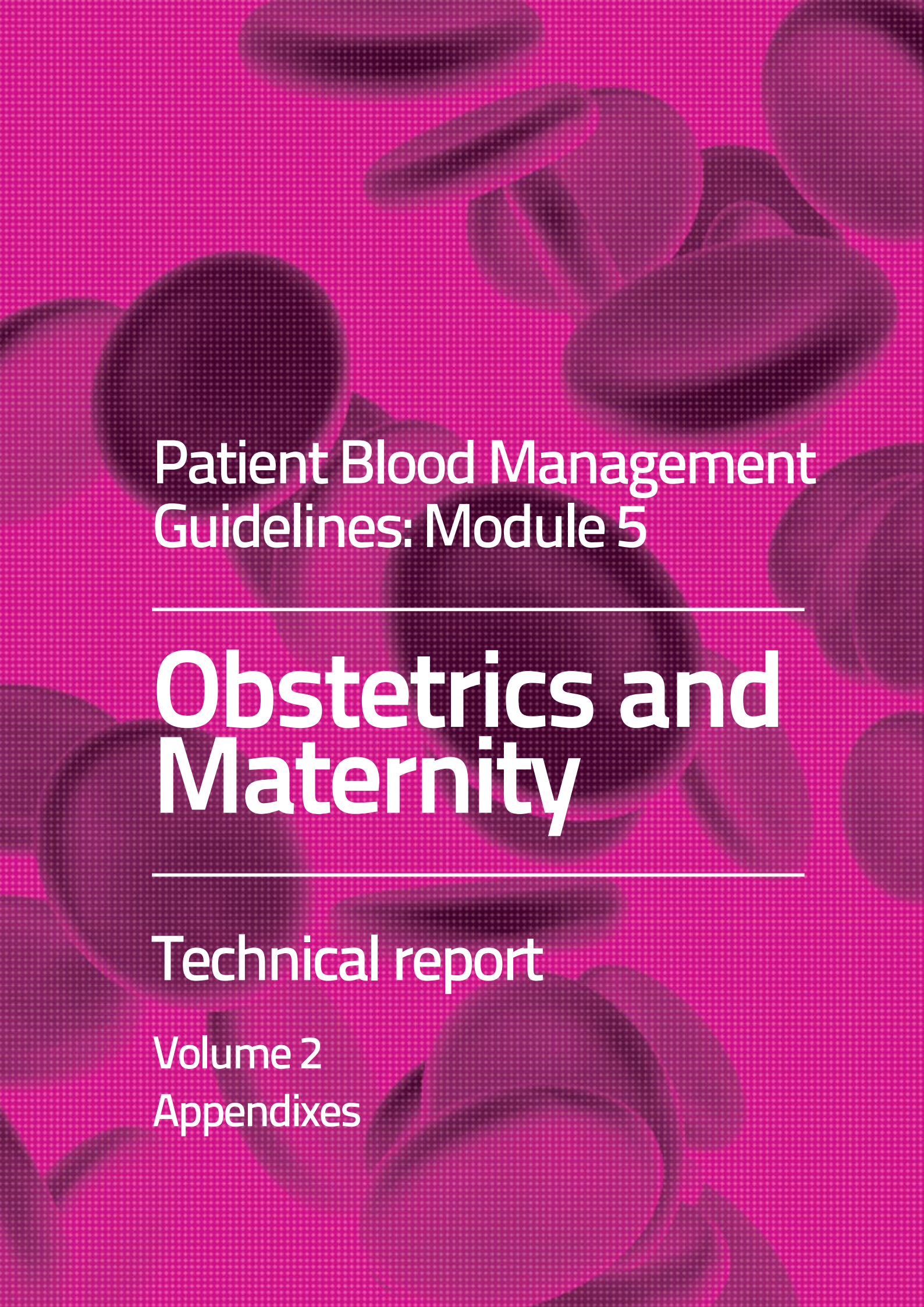

Patient Blood Management Guidelines: Module 5

Obstetrics and Maternity

Technical report

Volume 2
Appendixes

Note

This volume presents the appendixes (Appendix A to Appendix F) to a systematic literature review on obstetric and maternity patient blood management. Volume 1 presents the main body of evidence. These two volumes cover all research questions developed for this topic.

Contents

Tables

Appendix A Literature searches

A1 Literature search – Question 1

Table A1.1 EMBASE.com search for Level I, Level II and Level III evidence conducted 12 June 2013

#	Query	Results
#1	'meta analysis'/exp OR 'meta analysis' OR 'systematic review'/exp OR 'systematic review' OR 'pooled analysis' OR ('review'/exp OR 'review' AND (systemat* OR pool*))	203523
#2	'comparative study'/exp OR 'comparative study' OR 'clinical trial'/exp OR 'clinical trial' OR 'randomized controlled trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'single blind procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'placebo'/exp OR placebo* OR random* OR rct OR 'single blind' OR 'single blinded' OR 'double blind' OR 'double blinded' OR 'treble blind' OR 'treble blinded' OR 'triple blind' OR 'triple blinded' OR 'prospective study'/exp OR 'prospective study'	2768458
#3	'clinical study'/exp OR 'case control study'/exp OR 'family study'/exp OR 'longitudinal study'/exp OR 'retrospective study'/exp OR ('prospective study'/exp NOT 'randomized controlled trials'/exp) OR 'cohort analysis'/exp OR cohort NEXT/1 (study OR studies) OR 'case control' NEXT/1 (study OR studies) OR 'follow up' NEXT/1 (study OR studies) OR observational NEXT/1 (study OR studies) OR epidemiologic* NEXT/1 (study OR studies) OR 'cross sectional' NEXT/1 (study OR studies)	6580388
#4	'blood transfusion'/exp OR (blood NEAR/4 transfus*):de,ab,ti OR 'erythrocyte transfusion':de,ab,ti OR 'erythrocyte transfusions':de,ab,ti OR (('red blood cell' OR 'rbc' OR 'red cell') NEAR/1 transfusion*):de,ab,ti OR (('red blood cell' OR 'rbc') NEAR/1 exchange*):de,ab,ti OR (('red cell' OR 'red cells') NEAR/3 exchange*):de,ab,ti	140112
#5	'restrictive transfusion trigger':de,ab,ti OR (restrictive NEAR/3 transfus*):de,ab,ti OR (low NEAR/3 transfusion*):de,ab,ti	967
#6	liberal:de,ab,ti AND transfus*:de,ab,ti OR (high NEAR/3 transfusion*):de,ab,ti	1130
#7	'hemoglobin blood level'/exp OR (transfusion NEAR/1 (threshold* OR trigger* OR strateg* OR polic* OR practice* OR protocol* OR guideline*)):de,ab,ti OR ('hemoglobin'/exp OR haemoglobin:de,ab,ti OR hemoglobin:de,ab,ti AND (level*:de,ab,ti OR threshold*:de,ab,ti OR concentration*:de,ab,ti OR content:de,ab,ti)) OR 'blood hemoglobin':de,ab,ti OR 'blood haemoglobin':de,ab,ti OR 'plasma hemoglobin':de,ab,ti OR 'plasma haemoglobin':de,ab,ti OR 'serum hemoglobin':de,ab,ti OR 'serum haemoglobin':de,ab,ti OR 'hematocrit'/exp OR 'hct':de,ab,ti OR 'haematocrit':de,ab,ti OR 'hemocrit':de,ab,ti	172764
#8	#4 OR #5 OR #6 OR #7	296654
#9	'obstetrics'/exp OR 'obstetric care'/exp OR 'pregnancy'/exp OR 'pregnancy disorder'/exp OR 'fetus'/exp OR 'prenatal disorder'/exp OR 'obstetric':de,ab,ti OR 'obstetrics':de,ab,ti OR 'fetus':de,ab,ti OR 'fetal':de,ab,ti OR 'foetus':de,ab,ti OR 'foetal':de,ab,ti OR 'pregnancy':de,ab,ti OR 'antenatal':de,ab,ti OR 'ante natal':de,ab,ti OR 'ante-natal':de,ab,ti OR 'prenatal':de,ab,ti OR 'pre natal':de,ab,ti OR 'pre-natal':de,ab,ti OR 'postnatal':de,ab,ti OR 'post natal':de,ab,ti OR 'post-natal':de,ab,ti OR 'perinatal':de,ab,ti OR 'peri natal':de,ab,ti OR 'peri-natal':de,ab,ti OR prepartum:de,ab,ti OR 'pre partum':de,ab,ti OR 'pre-partum':de,ab,ti OR postpartum:de,ab,ti OR 'post partum':de,ab,ti OR 'post-partum':de,ab,ti OR intrapartum:de,ab,ti OR 'intra partum':de,ab,ti OR 'intra-partum':de,ab,ti OR maternal:de,ab,ti	1313033
Level I Results		
#10	#1 AND #8 AND #9 AND [1985-2013]/py	553
Level II Results		

#11	#2 AND #8 AND #9 AND [1985-2013]/py	4584
#12	#11 NOT #10	4225
#13	#3 AND #8 AND #9 AND [1985-2013]/py	13263
Level III Results		
#14	#13 NOT #12	9913

Table A1.2 Cochrane library: search conducted 12 June 2013

#	Query	Results
#1	MeSH descriptor: [Erythrocyte Transfusion] explode all trees	442
#2	MeSH descriptor: [Blood Transfusion] explode all trees	3019
#3	blood near/3 transfusion	5300
#4	"erythrocyte transfusion" or "erythrocyte transfusions"	546
#5	("red blood cell" or rbc) near/1 transfusion*	446
#6	"red cell" near/1 transfusion*	222
#7	("red blood cell" or rbc) near/1 exchange	2
#8	("red cell" or "red cells") near/3 exchange	5
#9	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8)	5899
#10	(restrictive and transfus*)	81
#11	(restrictive or low) near/3 transfusion*	270
#12	(#10 or #11)	302
#13	(liberal and transfus*)	64
#14	(liberal or high) near/3 transfusion*	204
#15	(#13 or #14)	227
#16	"transfusion threshold" or "transfusion thresholds"	51
#17	transfusion near/1 trigger*	67
#18	"transfusion strategy" or "transfusion strategies"	52
#19	"transfusion policy" or "transfusion policies"	28
#20	"transfusion practice" or "transfusion practices"	61
#21	"transfusion protocol" or "transfusion protocols"	62
#22	transfusion near/1 guideline*	42
#23	"hemoglobin threshold" or "hemoglobin trigger"	7
#24	"hematocrit threshold" or "hematocrit trigger"	3
#25	"haemoglobin threshold" or "haemoglobin trigger"	9
#26	"haematocrit threshold" or "haematocrit trigger"	2
#27	"hb threshold" or "hb trigger"	8

#28	"hct threshold" or "hct trigger"	0
#29	"hemoglobin thresholds" or "hemoglobin triggers"	5
#30	"hematocrit thresholds" or "hematocrit triggers"	1
#31	"haemoglobin thresholds" or "haemoglobin triggers"	4
#32	"haematocrit thresholds" or "haematocrit triggers"	2
#33	"hb thresholds" or "hb triggers"	2
#34	"hct thresholds" or "hct triggers"	0
#35	(#16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34)	280
#36	(#9 or #12 or #15 or #35)	6018
#37	MeSH descriptor: [Obstetrics] explode all trees	120
#38	MeSH descriptor: [Pregnancy] explode all trees	5318
#39	MeSH descriptor: [Pregnancy Complications] explode all trees	6985
#40	MeSH descriptor: [Fetus] explode all trees	1404
#41	obstetric or obstetrics	19854
#42	fetus or foetus or fetal or foetal	7262
#43	pregnancy	23005
#44	antenatal or 'ante natal' or 'ante-natal'	1896
#45	prenatal or 'pre natal' or 'pre-natal'	3173
#46	postnatal or 'post natal' or 'post-natal'	2188
#47	perinatal or 'peri natal' or 'peri-natal'	3636
#48	prepartum or 'pre partum' or 'pre-partum'	202
#49	postpartum or 'post partum' or 'post-partum'	3715
#50	intrapartum or 'intra partum' or 'intra-partum'	778
#51	maternal	8372
#52	#37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51	40210
#53	#36 and #52	699
#54	#53 from 1985 to 2013, in Cochrane Reviews (Reviews and Protocols), Other Reviews, Technology Assessments and Economic Evaluations	371
#55	#53 from 1985 to 2013, in Trials, Methods Studies and Cochrane Groups	302

A2 Literature search – Question 2

Table A2.1 EMBASE.com search for Level I, Level II and Level III studies conducted 12 June 2013

#	Query	Results
#1	'meta analysis'/exp OR 'meta analysis' OR 'systematic review'/exp OR 'systematic review' OR 'pooled analysis' OR ('review'/exp OR 'review' AND (systemat* OR pool*))	203686
#2	'comparative study'/exp OR 'comparative study' OR 'clinical trial'/exp OR 'clinical trial' OR 'randomized controlled trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'single blind procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'placebo'/exp OR placebo* OR random* OR rct OR 'single blind' OR 'single blinded' OR 'double blind' OR 'double blinded' OR 'treble blind' OR 'treble blinded' OR 'triple blind' OR 'triple blinded' OR 'prospective study'/exp OR 'prospective study'	2769449
#3	'clinical study'/exp OR 'case control study'/exp OR 'family study'/exp OR 'longitudinal study'/exp OR 'retrospective study'/exp OR ('prospective study'/exp NOT 'randomized controlled trials'/exp) OR 'cohort analysis'/exp OR cohort NEXT/1 (study OR studies) OR 'case control' NEXT/1 (study OR studies) OR 'follow up' NEXT/1 (study OR studies) OR observational NEXT/1 (study OR studies) OR epidemiologic* NEXT/1 (study OR studies) OR 'cross sectional' NEXT/1 (study OR studies)	6582344
#4	'erythropoietin'/exp OR 'recombinant erythropoietin'/exp OR erthropoietin OR erythropoietin OR 'erythropoiesis stimulating' OR 'erythropoietic factor' OR hematopoietin OR hemopoietin OR haematopoietin OR haemopoietin OR darbepoetin OR rhuepo OR 'rhu epo' OR 'r hu epo' AND [1985-2013]/py	42466
#5	'iron'/exp OR iron OR ferrous NEXT/1 (sulfate OR fumarate) OR 'heme iron polypeptide' OR 'cosmofer' OR 'dexferrum' OR 'imferon' OR 'infed' OR '9004 66 4':rn OR '7720 78 7':rn AND [1970-2013]/py	236560
#6	#4 OR #5	271148
#7	'obstetrics'/exp OR 'obstetric care'/exp OR 'pregnancy'/exp OR 'pregnancy disorder'/exp OR 'fetus'/exp OR 'prenatal disorder'/exp OR 'obstetric':de,ab,ti OR 'obstetrics':de,ab,ti OR 'fetus':de,ab,ti OR 'fetal':de,ab,ti OR 'foetus':de,ab,ti OR 'foetal':de,ab,ti OR 'pregnancy':de,ab,ti OR 'antenatal':de,ab,ti OR 'ante natal':de,ab,ti OR 'ante-natal':de,ab,ti OR 'prenatal':de,ab,ti OR 'pre natal':de,ab,ti OR 'pre-natal':de,ab,ti OR 'postnatal':de,ab,ti OR 'post natal':de,ab,ti OR 'post-natal':de,ab,ti OR 'perinatal':de,ab,ti OR 'peri natal':de,ab,ti OR 'peri-natal':de,ab,ti OR prepartum:de,ab,ti OR 'pre partum':de,ab,ti OR 'pre-partum':de,ab,ti OR postpartum:de,ab,ti OR 'post partum':de,ab,ti OR 'post-partum':de,ab,ti OR intrapartum:de,ab,ti OR 'intra partum':de,ab,ti OR 'intra-partum':de,ab,ti OR maternal:de,ab,ti	1313357
Level I Results		
#8	#1 AND #6 AND #7	334
Level II Results		
#9	#2 AND #6 AND #7	2937
#10	#9 NOT #8	2732
#11	#3 AND #6 AND #7	5559
Level III Results		
#12	#11 NOT #10	3676

Table A2.2 Cochrane library database search conducted 12 June 2013

#	Query	Results
#1	MeSH descriptor: [Erythropoietin] explode all trees	1383
#2	MeSH descriptor: [Iron] explode all trees	1557
#3	(erthropoietin or "erythropoiesis stimulating factor")	3
#4	erythropoietic near/1 factor	0
#5	(hematopoietin or hemopoietin)	2
#6	(haematopoietin or haemopoietin)	1
#7	(rHuEPO or "rHu EPO" or "r Hu EPO")	383
#8	iron or ferrous next/1 (sulfate or fumarate) or 'heme iron polypeptide' or 'cosmofer' or 'dexferrum' or 'imferon' or 'infed'	4180
#9	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8)	5311
#10	MeSH descriptor: [Obstetrics] explode all trees	120
#11	MeSH descriptor: [Pregnancy] explode all trees	5318
#12	MeSH descriptor: [Pregnancy Complications] explode all trees	6985
#13	MeSH descriptor: [Fetus] explode all trees	1404
#14	obstetric or obstetrics	19854
#15	fetus or foetus or fetal or foetal	7262
#16	pregnancy	23005
#17	antenatal or 'ante natal' or 'ante-natal'	1896
#18	prenatal or 'pre natal' or 'pre-natal'	3173
#19	postnatal or 'post natal' or 'post-natal'	2188
#20	perinatal or 'peri natal' or 'peri-natal'	3636
#21	prepartum or 'pre partum' or 'pre-partum'	202
#22	postpartum or 'post partum' or 'post-partum'	3715
#23	intrapartum or 'intra partum' or 'intra-partum'	778
#24	maternal	8372
#25	(#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24)	40210
#26	#9 and #25	901
#27	#26 in Cochrane Reviews (Reviews and Protocols), Other Reviews, Technology Assessments and Economic Evaluations	236
#28	#26 in Trials, Methods Studies and Cochrane Groups	665

A3 Literature search – Question 3

Table A3.1 EMBASE.com search for Level I, II and III studies conducted 12 June 2013

#	Query	Results
#1	'meta analysis'/exp OR 'meta analysis' OR 'systematic review'/exp OR 'systematic review' OR 'pooled analysis' OR ('review'/exp OR 'review' AND (systemat* OR pool*))	203686
#2	'comparative study'/exp OR 'comparative study' OR 'clinical trial'/exp OR 'clinical trial' OR 'randomized controlled trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'single blind procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'placebo'/exp OR placebo* OR random* OR rct OR 'single blind' OR 'single blinded' OR 'double blind' OR 'double blinded' OR 'treble blind' OR 'treble blinded' OR 'triple blind' OR 'triple blinded' OR 'prospective study'/exp OR 'prospective study'	2769449
#3	'clinical study'/exp OR 'case control study'/exp OR 'family study'/exp OR 'longitudinal study'/exp OR 'retrospective study'/exp OR ('prospective study'/exp NOT 'randomized controlled trials'/exp) OR 'cohort analysis'/exp OR cohort NEXT/1 (study OR studies) OR 'case control' NEXT/1 (study OR studies) OR 'follow up' NEXT/1 (study OR studies) OR observational NEXT/1 (study OR studies) OR epidemiologic* NEXT/1 (study OR studies) OR 'cross sectional' NEXT/1 (study OR studies)	6582344
#4	'blood component'/exp OR blood NEXT/1 component* OR blood NEXT/1 product* OR transfusion NEXT/1 product* OR blood NEXT/1 constituent*	44108
#5	'fresh frozen plasma'/exp OR 'plasma'/exp OR 'fresh frozen plasma' OR ffp	106691
#6	'cryoprecipitate'/exp OR 'cryoprecipitate coagulum' OR cryoprecipitate OR 'cryo precipitate'	3523
#7	'fibrinogen'/exp OR fibrinogen OR 'factor 1' OR 'factor i'	174469
#8	#4 OR #5 OR #6 OR #7	313868
#9	'transfusion'/exp OR transfus* OR 'blood exchange' OR 'blood infusion' OR 'blood replacement' OR 'blood retransfusion' OR hemotherapy OR hematherapy OR hematotherapy OR haemotherapy OR haematherapy OR haematotherapy OR multitransfusion OR polytransfusion OR retransfusion OR 'transfusion blood' OR 'transfusion therapy'	302047
#10	#8 AND #9	49979
#11	'plasma transfusion'/exp OR 'plasma transfusion' OR 'plasma infusion' OR 'serum transfusion'	2988
#12	'thrombocyte transfusion'/exp OR ('thrombocyte'/exp AND ('blood transfusion'/exp OR 'transfusion'/exp)) OR 'platelet' NEAR/1 'transfusion' OR 'platelet' NEAR/1 'transfusions' OR 'transfusion' NEAR/3 'platelet' OR 'transfusion' NEAR/3 'platelets' OR 'thrombocyte transfusion' OR 'thrombocytic transfusion'	18415
#13	#10 OR #11 or #12	55168
#14	'obstetrics'/exp OR 'obstetric care'/exp OR 'pregnancy'/exp OR 'pregnancy disorder'/exp OR 'fetus'/exp OR 'prenatal disorder'/exp OR 'obstetric':de,ab,ti OR 'obstetrics':de,ab,ti OR 'fetus':de,ab,ti OR 'fetal':de,ab,ti OR 'foetus':de,ab,ti OR 'foetal':de,ab,ti OR 'pregnancy':de,ab,ti OR 'antenatal':de,ab,ti OR 'ante natal':de,ab,ti OR 'ante-natal':de,ab,ti OR 'prenatal':de,ab,ti OR 'pre natal':de,ab,ti OR 'pre-natal':de,ab,ti OR 'postnatal':de,ab,ti OR 'post natal':de,ab,ti OR 'post-natal':de,ab,ti OR 'perinatal':de,ab,ti OR 'peri natal':de,ab,ti OR 'peri-natal':de,ab,ti OR prepartum:de,ab,ti OR 'pre partum':de,ab,ti OR 'pre-partum':de,ab,ti OR postpartum:de,ab,ti OR 'post partum':de,ab,ti OR 'post-partum':de,ab,ti OR intrapartum:de,ab,ti OR 'intra partum':de,ab,ti OR 'intra-partum':de,ab,ti OR maternal:de,ab,ti	1313357
Level I Results		
#15	#1 AND #13 AND #14 AND [1985-2013]/py	155

Level II Results		
#16	#2 AND #13 AND #14 AND [1985-2013]/py	775
#17	#16 NOT #15	696
#18	#3 AND #13 AND #14 AND [1985-2013]/py	2819
Level III Results		
#19	#18 NOT #17	2288

Table A3.2 Cochrane library database search conducted 12 June 2013

#	Query	Results
#1	MeSH descriptor: [Blood Component Transfusion] explode all trees	785
#2	MeSH descriptor: [Blood Transfusion] explode all trees	3019
#3	*transfus*	8397
#4	"blood exchange" or "blood infusion"	57
#5	"blood replacement"	72
#6	hemotherapy or hematherapy or hematotherapy	62
#7	haemotherapy or haematherapy or haematotherapy	8
#8	(#1 or #2 or #3 or #4 or #5 or #6 or #7)	8654
#9	"blood component" or "blood components"	498
#10	"blood product" or "blood products"	797
#11	"transfusion product" or "transfusion products"	13
#12	"blood constituent" or "blood constituents"	18
#13	(#9 or #10 or #11 or #12)	1243
#14	(#8 and #13)	812
#15	MeSH descriptor: [Plasma] explode all trees	449
#16	"fresh frozen plasma" or FFP	452
#17	#15 or #16	801
#18	#8 and #17	379
#19	"plasma transfusion"	49
#20	"plasma infusion" or "serum transfusion"	20
#21	(#18 or #19 or #20)	413
#22	cryoprecipitate or "cryo precipitate"	85
#23	(#22 and #8)	56
#24	fibrinogen or "factor 1" or "factor I"	5250
#25	(#8 and #24)	375
#26	MeSH descriptor: [Platelet Transfusion] explode all trees	245

#27	MeSH descriptor: [Blood Platelets] explode all trees	1565
#28	(#8 and #27)	153
#29	platelet* near/3 transfusion*	685
#30	"thrombocyte transfusion" or "thrombocytic transfusion"	50
#31	(#26 or #28 or #29 or #30)	760
#32	(#14 or #21 or #23 or #25 or #31)	1859
#33	MeSH descriptor: [Obstetrics] explode all trees	120
#34	MeSH descriptor: [Pregnancy] explode all trees	5318
#35	MeSH descriptor: [Pregnancy Complications] explode all trees	6985
#36	MeSH descriptor: [Fetus] explode all trees	1404
#37	obstetric or obstetrics	19854
#38	fetus or foetus or fetal or foetal	7262
#39	pregnancy	23005
#40	antenatal or 'ante natal' or 'ante-natal'	1896
#41	prenatal or 'pre natal' or 'pre-natal'	3173
#42	postnatal or 'post natal' or 'post-natal'	2188
#43	perinatal or 'peri natal' or 'peri-natal'	3636
#44	prepartum or 'pre partum' or 'pre-partum'	202
#45	postpartum or 'post partum' or 'post-partum'	3715
#46	intrapartum or 'intra partum' or 'intra-partum'	778
#47	maternal	8372
#48	(#33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47)	40210
#49	#32 and #48 from 1985 to 2013	133
#50	#49 from 1985 to 2013, in Cochrane Reviews (Reviews and Protocols), Other Reviews, Technology Assessments and Economic Evaluations	107
#51	#49 from 1985 to 2013, in Trials, Methods Studies and Cochrane Groups	26

A4 Literature search – Question 4

Table A4.1 EMBASE.com search for Level I, II and III studies conducted 12 June 2013

#	Query	Results
#1	'meta analysis'/exp OR 'meta analysis' OR 'systematic review'/exp OR 'systematic review' OR 'pooled analysis' OR ('review'/exp OR 'review' AND (systemat* OR pool*))	203686
#2	'comparative study'/exp OR 'comparative study' OR 'clinical trial'/exp OR 'clinical trial' OR 'randomized controlled trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'single blind procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'placebo'/exp OR placebo* OR random* OR rct OR 'single blind' OR 'single blinded' OR 'double blind' OR 'double blinded' OR 'treble blind' OR 'treble blinded' OR 'triple blind' OR 'triple blinded' OR 'prospective study'/exp OR 'prospective study'	2769449
#3	'clinical study'/exp OR 'case control study'/exp OR 'family study'/exp OR 'longitudinal study'/exp OR 'retrospective study'/exp OR ('prospective study'/exp NOT 'randomized controlled trials'/exp) OR 'cohort analysis'/exp OR cohort NEXT/1 (study OR studies) OR 'case control' NEXT/1 (study OR studies) OR 'follow up' NEXT/1 (study OR studies) OR observational NEXT/1 (study OR studies) OR epidemiologic* NEXT/1 (study OR studies) OR 'cross sectional' NEXT/1 (study OR studies)	6582344
#4	'teg':de,ab,ti OR 'sonoclot':de,ab,ti OR 'rotem':de,ab,ti OR 'roteg':de,ab,ti OR hemocue OR 'international normalised ratio':de,ab,ti OR 'hemoglobin test':de,ab,ti OR 'hb test':de,ab,ti OR 'thromboelastograph':de,ab,ti OR 'thromboelastography':de,ab,ti OR 'thromboelastograpy':de,ab,ti OR 'hemoglobin blood level'/exp OR 'hemoglobin blood level' OR 'hemoglobin blood level':de,ab,ti OR 'thrombelastography':de,ab,ti OR 'haemoglobin blood level'/exp OR 'haemoglobin blood level'	30834
#5	'antifibrinolytic agent'/exp OR antifibrinolytic* OR 'anti fibrinolytic' OR 'anti fibrinolytics' OR antiplasmin* OR 'anti plasmin' OR 'anti plasmins' OR antifibrinolysin* OR 'anti fibrinolysin' OR 'anti fibrinolysins' OR 'fibrinolysis inhibitor'/exp OR 'fibrinolysis inhibitors' OR 'plasmin inhibitor'/exp OR 'plamin inhibitors' OR 'tranexamic acid'/exp OR 'tranexamic acid' OR 'cyklokapron'/exp OR 'cyklokapron' OR '1197 18 8':rn OR '701 54 2':rn	29299
#6	'blood salvage'/exp OR 'blood salvage' OR 'salvage therapy'/exp OR 'salvage therapy' OR 'cell salvage' OR 'erythrocyte salvage' OR 'cell saver' OR 'cell savers'	
#7	recombinant AND blood AND clotting AND factor AND 7a OR (blood AND clotting AND factor AND 7a AND recombinant AND 'protein'/exp) OR 'recombinant fviia':de OR 'recombinant activated factor vii':tn,ab,ti OR ('recombinant' NEXT/3 'viia'):tn,ab,ti OR ('recombinant' NEXT/3 'fviia'):tn,ab,ti OR 'recombinant f viia':tn,ab,ti OR rfviia:tn,ab,ti OR 'r fviia':tn,ab,ti OR 'r f viia':tn,ab,ti OR rf7a:tn,ab,ti OR 'eptacog alfa':tn,ab,ti OR niastase:tn,ab,ti OR 'novo seven':tn,ab,ti OR novoseven:tn,ab,ti OR 'nn 1731':de,tn,ab,ti OR nn1731:tn,ab,ti	6283
#8	'blood clotting factor viia':tn,ab,ti OR 'coagulation factor viia':tn,ab,ti OR ('activated' NEXT/3 'factor vii'):tn,ab,ti OR ('activated' NEXT/3 'fvii'):tn,ab,ti OR acset:tn,ab,ti OR ('activated' NEXT/3 'factor 7'):tn,ab,ti OR ('activated' NEXT/3 'f7'):tn,ab,ti OR '98982 74 2':rn AND recombinant:ab,ti	1964
#9	#7 or #8	6346
#10	'interventional radiology'/exp OR 'balloon catheter'/exp OR 'balloon embolization'/exp OR 'artificial embolism'/exp OR 'interventional radiology' OR 'balloon embolisation' OR iliac AND balloon* NEAR/3 catheter* OR iliac AND balloon* NEAR/3 occlusion OR balloon* NEAR/3 emboli?ation	4360
#11	#4 OR #5 OR #6 OR #9 OR #10	88713
#12	'perinatal period'/exp OR 'obstetrics'/exp OR 'obstetric care'/exp OR 'pregnancy'/exp OR 'pregnancy disorder'/exp OR 'fetus'/exp OR 'prenatal disorder'/exp OR 'obstetric':de,ab,ti OR 'obstetrics':de,ab,ti OR 'fetus':de,ab,ti OR 'fetal':de,ab,ti OR 'foetus':de,ab,ti OR 'foetal':de,ab,ti OR 'pregnancy':de,ab,ti OR 'antenatal':de,ab,ti OR 'ante natal':de,ab,ti OR 'ante-natal':de,ab,ti OR 'prenatal':de,ab,ti OR 'pre natal':de,ab,ti OR 'pre-natal':de,ab,ti OR 'postnatal':de,ab,ti OR 'post natal':de,ab,ti OR 'post-natal':de,ab,ti OR 'perinatal':de,ab,ti OR 'peri natal':de,ab,ti OR 'peri-natal':de,ab,ti OR	1313357

	prepartum:de,ab,ti OR 'pre partum':de,ab,ti OR 'pre-partum':de,ab,ti OR postpartum:de,ab,ti OR 'post partum':de,ab,ti OR 'post-partum':de,ab,ti OR intrapartum:de,ab,ti OR 'intra partum':de,ab,ti OR 'intra-partum':de,ab,ti OR maternal:de,ab,ti	
Level I Results		
#13	#1 AND #11 AND #12 AND [1985-2013]/py	158
Level II Results		
#14	#2 AND #11 AND #12 AND [1985-2013]/py	1140
#15	#14 NOT #13	1033
#16	#3 AND #11 AND #12 AND [1985-2013]/py	2851
Level III Results		
#17	#16 NOT #15	2002

Table A4.2 Cochrane library database search conducted 12 June 2013

#	Query	Results
#1	MeSH descriptor: [Thrombelastography] explode all trees	146
#2	Sonoclot	12
#3	rotem	32
#4	roteg	6
#5	"international normalized ratio"	694
#6	"international normalised ratio"	210
#7	"haemoglobin test"	3
#8	"hemoglobin test"	3
#9	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8)	1035
#10	MeSH descriptor: [Antifibrinolytic Agents] explode all trees	379
#11	MeSH descriptor: [Tranexamic Acid] explode all trees	331
#12	(antifibrinolytic* or "anti fibrinolytic" or "anti fibrinolytics")	602
#13	(antiplasmin* or "anti plasmin" or "anti plasmins")	278
#14	(antifibrinolysin* or "anti fibrinolysin" or "anti fibrinolysins")	5
#15	"fibrinolysis inhibitor" or "fibrinolysis inhibitors"	36
#16	"plasmin inhibitor" or "plamin inhibitors"	59
#17	"tranexamic acid" or Cyklokapron	572
#18	(#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17)	1121
#19	MeSH descriptor: [Salvage Therapy] explode all trees	433
#20	"blood salvage" or "salvage therapy" or "cell salvage" or "erythrocyte salvage" or "cell saver" or "Cell savers"	873
#21	(#19 or #20)	873

#22	MeSH descriptor: [Factor VIIa] explode all trees	183
#23	MeSH descriptor: [Recombinant Proteins] explode all trees	6995
#24	#22 and #23	124
#25	"recombinant activated factor VII"	102
#26	"recombinant *2 VIIa" or "Recombinant *2 FVIIa"	99
#27	"recombinant F VIIa" or rFVIIa or "r FVIIa" or "r F VIIa" or rf7a	158
#28	"eptacog alfa" or niastase or "Novo Seven" or Novoseven	74
#29	"nn 1731" or nn1731	3
#30	"blood clotting factor viia" or "coagulation factor viia"	8
#31	Activated near/2 ("Factor VII" or "FVII")	187
#32	Activated near/2 ("Factor 7" or "F7")	2
#33	acset 1	1
#34	(#30 or #31 or #32 or #33)	196
#35	recombinant	11357
#36	(#34 and #35)	139
#37	(#24 or #25 or #26 or #27 or #28 or #29 or #36)	252
#38	MeSH descriptor: [Radiology, Interventional] explode all trees	36
#39	MeSH descriptor: [Radiography, Interventional] explode all trees	163
#40	MeSH descriptor: [Balloon Occlusion] explode all trees	63
#41	'interventional radiology'	629
#42	iliac and balloon* near/3 catheter*	6
#43	iliac and balloon* near/3 occlusion	4
#44	emboli?ation	902
#45	#38 or #39 or #40 or #41 or #42 or #43 or #44	1585
#46	#9 or #18 or #21 or #37 or #45	4728
#47	MeSH descriptor: [Obstetrics] explode all trees	120
#48	MeSH descriptor: [Pregnancy] explode all trees	5318
#49	MeSH descriptor: [Pregnancy Complications] explode all trees	6985
#50	MeSH descriptor: [Peripartum Period] explode all trees	5
#51	MeSH descriptor: [Fetus] explode all trees	1404
#52	obstetric or obstetrics or childbirth or "child birth"	20513
#53	fetus or foetus or fetal or foetal	7262
#54	pregnancy	23006
#55	peripartum or 'peri partum' or 'peri-partum'	162
#56	antenatal or 'ante natal' or 'ante-natal'	1896

#57	prenatal or 'pre natal' or 'pre-natal'	3173
#58	postnatal or 'post natal' or 'post-natal'	2188
#59	perinatal or 'peri natal' or 'peri-natal'	3636
#60	prepartum or 'pre partum' or 'pre-partum'	202
#61	postpartum or 'post partum' or 'post-partum'	3715
#62	intrapartum or 'intra partum' or 'intra-partum'	778
#63	maternal	8372
#64	(#47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63)	40316
#65	#46 and #64 from 1985 to 2013	308
#66	#65 from 1985 to 2013, in Cochrane Reviews (Reviews and Protocols), Other Reviews, Technology Assessments and Economic Evaluations	172
#67	#65 from 1985 to 2013, in Trials, Methods Studies and Cochrane Groups	136

Appendix B Excluded studies

This appendix documents studies that met inclusion criteria determined by PICO criteria, but were later excluded. These studies, and their reasons for exclusion, are listed below.

B1 Studies excluded from Question 1

Level I evidence

The following studies were excluded for reasons other than not meeting the PICO criteria:

Article not in English

Irita, K. and Inada, E. (2011) Guidelines for management of critical bleeding in obstetrics. *Jpn.J.Anesthesiol.* **60** (1) 14-2

No usable data

Alexander, J, Peter W. Thomas, and Sanghera, J. (2002) Treatments for secondary postpartum haemorrhage. *Cochrane Database of Systematic Reviews* [no RCTs identified]

Dodd, J., M. R. Dare, and P. Middleton. Treatment for women with postpartum iron deficiency anaemia. *Cochrane database of systematic reviews (Online)*.**4** (2004): CD004222. [no RCTs identified]

Henriquez, Dacia, et al. (2011) Treatment of valvular heart disease during pregnancy for improving maternal and neonatal outcome. *Cochrane Database of Systematic Reviews*) [no RCTs identified]

Leduc, D., Senikas, V., Lalonde, A. B., Ballerman, C., Biringer, A., Delaney, M., Duperron, L., Girard, I., Jones, D., Lee, L. S., Shepherd, D., and Wilson, K. (2009) Active management of the third stage of labour: prevention and treatment of postpartum hemorrhage. *J Obstet Gynaecol Can* **31** (10) 980-993 [Guidelines]

Marti-Carvajal, A. J., Pena-Marti, G. E., Comunian-Carrasco, G., and Marti-Pena, A. J (2009). Interventions for treating painful sickle cell crisis during pregnancy. Cochrane Database Syst.Rev. **4** [no RCTs identified]

Neilson, James P. (2003) Interventions for treating placental abruption. *Cochrane Database of Systematic Reviews* [no RCTs identified]

Su, L. L. and Chong, Y. S. (2012) Massive obstetric haemorrhage with disseminated intravascular coagulopathy. *Best Pract.Res.Clin.Obstet.Gynaecol.* **26** (1) 77-90 [Guidelines]

No usable data (clinical practice guidelines - secondary sources)

British Committee for Standards in Haematology (2009) Guidelines for the diagnosis and management of aplastic anaemia. *NGC:007592* [Guidelines]

Dutch Institute for Healthcare Improvement CBO (2011) Chronic anaemia. In: Blood transfusion guideline. *NGC:009176* [Guidelines]

Dutch Institute for Healthcare Improvement CBO (2011) Transfusion policy for acute anaemia. In: Blood transfusiion guideline. *NGC:009177* [Guidelines]

Royal Australian and New Zealand College of Obstetricians and Gynaecologists (2011) Management of postpartum haemorrhage. *C-Obs 43* [Guidelines]

Royal College of Obstetricians and Gynaecologists (2008) Blood transfusions in obstetrics. *Green-top guideline no.47* [Guidelines]

Royal College of Obstetricians and Gynaecologists (2009) Prevention and management of postpartum haemorrhage. *NGC:008394* [Guidelines]

Royal College of Obstetricians and Gynaecologists (2011) Antepartum haemorrhage. *NGC:008986* [Guidelines]

Royal College of Obstetricians and Gynaecologists (2011) Management of sickle cell disease in pregnancy. *NGC:008805* [Guidelines]

Withdrawn/Superseded

Mahomed, K. (2000) Prophylactic versus selective blood transfusion for sickle cell anaemia during pregnancy. *Cochrane database of systematic reviews (Online).***2** : CD000040.

Mahomed, Kassam. (2006) Prophylactic versus selective blood transfusion for sickle cell anaemia during pregnancy. *Cochrane Database of Systematic Reviews (Online)*

Mahomed, K. (2007) Prophylactic versus selective blood transfusion for sickle cell anaemia during pregnancy. *Cochrane database of systematic reviews (Online)*.**3** (2007): CD000040.

Level II evidence

The following studies were excluded for reasons other than not meeting the PICO criteria:

Article not in English

Jablonski, J., Moniuszko-Jakoniuk, J., Kocmierska-Grodzka, D., and Miniuk, K. (1986) Evaluation of iron metabolism in pregnant and non-pregnant students of the Bialystok Medical Academy. *Rocz Akad Med Im Juliana Marchlewskiego Bialymst* **31-32** 101-110

Jansen, A. J. G., Duvekot, J. J., Essink-Bot, M. L., Hop, W. C. J., and Van Rhenen, D. J. (2007) Multicentre clinical study into the optimal blood transfusion policy in patients with postpartum haemorrhage: The 'Wellbeing of obstetric patients on minimal blood transfusions' (WOMB) study. *Ned Tijdschr Geneeskd* **151** (39) 2170-2172

Knottnerus, J. A., Delgado, L. R., Knipschild, P. G., Essed, G. G., and Smits, F. (1988) Hemoglobin levels, hematocrit and pregnancy outcome. *Ned Tijdschr Geneeskd* **132** (16) 719-723

Markin, S. A., Khamdamova, F. K., and Rymareva, V. I. (1988) Variants of corrective therapy in puerperants with anemia and a history of pathologic blood loss. *Akush Ginekol (Sofiia)* (9) 36-39

Proshina, I. V. and Piastunovich, K. A. (1988) Programs of infusion and transfusion therapy for obstetric and gynecologic patients in the early postoperative period. *Anesteziol Reanimatol* (5) 50-54

Saburov, K. S. and Khamdamova, F. K. (1990) Current state of the problem of anemia in pregnancy and the corrective therapy of postpartum hemorrhage. *Akush Ginekol (Sofiia)* (7) 10-12

Strizhakov, A. N., Bunin, A. T., and Baev, O. R. (1988) Status of central hemodynamics in puerperants with postpartum hemorrhage in relation to the characteristics of infusion therapy. *Akush Ginekol (Sofiia)* (9) 30-34

Vorob'ev, A. I., Gorodetskii, V. M., Vasil'ev, S. A., Panchenkov, N. R., and Fomin, M. D. (1999) Acute massive hemorrhage and disseminated intravascular coagulation. *Ter.Arkh.* **71** (7) 5-12

Zarubina, E. N., Tvorogov, P. A., and Barinov, V. G. (1995) Prevention and treatment of hemorrhage in obstetrical hospitals. *Akush Ginekol (Sofiia)* (4) 19-22

Zavarzina, O. O., Markin, S. A., and Smirnova, L. I. (1987) Replacement of blood loss during scheduled cesarean section. *Akush Ginekol (Sofiia)* (2) 12-15

No usable data

Adukauskiene, D., Veikutiene, A., Adukauskaite, A., Veikutis, V., and Rimaitis, K. (2010) The usage of blood components in obstetrics. *Medicina (Argentina)* **46** (8) 561-567 [Guidelines]

Fischerova, D. (2009) Urgent care in gynaecology: Resuscitation and management of sepsis and acute blood loss. *Best Practice and Research: Clinical Obstetrics and Gynaecology* **23** (5) 679-690 [Guidelines]

Mousa, H. A. and Walkinshaw, S. (2001) Major postpartum haemorrhage. *Curr.Opin.Obstet.Gynecol.* **13** (6) 595-603 [Guidelines]

Prick, B. W., Steegers, E. A. P., Jansen, A. G., Hop, W. C. J., Essink-Bot, M. L., Peters, N. C. J., Uyl-de Groot, C. A., Papatsonis, D. N. M., Akerboom, B. M. C., Metz, G. C. H., Bremer, H. A., Van Loon, A. J., Stigter, R. H., Van Der Post, J. A. M., Van Alphen, M., Porath, M., Rijnders, R. J. P., Spaanderman, M. E. A., Schippers, D. H., Bloemenkamp, K. W. M., Boers, K. E., Scheepers, H. C. J., Roumen, F. J. M. E., Kwee, A., Schuitemaker, N. W. E., Mol, B. W. J., Van Rhenen, D. J., and Duvekot, J. J. (2010) Well being of obstetric patients on minimal blood transfusions (WOMB trial). BMC Pregnancy Childbirth 10 [protocol only]

Prick, B. W., Jansen, A. J. G., Steegers, E. A. P., Hop, W. C. J., Essink-Bot, M. L., De Uyl-Groot, C. A., Akerboom, B. M. C., Van Alphen, M., Bloemenkamp, K. W. M., Boers, K. E., Bremer, H. A., Kwee, A., Van Loon, A. J., Metz, G. C. H., Papatsonis, D. N. M., Van Der Post, J. A. M., Porath, M., Rijnders, R. J. P., Roumen, F. J. M. E., Scheepers, H. C. J., Schippers, D. H., Schuitemaker, N. W. E., Spaanderman, M. E. A., Stigter, R. H., Mol, B. W. J., Van Rhenen, D. J., and Duvekot, J. (2012) Health related quality of life in patients with acute anemia after primary postpartum hemorrhage: A randomized controlled trial of red blood cell transfusion vs expectant management: The womb study. Vox Sang. 103 35- [full results not reported]

Prick, B. W., Gerard Jansen, A. J., Steegers, E. A. P., Hop, W. C. J., Essink-Bot, M. L., Uyl-de Groot, C. A., Papatsonis, D. N. M., Akerboom, B. M. C., Metz, G. C. H., Bremer, H. A., Van Loon, A. J., Stigter, R. H., Van Der Post, J. A. M., Van Alphen, M., Porath, M., Rijnders, R. J. P., Spaanderman, M. E. A., Schippers, D. H., Bloemenkamp, K. W. M., Boers, K. E., Scheepers, H. C. J., Roumen, F. J. M. E., Kwee, A., Schuitemaker, N. W. E., Mol, B. W. J., Van Rhenen, D. J., and Duvekot, J. J. (2012) RBC transfusion leads to an improvement of physical fatigue in women with acute postpartum anemia: The WOMB study (NCT00335023). AM.J.OBSTET.GYNECOL. 206 (1) S41-S42 [full results not reported]

Selo-Ojeme, D. O. (2002) Primary postpartum haemorrhage. *J.Obstet.Gynaecol.* **22** (5) 463-469 [Guidelines]

Level III evidence

The following studies were excluded for reasons other than not meeting the PICO criteria:

Article not in English

Antipenskaya, L. V. (1988) Immunomodulating action of blood transfusion in habitual abortion. *Immunologiya* (5) 61-65

Attal, J. P., Lafay-Pillet, M. C., and Taurelle, R. (1987) The value of systematic prophylactic blood transfusions in the outcome of pregnancies in patients with severe sickle cell anemia. Study of 63 deliveries in Guadeloupe. *J Gynecol Obstet Biol Reprod (Paris)* **16** (6) 787-793

Driss, F., Tertian, G., Becquemont, L., Haddad, B., Cynober, T., Raphael, M., and Tchernia, G. (2007) Management of high risk pregnancy in sickle cell disease by a strategy of prophylactic red cell transfusion or automated red cell exchange. *Transfus.Clin.Biol.* **14** (4) 386-392

Dupont, C., Deneux-Tharaux, C., Cortet, M., Colin, C., Touzet, S., Rabilloud, M., Lansac, J., Harvey, T., Tessier, V., Chauleur, C., Pennehouat, G., Morin, X., Bouvier-Colle, M. H., and Rudigoz, R. C. (2012) Practices for management of grave postpartum haemorrhage after vaginal delivery: A population-based study in 106 French maternity units. *J Gynecol Obstet Biol Reprod.* **41** (3) 279-289

Fernandez, H. (1995) Hemorrhages in obstetrics. *Reprod.Hum.Horm.* **8** (1-2) 39-46

Gomez Garcia, I. M., Avila Gordo, C., Morales Rodriguez, M. R., and Echevarria Moreno, M. (2006) Postpartum rupture of a healthy uterus. *Rev Esp Anestesiol Reanim* **53** (3) 201-202

Italiano, C., Fender, M., Masson, M., Schwartz-Haehnel, I., and Gschaedler, R. (1993) Deferred autologous transfusion in obstetrics. *Cah Anesthesiol* **41** (3) 227-229

Ozkan Seyhan, T., Orhan Sungur, M., Demircan, F., Kalelioglu, I., Iyibozkurt, A. C., and Senturk, M. (2012) Perioperative anaesthetic approach for placenta accreta cases (a retrospective analysis). *Anestezi Derg.* **20** (4) 223-232

Rath, W. (2011) [Postpartum Haemorrhage (PPH): "too little is done too late"!]. *Z Geburtshilfe Neonatol* **215** (5) 177-181

Weissenbacher, E. R., Wachter, I., Gutschow, K., Krebs, N., and Mempel, W. (1989) Postpartal infection after cesarean section due to perioperative blood transfusion. *ARCH.GYNECOL.OBSTET.* **245** (1-4) 305-307

No usable data

Osei, ED., Odoi, AT., Owusu-Ofori, S., and Allain, JP. (2013) Appropriateness of blood product transfusion in the Obstetrics and Gynaecology (O&G) department of a tertiary hospital in West Africa. *Transfus Med* **23** (3) 160-166

Rouse, D. J., MacPherson, C., Landon, M., Varner, M. W., Leveno, K. J., Moawad, A. H., Spong, C. Y., Caritis, S. N., Meis, P. J., Wapner, R. J., Sorokin, Y., Miodovnik, M., Carpenter, M., Peaceman, A. M., O'Sullivan, M. J., Sibai, B. M., Langer, O., Thorp, J. M., Ramin, S. M., and Mercer, B. M. (2006) Blood transfusion and cesarean delivery. *Obstet.Gynecol.* **108** (4) 891-897 [study evaluates risks for RBC transfusion]

Included < 100 subjects

Chigbu, B., Onwere, S., Kamanu, C., Aluka, C., Okoro, O., Feyi-Waboso, P., and Onichakwe, C. (2009) Lessons learned from the outcome of bloodless emergency laparotomies on Jehovah's Witness women presenting in the extremis with ruptured uterus. *Arch.Gynecol.Obstet.* **279** (4) 469-472

Howard, R. J., Tuck, S. M., and Pearson, T. C. (1995) Pregnancy in sickle cell disease in the UK: Results of a multicentre survey of the effect of prophylactic blood transfusion on maternal and fetal outcome. *Br.J.Obstet.Gynaecol.* **102** (12) 947-951

Tuck, S. M., James, C. E., and Brewster, E. M. (1987) Prophylactic blood transfusion in maternal sickle cell syndromes. *Br.J.Obstet.Gynaecol.* **94** (2) 121-125

B2 Studies excluded from Question 2

Level I evidence

The following studies were excluded for reasons other than not meeting the PICO criteria:

Article not in English

Berkane, N. and Uzan, S. (2004) The use of supplements in pregnancy. *J Gynecol Obstet Biol Reprod (Paris)* **33** (1 Suppl) S33-S36

Macedo, A. and Cardoso, S. (2010) Routine iron supplementation in pregnancy. *Acta Med.Port.* **23** (5) 785-792

Paesano, R., Pietropaoli, M., Gessani, S., and Valenti, P. (2011) [Activity of oral lactoferrin into systematic iron homeostasis in pregnant women suffering from iron deficiency and iron deficiency anemia]. *Akush Ginekol (Sofiia)* **50** (6) 51-52

Sachet, P. (1997) Supplementations during pregnancy. Consequences of iron deficiency, iron excess and the role of routine iron supplementation. *J.Gynecol.Obstet.Biol.Reprod.* **26** (SUPPL. 3) 59-66

Duplicate data

Barros, F. C., Bhutta, Z. A., Batra, M., Hansen, T. N., Victora, C. G., and Rubens, C. E. (2010) Global report on preterm birth and stillbirth (3 of 7): Evidence for effectiveness of interventions. *BMC Pregnancy Childbirth* **10** (SUPPL. 1)

Bhutta, Z. A., Lassi, Z. S., Blanc, A., and Donnay, F. (2010) Linkages Among Reproductive Health, Maternal Health, and Perinatal Outcomes. *Semin.Perinatol.* **34** (6) 434-445

Collin, S. M., Baggaley, R. F., Pittrof, R., and Filippi, V. (2007) Could a simple antenatal package combining micronutritional supplementation with presumptive treatment of infection prevent maternal deaths in sub-Saharan Africa? *BMC Pregnancy Childbirth* **7**

Dunlop, A. L., Kramer, M. R., Hogue, C. J. R., Menon, R., and Ramakrishan, U. (2011) Racial disparities in preterm birth: An overview of the potential role of nutrient deficiencies. *Acta Obstet.Gynecol.Scand.* **90** (12) 1332-1341

Imdad, A. and Bhutta, Z. A. (2012) Routine iron/folate supplementation during pregnancy: Effect on maternal anaemia and birth outcomes. *Paediatr.Perinat.Epidemiol.* **26** (SUPPL. 1) 168-177

Kulier, R., De Onis, M., Gulmezoglu, A. M., and Villar, J. (1998) Nutritional interventions for the prevention of maternal morbidity. *Int.J.Gynecol.Obstet.* **63** (3) 231-246

Parker, J. A., Barroso, F., Stanworth, S. J., Spiby, H., Hopewell, S., Doree, C. J., Renfrew, M. J., and Allard, S. (2012) Gaps in the evidence for prevention and treatment of maternal anaemia: a review of systematic reviews. *BMC Pregnancy Childbirth* **12**

Yakoob, M. Y. and Bhutta, Z. A. (2011) Effect of routine iron supplementation with or without folic acid on anemia during pregnancy. *BMC public health* **11 Suppl 3** S21-

No usable data

Hemminki, E. and Starfield, B. (1978) Routine administration of iron and vitamins during pregnancy: Review of controlled clinical trials. *Br.J.Obstet.Gynaecol.* **85** (6) 404-410 [quantitative results not reported]

Kotto-Kome, A. C., Calhoun, D. A., Montenegro, R., Sosa, R., Maldonado, L., and Christensen, R. D. (2004) Effect of administering recombinant erythropoietin to women with postpartum anemia: A meta-analysis. *J.Perinatol.* **24** (1) 11-15 [detailed results not provided]

Middleton, P. F., Lassi, Z. S., Tran, T. S., Bhutta, Z., Bubner, T. K., Flenady, V., and Crowther, C. A. (2013) Nutrition interventions and programs for reducing mortality and morbidity in pregnant and lactating women and women of reproductive age: A systematic review. *J.Paediatr.Child Health* **49** 71- [quantitative results not reported]

Moore, R. A., Gaskell, H., Rose, P., and Allan, J. (2011) Meta-analysis of efficacy and safety of intravenous ferric carboxymaltose (Ferinject) from clinical trial reports and published trial data. *BMC Blood Disord.* **11** [detailed results not provided]

Villar J, Merialdi M Gulmezoglu M Abalos E Carroli G Kulier R et al. (2003) Nutritional interventions during pregnancy for the prevention or treatment of maternal morbidity and preterm delivery: an overview of randomized controlled trials. J Nutr 133[5 (Suppl 1)], S1606-S1625. [detailed results not provided]

Superseded/withdrawn

Cuervo, L. G. and Mahomed, K. (2001) Treatments for iron deficiency anaemia in pregnancy. Cochrane Database Syst Rev **2:**CD003094-

Haider, B. A. and Bhutta, Z. A. (2006) Multiple-micronutrient supplementation for women during pregnancy. Cochrane Database Syst Rev **4**

Mahomed, K. (2000). Iron supplementation in pregnancy. Cochrane Database Syst Rev **2**:CD000117.

Mahomed, K. (2000). Iron and folate supplementation in pregnancy. Cochrane Database Syst Rev **2**:CD001135

Mahomed, Kassam (2006) Iron supplementation in pregnancy. Cochrane Database Syst.Rev.

Mahomed, Kassam (2006) Iron and folate supplementation in pregnancy. Cochrane Database Syst Rev

Mahomed. K. (2007). WITHDRAWN: Iron supplementation in pregnancy. Cochrane Database Syst Rev **3**:CD000117

Mahomed. K. (2007). WITHDRAWN: Iron and folate supplementation in pregnancy. Cochrane Database Syst Rev **3**:CD001135

Pena-Rosas, J. P. and Viteri, F. E. (2006) Effects of routine oral iron supplementation with or without folic acid for women during pregnancy. Cochrane Database Syst Rev **3**:CD004736-

Pena-Rosas, J. P. and Viteri, F. E. (2009) Effects and safety of preventive oral iron or iron+folic acid supplementation for women during pregnancy. Cochrane Database Syst Rev **4**:CD004736-

Reveiz, L., Gyte, G. M., and Cuervo, L. G. (2007) Treatments for iron-deficiency anaemia in pregnancy. Cochrane Database Syst Rev **2**:CD003094-

Sloan N, Jordan E Winikoff B. (2002) Effects of iron supplementation on maternal hemotologic status in pregnancy. Am J Public Health **92**[2], 288-293

No usable data (clinical practice guidelines only - secondary sources)

American College of Obstetricians and Gynecologists. Anemia in pregnancy. (2008) *NGC:006764* [Guidelines]

Department of Defence - Department of Veterans Affairs - Veterans Health Administration. Va/DoD clinical practice guidelines for management of pregnancy. (2009) *NGC:007714* [Guidelines]

Dutch Institute for Healthcare Improvement CBO (2011) Chronic anaemia. In: Blood transfusion guideline. *NGC:009176* [Guidelines]

National Collaborating Centre for Women's and Children's Health (2008) Antenatal care. Routine care for the healthy pregnant woman. *NGC:007174* [Guidelines]

Royal College of Obstetricians and Gynaecologists (2011) Management of sickle cell disease in pregnancy. *NGC:008805* [Guidelines]

Level II evidence – oral and/or parenteral iron therapy

The following studies were excluded for reasons other than not meeting the PICO criteria:

Article not in English

Bencaiova, G., Mandach, U., and Zimmerman, R. (2007). Optimal prophylaxis of iron deficiency and iron-deficiency anemia during pregnancy: a randomized study [abstract]. *Gynakologisch.geburtshilfliche Rundschau.* 47:140.

Binder, T., Zahumensky, J., Feldmar, P., Dvorska, M., and Zmrhalova, B. (2007) Intravenous treatment of pospartal anemia with trivalent ferrum preparation. *Ceska Gynekol.* **72** (3) 169-174

Bozhinova, S., Penkov, V., and Bogdanova, A. (2004). Ferro-Folgamma--a drug for treatment and prophylaxis of iron deficiency anemia in pregnant women. *Akush Ginekol (Sofiia)* **43** Suppl 1:15-18.

Guerra Merino, S., Lopez Picado, A., Munoz Hernandez, H., Marin Mesa, J. M., Lete Lasa, I., and Aizpuru Barandiaran, F. (2012) Randomized clinical trial to evaluate the effectiveness of two routes of iron administration, oral and intravenous, in the treatment of postpartum iron deficiency anemia. *Clin.Invest.Ginecol.Obstet.* **39** (5) 190-195

Kreutzkamp, B. (2009). Postpartum iron deficiency anemia: Intravenous ferric carboxymaltose is superior to oral iron substitution. *Med.Monatsschr.Pharm.* **32** (7):273-274.

Stoianova, V. (2006). Tardyferon in obstetric and gynecological practice. *Akusherstvo i ginekologic* **45** Suppl 3:76-77.

Duplicate data (study already included in Level I review)

Lee JI, Lee JA, Lim HS (2005) Effect of time of initiation and dose of prenatal iron and folic acid supplementation on iron and folate nutriture of Korean women during pregnancy. *The American journal of clinical nutrition* **82,** 843-849. [included in Penas-Rosas, 2012]

Siega-Riz AM, Hartzema AG, Turnbull C, Thorp J, McDonald T, Cogswell ME (2006) The effects of prophylactic iron given in prenatal supplements on iron status and birth outcomes: A randomized controlled trial. *American Journal of Obstetrics and Gynecology* **194,** 512-519. [included in Penas-Rosas, 2012]

Ziaei S, Norrozi M, Faghihzadeh S, Jafarbegloo E (2007) A randomised placebo-controlled trial to determine the effect of iron supplementation on pregnancy outcome in pregnant women with haemoglobin (greater-than or equal to) 13.2 g/dl. *BJOG: An International Journal of Obstetrics and Gynaecology* **114,** 684-688. [included in Penas-Rosas, 2012]

Ziaei S, Norrozi M, Faghihzadeh S, Jafarbegloo E (2007) A randomized placebo-controlled trial to determine the effect of iron supplementation on pregnancy outcome in pregnant women with hemoglobin >13.2 g/dL. *Obstetrical and Gynecological Survey* **62,** 574-576. [included in Penas-Rosas, 2012]

Ziaei S, Norrozi M, Faghihzadeh S, Jafarbegloo E (2007) Erratum: A randomised placebo-controlled trial to determine the effect of iron supplementation on pregnancy outcome in pregnant women with haemoglobin (greater-than or equal to)13.2 g/dl (BJOG: An International Journal of Obstetrics and Gynaecology (2007) 114, (684-688)). *BJOG: An International Journal of Obstetrics and Gynaecology* **114,** 1311. [included in Penas-Rosas, 2012]

Christian P, Darmstadt GL, Wu L, Khatry SK, LeClerq SC, Katz J, West J, Adhikari RK (2008) The effect of maternal micronutrient supplementation on early neonatal morbidity in rural Nepal: A randomised, controlled, community trial. *Archives of Disease in Childhood* **93,** 660-664. [included in Penas-Rosas, 2012]

Zeng L, Dibley MJ, Cheng Y, Dang S, Chang S, Kong L, Yan H (2008) Impact of micronutrient supplementation during pregnancy on birth weight, duration of gestation, and perinatal mortality in rural western China: Double blind cluster randomised controlled trial. *BMJ* **337,** 1211-1215. [included in Penas-Rosas, 2012]

Ziaei S, Mehrnia M, Faghihzadeh S (2008) Iron status markers in nonanemic pregnant women with and without iron supplementation. *International Journal of Gynecology and Obstetrics* **100,** 130-132. [included in Penas-Rosas, 2012]

Chan KKL, Chan BCP, Lam KF, Tam S, Lao TT (2009) Iron supplement in pregnancy and development of gestational diabetes - A randomised placebo-controlled trial. *BJOG: An International Journal of Obstetrics and Gynaecology* **116,** 789-797. [included in Penas-Rosas, 2012]

Sun YY, Ma AG, Yang F, Zhang FZ, Luo YB, Jiang DC, Han XX, Liang H (2010) A combination of iron and retinol supplementation benefits iron status, IL-2 level and lymphocyte proliferation in anemic pregnant women. *Asia Pacific Journal of Clinical Nutrition* **19,** 513-519. [included in Penas-Rosas, 2012]

Falahi E, Akbari S, Ebrahimzade F, Gargari BP (2011) Impact of prophylactic iron supplementation in healthy pregnant women on maternal iron status and birth outcome. *Food and Nutrition Bulletin* **32,** 213-217. [included in Penas-Rosas, 2012]

Han XX, Sun YY, Ma AG, Yang F, Zhang FZ, Jiang DC, Li Y (2011) Moderate NaFeEDTA and ferrous sulfate supplementation can improve both hematologic status and oxidative stress in anemic pregnant women. *Asia Pacific Journal of Clinical Nutrition* **20,** 514-520. [included in Penas-Rosas, 2012]

Ouladsahebmadarek E, Sayyah-Melli M, Taghavi S, Abbasalizadeh S, Seyedhejazie M (2011) The effect of supplemental iron elimination on pregnancy outcome. *Pakistan Journal of Medical Sciences* **27,** 641-645. [included in Penas-Rosas, 2012]

De Souza AI, Batista Filho M, Cardoso Ferreira LO, Natal Figueiroa J (2004) The effectiveness of three regimens using ferrous sulfate to treat anemia in pregnant women. *Revista Panamericana de Salud Publica/Pan American Journal of Public Health* **15,** 313-319. [included in Reveiz, 2011]

Zutschi V, Batra S, Ahmad SS, Khera N, Chauhan G, Gandhi G, Sachdeva P (2004) Injectable iron supplementation instead of oral therapy for antenatal care. *Journal of Obstetrics and Gynecology of India* **54,** 37-38. [included in Reveiz, 2011]

Al RA, Unlubilgin E, Kandemir O, Yalvac S, Cakir L, Haberal A (2005) Intravenous versus oral iron for treatment of anemia in pregnancy: A randomized trial. *Obstetrics and Gynecology* **106,** 1335-1340. [included in Reveiz, 2011]

Bayoumeu F, Subiran BC, Baka NE, Legagneur H, Monnier BP, Laxenaire MC (2005) Iron therapy in iron deficiency anemia in pregnancy: intravenous route versus oral route. *European journal of obstetrics, gynecology, and reproductive biology* **123,** S15-S19. [included in Reveiz, 2011]

Kumar A, Jain S, Singh NP, Singh T (2005) Oral versus high dose parenteral iron supplementation in pregnancy. *International Journal of Gynecology and Obstetrics* **89,** 7-13. [included in Reveiz, 2011]

Tomar R, Dubey K, Pandit U (2006) Comparative study - efficacy, safety, compliance of intravenous iron and intra muscular iron in severe iron deficiency [abstract]. *49th All India Congress of Obstetrics and Gynaecology*. [included in Reveiz, 2011]

Saha L, Pandhi P, Gopalan S, Malhotra S, Saha PK (2007) Comparison of efficacy, tolerability, and cost of iron polymaltose complex with ferrous sulphate in the treatment of iron deficiency anemia in pregnant women. *MedGenMed : Medscape general medicine* **9,** 1. [included in Reveiz, 2011]

Nappi C, Tommaselli GA, Morra I, Massaro M, Formisano C, Di Carlo C (2009) Efficacy and tolerability of oral bovine lactoferrin compared to ferrous sulfate in pregnant women with iron deficiency anemia: A prospective controlled randomized study. *Acta Obstetricia et Gynecologica Scandinavica* **88,** 1031-1035. [included in Reveiz, 2011]

Zhou SJ, Gibson RA, Crowther CA, Makrides M (2009) Should we lower the dose of iron when treating anaemia in pregnancy? A randomized dose-response trial. *European Journal of Clinical Nutrition* **63,** 183-190. [included in Reveiz, 2011]

Khalafallah A, Dennis A, Bates J, Bates G, Robertson IK, Smith L, Ball MJ, Seaton D, Brain T, Rasko JEJ (2010) A prospective randomized, controlled trial of intravenous versus oral iron for moderate iron deficiency anaemia of pregnancy. *Journal of Internal Medicine* **268,** 286-295. [included in Reveiz, 2011]

Digumarthi L, Cheruku V (2008) Comparison of intravenous versus oral iron in iron deficiency anaemia of pregnancy. *BJOG* **115,** 53. [included in Reveiz, 2011]

Krafft A, Breymann C (2011) Iron sucrose with and without recombinant erythropoietin for the treatment of severe postpartum anemia: A prospective, randomized, open-label study. *Journal of Obstetrics and Gynaecology Research* **37,** 119-124. [included in ESA review]

Study not complete/result not yet published

A 6-week Randomised, Open Comparative, Multi-centre Study of Intravenous Ferric Carboxymaltose (Ferinject) and Oral Iron (Duroferon) for Treatment of Post Partum Anemia (2009). *NCT00929409* [study terminated/poor recruitment]

Low Dose Intravenous Versus Oral Iron for Iron Deficiency Anemia Starting Late in Pregnancy: A Randomized Controlled Trial (2008). *NCT00746551* [study complete/no results published]

An Open-label, Multicentre, Randomised, 2-arm Study to Investigate the Comparative Efficacy and Safety of Intravenous Ferric Carboxymaltose Versus Oral Iron for the Treatment of Iron Deficiency Anaemia in Pregnant Women (2010). *NCT01131624*. [ongoing]

Treatment of Women after Postpartum Haemorrhage. A Randomized Comparative, Open-Label Study of Intravenous Iron Isomaltoside 1000 (Monofer®) Administered by High Single Dose Infusions or Standard Medical Care in Women after Postpartum Haemorrhage - P-Monofer-PP-01 (2013). *EUCTR2012-005782-12-DK* [ongoing]

Use of Iron Isomaltoside 1000 (Monofer) in Postpartum Anemia (2013). *NCT01628770* [ongoing]

Unable to be retrieved

Naz, N., Mashoori, G. R., Zehra, T., Chaudhry, A., and Ri, J. L. (2008) Intravenous iron sucrose versus oral ferrous sulphate for treatment of iron deficiency anemia in pregnancy. *Medical Channel.* **14** 55-58

Level II evidence – ESAs

The following studies were excluded for reasons other than not meeting the PICO criteria:

Duplicate data (study already included in Level I review)

Breymann, C., Zimmermann, R., Huch, R., and Huch, A. (1996). Use of recombinant human erythropoietin in combination with parenteral iron in the treatment of postpartum anaemia. *European Journal of Clinical Investigation* 26 (2):123-130.

Breymann, C., Visca, E., Huch, R., and Huch, A. (2001). Efficacy and safety of intravenously administered iron sucrose with and without adjuvant recombinant human erythropoietin for the treatment of resistant iron-deficiency anemia during pregnancy. American Journal of Obstetrics and Gynecology 184 (4):662-667.

Breymann, C., Richter, C., Huttner, C., Huch, R., and Huch, A. (2000). Effectiveness of recombinant erythropoietin and iron sucrose vs. iron therapy only, in patients with postpartum anaemia and blunted erythropoiesis. *European Journal of Clinical Investigation* 30 (2):154-161.

Lebrecht, A., Haberlin, F., and Eberhard, J. (1995). Anemia in puerperium; parenteral iron substitution renders erythropoietin therapy dispensable. *Geburtshilfe und Frauenheilkunde* 55 (3):167-170.

Makrydimas, G., Lolis, D., Lialios, G., Tsiara, S., Georgiou, I., and Bourantas, K. L. (1998). Recombinant human erythropoietin treatment of postpartum anemiaPreliminary results. *European Journal of Obstetrics Gynecology and Reproductive Biology* 81 (1):27-31.

Zimmermann, R., Breymann, C., Richter, C., Huch, R., and Huch, A. (1995). rhEPO treatment of postpartum anemia. *Journal of Perinatal Medicine* 23 (1-2):111-117.

Level III evidence – ESAs

Included <100 subjects

Hatzis T, Cardamakis E, Tsapanos V, Kourounis G, Linardos N, Mantouvalos H, Tzingounis V (2003) The effects of recombinant human erythropoietin given immediately after delivery to women with anaemia. *Current Medical Research and Opinion* **19,** 346-349. [N=74]

Oropeza G, Romero G, Cruz R, Castillo C, Torres M, Hernandez A, Rosas A, Pol G, Jaen D (2004) Combined iron sucrose and erithropoietin versus ferrous sulphate and its effects on the maternal-foetal binomia. *Clinica e Investigacion en Ginecologia y Obstetricia* **31,** 44-54. [N=40]

Krafft A, Bencaiova G, Breymann C (2009) Selective use of recombinant human erythropoietin in pregnant patients with severe anemia or nonresponsive to iron sucrose alone. *Fetal Diagnosis and Therapy* **25,** 239-245. [N=84]

B3 Studies excluded from Question 3

Level I evidence

The following studies were excluded for reasons other than not meeting the PICO criteria:

Article not in English

Irita, K., and Inada, E. (2011). Guidelines for management of critical bleeding in obstetrics. *Jpn.J.Anesthesiol.* 60 (1):14-22.

No usable data

George, J. N., Woolf, S. H., Raskob, G. E., Wasser, J. S., Aledort, L. M., Ballem, P. J., Blanchette, V. S., Bussel, J. B., Cines, D. B., Kelton, J. G., Lichtin, A. E., McMillan, R., Okerbloom, J. A., Regan, D. H., and Warrier, I. (1996) Idiopathic thrombocytopenic purpura: A practice guideline developed by explicit methods for the American Society of Hematology. *Blood* **88** (1) 3-40 [Guidelines]

Marsh, J. C. W., Ball, S. E., Cavenagh, J., Darbyshire, P., Dokal, I., Gordon-Smith, E. C., Keidan, J., Laurie, A., Martin, A., Mercieca, J., Killick, S. B., Stewart, R., and Yin, J. A. L. (2009) Guidelines for the diagnosis and management of aplastic anaemia. *Br.J.Haematol.* **147** (1) 43-70 [Guidelines]

Martí-Carvajal, Arturo J., Comunián, Carrasco Gabriella, and Peña-Martí, Guiomar E. (2011) Haematological interventions for treating disseminated intravascular coagulation during pregnancy and postpartum. *Cochrane.Database.of Systematic.Reviews.* [no RCTs identified]

Michael, Mini, Elliott, Elizabeth J., Ridley, Greta F., Hodson, Elisabeth M., and Craig, Jonathan C. (2009) Interventions for haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura. *Cochrane.Database.of Systematic.Reviews.* [no RCTs identified]

Neilson, James P. (2003) Interventions for treating placental abruption. *Cochrane.Database.of Systematic.Reviews.* [no RCTs identified]

Parker, C., Omine, M., Richards, S., Nishimura, J. I., Bessler, M., Ware, R., Hillmen, P., Luzzatto, L., Young, N., Kinoshita, T., Rosse, W., and Socie, G. (2005) Diagnosis and management of paroxysmal nocturnal hemoglobinuria. *Blood* **106** (12) 3699-3709 [Guidelines]

No usable data (clinical practice guidelines only – secondary sources)

Dutch Institute for Healthcare Improvement CBO (2011) Platelet and plasma transfusion policy. In: Blood transfusion guideline. *NGC:009178* [Guidelines]

Royal College of Obstetricians and Gynaecologists (2008) Blood transfusions in obstetrics. *Green-top guideline no.47* [Guidelines]

Royal College of Obstetricians and Gynaecologists (2009) Prevention and management of postpartum haemorrhage. *NGC:008394* [Guidelines]

Royal College of Obstetricians and Gynaecologists (2011) Antepartum haemorrhage. *NGC:008986* [Guidelines]

Level II evidence

The following studies were excluded for reasons other than not meeting the PICO criteria:

No usable data

Wikkelsoe AJ, Afshari A, Stensballe J, Langhoff-Roos J, Albrechtsen C, Ekelund K, Hanke G, Sharif HF, Mitchell AU, Svare J, Troelstrup A, Pedersen LM, Lauenborg J, Madsen MG, Bodker B, Moller AM (2012) The FIB-PPH trial: fibrinogen concentrate as initial treatment for postpartum haemorrhage: study protocol for a randomised controlled trial. *Trials* **13**. [protocol only]

Study not complete/result not yet published

Fibrinogen Concentrate as Initial Treatment for Postpartum Haemorrhage: A Randomised Clinically Controlled Trial (FIB-PPH) (2011). *NCT01359878* [ongoing]

Level III evidence

No studies were excluded for reasons other than not meeting the PICO criteria.

B4 Studies excluded from Question 4

Level I evidence

The following studies were excluded for reasons other than not meeting the PICO criteria:

No usable data

Afshari A, Wikkelsø A, Brok J, Møller AM, Wetterslev J (2011) Thrombelastography (TEG) or thromboelastometry (ROTEM) to monitor haemotherapy versus usual care in patients with massive transfusion. Cochrane Database Syst Rev. [no RCTs found]

Anonymous. (2005). Intraoperative blood cell salvage in obstetrics. Summary of National Institute for Health and Clinical Excellence (NICE) Interventional Procedure Guidance 144. *Health Technology Assessment.Database* 2- [Structured abstract]

Anonymous. (2012). A randomised controlled trial of intra-operative cell salvage during caesarean section in women at risk of haemorrhage (Project record). *Health Technology Assessment.Database*.

Connell J.E., and Mahomed, K. (2009) Medical methods for preventing blood loss at caesarean section. *Cochrane Database Syst.Rev*. [protocol only]

Dason S., Dilauro, M., and Athreya, S. (2011). Prophylactic balloon occlusion of internal iliac arteries in women with placenta accrete: A literature review and analysis. *J.Vasc.Intervent.Radiol.* **22** (3):S147. [abstract]

Dilauro, M. D., Dason, S., and Athreya, S. (2012). Prophylactic balloon occlusion of internal iliac arteries in women with placenta accreta: Literature review and analysis. *Clin.Radiol.* **67** (6):515-520. [quantitative results not repored]

Ferrer, P., Roberts, I., Sydenham, E., Blackhall, K., and Shakur, H. (2009) Anti-fibrinolytic agents in post partum haemorrhage: A systematic review. *BMC Pregnancy Childbirth* **9** [outcome data does meet our PICO criteria]

Johansen, M., Wikkelsø, A., Lunde, J., Wetterslev, J., and Afshari, A. (2013). Prothrombin complex concentrate for perioperative reversal of vitamin K antagonist treatment in bleeding and non-bleeding patients requiring acute surgical intervention. *Cochrane Database Syst.Rev.* [protocol only]

Ker, K., Beecher, D., and Roberts, I. (2013). Topical application of tranexamic acid for the reduction of bleeding. *Cochrane Database Syst.Rev.*. [protocol only]

Leduc, D., Senikas, V., Lalonde, A. B., Ballerman, C., Biringer, A., Delaney, M., Duperron, L., Girard, I., Jones, D., Lee, L. S., Shepherd, D., and Wilson, K. (2009) Active management of the third stage of labour: prevention and treatment of postpartum hemorrhage. *J Obstet Gynaecol Can* **31** (10) 980-993 [Guidelines]

Marti-Carvajal, A. J., Comunian-Carrasco, G., and Pena-Marti, G. E. (2011). Haematological interventions for treating disseminated intravascular coagulation during pregnancy and postpartum. *Cochrane Database Syst Rev* **3**:CD008577. [no RCTs identified]

National Institute for CIinical Excellence (2004). Interventional procedure overview of intraoperative blood cell salvage in obstetric procedures. Available from www.nice.org.uk/ip040overview [overview]

Novikova, N. and Hofmeyr, G. J. (2010) Tranexamic acid for preventing postpartum haemorrhage. *Cochrane Database Syst Rev* **7** CD007872- [outcome data does not meet our PICO criteria]

Yaju, Y., Kataoka, Y., Eto, H., Horiuchi, S., and Mori, R. (2011). Prophylactic interventions after delivery of placenta for reducing bleeding during the postnatal period. *Cochrane Database Syst.Rev*. [protocol only]

No usable data (clinical practice guidelines only – secondary sources)

Dutch Institute for Healthcare Improvement (2011) Transfusion policy for acute anaemia. In: Blood transfusiion guideline. *NGC:009177*. [Guidelines].

Dutch Institute for Healthcare Improvement (2011) Blood saving techniques and medications. In: Blood transfuion guideline. *NGC:009180.* [Guidelines]

Dutch Institute for Healthcare Improvement (2011) Platelet and plasma transfusion policy. In: Blood transfusion guideline. *NGC:009178.* [Guidelines]

National Institute for Health and Clinical Excellence (2005) Intraoperative blood cell salvage in obstetrics. *IPG144* [Guidelines]

Royal College of Obstetricians and Gynaecologists (2008) Blood transfusions in obstetrics. *Green-top guideline no.47* [Guidelines]

Royal Australian and New Zealand College of Obstetricians and Gynaecologists (2011) Management of postpartum haemorrhage. *C-Obs 43* [Guidelines]

Royal College of Obstetricians and Gynaecologists. (2011) Placenta praevia, placenta praevia accretra and vasa praevia: diagnosis and management. [Guidelines]

Withdrawn/superseded

Novikova, N., and Hofmeyr, G. J. (2009). Tranexamic acid for preventing postpartum haemorrhage. *Cochran*e *Database Syst.Rev.* **4**.

Article not able to be retrieved

HAYES Inc. (2011). Intrauterine balloon tamponade for the management of postpartum hemorrhage (Structured abstract). *Health Technology Assessment.Database*.

Level II evidence

The following studies were excluded for reasons other than not meeting the PICO criteria:

Article not in English

Yang, H., Zheng, S., and Shi, C. (2001). Clinical study on the efficacy of tranexamic acid in reducing postpartum blood lose: a randomized, comparative, multicenter trial. *Zhonghua fu chan ke za zhi* **36** (10):590-592.

Tetruashvili, N. K. (2007). Hemostatic therapy for hemorrhages during first and second trimesters. *Anesteziol Reanimatol* (6):46-48.

No usable data

Shakur, H., Elbourne, D., Gulmezoglu, M., Alfirevic, Z., Ronsmans, C., Allen, E., and Roberts, I. (2010). The WOMAN Trial (World Maternal Antifibrinolytic Trial): tranexamic acid for the treatment of postpartum haemorrhage: an international randomised, double blind placebo controlled trial. *Trials* **11**:40. [protocol only]

Duplicate data (Study identified in Level II)

Intravenous tranexamic acid use in elective caesarean section: Does it reduce blood loss? A prospective randomised double-blind placebo controlled study (2009). *ISRCTN42314355* [Study complete. See Gungorduk, 2011)

Can we Use Intravenous Injection of Tranexamic Acid in Routine Practice With Active Management of the Third Stage of Labor? (2011) *NCT01338454*. [Study complete. See Gungorduk, 2013]

Can Tranexamic Acid Reduce Bleeding After Post Partum Hemorrhage in Cesarean Section Delivery. (2011). *NCT01599468* [Study complete. See Ducloy-Bouthers, 2011]

Study not complete / results not yet published

Recombinant Human Activated Factor VII as Salvage Therapy in Women With Severe Postpartum Hemorrhage (2007). *NCT00370877* [Study complete. Results published as abstract. See Lavigne-Lissalde, 2013]

Tranexamic Acid for the Treatment of Postpartum Haemorrhage: An International Randomised, Double Blind, Placebo Controlled Trial (WOrld Maternal ANtifibrinolytic Trial (WOMAN)). *NCT00872469* [ongoing]

Balloon Catheter for Occlusion of the Pelvic Vasculature as an Adjuvant Therapy in Cases of Placenta Accreta (2011). *NCT01373255* [ongoing]

Cell SALVage in Obstetrics. A randomised controlled trial of intra-operative cell salvage during caesarean section in women at risk of haemorrhage (2012). *ISRCTN66118656* [ongoing]

Level III evidence

The following studies were excluded for reasons other than not meeting the PICO criteria:

Article not in English

Seidlova, D., Blatny, J., Penka, M., Ovesna, P., Brabec, P., Sevcik, P., Ventruba, P., and Cerny, V. (2010. Recombinant activated factor VII in the treatment of life threatening post-partum haemorrhage; Registry UniSeven in the Czech Republic. *Ceska Gynekol.* **75** (4):297-305.

Appendix C Literature screening results

C1 Search results – Question 1

Literature search for Level I studies	Number of citations
Number of citations identified	924
Citations excluded after title/abstract review:	
Duplicate citation	68
Non-human study	2
Wrong population	122
Wrong intervention	584
Wrong outcomes	63
Wrong publication type	56
Wrong study type (Level III-2)	1
Wrong study type (Level III-3 or below)	11
Withdrawn	3
Number of studies included for full text review	14
Studies excluded after full text review:	
Wrong population	3
Wrong intervention	2
Wrong publication type	1
Publication not in English	1
No usable data	7
Number of eligible reviews	0

Literature search for Level II studies	Number of citations
Number of citations identified	4527
Citations excluded after title/abstract review:	
Duplicate citation	211
Non-human study	195
Wrong population	940
Wrong intervention	2322
Wrong comparator	2
Wrong outcomes	487
Wrong publication type	285
Wrong study type (Level III)	11
Wrong study type (Level IV or below)	37
Number of studies included for full text review	37
Studies excluded after full text review:	
Wrong population	1
Wrong intervention	7
Wrong outcomes	1
Wrong publication type	8
Wrong study type (Level III-2)	1
Wrong study type (Level III-3 or below)	1
Publication not in English	10
No usable data	7
Number of eligible studies	1

Literature search for Level III studies	Number of citations
Number of citations identified	9913
Citations excluded after title/abstract review:	
Duplicate citation	75
Non-human study	24
Wrong population	2773
Wrong intervention	4268
Wrong comparator	134
Wrong outcomes	783
Wrong publication type	195
Wrong study type (Level I)	1
Wrong study type (Level III-3 or below)	1599
Sample size (N≤100)	3
Citations included from other sources:	
From Level I and II databases after title/abstract review (excluding duplicates)	9
Number of studies included for full text review	67
Studies excluded after full text review:	
Wrong population	2
Wrong intervention	26
Wrong comparator	6
Wrong outcomes	4
Wrong outcomes (only secondary outcomes)	1
Wrong publication type	14
No usable data	1
Publication not in English	10
Sample size (N≤100)	3
Final number of eligible studies	0

Literature search of secondary databases and handsearching	
Number of citations identified - PreMedline	108
Citations excluded after title/abstract review:	
Publication not in English	16
Wrong population	17
Wrong intervention	46
Wrong comparator	3
Wrong outcomes	9
Wrong publication type	5
Wrong study type (Level IV or below)	11
Citations included from other sources:	
HTA websites / Guideline databases	14
Clinical trial registries	1
Number of studies included for full text review	16
Studies excluded after full text review:	
Wrong population	3
Wrong intervention	3
No usable data (Clinical practice guidelines only)	8
No usable data (Level III study)	1
Duplicate (Level II study already identified)	1
Final number of eligible studies	0

C2 Search results – Question 2

Literature search for Level I studies	Number of citations
Total number of citations identified	570
Citations excluded after title/abstract review:	
Duplicate citation	39
Non-human study	3
Wrong population	69
Wrong intervention	280
Wrong outcomes	54
Wrong publication type	69
Wrong study type (Level III-2)	1
Withdrawn/superseded	4
Citations included from other sources:	
From Level II and Level III databases (excluding duplicates)	1
Number of studies reviewed in full text	52
Studies excluded after full text review:	
Wrong intervention	6
Wrong comparator	11
Wrong publication type	7
Wrong study type (systematic review of systematic reviews)	1
Wrong study type (Level II)	1
Publication not in English	4
No usable data	4
Withdrawn/superseded	7
Duplicate data	8
Final number of eligible reviews	3

Literature search for Level II studies	Number of citations
Number of citations identified	3397
Citations excluded after title/abstract review:	
Publication data prior to 1970	7
Duplicate citation	504
Non-human study	204
Wrong population	646
Wrong intervention	1196
Wrong outcome	272
Wrong publication type	110
Wrong study type (Level I)	1
Wrong study type (Level III-2)	23
Wrong study type (Level III-3 or below)	31
Number of studies identified for full text review	403

Literature search for Level II studies (screening for IV and IM iron only)	Number of citations
Number of citations re-screened for IV and IM iron only	391
Citations excluded after title/abstract review	
Publication date prior to 2003	220
Duplicate citation	3
Wrong intervention (not iron)	39
Wrong intervention (not IV or IM iron)	10
Wrong comparator	50
Wrong publication type	10
Wrong study type (Level III or below)	1
Duplicate data (study included in ESA review)	1
Duplicate data (study included in Level I review – Reveiz, 2011)	11
Duplicate data (study included in Level I review – Pena-Rosas, 2012)	13
Publication not in English (no abstract)	4
Number of eligible RCTs for IV or IM iron	29
Studies excluded after full text review:	
Wrong publication type	10
Publication not in English	2
Unable to be retrieved	1
Citations included from other sources:	
From systematic review published after literature search date	1
Final number of eligible RCTs of IV and IM iron	17

Literature search for Level II studies (selective screening for ESAs)	Number of citations
Number of articles screened for ESAs	29
Citations excluded after full text review	
Wrong population	1
Wrong intervention (not ESAs)	8
Wrong comparator	2
Wrong publication type	4
Duplicate data (study included in Level I review – Dodd, 2004)	5
Duplicate data (study included in Level I review – Reveiz, 2011)	1
Number of RCTs reviewed in full text for ESAs	8
Citations excluded after full text review:	
Wrong population	1
Wrong intervention	1
Wrong publication type	3
Wrong study level (Level III or below)	1
Number of eligible RCTs for ESAs	2

Literature search for Level III studies	Number of citations
Number of citations identified	3676
Citations excluded after title/abstract review:	
Duplicate citation	35
Non-human study	23
Wrong population	1394
Wrong intervention	1390
Wrong comparator	49
Wrong outcomes	104
Wrong publication type	98
Wrong study type (Level I)	8
Wrong study type (Level II)	2
Wrong study type (Level III-3 or below)	453
Sample size (n<100)	3
Publication not in English	1
Citations included from other sources:	
From Level I and Level II databases after title/abstract review (excluding duplicates)	23
Number of studies identified for full text review	139

Literature search for Level III studies (selective screening for ESAs)	Number of citations
Number of articles screened for ESAs	15
Wrong population	2
Wrong intervention	1
Wrong study type (Level I)	2
Wrong study type (Level IV)	1
Wrong publication type	6
Sample size (n<100)	3
Final number of eligible studies for ESAs	0

Literature search for Level III studies (selective screening for iron and outcome of mortality)	Number of citations
Number of articles screened for iron	139
Article not in English	17
Wrong intervention (study examines EPO only)	12
Wrong intervention (study examines micronutrients, no intervention, or other)	9
Wrong comparator	11
Wrong study type (Level I)	4
Wrong study type (Level II)	2
Wrong study type (Level III-3 or below)	2
Wrong outcome (study does not assess mortality)	76
Wrong publication type	3
Not able to be retrieved	1
Final number of eligible studies for iron (outcome of mortality)	2

Literature search of secondary databases and handsearching	
Citations included from other sources: PreMedline HTA websites / Guideline databases Clinical trial registries Handsearching	37 2 19 12 4
Studies excluded after abstract/title review: Wrong population Wrong intervention	 5 12
Number of studies reviewed in full text (secondary databases and handsearching)	20
Studies excluded after full text review: Duplicate citation Wrong intervention Wrong outcomes No usable data No usable data (Clinical practice guidelines only) Study not complete/results not yet published Study terminated Duplicate data (study already identified in Level II) Superseded	 1 1 1 1 7 4 1 3 1
Final number of eligible studies	0

C3 Search results – Question 3

Literature search for Level I studies	Number of citations
Number of citations identified	262
Citations excluded after title/abstract review:	
Duplicate citation	5
Publication not in English	1
Wrong population	101
Wrong intervention	86
Wrong publication type	16
Wrong study type (Level III-3 or below)	24
Citations included from other sources:	
From Level II and Level III databases after abstract/title screen (excluding duplicates)	2
From Level II database after full text review	3
Number of studies reviewed in full text	34
Studies excluded after full text review:	
Wrong population	8
Wrong intervention	4
Wrong outcomes	2
Wrong publication type	13
Wrong study type (Level IV or below)	1
No usable data	6
Final number of eligible reviews	0

Literature search for Level II studies	Number of citations
Total number of citations identified	722
Citations excluded after title/abstract review:	
Duplicate citation	17
Publication not in English	10
Non-human study	14
Wrong population	311
Wrong intervention	151
Wrong comparator	1
Wrong publication type	125
Wrong study type (Level I)	1
Wrong study type (Level III-2)	9
Wrong study type (Level III-3 or below)	37
Number of studies reviewed in full text	46
Studies excluded after full text review:	
Wrong population	15
Wrong intervention	8
Wrong publication type	16
Wrong study type (Level I)	3
Wrong study type (Level III or below)	3
No usable data (protocol only)	1
Final number of eligible studies	0

Literature search for Level III studies	Number of citations
Number of citations identified	2288
Citations excluded after title/abstract review:	
Duplicate citation	9
Publication not in English	7
Non-human study	9
Wrong population	945
Wrong intervention	319
Wrong comparator	1
Wrong outcomes	1
Wrong publication type	71
Wrong study type (Level I)	1
Wrong study type (Level III-3 or below)	840
Citations included from other sources:	
From Level I and Level II databases after title/abstract review (excluding duplicates)	9
From Level II database after full text review	3
Number of studies reviewed in full text	97
Studies excluded after full text review:	
Wrong population	9
Wrong intervention	21
Wrong comparator	5
Wrong outcomes	5
Wrong publication type	26
Wrong study type (Level III-3 or below)	29
Final number of eligible studies	2

Literature search of secondary databases and handsearching	
Number of citations identified - PreMedline	15
Studies excluded after abstract/title review:	
Publication not in English	4
Wrong population	3
Wrong intervention	3
Wrong outcomes	1
Wrong study type (Level IV or below)	4
Citations included from other sources:	
HTA websites / Guideline databases	28
Clinical trial registries	2
Number of studies reviewed in full text (secondary databases and handsearching)	30
Studies excluded after full text review:	
Duplicate citation	2
Wrong population	6
Wrong intervention	14
Wrong outcomes	3
No usable data (Clinical practice guidelines only)	4
Study not complete/results not yet published	1
Final number of eligible studies	0

C4 Search results – Question 4

Literature search for Level I studies	Number of citations
Number of citations identified	330
Citations excluded after title/abstract review:	
Duplicate citation	15
Non-human study	3
Wrong population	217
Wrong intervention	46
Wrong outcomes	7
Wrong publication type	19
Wrong study type (Level III-3 or below)	2
No usable data	7
Withdrawn/superseded	1
Number of studies included after title/abstract review	15
Citations included from other sources:	
From Level I and Level II databases after title/abstract review (excluding duplicates)	6
Number of studies reviewed in full text	21
Studies excluded after full text review:	
Wrong comparator	1
Wrong outcomes	1
Wrong publication type	5
Wrong study type (Level III)	3
Wrong study type (Level IV or below)	5
No usable data	5
Article not able to be retrieved	1
Final number of eligible reviews	0

Literature search for Level II studies	Number of citations
Number of citations identified	1169
Citations excluded after title/abstract review:	
Duplicate citation	29
Non-human study	22
Wrong population	560
Wrong intervention	338
Wrong comparator	14
Wrong outcomes	39
Wrong publication type	109
Wrong study type (Level I)	3
Wrong study type (Level III-2)	10
Wrong study type (Level III-3 or below)	16
Publication not in English	2
No usable data (protocol only)	1
Number of studies reviewed in full text	26
Studies excluded after full text review:	
Wrong intervention	1
Wrong outcomes	3
Wrong publication type (reviews, editorials)	6
Wrong publication type (conference abstracts)	9
Final number of eligible studies	7

Literature search for Level III studies	Number of citations
Total number of citations identified	2002
Citations excluded after title/abstract review:	
Duplicate citation	10
Publication not in English	1
Non-human study	6
Wrong population	1340
Wrong intervention	242
Wrong comparator	8
Wrong outcomes	115
Wrong publication type	46
Wrong study type (Level I)	7
Wrong study type (Level II, protocol only)	1
Wrong study type (Level III-3 or below)	203
No usable data	1
Number of studies included after title/abstract review	20
Citations included from other sources:	
From Level I and Level II databases after title/abstract review (excluding duplicates)	9
From Level I database (systematic reviews of Level III studies)	4
Number of studies reviewed in full text	33
Studies excluded after full text review:	
Wrong intervention	1
Wrong comparator	1
Wrong outcomes	1
Wrong publication type (conference abstract)	9
Wrong study type (Level III-3)	2
Wrong study type (Level IV or below)	8
Article not in English	1
Final number of eligible studies	10

Number of studies reviewed in full text (secondary databases and handsearching)	33
Number of citations identified - PreMedline	0
Citations included from other databases	
HTA websites / Guideline databases	9
Clinical trial registries	19
Handsearching	5
Number of studies reviewed in full text (secondary databases and handsearching)	33
Studies excluded after full text review:	
Wrong population	1
Wrong intervention	12
Wrong comparator	1
Wrong outcomes	2
Wrong publication type (reviews, editorials)	1
Duplicate data (study already identified)	3
No usable data (Clinical practice guidelines only)	7
No usable data (study not complete)	3
No usable data (study complete, not yet published)	1
Final number of eligible studies	2
Level II study	1
Level III study	1

Appendix D Evidence matrixes

Evidence matrixes are presented below for each intervention, subpopulation and outcome identified within each question of this module.

Where no evidence was found for a particular intervention, subpopulation or outcome, no evidence statement form has been presented and in the systematic review (Volume 1) the corresponding evidence statements are described as 'unknown'. These evidence statements are not numbered or included in the main body of the guideline.

Where applicable, the complete set of evidence statement forms is followed by a separate form that contains any recommendations which were formulated from the evidence base.

Recommendations were not made where the effect of the intervention was unknown or uncertain or where the underpinning evidence would have led to a Grade D recommendation. Instead, consensus-based practice points were made (see **Section 2.5.2**, Volume 1).

D1 Evidence – Question 1

Table D1.A Key question: What is the effect of prophylactic RBC transfusion vs transfusion for medical or obstetric indications on maternal and perinatal mortality in pregnant women with sickle cell disease?		Evidence table ref: D1.A
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level II study (Koshy et al 1988) of fair quality in women with sickle cell disease.	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Koshy et al (1988) reported six perinatal deaths, four stillbirths and two neonatal deaths in the prophylactic RBC transfusion group compared with two perinatal deaths and two neonatal deaths in the restrictive RBC transfusion group. The differences between the two randomised groups were not statistically significant but perinatal mortality was reported to approach statistical significance.This trend was removed when patients with twins (three patients vs one) or previous perinatal death (six patients vs one) were excluded from the analysis. There were no maternal deaths, but this is not surprising, given that the study was underpowered to measure the effect of treatment on mortality.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is directly generalisable to pregnant women with sickle cell anaemia.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in the USA between 1979-1986 therefore the evidence is probably applicable to the Australian health care system with some caveats	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats

	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Authors report adjusted analysis for multiple gestation and perinatal mortality as baseline characteristics for these measures were notably different between the intervention and comparator groups (numbers too small to detect statistically significant deviation). The difference in perinatal mortality between pregnancies with multiple fetuses or had previously ended in perinatal death and those pregnancies that did not was significant (P<0.0001).

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES1.2 In pregnant women with sickle cell disease, the effect of prophylactic RBC transfusion on maternal and perinatal mortality is uncertain

Table D1.B Key question: What is the effect of prophylactic RBC transfusion vs transfusion for medical or obstetric indications on measures of fetal outcomes (birth weight/gestation/ preterm delivery) in pregnant women with sickle cell disease?		Evidence table ref: D1.B
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level II study (Koshy et al 1988) of fair quality.	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Koshy et al (1988) reported no significant difference between treatment groups for birth weight or preterm delivery. A statistically significant difference (P<0.05) favouring restrictive RBC transfusion was reported for gestational age at delivery; however this difference did not remain significant after adjustment for previous perinatal mortality and multiple birth.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Evidence is directly generalisable to pregnant women with sickle cell anaemia.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in the USA between 1979-1986 therefore the evidence is probably applicable to the Australian health care system with some caveats	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Authors report adjusted analysis for multiple gestation and perinatal mortality as baseline characteristics for these measures were notably different between the intervention and comparator groups (numbers too small to detect statistically significant deviation). The difference in perinatal mortality between pregnancies with multiple fetuses or had previously ended in perinatal death and those pregnancies that did not was significant (P<0.0001).

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES1.3 In pregnant women with sickle cell disease, the effect of prophylactic RBC transfusions on measures of fetal outcomes is uncertain.

D2 Evidence – Question 2

Oral and/or parenteral iron

Table D2.E Key question: In maternity patients, what is the effect of oral iron vs no treatment or placebo on transfusion incidence?		Evidence table ref: D2.E
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One Level I study of good quality (Pena-Rosas et al 2012) identified one RCT (Puolakka 1980) with unclear risk of bias.	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pena-Rosas et al (2012) reported no significant difference in the number of transfusions provided: 0/16 (0%) vs 1/16 (6.3%); RR 0.33; 95% CI: 0.01, 7.62.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study included pregnant women of any gestational age and parity (Pena-Rosas et al 2012).	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study included one RCT conducted in Finland (Pena-Rosas et al 2012).	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The inclusion of the trial by Heminiki (1991) was questioned by the CRG and subsequently removed from the analysis (for wrong comparator). The trial gives 100mg daily to women in the control group if haematocrit levels fell below 0.32. The CRG considered this to be routine oral iron therapy compared to a targeted oral iron therapy (i.e. not no treatment/placebo), therefore the study did not meet our PICO criteria.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES2.1 In pregnant women, the effect of routine oral iron compared to no treatment or placebo on transfusion incidence is uncertain

Table D2.F Key question: In maternity patients, what is the effect of intravenous iron vs oral iron on transfusion incidence?			Evidence table ref: D2.F
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Level I evidence: One Level I study of good quality (Reveiz et al 2011) which includes three RCTs with high or unclear risk of bias Level II evidence: Three Level II studies, two of fair quality (Gupta et al 2013; Van Wyck et al 2007) and one of poor quality (Breymann et el 2008;). During pregnancy (Reveiz et al 2011; Gupta et al 2013) Postpartum (Breymann et al 2008; Van Wyck et al 2007)	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
None of the studies reported any significant differences in transfusion incidence. Reveiz et al (2011) found no difference in blood transfusions required, Breymann et al (2008) did not report significance and Gupta et al (2013) and Van Wyck et al (2007) did not report any events in either study group.	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
Reveiz et al (2011) did not find any significant difference in blood transfusions required: 0/84 (0%) vs 4/83 (4.8%); RR 0.27; 95% CI 0.05, 1.59; P=0.15. Breymann et al (2008) did not report on significance: 1/227 (0.4%) vs 0 (0%). Gupta et al (2013) and Van Wyck et al (2007) did not report any transfusions in either study group: 0/50 (0%) vs 0/50 (0%) and 0/182 (0%) vs 0/179 (0%).	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The Level I study included pregnant women with a haemoglobin value less than 11g/dL (Reveiz et al 2011). The Level II studies included women with postpartum iron deficiency anaemia (Breymann et al 2008), pregnant women with anaemia (Gupta et al 2013) and women with postpartum anaemia (Van Wyck et al 2007).	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The Level I study included RCTs conducted in France and Turkey (Reveiz et al 2011). The Level II studies were conducted in multiple centres in Poland, Romania and the Russian Federation (Breymann et al 2008), a single centre in India (Gupta et al 2013) and multiple centres the USA and Mexico (Van Wyck et al 2007).	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2. Consistency	A	All studies consistent
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES2.3 In maternity patients with iron deficiency anaemia, the effect of IV iron compared to oral iron on transfusion incidence is uncertain

DP; during pregnancy, PP; postpartum

Table D2.G Key question: In maternity patients, what is the effect of intravenous iron + oral iron vs oral iron on transfusion incidence?			Evidence table ref: D2.G
1. Evidence base (*number of studies, level of evidence and risk of bias in the included studies)*			
Includes two Level II studies, one of fair quality (Westad et al 2008) and one of poor quality (Neeru et al 2012). During pregnancy (Neeru et al 2012) Postpartum (Westad et al 2008)	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency (if only one study was available, rank this component as 'not applicable')			
NA	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact (Indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)			
Neeru et al did not report significance but found 4/50 (8.0%) participants in the intravenous iron with oral iron group received blood transfusions. Westad et al (2008) did not find any significant difference in the incidence of transfusion: 4/58 (6.9%) vs 10/70 (14.3%); P=0.18.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability (How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)			
Neeru et al (2012) included pregnant women with iron deficiency anaemia. Westad et al (2008) included women with postpartum anaemia.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability (Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)			
Neeru et al (2012) was conducted in a single centre in India. Westad et al (2008) was conducted in multiple centres in Norway.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*			
Dosage of IV iron and timing of outcome measurements reported differently in these trials and those comparing IV iron with oral iron alone. Also uncertainties surrounding compliance with oral iron therapy. For example, Westad et al (2008) reported that compliance with oral iron was poor, stating that less than 50% of the required dose was taken by patients in both arms of the study.			

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2. Consistency	A	All studies consistent
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES2.4 In maternity patients with anaemia, the effect of IV iron plus oral iron compared to oral iron alone on transfusion incidence is uncertain.

Abbreviations: DP; during pregnancy, PP; postpartum

Table D2.H Key question: In maternity patients, what is the effect of intravenous iron + folic acid vs oral iron + folic acid on transfusion incidence?			Evidence table ref: D2.H
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Three Level II studies of fair quality (Bencaiova et al 2009; Froessler et al 2013; Kochhar et al 2013). Non-anaemic pregnant women (Bencaiova et al 2009) Iron deficiency anaemia (Froessler et al 2013) Moderate iron deficiency anaemia (Kochhar et al 2013)	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
Two of the studies reported no significant difference in transfusion requirement (Bencaiova et al 2009; Froessler et al 2013)and one did not report on significance (Kochhar et al 2013).	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
Bencaiova et al (2009) reported no significant difference in transfusion requirement (examining two and three doses of intravenous iron respectively): 1/61 (1.6%) and 0/49 (0%) vs 1/119 (0.8%); P=1.00. Froessler et al (2013) found no significant differences in red blood cell transfusion in an antenatal cohort: 0.8% vs 3.0% and a postnatal cohort: 0% vs 2.2%.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
Bencaiova et al (2009) included non-anaemic pregnant women, Froessler et al (2013) included both pregnant and post lower segment caesarean section women with iron deficiency anaemia and Kochhar et al (2013) included pregnant women with moderate iron deficiency anaemia.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
Two of the studies were conducted in single-centres in Switzerland and Australia (Bencaiova et al 2009; Froessler et al 2013) and one was conducted in two hospitals in India (Kochhar et al 2013).	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*			
Potential suboptimal dose of IV iron in studies by Froessler (2013) and Bencaovia. (2009)			

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*		
Component	Rating	Description
1. Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2. Consistency	A	All studies consistent
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats
EVIDENCE STATEMENT ES2.5 In maternity patients, the effect of IV iron plus folic acid compared to oral iron plus folic acid on transfusion incidence is uncertain		

Table D2.I Key question: In maternity patients, what is the effect of intravenous iron vs intramuscular iron + oral iron on transfusion incidence?			Evidence table ref: D2.I
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
One Level II study of poor quality (Hashmi et al 2006).	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
Not applicableA	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
Hashmi et al (2006) did not report any transfusions in either study group: 0/50 (0%) vs 0/50 (0%).	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The study included women with iron deficiency anaemia (both pregnant and postpartum) (Hashmi et al 2006).	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The study was conducted in a single centre in Pakistan (Hashmi et al 2006).	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*			

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES2.7 In maternity patients with iron deficiency anaemia, the effect of IV iron compared to IM iron plus oral iron on transfusion incidence is uncertain

Table D2.J Key question: In pregnant women, what is the effect of oral iron vs no treatment or placebo on laboratory measures?				Evidence table ref: D2.J
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*				
One Level I study of good quality (Pena-Rosas et al 2012) included 14 trials that examined the outcome of maternal anaemia (MA),6 trials that examined the outcome of maternal iron deficiency anaemia (MIDA), and seven trials that examined the outcome of anaemia postpartum (AP).	MA	MIDA	AP	
	A	A	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias
	B	B	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	C	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	D	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*				
Pena-Rosas et al (2012) reported significant differences in laboratory measures favouring oral such as maternal anaemia at or near term, maternal iron deficiency anaemia at or near term and maternal haemoglobin concentration.	A	A	A	All studies consistent
	B	B	B	Most studies consistent and inconsistency can be explained
	C	C	C	Some inconsistency, reflecting genuine uncertainty around question
	D	D	D	Evidence is inconsistent
	NA	NA	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*				
Pena-Rosas et al (2012) found a significant effect favouring iron for anaemia at term: 142/1131 (12.6%) vs 345/1005 (34.3%); RR 0.29; 95% CI 0.19, 0.47; P < 0.0001, maternal iron deficiency anaemia at term: 25/572 (4.4%) vs 68/516 (13.2%); RR 0.33; 95% CI 0.16, 0.69; P=0.0030 and maternal haemoglobin concentration at or near term (g/L): MD 8.95; 95% CI 6.37, 11.53; P < 0.00001.	A	A	A	Very large
	B	B	B	Substantial
	C	C	C	Moderate
	D	D	D	Slight/Restricted
	NA	NA	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*				
The study included women of any gestational age and parity (Pena-Rosas et al 2012;).	A	A	A	Evidence directly generalisable to target population
	B	B	B	Evidence directly generalisable to target population with some caveats
	C	C	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	D	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*				
The study included RCTs conducted in England, USA, Australia, Canada, Norway, France, Denmark, Finland, Netherlands, Belgium, China, South Korea, Niger, Myanmar, Gambia and Iran (Pena-Rosas et al 2012).	A	A	A	Evidence directly applicable to Australian healthcare context
	B	B	B	Evidence applicable to Australian healthcare context with few caveats
	C	C	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	D	D	Evidence not applicable to Australian healthcare context
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*				

There were concerns about definitions of anaemia and inclusion of non-anaemic patients in studies. High heterogeneity for pooled results.

The inclusion of the trial by Heminiki (1991) was questioned by the CRG and subsequently removed from the analysis (for wrong comparator). The trial gave 100mg daily oral iron to women in the control group if haematocrit levels fell below 0.32. The CRG considered this to be routine oral iron therapy compared to a targeted iron therapy (i.e. not no treatment/placebo); therefore the trial did not meet our PICO criteria.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	MA	MIDA	AP	Description
1. Evidence base	A	A	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias
2. Consistency	B	B	D	B - Most studies consistent and inconsistency can be explained D - Evidence is inconsistent
3. Clinical impact	C	C	NA	C - Moderate NA - Not applicable/no difference/underpowered
4. Generalisability	C	C	B	C - Evidence not directly generalisable to the target population but could be sensibly applied B - Evidence directly generalisable to target population with some caveats
5. Applicability	C	C	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES2.8 In pregnant women, oral iron reduces maternal anaemia (haemoglobin < 110g/L) at 34 weeks gestation or more compared to no treatment or placebo

ES2.9 In pregnant women, oral iron reduces maternal iron deficiency anaemia (haemoglobin < 110g/L) at 34 weeks gestation or more compared to no treatment or placebo

ES2.10 In pregnant women, the effect of oral iron compared to no treatment or placebo on postpartum anaemia (haemoglobin <110 g/L) is uncertain

Abbreviations: AP; anaemia postpartum; MA; maternal anaemia, MIDA; maternal iron deficiency anaemia

Table D2.K Key question: In pregnant women with iron deficiency anaemia, what is the effect of oral iron vs no treatment or placebo on laboratory measures?			Evidence table ref: D2.K
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
One Level I study of good quality (Reveiz et al 2011) that included two RCTs (Suhamo 1993, Sun 2010) with low or unclear risk of bias	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
The included RCTs are consistent.	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
Reveiz et al (2011) found significant differences favouring iron for measures of anaemia during the second trimester: 20/63 (31.7%) vs 52/62 (83.9%); RR 0.38; 95% CI 0.26, 0.55, haemoglobin: MD 1.34; 95% CI 0.27, 2.42 and ferritin: 3.3 ± 0.5 vs 2.6 ± 0.5; MD 0.70; 95% CI 0.52, 0.88.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The study included pregnant women with a haemoglobin value less than 11g/dL (Reveiz et al 2011).	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The study included RCTs conducted in Indonesia and China (Reveiz et al 2012).	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*			

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2. Consistency	A	All studies consistent
3. Clinical impact	C	Moderate
4. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES2.11 In pregnant women with iron deficiency anaemia, oral iron improves laboratory values (haemoglobin and serum ferritin) and reduces anaemia (haemoglobin <110g/L) compared to no treatment or placebo

Table D2.L Key question: In maternity patients, what is the effect of oral iron + folic acid vs no treatment or placebo on laboratory measures?					Evidence table ref: D2.L
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*					
	MA	MIDA	AP	SA	
One Level I study of good quality (Pena-Rosas et al 2012) identified 3 RCTs (Barton 1994, Batu 1976, Chisholm 1966) with low/unclear risk of bias that reported MA, 1 RCT reported MIDA (Lee 2005), 2 RCTs reported AP (Christian 2003, Lee 2005) and 4 RCTs reported SA (Barton 1994, Batu 1976, Christian 2003, Lee 2005).	A	A	A	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias
	B	B	B	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	C	C	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	D	D	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*					
The study reported significant differences in laboratory measures such as maternal anaemia at or near term and haemoglobin concentration (Pena-Rosas et al 2012).	A	A	A	A	All studies consistent
	B	B	B	B	Most studies consistent and inconsistency can be explained
	C	C	C	C	Some inconsistency, reflecting genuine uncertainty around question
	D	D	D	D	Evidence is inconsistent
	NA	NA	NA	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*					
Pena-Rosas et al (2012) found a significant difference favouring iron and folic acid for anaemia at term: 15/208 (7.2%) vs 39/138 (28.3%); RR 0.34; 95% CI 0.21, 0.54; P < 0.00001 and maternal mean haemoglobin concentration at or near term (g/L): MD 16.13; 95% CI 12.74, 19.52; P < 0.00001	A	A	A	A	Very large
	B	B	B	B	Substantial
	C	C	C	C	Moderate
	D	D	D	D	Slight/Restricted
	NA	NA	NA	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*					
The study included women of any gestational age and parity (Pena-Rosas et al 2012).	A	A	A	A	Evidence directly generalisable to target population
	B	B	B	B	Evidence directly generalisable to target population with some caveats
	C	C	C	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	D	D	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*					
The study included RCTs conducted in Ireland, England, Myanmar, South Korea and Nepal (Pena-Rosas et al 2012).	A	A	A	A	Evidence directly applicable to Australian healthcare context
	B	B	B	B	Evidence applicable to Australian healthcare context with few caveats
	C	C	C	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	D	D	D	Evidence not applicable to Australian healthcare context
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*					
Paper by Lee (2005) was queried by CRG as to methods for definition of outcome (maternal iron deficiency anaemia)					

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	MA	MIDA	AP	SA	Description
1. Evidence base	A	C	D	C	A - One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias C - One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias D - Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	B	NA	B	B	B - Most studies consistent and inconsistency can be explained NA - Not applicable (one study only)
3. Clinical impact	C	NA	NA	NA	C - Moderate NA - Not applicable/no difference/underpowered
4. Generalisability	A	A	B	B	A - Evidence directly generalisable to target population B - Evidence directly generalisable to target population with some caveats
5. Applicability	C	C	D	D	C - Evidence probably applicable to Australian healthcare context with some caveats D - Evidence not applicable to Australian healthcare context

EVIDENCE STATEMENTS

ES2.12 In pregnant women, oral iron plus folic acid reduces maternal anaemia (haemoglobin < 110g/L) at 34 weeks gestation or more compared to no treatment or placebo

ES2.13 In pregnant women, the effect of oral iron plus folic acid compared to no treatment or placebo on maternal iron deficiency anaemia is uncertain

ES2.14 In pregnant women, oral iron plus folic acid reduces moderate anaemia postpartum (haemoglobin between 80 g/L and 110 g/L) compared to no treatment or placebo

ES2.15 In pregnant women, the effect of oral iron plus folic acid compared to no treatment or placebo on severe anaemia (haemoglobin <80 g/L) is uncertain

AP; anaemia postpartum, MA; maternal anaemia, MIDA; maternal iron deficiency anaemia, SA; severe anaemia

Table D2.M Key question: In maternity patients, what is the effect of intravenous iron vs oral iron on laboratory measures?			Evidence table ref: D2.M
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
During pregnancy: One Level I study of good quality (Reveiz et al 2011) that included three RCTs with high or unclear risk of bias. One additional Level II study of fair quality (Gupta et al 2013) was identified. Postpartum: Eight Level II studies, four of fair quality (Bhandal et al 2006; Jain et al 2013; Seid et al 2008; Van Wyck et al 2007) and four of poor quality (Breymann et al 2008; Giannoulis et al 2009; Mumtaz et al 2011; Verma et al 2011).	DP	PP	
	A	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias
	B	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
Reveiz et al (2011) reported significant differences favouring intravenous iron for haemoglobin levels at birth and at 4 weeks. All of the Level II studies reported significant results favouring intravenous iron for laboratory measures including: haemoglobin, haematocrit and ferritin levels. Some also reported non-significant results or did not report on significance.	A	A	All studies consistent
	B	B	Most studies consistent and inconsistency can be explained
	C	C	Some inconsistency, reflecting genuine uncertainty around question
	D	D	Evidence is inconsistent
	NA	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
During pregnancy: Reveiz et al (2011) found a significant difference favouring intravenous iron for maternal haemoglobin at birth (g/dL): 12.01 ± 0.88 vs 11.26 ± 1.1; MD 0.75; 95% CI 0.34, 1.16; P=0.00035 and mean maternal haemoglobin at 4 weeks (g/dL): MD 0.44; 95% CI 0.05, 0.82; P=0.027. Postpartum: Bhandal et al (2006) reported significant differences favouring intravenous iron for haemoglobin levels (g/dL) at days 5 and 14, and for ferritin levels (µg/L) at days 5, 14, and 40. Seid et al (2008) found significant differences in the change from baseline value to day 42 for haemoglobin (g/dL), haematocrit, and ferritin (ng/mL), all of which favoured intravenous iron. The remaining Level II studies reported similar results (Breymann et al 2008; Giannoulis et al 2009; Gupta et al 2013; Jain et al 2013; Mumtaz et al 2011; Van Wyck et al 2007; Verma et al 2011).	A	A	Very large
	B	B	Substantial
	C	C	Moderate
	D	D	Slight/Restricted
	NA	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
During pregnancy: The Level I study included pregnant women with a haemoglobin value less than 11g/dL (Reveiz et al 2011). The Level II study included pregnant women with anaemia (Gupta et al 2013). Postpartum: Three RCTs included women with postpartum anaemia (Jain et al 2013; Seid et al 2008, Van Wyck et al 2007), four RCTs included women with postpartum iron deficiency anaemia (Bhandal et al 2006; Breymann et al 2008; Mumtaz et al 2011; Verma et al 2011), and one RCT included women with severe postpartum iron deficiency anaemia (Giannoulis et al 2009)	A	A	Evidence directly generalisable to target population
	B	B	Evidence directly generalisable to target population with some caveats
	C	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			

During pregnancy: The Level I study included RCTs conducted in France and Turkey (Reveiz et al 2011). The Level II study was a conducted in a single centre in India (Gupta et al 2013) Postpartum: The Level II studies were conducted in a single centre in the UK (Bhandal et al 2006), multiple centres in Poland, Romania and the Russian Federation (Breymann et al 2008), a single centre in Greece (Giannoulis et al 2009), a single centre in India (Jain et al 2013; Verma et al 2011), two hospitals in Pakistan (Mumtaz et al 2011), multiple centres in the USA (Seid et al 2008), or multiple centres in the USA and Mexico (Van Wyck et al 2007).	A	A	Evidence directly applicable to Australian healthcare context
	B	B	Evidence applicable to Australian healthcare context with few caveats
	C	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

CRG noted a high variability of anaemia and iron deficiency and different doses of iron in included trials. Participants in one trial (Gupta, 2013) were also receiving mebendazole.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	DP	PP	Description
1. Evidence base	C	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2. Consistency	B	B	Most studies consistent and inconsistency can be explained
3. Clinical impact	C	C	Moderate
4. Generalisability	B	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES2.16 In maternity patients with iron deficiency anaemia, IV iron may lead to more rapid correction of laboratory measures (haemoglobin and ferritin) than oral iron; however, at completion of therapy haemoglobin levels were similar in both groups but ferritin continued to be higher with IV iron

Table D2.N Key question: In maternity patients, what is the effect of intravenous iron + oral iron vs oral iron on laboratory measures?			Evidence table ref: D2.N
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
During pregnancy: One Level I study of good quality (Reveiz et al 2011) identified one RCT (Khalafallah 2010) with low/unclear risk of bias. One additional Level II study of poor quality (Neeru et al 2012) found. Postpartum: One Level II study of fair quality (Westad et al 2008)	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
During pregnancy: Reveiz et al (2011) reported significant differences favouring intravenous iron and oral iron for haemoglobin levels before and after delivery. Neeru et al (2012) found significant differences favouring intravenous iron with oral iron for changes in haemoglobin and ferritin. Postpartum: Westad et al (2008) did not find any significant differences in haemoglobin levels but did report a significant difference in ferritin levels at 4 weeks.	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
During pregnancy: Reveiz et al (2011) found a significant difference favouring intravenous iron and oral iron for: mean predelivery maternal haemoglobin (g/dL): MD 0.48; 95% CI 0.21, 0.75, P=0.00042 and mean maternal haemoglobin after delivery (g/dL): MD 0.39; 95% CI 0.02, 0.76, P=0.037. Neeru (2012) reported significant differences for percentage changes in haemoglobin and ferritin. Postpartum: Westad et al (2008) reported a significant difference favouring intravenous iron plus oral iron for ferritin (µg/L) increase after 4 weeks: 13.7 ± 24.4 vs 4.2 ± 15.5; P < 0.001.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
During pregnancy: The Level I study included pregnant women with a haemoglobin value less than 11g/dL (Reveiz et al 2011). The Level II study included pregnant women with iron deficiency anaemia (Neeru et al 2012) Pospartum: The RCT included women with postpartum anaemia (Westad et al 2008).	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The Level I study included one RCT conducted in Australia (Reveiz et al 2011). The Level II studies were conducted in a single centre in India (Neeru et al 2012) and multiple centres in Norway (Westad et al 2008).	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

While there is significant effect observed, there the clinical significance is uncertain. Generalisability to Australian population queried as included population in Khalafallah trial does not meet standard definition of iron deficiency anaemia. Conflicting results due to timing of measurements of outcomes, doses used and uncertainties about compliance.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical impact	C	Moderate
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES2.17 In maternity patients with anaemia the superiority of IV iron plus oral iron compared to oral iron alone on increasing haemoglobin or ferritin levels is uncertain

Abbreviations: DP; during pregnancy, PP; postpartum

Table D2.O Key question: In maternity patients, what is the effect of intravenous iron vs oral iron + folic acid on laboratory measures?			Evidence table ref: D2.O
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
One Level II study of fair quality (Deeba et al 2012).	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
NA	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
The study found significant differences in haemoglobin and ferritin levels after 2, 4 and 6 weeks favouring intravenous iron (Deeba et al 2012). At 6 weeks the haemoglobin (g/dL) results were: 10.79 ± 0.8432 vs 9.903 ± 0.8848; P=0.000 and ferritin (ng/mL) results: 86.98 ± 19.939 vs 34.78 ± 8.793; P=0.000 (Deeba et al 2012).	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The study included pregnant women with iron deficiency anaemia (Deeba et al 2012).	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The study was conducted in a single centre in India (Deeba et al 2012).	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

CRG noted that the dose of IV iron calculated according to iron deficit. Evidence is from a single RCT. Clinical significance of the effect is assumed to be moderate but it is noted that laboratory measures are secondary outcome measures.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	C	Moderate
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES2.18 In maternity patients with iron deficiency anaemia, IV iron is more effective at increasing haemoglobin and ferritin levels than oral iron plus folic acid.

Table D2.P Key question: In maternity patients, what is the effect of intravenous iron + folic acid vs oral iron + folic acid on laboratory measures?				Evidence table ref: D2.P
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*				
Three Level II studies of fair quality (Bencaiova et al 2009; Froessler et al 2013; Kochhar et al 2013). Non-anaemic pregnant women (Bencaiova et al 2009) Antenatal Iron deficiency anaemia (Froessler et al 2013, Kochhar et al 2013) Postpartum iron deficiency anaemia (Froessler et al 2013,	NA	ID	PP	
	A	A	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias
	B	B	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	C	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	D	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*				
Non-anaemic pregnant women: One study Antenatal iron deficiency anaemia: Studies not consistent but can be explained. Froessler used suboptimal dose of IV iron and population with mild iron deficiency anaemia.	A	A	A	All studies consistent
	B	B	B	Most studies consistent and inconsistency can be explained
	C	C	C	Some inconsistency, reflecting genuine uncertainty around question
	D	D	D	Evidence is inconsistent
	NA	NA	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*				
Bencaiova et al (2009) found a significant difference in ferritin before delivery (µg/L) favouring intravenous iron with folic acid: 50 (4-266) vs 21 (4-82); P < 0.001. Froessler et al (2013) reported a significant difference favouring intravenous iron with folic acid for ferritin after delivery (µg/L) at day 14 only: 71 (26-120) vs 38 (20-54); P=0.004. Kochhar et al (2013) reported significant differences in both haemoglobin levels at days 21, 30 and delivery and ferritin levels at day 30 and delivery. No other significant differences were reported.	A	A	A	Very large
	B	B	B	Substantial
	C	C	C	Moderate
	D	D	D	Slight/Restricted
	NA	NA	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*				
Bencaiova et al (2009) included non-anaemic pregnant women, Froessler et al (2013) included both pregnant and post lower segment caesarean section women with iron deficiency anaemia and Kochhar et al (2013) included pregnant women with moderate iron deficiency anaemia.	A	A	A	Evidence directly generalisable to target population
	B	B	B	Evidence directly generalisable to target population with some caveats
	C	C	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	D	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*				
Two of the studies were conducted in single-centres in Switzerland and Australia (Bencaiova et al 2009; Froessler et al 2013) and one was conducted in two hospitals in India (Kochhar et al 2013).	A	A	A	Evidence directly applicable to Australian healthcare context
	B	B	B	Evidence applicable to Australian healthcare context with few caveats
	C	C	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	D	D	Evidence not applicable to Australian healthcare context
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*				
Definition of anaemia used differs between studies (Froessler, 2013; Kocchar, 2013).				

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	NA	AP	PP	Description
1. Evidence base	C	C	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2. Consistency	NA	B	NA	NA - Not applicable (one study only) B - Most studies consistent and inconsistency can be explained
3. Clinical impact	D	C	D	D - Slight/Restricted C - Moderate
4. Generalisability	A	A	A	Evidence directly generalisable to target population
5. Applicability	B	B	A	B - Evidence applicable to Australian healthcare context with few caveats A - Evidence applicable to Australian healthcare context

EVIDENCE STATEMENT

ES2.19 In non-anaemic pregnant women, prophylactic IV iron plus folic acid compared to oral iron plus folic acid does not improve haemoglobin levels but does increase ferritin levels before delivery

ES2.20 In pregnant women with iron deficiency anaemia, IV iron plus folic acid was more effective than oral iron plus folic acid at increasing haemoglobin and ferritin levels

ES2.21 In women with postpartum iron deficiency anaemia, IV iron plus folic acid was no more effective than oral iron plus folic acid at increasing haemoglobin levels but was more effective in increasing ferritin levels

Abbreviations: ID; iron deficiency, MID; moderate iron deficiency, NA; not anaemic

Table D2.Q Key question: In maternity patients, what is the effect of intravenous iron vs intramuscular iron on laboratory measures?			Evidence table ref: D2.Q
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
One Level II study of poor quality (Singh et al 2013).	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
Singh et al (2013) did not report significance for all outcomes but did find a significant difference in haemoglobin values after 2 and 4 weeks of therapy.	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
Singh et al (2013) reported a significant difference for haemoglobin (g/dL) after 2 weeks of therapy: 8.79 vs 7.74; P < 0.01 and 4 weeks of therapy: 10.01 vs 8.81; P < 0.01.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The Level II study included pregnant women with haemoglobin ≤8g/dL (Singh et al 2013).	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The Level II study was conducted in a single centre in India (Singh et al 2013).	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*			

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	C	Moderate
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES2.24 In pregnant women with iron deficiency anaemia, IV iron is more effective than IM iron in increasing haemoglobin levels

Table D2.R Key question: In maternity patients, what is the effect of intravenous iron vs intramuscular iron + oral iron on laboratory measures?			Evidence table ref: D2.R
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
One Level I study of good quality (Reveiz et al 2011) which includes one RCT (Wali 2002) with high/unclear risk of bias. One Level II study of poor quality (Hashmi et al 2006).	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
Reveiz et al (2011) and Hashmi et al (2006) found several significant differences in laboratory measures which favoured IV iron.	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
Reveiz et al (2011) found a significant difference favouring intravenous iron for: maternal haemoglobin level at birth (following IV iron sucrose 500mg): 11.8 ± 1.1 vs 10.2 ± 1.2; MD 1.60; 95% CI 0.87, 2.33; P=0.000017 and haemoglobin level at delivery (following IV iron sucrose 200mg) 11.3 ± 0.9 vs 10.2 ±1.2; MD 1.10; 95% CI 0.49, 1.71; P=0.00044. Hashmi et al (2006) reported a significant difference favouring intravenous iron for the percentage of participants achieving target haemoglobin: 80% vs 20%; P < 0.05. The study did not report on significance for initial rise in haemoglobin (g/dL): 2.6 ± 0.9 vs 1.2 ± 0.8, post therapy final haemoglobin (g/dL): 12.1 ± 0.9 vs 10.0 ± 1.4 or final rise of haemoglobin at delivery (g/dL): 4.6 ± 0.3 vs 2.2 ± 0.5.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The Level I study included pregnant women with a haemoglobin value less than 11g/dL (Reveiz et al 2011). The Level II study included women with iron deficiency anaemia (both pregnant and postpartum) (Hashmi et al 2006).	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The Level I study included one RCT conducted in Pakistan (Reveiz et al 2011). The Level II study was conducted in a single centre in Pakistan (Hashmi et al 2006).	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	A	All studies consistent
3. Clinical impact	C	Moderate
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES2.25 In pregnant women with iron deficiency anaemia, IV iron increases haemoglobin levels more than IM iron plus oral iron

Table D2.S Key question: In maternity patients, what is the effect of intramuscular iron vs oral iron on laboratory measures?			Evidence table ref: D2.S
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
One Level I study of good quality (Reveiz et al 2011) which includes two RCTs with low or unclear risk of bias(Ogunbode 1980; Zutschi 2004)	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
The included RCTs are consistent.	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
Reveiz et al (2011) reported a significant difference favouring intramuscular iron for several outcomes including: not anaemic at term: 76/100 (76.0%) vs 62/100 (62.0%); RR 1.23; 95% CI 1.01, 1.48; P=0.035, mean maternal haemoglobin at birth (g/dL): 10.5 ± 0.84 vs 9.96 ± 0.89; MD 0.54; 95% CI 0.30, 0.78; P=0.000010 and mean maternal haematocrit level at birth (%): 31.2 ± 2.6 vs 29.8 ± 2.7; MD 1.40; 95% CI 0.67, 2.13; P=0.00019.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The studies included pregnant women with a haemoglobin value less than 11g/dL (Reveiz et al 2011).	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The study included RCTs conducted in India and Nigeria (Reveiz et al 2011).	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*			
Concerns exist about compliance with oral iron therapy.			

EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*		
Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	A	All studies consistent
3. Clinical impact	D	Slight/Restricted
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats
EVIDENCE STATEMENT ES2.23 In pregnant women with iron deficiency anaemia, IM iron may increase maternal haemoglobin and haematocrit compared to oral iron		

Table D2.T Key question: In maternity patients, what is the effect of intramuscular iron vs oral iron + folic acid on laboratory measures?		Evidence table ref: D2.T
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One Level I study of good quality (Reveiz et al 2011) which includes one RCT (Kumar, 2005) with high/unclear risk of bias	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Reveiz et al (2011) reported a significant difference favouring oral iron and folic acid in mean haemoglobin at 36 weeks (g/dL): 10.94 ± 0.56 vs 11.2 ± 0.82; MD -0.26; 95% CI -0.48, -0.04; P=0.023 but no other significant differences were reported.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study included pregnant women with a haemoglobin value less than 11g/dL (Reveiz et al 2011).	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study included one RCT conducted in India.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		

Comparable dose of oral iron but suboptimal dose of IM iron given.
Per-protocol analysis only. Noted withdrawals were different for women receiving oral treatment (13.5%) and those receiving IM treatment (38.5%).

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	D	Slight/Restricted
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	D	Evidence not applicable to Australian healthcare context

EVIDENCE STATEMENT

ES2.22 In pregnant women with iron deficiency anaemia, the effect of IM iron compared to oral iron plus folic acid on laboratory measures is uncertain

Table D2.U Key question: In maternity patients, what is the effect of oral iron vs no treatment or placebo on measures of fetal outcome?				Evidence table ref: D2.U
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*				
One Level I study of good quality (Pena-Rosas et al 2012) included 7 RCTs with low/unclear risk of bias.	LB	PB		
	A	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*				
Pena-Rosas et al (2012) did not report any significant differences.	A	A	All studies consistent	
	B	B	Most studies consistent and inconsistency can be explained	
	C	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	D	Evidence is inconsistent	
	NA	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*				
Pena-Rosas et al (2012) did not report any significant differences in low birthweight: 25/582 (4.3%) vs 38/554 (6.9%); RR 0.63; 95% CI 0.30, 1.32; P=0.22 or preterm birth: 57/582 (6.7%) vs 70/861 (8.1%); RR 0.82; 95% CI 0.58, 1.14; P=0.24. No other significant differences were reported.	A	A	Very large	
	B	B	Substantial	
	C	C	Moderate	
	D	D	Slight/Restricted	
	NA	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*				
The study included women of any gestational age and parity (Pena-Rosas et al 2012).	A	A	Evidence directly generalisable to target population	
	B	B	Evidence directly generalisable to target population with some caveats	
	C	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*				
The study included RCTs conducted in England, USA, Australia, Norway, Iran, Gambia and Hong Kong (Pena-Rosas et al 2012).	A	A	Evidence directly applicable to Australian healthcare context	
	B	B	Evidence applicable to Australian healthcare context with few caveats	
	C	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	D	Evidence not applicable to Australian healthcare context	
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*				

The inclusion of the trial by Heminiki (1991) was questioned by the CRG and subsequently removed from the analysis (for wrong comparator). The trial gave 100mg daily oral iron to women in the control group if haematocrit levels fell below 0.32. The CRG considered this to be routine oral iron therapy compared to a targeted iron therapy (i.e. not no treatment/placebo); therefore the trial did not meet our PICO criteria.
No evidence of effect but queries around overall sample size (underpowered)

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	LB	PB	Description
1. Evidence base	B	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2. Consistency	A	A	All studies consistent
3. Clinical impact	NA	NA	Not applicable/no difference/underpowered
4. Generalisability	A	A	Evidence directly generalisable to target population
5. Applicability	B	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES2.26 In pregnant women, the effect of oral iron compared to no treatment or placebo on the incidence of low birth weight (<2500 g), very low birth weight (<1500 g) and preterm birth is uncertain

Abbreviations: LB, low birthweight, PB, preterm birth

Table D2.V Key question: In maternity patients, what is the effect of oral iron + folic acid vs no treatment or placebo on measures of fetal outcome?			Evidence table ref: D2.V
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
One Level I study of good quality (Pena-Rosas et al 2012) identified 3 RCTs each with unclear risk of bias (Christian 2003, Lee 2005, Taylor 1982).	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
The study found a significant difference favouring iron and folic for mean birthweight but no other significant differences were reported (Pena-Rosas et al 2012).	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
Pena-Rosas et al (2012) found a significant difference favouring iron and folic acid for weight at birth (g): MD 57.73; 95% CI 7.66, 107.79; P=0.024 (2 RCTs) but not low birthweight (<2500g): 220/659 (33.4%) vs 262/652 (40.2%); RR 1.07; 95% CI 0.31, 3.74; P=0.91 or preterm birth: 149/768 (19.4%) vs 140/729 (19.2%); RR 1.55; 95% CI 0.40, 6.00; P=0.53. No other significant differences were reported (Pena-Rosas et al 2012).	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The study included women of any gestational age and parity (Pena-Rosas et al 2012).	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The study included RCTs conducted in England, Nepal and South Korea (Pena-Rosas et al 2012).	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*			

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	B	One or two Level II studies with a low risk of bias
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	D	Evidence not applicable to Australian healthcare context

EVIDENCE STATEMENT

ES2.27 In pregnant women, the effect of oral iron plus folic acid compared to no treatment or placebo on measures of fetal outcomes (low birthweight, incidence of preterm birth and small-for-gestational age) is uncertain

Table D2.W Key question: In maternity patients, what is the effect of intravenous iron vs oral iron on measures of fetal outcome?			Evidence table ref: D2.W
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Level I evidence: One Level I study of good quality (Reveiz et al 2011) which includes three RCTs with low or unclear risk of bias (Al 2005, Bayoumeu 2002, Singh, 1998) Level II evidence: One Level II study of fair quality (Gupta et al 2013).	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
Neither study recorded any significant differences in fetal outcomes (Reveiz et al 2011; Gupta et al 2013).	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
In one RCT, no events were recorded in either study group for preterm labour or low birthweight (<2500g) and there was no significant differences eported for small-for-gestational age: 8/50 (16.0%) vs 5/50 (10.0%); P=0.38 (Reveiz et al 2011). Three RCTs found no significant difference for neonatal weight at birth (g): MD 54.29; 95% CI -170.11, 278.68; P=0.64 (Reveiz et al 2011). Heterogeneity was substantial. Gupta et al (2013) did not report any significant differences in period of gestation (weeks): 38.48 ± 1.36 vs 38.31 ± 1.47 or birthweight (g): 2607 ± 253.28 vs 2568 ± 244.19.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The Level I study included pregnant women with a haemoglobin value less than 11g/dL or toerh tests for anaemia attributed to iron deficiency (Reveiz et al 2011). The Level II study included pregnant women with anaemia (Hb 7-9 g/dL) and ferritin <15ng/ml) (Gupta et al 2013).	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The Level I study included RCTs conducted in France, Turkey and Singapore (Reveiz et al 2011). The Level II study was conducted in a single centre in India (Gupta et al 2013).	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*			

Gupta (2013) participants also received mebendazole.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2. Consistency	A	All studies consistent
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES2.28 In maternity patients with iron deficiency anaemia, the effect of IV iron compared to oral iron on measures of fetal outcomes is uncertain

Table D2.X Key question: In maternity patients, what is the effect of intravenous iron + folic acid vs oral iron + folic acid on measures of fetal outcome?			Evidence table ref: D2.X
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Two Level II studies of fair quality (Bencaiova et al 2009; Kochhar et al 2013). Non-anaemic pregnant women (Bencaiova et al 2009) Women with iron deficiency anaemia during pregnancy (Kochhar et al 2013)	NA	MID	
	A	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias
	B	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
NA	A	A	All studies consistent
	B	B	Most studies consistent and inconsistency can be explained
	C	C	Some inconsistency, reflecting genuine uncertainty around question
	D	D	Evidence is inconsistent
	NA	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
Neither study reported any significant differences in birthweight or gestational age at delivery. Bencaiova et al (2009) found no difference in birthweight (g) (examining two and three doses of intravenous iron respectively): 3325 ± 482 and 3178 ± 705 vs 3361 ± 567; P=0.131. Kochhar et al (2013) reported similar results: 2870 ± 680 vs 2695 ± 765.	A	A	Very large
	B	B	Substantial
	C	C	Moderate
	D	D	Slight/Restricted
	NA	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
Bencaiova et al (2009) included non-anaemic pregnant women and Kochhar et al (2013) included pregnant women with moderate iron deficiency anaemia.	A	A	Evidence directly generalisable to target population
	B	B	Evidence directly generalisable to target population with some caveats
	C	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
One study was conducted in a single centre in Switzerland (Bencaiova et al 2009) and one was conducted in two hospitals in India (Kochhar et al 2013).	A	A	Evidence directly applicable to Australian healthcare context
	B	B	Evidence applicable to Australian healthcare context with few caveats
	C	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	D	Evidence not applicable to Australian healthcare context
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*			
Potential suboptimal dose of IV iron in study by Bencaovia (2009).			

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	NA	AP	Description
1. Evidence base	C	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2. Consistency	NA	NA	Not applicable (one study only)
3. Clinical impact	NA	NA	Not applicable/no difference/underpowered
4. Generalisability	A	A	Evidence directly generalisable to target population
5. Applicability	B	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES2.29 In non-anaemic pregnant women, the effect of prophylactic IV iron plus folic acid compared with oral iron plus folic acid on measures of fetal outcomes is uncertain

ES2.30 In pregnant women with iron deficiency anaemia, the effect of IV iron plus folic acid compared with oral iron plus folic acid on measures of fetal outcomes is uncertain

Abbreviations: MID, moderate iron deficiency; NA, not anaemic

Table D2.Y Key question: In maternity patients, what is the effect of intramuscular iron vs oral iron + folic acid on measures of fetal outcome?			Evidence table ref: D2.Y
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
One Level I study of good quality (Reveiz et al 2011) which includes one RCT with high/unclear risk of bias (Kumar, 2005).	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
NA	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
Reveiz et al (2011) did not report any significant difference in fetal outcomes. Mean birthweight (g): 2610 ± 420 vs 2630 ± 480; MD -20.00, 95% CI -164.35, 124.35.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The study included pregnant women with a haemoglobin value less than 11g/dL (Reveiz et al 2011).	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The study included one RCT conducted in India (Reveiz et al 2011).	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*			

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	A	Evidence directly generalisable to target population with some caveats
5. Applicability	D	Evidence not applicable to Australian healthcare context

EVIDENCE STATEMENT

ES2.34 In pregnant women with iron deficiency anaemia, the effect of IM iron compared to oral iron plus folic acid on birthweight is uncertain

Table D2.Z Key question: In maternity patents, what is the effect of oral iron vs no treatment or placebo on mortality?			Evidence table ref: D2.Z
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
	MM	PM	
Maternal mortality: One Level I study of good quality (Pena-Rosas et al 2012) identified one RCT (Eskeland, 1997) with unclear risk of bias. **Perinatal mortality:** One Level III study of fair quality (McCaw-Binns et al 1994) that reported on perinatal mortality.	A	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias
	B	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
NA.	A	A	All studies consistent
	B	B	Most studies consistent and inconsistency can be explained
	C	C	Some inconsistency, reflecting genuine uncertainty around question
	D	D	Evidence is inconsistent
	NA	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
Maternal mortality: No maternal deaths were reported in either treatment arms: 0/24 (0%) vs 0/23 (0%), but the study was underpowered for this outcome (Pena-Rosas et al 2012). **Perinatal mortality:** McCaw-Binns et al (1994) reported significant differences favouring oral iron for antepartum fetal deaths: OR 1.42; 95% CI 1.09, 1.84; P < 0.01 and all perinatal deaths: OR 1.26; 95% CI 1.07, 1.50; P < 0.01 after adjustments for confounders. Although an effect favouring iron was observed in the unadjusted analyses for deaths from immaturity and intrapartum asphyxia, the significance of these effects were not maintained after adjustments for potential confounders.	A	A	Very large
	B	B	Substantial
	C	C	Moderate
	D	D	Slight/Restricted
	NA	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The study identified by Pena-Rosas et al (2012) included women of any gestational age and parity. The Level III study included all pregnant women delivering over a defined time period (McCaw-Binns et al 1994).	A	A	Evidence directly generalisable to target population
	B	B	Evidence directly generalisable to target population with some caveats
	C	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
Pena-Rosas et al 2012 included one RCT conducted in Norway. The Level III study was conducted in Jamaica (McCaw-Binns et al 1994).	A	A	Evidence directly applicable to Australian healthcare context
	B	B	Evidence applicable to Australian healthcare context with few caveats
	C	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The inclusion of the trial by Heminiki (1991) was questioned by the CRG and subsequently removed from the analysis (for wrong comparator). The trial gave 100mg daily oral iron to women in the control group if haematocrit levels fell below 0.32. The CRG considered this to be routine oral iron therapy compared to a targeted iron therapy (i.e. not no treatment/placebo); therefore the trial did not meet our PICO criteria.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating		Description
	MM	PM	
1. Evidence base	C	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2. Consistency	NA	NA	Not applicable (one study only)
3. Clinical impact	NA	C	NA - Not applicable/no difference/underpowered C - Moderate
4. Generalisability	A	C	A - Evidence directly generalisable to target population C - Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	B	C	B - Evidence applicable to Australian healthcare context with few caveats C - Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES2.35 In pregnant women, the effect of oral iron compared to no treatment or placebo on maternal mortality is uncertain

ES2.36 In pregnant women, the effect of oral iron compared to no treatment or placebo on perinatal and neonatal mortality is uncertain

Abbreviations: MM, maternal mortality; PM, perinatal mortality

Table D2.AA Key question: In maternity patients, what is the effect of oral iron + folic acid vs no treatment or placebo on mortality?		Evidence table ref: D2.AA
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level I evidence: One Level I study of good quality (Pena-Rosas et al 2012) which included four RCTs with low or unclear risk of bias that reported on maternal (1 trial) or neonatal deaths (3 trials). Level III evidence: One Level III study of fair quality (Titaley et al 2012) reported on neonatal mortality.	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
The included RCTs in Pena-Rosas et al (2012) were consistent; reporting no significant difference betweeen treatment groups for either maternal deaths or neonatal deaths. Titaley et al (2012) reported a significant difference favouring iron + folic acid for both early and all neonatal mortality.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pena-Rosas et al (2012) did not report any significant differences in maternal death: 0/111 (0%) vs 0/20 (0%) or neonatal death: 29/849 (3.4%) vs 40/944 (4.2%); RR 0.81; 95% CI 0.51, 1.30. Titaley et al (2012) reported significant differences favouring iron and folic acid for early neonatal mortality: HR 0.48; 95% CI 0.30, 0.79; P < 0.01 and all neonatal mortality: HR 0.51; 95% CI 0.33, 0.79; P < 0.01, which was sustained after adjustments for confounders, but he clinical impact could not be determined. (see note below)	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The RCTs included by Pena-Rosas et al 2012 included women of any gestational age and parity. The Level III study included women of reproductive age (15-49 years) (Titaley et al 2012).	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The RCTs included by Pena-Rosas et al 2012 were conducted in England, Ireland, Nepal and South Korea. The Level III study was conducted in Indonesia (Titaley et al 2012).	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		

Titaley et al 2012 - most common formulation used in Indonesia is iron 60 mg and folic acid 0.25 mg and mothers are recommended to attend four antenatal visits only. A mother was classified as using antenatal iron/folic acid if they reported taking tablets for at least one day. Information used in the analysis was collected from the mothers, relying on their recollection of supplement use, meaning there is potential for recall and misclassification bias. Further, only surviving mothers were included, which might lead to an underestimate of neonatal deaths.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	C	Evidence probably applicable to Australian healthcare context

EVIDENCE STATEMENT

ES2.37 In pregnant women, the effect of oral iron plus folic acid compared to no treatment or placebo on maternal and neonatal mortality is uncertain

Table D2.AB Key question: In maternity patients, what is the effect of intravenous iron vs oral iron on mortality?			Evidence table ref: D2.AB
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
One Level I study of good quality (Reveiz et al 2011) which includes two RCTs (Bayoumeu, 2002; Singh 1998) with low or unclear risk of bias.	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
None of the included RCTs reported any events in either study group.	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
No events were recorded in either study group for maternal mortality: 0/50 (0%) vs 0/50 (0%) and neonatal mortality: 0/74 (0%) vs 0/73 (0%)(Reveiz et al 2011), however the studies were underpowered for this outcome.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The study included pregnant women with a haemoglobin value less than 11g/dL or other test fo anaemia attributed to iron deficiency (Reveiz et al 2011).	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The study included RCTs conducted in France and Singapore (Reveiz et al 2011).	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*			

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2. Consistency	A	All studies consistent
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES2.38 In maternity patients with iron deficiency anaemia, the effect of IV iron compared to oral iron on maternal and perinatal mortality is uncertain

Recommendations

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.* R1 The routine administration of iron supplementation to all pregnant women is not recommended[a] [a] in accordance with *Clinical practice guidelines: Antenatal care – Module 1*	GRADE OF RECOMMENDATION C	RELEVANT ESF(S) D2.E, D2.J, D2.K, D2.U and D2.Z

UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*
CRG concerned about lack of applicability of trials to the Australian health care setting. There is insufficient high-quality data to suggest iron benefits the health of the woman or baby. Conflicting evidence of effect for iron vs iron (+/- folate) for preterm births/birthweight does not reach statistical significance, there is insufficient high-quality data for perinatal mortality and a lack of evidence for maternal mortality. Note: Studies that report iron associated with increased birth weight are confounded by inclusion of other micronutrients in the intervention/comparator or are associated with use of iron as part of a population health intervention, rather than specific supplement. Research gaps on haemoglobin levels and clinical benefits.

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	YES
	NO
Are there any resource implications associated with implementing this recommendation?	YES
	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES
	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation?	YES
	NO

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.* R2 The administration of iron to pregnant women with iron deficiency anaemia is recommended; IV iron is preferred when rapid restoration of haemoglobin and iron stores is required	GRADE OF RECOMMENDATION C	RELEVANT ESF(S) D2.E, D2.F, D2.G, D2.I, D2.J, D2.K, D2.M, D2.N, D2.Q, D2.R, D2.S, D2.U, D2.W, D2.Z and D2.AB
UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*		
IV iron leads to a more rapid increase in these values than other routes of administration. Compliance and intolerance of oral iron preparations can limit efficacy. Insufficient evidence on dose, compliance, fetal outcomes, IM iron (implications for rural and indigenous population). Increase IV use may be mitigated by screening for iron deficiency during pregnancy.		
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care? The recommendation has the potential to increase the utilisation of iron supplementation (oral and IV) in women with IDA		YES NO
Are there any resource implications associated with implementing this recommendation? Small increase in testing for IDA, drug use, training and development of staff, better communication and hand over between healthcare workers may occur, however this is not certain.		YES NO
Will the implementation of this recommendation require changes in the way care is currently organised? Some aspects of care will require increased access in remote areas.		YES NO
Are the guideline development group aware of any barriers to the implementation of this recommendation? Cost of intervention and training of health care workers.		YES NO

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.* R3 In maternity patients who require iron therapy for the treatment of anaemia, the routine addition of folic acid is not recommended[a]. [a] Folic acid should be administered for the prevention of neural tube defects, in accordance with *Clinical practice guidelines: Antenatal care – Module 1*	GRADE OF RECOMMENDATION C	RELEVANT ESF(S) D2.H, D2.L, D2.O, D2.P, D2.T, D2.V, D2.X, D2.Y and D2.AA
UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.* There is insufficient high-quality data to suggest iron plus folic acid benefits the health of the woman or baby.		
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care?		YES
		NO
Are there any resource implications associated with implementing this recommendation?		YES
		NO
Will the implementation of this recommendation require changes in the way care is currently organised?		YES
		NO
Are the guideline development group aware of any barriers to the implementation of this recommendation?		YES
		NO

ESAs

Table D2.A Key question: In maternity patients, what is the effect of ESAs + iron vs iron on transfusion incidence?			Evidence table ref: D2.A
1. Evidence base (*number of studies, level of evidence and risk of bias in the included studies)*			
	DP	PP	
Level I evidence Two Level I studies of good quality included three RCTs with low or unclear risk of bias: During pregnancy (Reveiz et al 2011), Postpartum (Dodd et al 2004) Level II evidence One Level II study of fair quality (Krafft et al 2011).	A	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias
	B	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
One study reported no significant difference (Dodd et al 2004), while the other two studies did not record any events in either study group (Reveiz et al 2011, Krafft et al 2011).	A	A	All studies consistent
	B	B	Most studies consistent and inconsistency can be explained
	C	C	Some inconsistency, reflecting genuine uncertainty around question
	D	D	Evidence is inconsistent
	NA	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
Dodd et al 2004: 0/60 (0%) vs 2/40 (5%); RR 0.20; 95% CI: 0.01, 3.92; no difference.	A	A	Very large
	B	B	Substantial
	C	C	Moderate
	D	D	Slight/Restricted
	NA	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
One Level I study included women with a postpartum haemoglobin value less than 12g/dL up to six weeks after birth (Dodd et al 2004) and the other included women with iron deficient anaemia in pregnancy with haemoglobin value less than 11g/dL (Reveiz et al 2011). The Level II study included postpartum women with haemoglobin less than 8.5g/dL (Krafft et al 2011).	A	A	Evidence directly generalisable to target population
	B	B	Evidence directly generalisable to target population with some caveats
	C	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The Level I studies were conducted in a variety of counties including France (Dodd et al 2004; Reveiz et al 2011). The Level II study was conducted in a single centre in Switzerland (Krafft et al 2011).	A	A	Evidence directly applicable to Australian healthcare context
	B	B	Evidence applicable to Australian healthcare context with few caveats
	C	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Inclusion criteria of <11g/dL (during pregnancy) or <12g/dL (postpartum) would not be routinely treated with ESAs in Australian population.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	DP	PP	Description
1. Evidence base	B	B	One or two Level II studies with a low risk of bias
2. Consistency	NA	B	NA - Not applicable (one study only) Most studies consistent and inconsistency can be explained
3. Clinical impact	NA	NA	Not applicable/no difference/underpowered
4. Generalisability	C	C	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	B	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES2.43 In women with iron deficiency anaemia in pregnancy, the effect on transfusion incidence of adding ESAs to iron is uncertain

ES2.44 In women with postpartum iron deficiency anaemia, the effect on transfusion incidence of adding ESAs to iron is uncertain

Abbreviations: DP, during pregnancy; PP, postpartum

Table D2.B Key question: In maternity patients, what is the effect of ESAs + iron vs iron on laboratory measures?			Evidence table ref: D2.B
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Level I evidence Two Level I studies of good quality which include five RCTs with low or unclear risk of bias; During pregnancy (Reveiz et al 2011), Postpartum (Dodd et al 2004) Level II evidence Two Level II studies of fair quality (Krafft et al 2011; Wagstrom et al 2007).	DP	PP	
	A	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias
	B	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
One Level I study reported a significant difference in haemoglobin levels within two weeks after treatment, which favoured the comparator but no other significant results (Dodd et al 2004). One Level II study found a significant difference in haemoglobin favouring erythropoietin plus iron (Krafft et al 2011). The other two studies not did report any differences (Reveiz et al 2011; Wagstrom et al 2007).	A	A	All studies consistent
	B	B	Most studies consistent and inconsistency can be explained
	C	C	Some inconsistency, reflecting genuine uncertainty around question
	D	D	Evidence is inconsistent
	NA	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
Dodd et al (2004) found a significant difference favouring the comparator (iron) in haemoglobin (g/dL) levels within two weeks after treatment: 10.7 ± 1.1 vs 11.25 ± 0.55; MD -0.55; 95% CI: -0.99, -0.11 but no other significant results. Reveiz et al (2011) did not report any differences. Krafft et al (2011) found a significant difference favouring erythropoietin with iron but did not report any other differences. Wagstrom et al (2007) did not report any significant differences between the groups.	A	A	Very large
	B	B	Substantial
	C	C	Moderate
	D	D	Slight/Restricted
	NA	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
One Level I study included postpartum women with a haemoglobin value less than 12g/dL (Dodd et al 2004) and the other included women during pregnancy with a haemoglobin value less than 11g/dL (Reveiz et al 2011). One Level II study included postpartum women with haemoglobin less than 8.5g/dL (Krafft et al 2011) and the other included postpartum women with haemoglobin less than or equal to 80g/L (Wagstrom et al 2007).	A	A	Evidence directly generalisable to target population
	B	B	Evidence directly generalisable to target population with some caveats
	C	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The two Level I studies included RCTs conducted in a variety of countries including France (Dodd et al 2004; Reveiz et al 2011). One of the Level II studies was conducted in Switzerland (Krafft et al 2011) and the other in Sweden (Wagstrom et al 2007).	A	A	Evidence directly applicable to Australian healthcare context
	B	B	Evidence applicable to Australian healthcare context with few caveats
	C	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	D	Evidence not applicable to Australian healthcare context
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*			

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	DP	PP	Description
1. Evidence base	B	B	One or two Level II studies with a low risk of bias
2. Consistency	NA	C	NA - Not applicable (one study only) C - Some inconsistency, reflecting genuine uncertainty around question
3. Clinical impact	NA	D	NA – Not applicable/no difference/underpowered D - Slight/Restricted
4. Generalisability	C	B	C - Evidence not directly generalisable to the target population but could be sensibly applied B - Evidence directly generalisable to target population with some caveats
5. Applicability	B	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES2.45 In women with iron deficiency anaemia in pregnancy, the effect on laboratory values of adding ESAs to iron is uncertain

ES2.46 In women with postpartum iron deficiency anaemia, the effect on laboratory values of adding ESAs to iron is uncertain

Abbreviations: DP, during pregnancy; PP, postpartum

Table D2.C Key question: In maternity patients, what is the effect of ESAs + iron vs iron on thromboembolic events?			Evidence table ref: D2.C
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Level I evidence: One Level I study of good quality (Dodd et al 2004), which includes two RCTs with unclear risk of bias. Level II evidence: One Level II study of fair quality (Krafft et al 2011).	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
Neither study reported any events in either study group (Dodd et al 2004; Krafft et al 2011).	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
No events were reported in either study group: Dodd et al 2004: 0/64 (0%) vs 0/32 (0%); RR 0.0; 95% CI: 0.0, 0.0	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The Level I study included women with a haemoglobin value less than 12g/dL (Dodd et al 2004). The Level II study included postpartum women with haemoglobin less than 8.5g/dL (Krafft et al 2011).	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The Level I study included RCTs conducted in a variety of countries (Dodd et al 2004). The Level II study was conducted in a single centre in Switzerland (Krafft et al 2011).	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*			

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	B	One or two Level II studies with a low risk of bias
2. Consistency	A	All studies consistent
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES2.48 In women with postpartum iron deficiency anaemia, the effect on thromboembolic events of adding ESAs to iron is uncertain

Table D2.D Key question: In maternity patients, what is the effect of ESAs + iron vs iron on measures of fetal outcome?			Evidence table ref: D2.D
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
One Level I study of good quality (Reveiz et al 2011), which includes one RCT with low/unclear risk of bias.	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
NA	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
The study did not report a difference in births before 37 weeks or birthweight: Birth (< 37 weeks): 0/20 (0%) vs 1/20 (5%); RR 0.33; 95% CI: 0.01, 7.72 Birthweight (g): 3332 ± 282 vs 3462 ± 497; MD -130.00, 95% CI: -380.44, 120.44	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The study included pregnant women with a haemoglobin value less than 11g/dL (Reveiz et al 2011).	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The study included one RCT conducted in France (Reveiz et al 2011).	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*			
EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*			

Component	Rating	Description
1. Evidence base	B	One or two Level II studies with a low risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES2.49 In women with iron deficiency anaemia in pregnancy, the effect on fetal outcomes of adding ESAs to iron is uncertain

Recommendations

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.* R4 ESAs should not be routinely used in maternity patients	GRADE OF RECOMMENDATION C	RELEVANT ESF(S) D2.A, D2.B, D2.C and D2.D
UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.* In other adult populations, there is evidence that ESAs may increase the risks of mortality and thromboembolic events. (see R2 in *Patient Blood Management Guidelines: Module 3 - Medical*). There is insufficient high quality data about the use of ESAs in maternity patients.		
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care?		YES / NO
Are there any resource implications associated with implementing this recommendation?		YES / NO
Will the implementation of this recommendation require changes in the way care is currently organised?		YES / NO
Are the guideline development group aware of any barriers to the implementation of this recommendation?		YES / NO

D3 Evidence – Question 3

Fresh frozen plasma

Table D3.A Key question: In patients with postpartum haemorrhage and maternity patients with an abnormal coagulation profile who are at risk of bleeding, what is the effect of fresh frozen plasma on maternal mortality?		Evidence table ref: D3.A
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes two Level III-2 studies (Pasquier 2013, fair; Reyal 2004, fair). The study by Pasquier et al included patients with severe postpartum haemorrhage and the study by Reyal et al included patients with and without haemorrhagic complications.	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
There was no maternal mortality reported in the fresh frozen plasma arm of both studies. In the Pasquier et al study, no maternal mortality was reported in the 'no fresh frozen plasma' arm; and no results reported for the 'no fresh frozen plasma' arm in the Reyal et al study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
No difference was reported between treatment arms in either study. In the Reyal et al study, out of the 44 patients who received transfusion, only 24 received fresh frozen plasma (19 patients received red blood cells and fresh frozen plasma, 5 patients received fresh frozen plasma only, 20 patients received red blood cells only).	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The Pasquier et al study was conducted in women with severe postpartum haemorrhage (>500 mL) who delivered after 24 weeks gestation, were treated with sulprostone and required transfusion with RBC within 6 hours of delivery. Therefore,	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied

results may not be directly generalisable to all bleeding and non-bleeding maternity patients. The Reyal et al study was conducted in women who had singleton or multiple pregnancy, delivery >24 weeks of amenorrhea. Cases were also selected based on having a haemorrhagic complication and all patients were from a medical unit located in a paediatrics hospital with a neonatal intensive care unit and significant prenatal diagnosis activity; therefore the authors claim that the patients compose a high risk population. Results may not be directly generalisable to all bleeding and non-bleeding maternity patients.	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Both studies were performed in France; therefore, the results are likely to be applicable to the Australian healthcare setting due to comparable availability of resources.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The Reyal et al study comprised a retrospective review of hospital records from January 1992 to December 1998; approaches to practice may have changed since this time.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	A	All studies consistent
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES3.1 In patients with postpartum haemorrhage the effect of fresh frozen plasma on maternal mortality is uncertain.

ES3.5 In maternity patients with an abnormal coagulation profile who are at risk of bleeding, the effect of fresh frozen plasma on maternal mortality is uncertain.

Table D3.B Key question: In patients with postpartum haemorrhage, what is the effect of fresh frozen plasma on transfusion requirements?			Evidence table ref: D3.B
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Includes one Level III-2 study (Pasquier 2013, fair).	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
NA	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
The result for mean (SD) volume of blood products transfused favours no fresh frozen plasma. However, the results for median (IQR) are comparable between treatment arms.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The Pasquier et al study was conducted in women with severe postpartum haemorrhage (>500 mL) who delivered after 24 weeks gestation, were treated with sulprostone and required transfusion with RBC within 6 hours of delivery. Therefore, results may not be directly generalisable to all bleeding and non-bleeding maternity patients.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The study was performed in France; therefore, the results are likely to be applicable to the Australian healthcare setting due to comparable availability of resources.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*			
NA			

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	D	Slight/Restricted
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES3.2 In patients with postpartum haemorrhage, the effect of fresh frozen plasma on transfusion requirements is uncertain.

Abbreviations: IQR, interquartile range; SD, standard deviation

Table D3.C Key question: In patients with postpartum haemorrhage, what is the effect of fresh frozen plasma on the need for additional interventions to control bleeding?		Evidence table ref: D3.C
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level III-2 study (Pasquier 2013, fair).	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
A total of 23 (56%) patients in the FFP arm required at least one additional intervention (embolisation and/or arterial ligation and/or hysterectomy) and 29 patients (29%) who did not received FFP required at least one additional intervention to control bleeding . The significance of this was not reported, however subjects who received FFP were prone to severity bias with the decision to transfuse FFP at the discretion of the anaesthetist.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study was conducted in women with severe postpartum haemorrhage (>500 mL) who delivered after 24 weeks gestation, were treated with sulprostone and required transfusion with RBC within 6 hours of delivery prior to therapy with fresh frozen plasma. Therefore, results may not be directly generalisable to all maternity patients (including bleeding maternity patients).	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was performed in France; therefore, the results are likely to be applicable to the Australian healthcare setting due to comparable availability of resources.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		
NA		

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES3.4 In patients with postpartum haemorrhage, the effect of fresh frozen plasma on the need for additional interventions to control bleeding is uncertain.

Combination or fixed ratio therapy

Table D3.D Key question: In patients with postpartum haemorrhage, what is the effect of combination or fixed ratio therapy (fresh frozen plasma, cryoprecipitate, fibrinogen concentrate and/or platelet transfusion), on transfusion requirements?		Evidence table ref: D3.D
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level III-2 study (Pasquier 2013, Fair) comparing high FFP:RBC ratio (> 1 U of FFP for every 2 U of packed RBC) with low FFP:RBC ratio (≤ 1 U of FFP for every 2 U of packed RBCs).	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study identified.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
No difference detected between treatment arms	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study was conducted in women with severe postpartum haemorrhage (>500 mL) who delivered after 24 weeks gestation, were treated with sulprostone and required transfusion with RBC within 6 hours of delivery prior to therapy with fresh frozen plasma. Therefore, results may not be directly generalisable to all maternity patients (including bleeding maternity patients).	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was performed in France; therefore, the results are likely to be applicable to the Australian healthcare setting due to comparable availability of resources	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES3.17 In patients with postpartum haemorrhage, the effect of combination or fixed ratio therapy (fresh frozen plasma, cryoprecipitate, fibrinogen concentrate and/or platelet transfusion), on transfusion requirements is uncertain.

Abbreviations: FFP, fresh frozen plasma; RBC, red blood cell; U, unit

Table D3.E Key question: In patients with postpartum haemorrhage, what is the effect of combination or fixed ratio therapy (fresh frozen plasma, cryoprecipitate, fibrinogen concentrate and/or platelet transfusion), on the need for additional interventions to control bleeding?		Evidence table ref: D3.E
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level III-2 study (Pasquier 2013, Fair) comparing high FFP:RBC ratio (> 1 U of FFP for every 2 U of packed RBC) with low FFP:RBC ratio (≤ 1 U of FFP for every 2 U of packed RBCs).	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Only one study identified.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
A high FFP:RBC ratio was associated with fewer requirements for additional interventions to control bleeding (embolisation and/or arterial ligation and/or hysterectomy). OR (95% CI): 1.58 (1.19-2.10), P=0.003. However, transfusion of FFP was dependent on clinical assessment and laboratory coagulation results. Therefore, results between the two patient groups may be subject to selection bias.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study was conducted in women with severe postpartum haemorrhage (>500 mL) who delivered after 24 weeks gestation, were treated with sulprostone and required transfusion with RBC within 6 hours of delivery prior to therapy with fresh frozen plasma. Therefore, results may not be directly generalisable to all maternity patients (including bleeding maternity patients).	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was performed in France; therefore, the results are likely to be applicable to the Australian healthcare setting due to comparable availability of resources.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	D	Slight/Restricted
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES3.18 In patients with postpartum haemorrhage, the effect of combination or fixed ratio therapy (fresh frozen plasma, cryoprecipitate, fibrinogen concentrate and/or platelet transfusion), on the need for additional interventions to control bleeding is uncertain.

Abbreviations: FFP, fresh frozen plasma; OR, odds ratio; RBC, red blood cell; U, unit

D4 Evidence – Question 4

Intraoperative cell salvage

Table D4.A Key question: In maternity patients who have placenta previa or who refuse transfusion, what is the effect of intraoperative cell salvage on transfusion requirements?		Evidence table ref: D4.A
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level III study (Malik 2010, poor).	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
In total, 31 units of homologous blood were transfused in the cell salvage group (n=77) compared to 29 units in the non-cell salvage group (n=70). Also, the study did not report the proportion of patients who had placenta previa, the proportion of patients in whom transfusion is not an option, or whether or not some patients fell into both categories.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study was conducted in patients who are Jehovah's Witnesses or who had placenta previa. All of the patients underwent caesarean section. It was unclear what proportion of the study population had placenta previa and how many were included because they were Jehovah's Witnesses; therefore it is hard to judge to which patient populations the results may be generalisable.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study institution (in the UK) had a limited number of staff trained in cell salvage (particularly out-of-hours). Therefore, the amount of blood salvaged was very low[a] and the applicability of the results warrant further consideration in settings where the	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats

intervention can be carried out more effectively. The applicability of the results also depends on other features of the study (i.e. that a double suction salvage method was used, and that the collection in the cell salvage chamber did not start until after delivery of the baby and placenta). Those factors also need to be considered in the context of the Australian healthcare system.	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Cell salvage was more likely to be used if massive blood loss was anticipated (e.g. in multiparous women with a higher risk of obstetric haemorrhage).
Potential important differences existed between the treatment groups at baseline – 27.3% of patients in the cell salvage group had an emergency caesarean compared to 60.0% in the comparator group.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	D	Evidence not directly generalisable to the target population and hard to judge whether it is sensible to apply
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES4.5 In maternity patients who have placenta previa or refuse transfusion, the effect of intraoperative cell salvage compared with no intraoperative cell salvage on transfusion requirements is uncertain.

a Mean: 95.5 ml, median: 0 ml, range: 0-1,800 ml. The median indicated that at least half of the patients in the cell salvage group had no blood salvaged. In addition, across the intervention arm, only 13 units of blood were processed and re-transfused.

Table D4.B Key question: In maternity patients who have placenta previa or who refuse transfusion, what is the effect of intraoperative cell salvage on the need for additional interventions to control bleeding?			Evidence table ref: D4.B
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Includes one Level III study (Malik 2010, poor)	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
NA	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
The use of additional interventions to control bleeding was measured via the number of patients who returned to theatre. There were no patients (0/77) in the intervention arm who had to return to theatre. The equivalent outcome was not reported for the control arm. Also, the study did not report the proportion of patients who had placenta previa, the proportion of patients in whom transfusion is not an option, or whether or not some patients fell into both categories.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The study was conducted in patients who had placenta previa or who refuse transfusion. In addition, all of the patients underwent caesarean section. Therefore, results are not generalisable to all maternity patients.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The study institution (in the UK) had a limited number of staff trained in cell salvage (particularly out-of-hours). Therefore, the amount of blood salvaged was very low[a] and the applicability of the results may warrant further consideration, particularly in settings where the intervention can be carried out more effectively.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*			
Cell salvage was more likely to be used if massive blood loss was anticipated (e.g. in multiparous women with a higher risk of obstetric haemorrhage). Potential important differences existed between the treatment groups at baseline – 27.3% of patients in the cell salvage group had an emergency caesarean compared to 60.0% in the comparator group.			

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component		Rating	Description
1.	Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2.	Consistency	NA	Not applicable (one study only)
3.	Clinical impact	NA	Not applicable/no difference/underpowered
4.	Generalisability	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5.	Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES4.6 In maternity patients who have placenta previa or refuse transfusion, the effect of intraoperative cell salvage compared with no intraoperative cell salvage on the need for additional interventions to control bleeding is uncertain.

a Mean: 95.5 ml, median: 0 ml, range: 0–1,800 ml. The median indicated that at least half of the patients in the cell salvage group had no blood salvaged. In addition, across the intervention arm, only 13 units of blood were processed and re-transfused.

Table D4.C Key question: In maternity patients who have placenta previa or who refuse transfusion, what is the effect of intraoperative cell salvage on thromboembolic events?			Evidence table ref: D4.C
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Includes one Level III study (Malik 2010, poor)	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
NA	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
No patients (0/77) in the intervention arm had a thromboembolism. The equivalent outcome was not reported for the control arm. Also, the study did not report the proportion of patients who had placenta previa, the proportion of patients in whom transfusion is not an option, or whether or not some patients fell into both categories.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The study was conducted in patients who are Jehovah's Witnesses or who had placenta previa. In addition, all of the patients underwent caesarean section. Therefore, results are not generalisable to all maternity patients.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The study institution (in the UK) had a limited number of staff trained in cell salvage (particularly out-of-hours). Therefore, the amount of blood salvaged was relatively low and the applicability of the results might need to be considered in settings where the intervention can be carried out in a more effective manner.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*			
Cell salvage was more likely to be used if massive blood loss was anticipated (e.g. in multiparous women with a higher risk of obstetric haemorrhage). Potential important differences existed between the treatment groups at baseline – 27.3% of patients in the cell salvage group had an emergency caesarean compared to 60.0% in the comparator group. Follow-up was not reported, but assumed to be for duration of hospital stay. This may not be an adequate period to detect thromboembolic outcomes.			

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES4.8 In maternity patients who have placenta previa or refuse transfusion, the effect of intraoperative cell salvage compared with no intraoperative cell salvage on thromboembolic events is uncertain.

Interventional radiology

Table D4.D Key question: In women with suspected morbidly adherent placenta, what is the effect of preventative interventional radiology (iliac balloon catheters or embolisation only) on transfusion requirements?		Evidence table ref: D4.D
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Two systematic reviews (Dilauro 2012 and Omar 2013)[a] were used to identify three Level III studies (Shrivastava 2007, fair; Bodner 2006, fair; Levine 1999, poor). An additional Level III study (Ballas 2012, fair) was also deemed eligible for inclusion.	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Transfusion dose/volume: Generally no significant difference across four studies. However, in a subgroup analysis in the study by Ballas comparing inflated vs uninflated balloon catheters, volume of PRBCs was significantly higher in the inflated group (P=0.02). Transfusion incidence: No significant difference in Ballas study for total cohort. However, in a subgroup analysis in the study by Ballas comparing inflated vs uninflated balloon catheters, transfusion incidence was significantly higher in the inflated group (P=0.005). Mass**ive transfusion (≥6 units PRBCs):** Favours balloon catheter (P=0.03) in Ballas study	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
In the Bodner study, the two treatment groups were divided by treatment referral patterns and therefore may be subject to selection bias. In the Shrivastava study, the method of diagnosis of placenta accreta or its subtypes varied considerably between the groups which may have introduced selection bias such that occlusive balloon catheters were placed in subjects with findings of more severe disease. In the Levine study, baseline characteristics were not reported by treatment group; therefore it was difficult to judge whether confounding may have been an issue. In the study by Ballas, a significantly greater percentage of those with balloon catheters had a predelivery diagnosis of invasive placentation which may indicate selection bias.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The studies were conducted in women with placenta accreta (or one of its variants). Therefore, results may not be generalisable to all maternity patients. In the Shrivastava study, around 90% of participants had placenta accreta or increta and the results may therefore not be directly generalisable to women with the more complicated variant, placenta percreta.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The four studies were conducted in the USA, where the level of healthcare is likely comparable to that in Australia. However, in the study by Shrivastava, the majority of patients in the cohort were Hispanic. Therefore, the results may be applied in the Australian context but with some caveats on ethnicity. Also, requires access to facilities where interventional radiology is available.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical impact	D	Slight/Restricted
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES4.9 In women with suspected morbidly adherent placenta, the effect of preventative interventional radiology (iliac balloon catheters or embolisation only) on transfusion requirements is uncertain.

a Results for the two systematic reviews were presented individually for the included Level III studies with no post hoc or pooled analyses reported. Overall conclusions of the systematic reviews were based on evidence from both Level III and Level IV studies. As no additional information was provided in the systematic review for the Level III studies other than what was presented in the primary studies, data for each of the individual studies deemed to be eligible for inclusion in the current guideline has been obtained from the primary studies.

Table D4.E Key question: In women with suspected morbidly adherent placenta, what is the effect of preventative interventional radiology (iliac balloon catheters or embolisation only) on the need for additional interventions to control bleeding?		Evidence table ref: D4.E
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One systematic review (Dilauro 2012)[a] was used to identify three Level III studies (Shrivastava 2007, fair; Bodner 2006, fair; Levine 1999, poor).	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Uterine artery ligation was reported in the Bodner study. A higher proportion of patients required uterine artery ligation in the intervention group (0/6, 0%) vs the comparator group (5/22, 23%). Need for reoperation[b] was reported in the study by Shrivastava. A higher proportion of patients required reoperation in the intervention group (4/19, 21%) vs the comparator group (6/50, 12%). Pelvic artery embolisation was reported in the Levine study. A higher proportion of patients required pelvic artery embolisation in the comparator group (1/4, 25%) vs the intervention group (0/5, 0%). Hysterectomy was reported as an outcome for the studies by Bodner and Levine. In the study by Bodner, the number of patients requiring hysterectomy in the control arm 22/22 (100%) and 5/6 (83%) and in the intervention arm; the patient not requiring hysterectomy instead had uterine curettage. In the study by Levine, delivery by caesarean hysterectomy was a requirement for being included in the comparator group. Therefore the number of patients requiring hysterectomy was 4/4 (100%). The number of patients requiring hysterectomy in the intervention group was 4/5 (80%) as one patient only required a caesarean section.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The sample size of the included studies was small (Shrivastava N=69; Bodner N=28; Levine N=9) and therefore likely to be underpowered to detect a difference in treatment effect. No statistically significant difference was reported.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The studies were conducted in women with placenta accreta (or one of its variants). Therefore, results may not be generalisable to all maternity patients. In the Shrivastava study, around 90% of participants had placenta accreta or increta and the results may therefore not be directly generalisable to women with the more complicated variant, placenta percreta	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The three studies were conducted in the USA, where the level of healthcare is likely comparable to that in Australia. However, in the study by Shrivastava, the majority of patients in the cohort were Hispanic. Therefore, the results may be applied in the Australian context but with some caveats on ethnicity. Also, requires access to facilities where interventional radiology is available.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Treatment groups in the Bodner study were divided by treatment referral patterns and therefore may be subject to selection bias. The referral bias meant that patients with a prenatal diagnosis of placenta accreta and especially those with a more complicated prenatal course, were more likely to fall into the interventional radiology group. Similarly, in the study by Shrivastava the method of diagnosis of placenta accreta or its subtypes varied considerably between the groups which may have introduced selection bias such that occlusive balloon catheters were placed in subjects with findings of more severe disease.
In the study by Levine, baseline characteristics were not reported by treatment group; therefore it was difficult to judge whether confounding may have been an issue.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component		Rating	Description
1.	Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2.	Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3.	Clinical impact	D	Slight/Restricted
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES4.10 In women with suspected morbidly adherent placenta, the effect of preventative interventional radiology (iliac balloon catheters or embolisation only) on the need for additional interventions to control bleeding is uncertain.

a Results for the systematic review were presented individually for the included Level III studies with no post hoc or pooled analyses reported. Overall conclusions of the systematic review were based on evidence from both Level III and Level IV studies. As no additional information was provided in the systematic review for the Level III studies other than what was presented in the primary studies, data for each of the individual studies deemed to be eligible for inclusion in the current guideline has been obtained from the primary studies.
b The authors did not specify what this entailed or for what purpose (i.e. may not have been specifically to control bleeding)

Table D4.F Key question: In women with suspected morbidly adherent placenta, what is the effect of preventative interventional radiology (iliac balloon catheters or embolisation only) on maternal mortality?		Evidence table ref: D4.F
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level III study (Bodner 2006, fair).	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
There were no maternal deaths reported in either treatment arm in the study (n/N: 0/6, interventional radiology; 0/22, no interventional radiology). However, due to the small sample size, it is unlikely that the study was statistically powered to detect a difference.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
This study was conducted in women with placenta accreta/percreta. Therefore, results may not be generalisable to all maternity patients.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in the USA, where the level of healthcare is likely to be comparable to that in Australia. As such, the findings are likely applicable but require access to healthcare facilities with interventional radiology.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		

Treatment groups in the Bodner study were divided by treatment referral patterns and therefore may be subject to selection bias. The referral bias meant that patients with a prenatal diagnosis of placenta accreta and especially those with a more complicated prenatal course, were more likely to fall into the interventional radiology group.

Specific trends relating to intraoperative strategies/protocols may vary between countries or hospitals and warrant consideration. In the study, occlusion balloons were inflated at the time of cord clamping and the results may therefore not be applicable in situations where different strategies with respect to the intraoperative utilisation/timing of occlusion balloon inflation have been adopted. In the present study, balloon occlusion preceded embolisation based on the belief that balloon occlusion would allow temporary control of haemorrhage.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES4.11 In women with suspected morbidly adherent placenta, the effect of preventative interventional radiology (iliac balloon catheters or embolisation only) on maternal mortality is uncertain.

Table D4.G Key question: In women with suspected morbidly adherent placenta, what is the effect of preventative interventional radiology (iliac balloon catheters or embolisation) on thromboembolic events?			Evidence table ref: D4.G
1. Evidence base (*number of studies, level of evidence and risk of bias in the included studies)*			
Includes two Level III studies (Bodner 2006, fair; Shrivastava 2007, fair).	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
The study by Bodner reported myocardial infarction for the comparator group (1/22, 5%); thromboembolic events were not reported for the interventional radiology group. The study by Shrivastava reported thrombosis for the interventional radiology group (2/19, 10.5%); thromboembolic events were not reported for the comparator group.	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
The results were presented for one treatment arm only within each in each study. Therefore, a measure of statistically significant difference between treatment arms was not reported.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability (*How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The studies were conducted in women with placenta accreta (or one of its variants). Therefore, results may not be generalisable to all maternity patients. In the Shrivastava study, around 90% of participants had placenta accreta or increta and the results may therefore not be directly generalisable to women with the more complicated variant, placenta percreta	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability (*Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
Both studies were conducted in the USA, where the level of healthcare is likely comparable to that in Australia. However, in the study by Shrivastava, the majority of patients in the cohort were Hispanic. Therefore, the results may be applied in the Australian context but with some caveats on ethnicity. Applicability is also dependent on access to healthcare facilities where interventional radiology is available.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*			
Treatment groups in the Bodner study were divided by treatment referral patterns and therefore may be subject to selection bias. The referral bias meant that patients with a prenatal diagnosis of placenta accreta and especially those with a more complicated prenatal course, were more likely to fall into the international radiology group. In the Shrivastava group, the method of diagnosis of placenta accreta or its subtypes varied considerably between the groups which may have introduced selection bias such that occlusive balloon catheters were placed in subjects with findings of more severe disease.			

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2. Consistency	D	Evidence is inconsistent
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES4.12 In women with suspected morbidly adherent placenta, the effect of preventative interventional radiology (iliac balloon catheters or embolisation) on thromboembolic events is uncertain.

Recombinant activated factor VII

Table D4.H Key question: In women with massive postpartum haemorrhage, what is the effect of recombinant activated factor VII (rFVIIa) on transfusion requirements?			Evidence table ref: D4.H
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Three Level III studies (Ahonen 2007, fair; Hossain 2007, fair; Kalina 2011, poor).	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
The results of the studies by Ahonen and Kalina mostly favoured no rFVIIa, whereas Hossain presented results that favoured the rFVIIa-treated patients (significantly less units of PRBC transfused). In the studies by Ahonen and Kalina there is a high chance that patients were treated with rFVIIa because they were more severely ill than those patients who did not receive rFVIIa (selection bias). In Kalina (2011), patients only received rFVIIa in circumstances where persistent coagulopathic bleeding existed after a massive transfusion pack (PRBC, FFP, cryoprecipitate, plateletpharesis) was transfused. In Ahonen (2007), guidelines at the study institution suggest that administration of rFVIIa should be considered when a patient has lost about 1.5 times her blood volume. In contrast, the use of rFVIIa in Hossain (2007) was more likely to be influenced by its availability than the severity of the patient and may, therefore, be less affected by selection bias.	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
The study by Ahonen (N=48) reported statistically significant differences in favour of no rFVIIa based on units of red blood cells (P=0.003) and platelets (P=0.014). The differences were also clinically significant. Ahonen reported no statistically significant difference between the groups based on the units of fresh frozen plasma transfused (P=0.074). The study by Kalina (N=27) also found that the rFVIIa group received significantly more units of red blood cells than the no rFVIIa group (P=0.004) and significantly more units of cryoprecipiate (P<0.001). No statistically significant differences were reported between the two treatment groups based on units of fresh frozen plasma or platelets transfused. In contrast, Hossain (N=34) found a significant difference in favour of rFVIIa (p=0.007) based on the units of packed red blood cells transfused.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The studies were conducted in women who suffered a massive postpartum haemorrhage (PPH) and may not be generalisable to all maternity patients or all women with PPH. All study participants were treated with background therapies as specified on	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	

massive transfusion/PPH protocols/guidelines. The results are therefore generalisable to women with massive PPH who are treated with standard management measures for massive PPH (eg. medical – PRBCs, FFP, cryoprecipitate, and/or surgical – internal iliac ligation, hysterectomy).	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*

The studies were conducted in Pakistan (Hossain 2007), Finland (Ahonen 2007) and the USA (Kalina 2011). The availability of rFVIIa is likely to vary dramatically between Pakistan and Australia; however, the level of healthcare and availability of resources in Finland and the USA should be comparable to that in Australia. Overall, the results should be generalisable to the Australian healthcare context, as all studies administered rFVIIa in combination with other medical and/or surgical measures outlined in massive PPH protocols/guidelines. It is likely that a similar approach to the treatment of massive PPH would be adopted in most Australian hospitals.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Baseline severity of illness:

Kalina 2011 – the treatment groups differed on baseline severity of illness – the rFVIIa group had significantly higher APACHE II scores compared with the no rFVIIa group

Hossain 2007 – the treatment groups differed on baseline haematological parameters (Hb, PT, aPTT) – the rFVIIa group had significantly worse parameters than the no rFVIIa group.

Administration of intervention:

Ahonen 2007 – according to guidelines at the study institution, rFVIIa should be considered when the patient has lost about 1.5 times her blood volume (i.e. potential selection bias in which more severely ill patients received rFVIIa)

Kalina 2011 – patients chosen to receive rFVIIa differed systematically from those in the control group – patients only received rFVIIa in circumstances where persistent coagulopathic bleeding existed after the first massive transfusion "pack" was transfused. This was inherent in the massive transfusion protocol at the study institution

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES4.17 In women with massive postpartum haemorrhage, the effect of recombinant activated factor VII compared with no recombinant activated factor VII on transfusion requirements is uncertain.

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; aPTT, activated partial thromboplastin; Hb, haemoglobin; PT, prothrombin; rFVIIa, recombinant activated factor VII

Table D4.I Key question: In women with massive postpartum haemorrhage, what is the effect of recombinant activated factor VII (rFVIIa) on the need for additional interventions to control bleeding?			Evidence table ref: D4.I
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Hysterectomy: Two Level III studies (Hossain 2007, fair; Kalina 2011, poor) Uterine artery embolisation: One Level III study (Kalina 2011, poor) Mixed interventions: One Level III study (Ahonen 2007, fair).	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
Hysterectomy: Both studies (Hossain 2007; Kalina 2011) reported no statistically significant difference between the number of patients who underwent hysterectomy in the rFVIIa group compared with the no rFVIIa group. The overall proportion of patients who underwent hysterectomy was higher in the study by Kalina 2011 (85.7% and 57.9% in the rFVIIa and no rFVIIa groups, respectively) compared with Hossain 2007 (61.1% and 37.5%, respectively). The significance of the difference is not known; however, the difference may reflect a more severely ill patient population in Kalina 2011 compared with Hossain 2007, or less resources to undertake hysterectomy in the study by Hossain 2007. Uterine artery embolisation: NA – only one study was available. The one available study (Kalina 2011) reported a higher proportion of patients requiring uterine artery embolisation in the rFVIIa group (2/7, 28.6%) compared with the no rFVIIa group (2/19, 10.5%). The difference between the groups was not significantly different (p=0.29). Mixed interventions: Ahonen (2007) reported additional interventions as one combined outcome i.e. all patients who required subsequent interventions to control bleeding (selective arterial embolisation, laparotomy for haemostasis, and/or arterial ligation) were reported together, making comparison with results from the other studies difficult. In total, 6 (23.1%) out of 26 patients had a 'poor' response to rFVIIa and required subsequent interventions.	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
Hysterectomy: The sample size of the included studies was small (Hossain N=34; Kalina N=27) and therefore likely to be underpowered to detect a difference in treatment effect. No statistically significant difference was reported. Uterine artery embolisation: The sample size of the included study was small (Kalina N=27) and therefore likely to be underpowered to detect a difference in treatment effect. No statistically significant difference was reported. Mixed interventions: Ahonen (2007) reported the need for additional interventions in the context of patients who had a 'poor' response to rFVIIa. As such the need for additional interventions to control bleeding is unknown for the control group and the clinical impact of rFVIIa cannot be assessed.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The studies were conducted in women who suffered a massive postpartum	A	Evidence directly generalisable to target population	

haemorrhage (PPH) and may not be generalisable to all maternity patients or all women with PPH. All study participants were treated with background therapies as specified by massive transfusion/PPH protocols/guidelines. The results are therefore generalisable to women with massive PPH who are treated with standard management measures for massive PPH (eg. medical – PRBCs, FFP, cryoprecipitate, and/or surgical – internal iliac ligation, hysterectomy).	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*

The studies were conducted in Pakistan (Hossain 2007), Finland (Ahonen 2007) and the USA (Kalina 2011). The availability of rFVIIa is likely to vary dramatically between Pakistan and Australia; however, the level of healthcare and availability of resources in Finland and the USA should be comparable to that in Australia. Overall, the results should be generalisable to the Australian healthcare context, as both studies administered rFVIIa in combination with medical and/or surgical measures outlined in a massive postpartum haemorrhage protocol. It is likely that a similar approach to the treatment of massive postpartum haemorrhage would be adopted in most Australian hospitals.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Baseline severity of illness:

Kalina 2011 – the treatment groups differed on baseline severity of illness – the rFVIIa group had significantly higher APACHE II scores compared with the no rFVIIa group

Hossain 2007 – the treatment groups differed on baseline haematological parameters (Hb, PT, aPTT) – the rFVIIa group had significantly worse parameters than the no rFVIIa group.

Administration of intervention:

Ahonen 2007 – according to guidelines at the study institution, rFVIIa should be considered when the patient has lost about 1.5 times her blood volume (i.e. potential selection bias in which more severely ill patients received rFVIIa)

Kalina 2011 – patients chosen to receive rFVIIa differed systematically from those in the control group – patients only received rFVIIa in circumstances where persistent coagulopathic bleeding existed after the first massive transfusion "pack" was transfused. This was inherent in the massive transfusion protocol at the study institution

Hossain 2007 – the decision to administer rFVIIa was based on availability at the time of the woman's haemorrhage; however, rFVIIa was only ever administered after other conventional methods failed, suggesting that the patients in the intervention group were more severely ill than those in the control group.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component		Rating	Description
1.	Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2.	Consistency	B	Most studies consistent and inconsistency can be explained
3.	Clinical impact	NA	Not applicable/no difference/underpowered
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES4.18 In women with massive postpartum haemorrhage, the effect of recombinant activated factor VII compared with no recombinant activated factor VII on the need for additional interventions to control bleeding (hysterectomy and uterine artery embolisation) is uncertain.

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; aPTT, activated partial thromboplastin; Hb, haemoglobin; PT, prothrombin; rFVIIa, recombinant activated factor VII

Table D4.J Key question: In women with massive postpartum haemorrhage, what is the effect of recombinant activated factor VII (rFVIIa) on maternal mortality?		Evidence table ref: D4.J
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Two Level III studies (Hossain 2007, fair; Kalina 2011, poor)	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
No maternal deaths were reported in the study by Kalina (2011). In contrast, Hossain (2007) reported five deaths (28%) out of 18 patients in the rFVIIa –treated group and eight deaths (50%) out of 16 patients in the group that did not receive rFVIIa. A potential reason for the inconsistency is the fact that the study by Hossain (2007) was conducted in Pakistan, compared to Kalina which was carried out in the USA. The hospital in Pakistan was is likely to have significantly less access to healthcare resources and additional interventions than the trauma centre in the USA, thus increasing the risk of maternal mortality. For example, the study institute in Pakistan did not have facilities for arterial embolisation and the study appeared to have a comparatively low rate of hysterectomy.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The sample size of the included studies was small (Hossain N=34; Kalina N=27) and therefore likely to be underpowered to detect a difference in treatment effect. Nonetheless, Hossain provided an adjusted odds ratio of 0.04 (95% CI 0.002, 0.83) using a logistic regression model. The odds ratio favoured treatment with rFVIIa and adjusted for haemoglobin and activated partial thromboplastin (chosen using a backward elimination strategy).	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The studies were conducted in women who suffered a massive postpartum haemorrhage (PPH) and may not be generalisable to all maternity patients or all women with PPH. All study participants were treated with background therapies as specified on massive transfusion/PPH protocols. The results are therefore generalisable to women with massive PPH who are treated with standard management measures for massive PPH (eg. medical – PRBCs, FFP, cryoprecipitate, and/or surgical – internal iliac ligation, hysterectomy).	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The studies were conducted in Pakistan (Hossain 2007) and the USA (Kalina 2011). The availability of rFVIIa is likely to vary dramatically between Pakistan and Australia; however, the level of healthcare and availability of resources in the USA should be	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats

comparable to that in Australia. Overall, the results should be generalisable to the Australian healthcare context, as both studies administered rFVIIa in combination with medical and/or surgical measures outlined in a massive PPH protocol. It is likely that a similar approach to the treatment of massive PPH would be adopted in most Australian hospitals.	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Baseline severity of illness:

Kalina 2011 – the treatment groups differed on baseline severity of illness – the rFVIIa group had significantly higher APACHE II scores compared with the no rFVIIa group

Hossain 2007 – the treatment groups differed on baseline haematological parameters (Hb, PT, aPTT) – the rFVIIa group had significantly worse parameters than the no rFVIIa group.

Administration of intervention:

Kalina 2011 – patients chosen to receive rFVIIa differed systematically from those in the control group – patients only received rFVIIa in circumstances where persistent coagulopathic bleeding existed after the first massive transfusion "pack" was transfused. This was inherent in the massive transfusion protocol at the study institution

Hossain 2007 – the decision to administer rFVIIa was based on availability at the time of the woman's haemorrhage; however, rFVIIa was only ever administered after other conventional methods failed, suggesting that the patients in the intervention group were more severely ill than those in the control group.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES4.19 In women with massive postpartum haemorrhage, the effect of recombinant activated factor VII compared with no recombinant activated factor VII on maternal mortality is uncertain.

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; aPTT, activated partial thromboplastin; Hb, haemoglobin; PT, prothrombin; rFVIIa, recombinant activated factor VII

Table D4.K Key question: In women with massive postpartum haemorrhage, what is the effect of recombinant activated factor VII (rFVIIa) on thromboembolic events?			Evidence table ref: D4.K
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Three Level III studies (Ahonen 2007, fair; Hossain 2007, fair; Kalina 2011, poor)	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
No thromboembolic events (thrombosis, pulmonary embolism, myocardial infarction) were reported in the rFVIIa or no rFVIIa arms of the studies by Hossain (2007) and Kalina (2011). In the study by Ahonen (2007) one health parturient experienced symptoms of a pulmonary embolism 17 hours after administration of rFVIIa and cessation of bleeding. No other thromboembolic events were reported.	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
The sample size of the included studies was small (Ahonen N=48; Hossain N=34; Kalina N=27) and therefore likely to be underpowered to detect a difference in treatment effect. Length of follow-up was not reported in Hossain and Kalina and may not have been long enough to observe thromboembolic events.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The studies were conducted in women who suffered a massive postpartum haemorrhage (PPH) and may not be generalisable to all maternity patients or all women with postpartum haemorrhage. All study participants were treated with background therapies as specified by massive transfusion/PPH protocols. The results are therefore generalisable to women with massive PPH who are treated with standard management measures for massive PPH (eg. medical – PRBCs, FFP, cryoprecipitate, and/or surgical – internal iliac ligation, hysterectomy).	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The studies were conducted in Pakistan (Hossain 2007), Finland (Ahonen 2007) and the USA (Kalina 2011). The availability of rFVIIa is likely to vary dramatically between Pakistan and Australia; however, the level of healthcare and availability of resources in Finland and the USA should be comparable to that in Australia. Overall, the results should be generalisable to the Australian healthcare context, as all studies administered rFVIIa in combination with other medical and/or surgical measures outlined in massive PPH protocols/guidelines. It is likely that a similar approach to the treatment of massive PPH would be adopted in most Australian hospitals.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*			

Baseline severity of illness:

Kalina 2011 – the treatment groups differed on baseline severity of illness – the rFVIIa group had significantly higher APACHE II scores compared with the no rFVIIa group

Hossain 2007 – the treatment groups differed on baseline haematological parameters (Hb, PT, aPTT) – the rFVIIa group had significantly worse parameters than the no rFVIIa group.

Administration of intervention:

Kalina 2011 – patients chosen to receive rFVIIa differed systematically from those in the control group – patients only received rFVIIa in circumstances where persistent coagulopathic bleeding existed after the first massive transfusion "pack" was transfused. This was inherent in the massive transfusion protocol at the study institution

Hossain 2007 – the decision to administer rFVIIa was based on availability at the time of the woman's haemorrhage; however, rFVIIa was only ever administered after other conventional methods failed, suggesting that the patients in the intervention group were more severely ill than those in the control group.

Ahonen 2007 – according to guidelines at the study institution, rFVIIa should be considered when the patient has lost about 1.5 times her blood volume (i.e. potential selection bias in which more severely ill patients received rFVIIa)

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component		Rating	Description
1.	Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2.	Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3.	Clinical impact	NA	Not applicable/no difference/underpowered
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES4.20 In women with massive postpartum haemorrhage, the effect of recombinant activated factor VII compared with no recombinant activated factor VII on thromboembolic events is uncertain.

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; rFVIIa, recombinant activated factor VII

Tranexamic acid

Table D4.L Key question: In women giving birth by caesarean delivery, what is the effect of the routine use of antifibrinolytic therapy (tranexamic acid only), on transfusion requirements?			Evidence table ref: D4.L
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Includes three Level II studies (Senturk 2013, good; Xu 2013, fair; Gungorduk 2011, good)	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
Transfusion incidence There was no significant difference between treatment arms in the studies by Senturk (nil in both groups) and Gungorduk (P=0.17). In the study by Xu, a statistically higher proportion of patients required transfusion in the 'no TXA' group (P=0.02) Transfusion dose/volume was only reported in the study by Gungorduk with similar mean units of packed red blood cells transfused in each treatment arm for transfused patients (TXA, 1.5 units vs no TXA 1.6 units)	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
The study by Xu found that a higher proportion of patients required transfusion in the 'no TXA' group RR [95% CI]: 0.41 [0.19, 0.89]. However, the transfusion incidence seen in both the control and intervention arms seemed very high when Hb levels and other clinical indicators were taken into account. For example, more than 20% of patients in the control arm received a blood transfusion. Also, the Hg threshold for transfusion and the number of patients that met the threshold does not match the number of patients transfused. As the dosage of TXA was not consistent across studies (ranging from 10mg/kg to 1g) the clinical impact of the intervention could not be determined.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The studies were conducted in women who underwent elective and/or urgent caesarean delivery; therefore, the evidence may not be directly generalisable to all maternity patients.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
Two studies were conducted in Turkey and one study was conducted in China. Therefore, the delivery of healthcare may not be directly applicable to the Australian healthcare context where treatment protocols and resources may vary.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

In two studies, the intervention group received 1 g of TXA administered intravenously over 5 minutes (Senturk, 2013; Gungorduk, 2011); whereas in the study by Xu patients In the intervention group received 10mg/kg TXA infused intravenously over 10 – 20 minutes.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES4.21 In women giving birth by caesarean delivery, the effect of the routine use of antifibrinolytic therapy (tranexamic acid only), on transfusion requirements is uncertain.

Table D4.M Key question: In women giving birth by vaginal delivery, what is the effect of the routine use of antifibrinolytic therapy (tranexamic acid only) on transfusion requirements?			Evidence table ref: D4.M
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Includes one Level II study (Gungorduk 2013, good)	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
NA	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
The study showed no statistically significant difference between treatment arms for the need for transfusion. The number of patients requiring blood transfusion was reported for TXA vs no TXA (1, 0.5% vs 3, 1.4%) and an overall RR [95% CI] of 3.01 [0.31-28.74]; P=0.37.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The study was conducted in women giving birth by vaginal delivery. Patients were also included if they had risk factors for PPH. Patients were excluded if they presented with placenta previa, placental abruption, had a caesarean section, uterine scarring, abnormal placentation, history of thromboembolic disease, heart, liver, or renal disorders.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The study was conducted in Turkey, where the delivery of healthcare may not be directly applicable to the Australian healthcare context.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*			
Patients in the intervention group received 1 g TXA administered intravenously at delivery over 5-minutes.			
EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*			

Component	Rating	Description
1. Evidence base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats
EVIDENCE STATEMENT ES4.22 In women giving birth by vaginal delivery, the effect of the routine use of antifibrinolytic therapy (tranexamic acid only) on transfusion requirements is uncertain.		

Table D4.N Key question: In women with postpartum haemorrhage after vaginal delivery, what is the effect of antifibrinolytic therapy (tranexamic acid only), on transfusion requirements?		Evidence table ref: D4.N
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level II study (Ducloy-Bouthors 2011, good)	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Transfusion incidence There was no statistically significant difference between treatment arms for transfusion incidence of packed red blood cells. However, a higher proportion of patients in the 'no TXA' group required transfusion of fibrinogen and fresh frozen plasma (P=0.001). Transfusion dose/volume There was no statistically significant difference for total units of packed red blood cells transfused before six hours; however, total units transfused through day 42 was significantly less for the TXA group for both the intention-to-treat (P<0.001) and per-protocol (P<0.001) analyses.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study was conducted in women with active, severe PPH after vaginal delivery defined as PPH >800 mL within 2 hours of vaginal delivery. Therefore, results may not be directly generalisable to obstetrics patients with different bleeding severities or clinical conditions.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in France and is therefore reasonably applicable to the Australian healthcare context, provided that patients receive similar adjuvant therapy (in the study, all patients were allowed PRBCs and colloids according to French guidelines; the use of additional procoagulant treatment was permitted in cases of intractable bleeding).	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		
Patients were administered a loading dose of 4 g TXA in 50 mL normal saline infused over 1 h, then 1 g/h over 6 h.		

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	D	Slight/Restricted
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES4.23 In women with postpartum haemorrhage after vaginal delivery, the effect of antifibrinolytic therapy (tranexamic acid only) on transfusion requirements is uncertain.

Table D4.O Key question: In women giving birth by caesarean delivery, what is the effect of the routine use of antifibrinolytic therapy (tranexamic acid only) on the need for additional interventions to control bleeding?			Evidence table ref: D4.O
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Includes two Level II studies (Senturk 2013, good; Gungorduk 2011, good)	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
Both studies reported nil requirements for additional interventions to control bleeding.	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
No difference was reported between treatment arms in either study.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The study by Senturk is generalisable to healthy maternity patients giving birth by elective or urgent caesarean section and therefore may not be generalisable to all maternity patients. The study by Gungorduk was limited by the exclusion of women at high risk for PPH.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The two studies were conducted in Turkey, where the delivery of healthcare may not be directly applicable to the Australian healthcare context.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

In the study by Senturk, oxytocin was administered to all patients after delivery, which may confound overall results.

In both studies, the intervention group received 1 g of TXA administered intravenously over 5 minutes (Senturk, 2013; Gungorduk, 2011)

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2. Consistency	A	All studies consistent
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES4.24 In women giving birth by caesarean delivery, the effect of the routine use of antifibrinolytic therapy (tranexamic acid only), on the need for additional interventions to prevent bleeding is uncertain.

Table D4.P Key question: In women giving birth by vaginal delivery, what is the effect of the routine use of antifibrinolytic therapy (tranexamic acid only) on the need for additional interventions to control bleeding?			Evidence table ref: D4.P
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Includes one Level II study (Gungorduk 2013, good)	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
NA	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
No difference was reported between treatment arms (nil requirements for additional surgical interventions to control bleeding in both groups).	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The study was conducted in maternity patients giving birth by vaginal delivery. Patients were also included if they had risk factors for PPH. Patients were excluded if they presented with placenta previa, placental abruption, had a caesarean section, uterine scarring, abnormal placentation, history of thromboembolic disease, heart, liver, or renal disorders.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The study was conducted in Turkey, where the delivery of healthcare may not be directly applicable to the Australian healthcare context.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*			
All patients in the cohort underwent 'active management' of the third stage of labour (prophylactic injection of oxytocin within 2 minutes of birth, early clamping of the umbilical cord, and controlled cord traction following delivery), which may have impacted the overall results. Patients in the intervention group received 1 g TXA administered intravenously at delivery over 5-minutes.			

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES4.25 In women giving birth by vaginal delivery, the effect of the routine use of antifibrinolytic therapy (tranexamic acid only) on the need for additional interventions to control bleeding is uncertain.

Table D4.Q Key question: In women with postpartum haemorrhage after vaginal delivery, what is the effect of antifibrinolytic therapy (tranexamic acid only) on the need for additional interventions to control bleeding?			Evidence table ref: D4.Q
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Includes one Level II study (Ducloy-Bouthors 2011, good).	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
NA	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
Tests for statistical significance in the intention-to-treat and per-protocol analyses showed no difference for arterial embolisation, surgical arterial ligature or hysterectomy and late postpartum curettage after day 7. However, the authors noted that the study was not powered to detect differences in the number of invasive procedures	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The study was conducted in women with active, severe PPH after vaginal delivery defined as PPH >800 mL within 2 hours of vaginal delivery. Therefore, results may not be directly generalisable to maternity patients with different bleeding severities or clinical conditions.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The study was conducted in France and is therefore reasonably applicable to the Australian healthcare context, provided that patients receive similar adjuvant therapy (in the study, all patients were allowed PRBCs and colloids according to French guidelines; the use of additional procoagulant treatment was permitted in cases of intractable bleeding).	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*			
Patients were administered a loading dose of 4 g TXA in 50 mL normal saline infused over 1 h, then 1 g/h over 6 h.			

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES4.26 In women with postpartum haemorrhage after vaginal delivery, the effect of antifibrinolytic therapy (tranexamic acid only) on the need for additional interventions to control bleeding is uncertain

Abbreviations: PRBC, packed red blood cell

Table D4.R Key question: In women giving birth by caesarean delivery, what is the effect of the routine use of antifibrinolytics (tranexamic acid only) on maternal mortality?			Evidence table ref: D4.R
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Includes one Level II study (Xu 2013, fair).	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
NA	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
Nil maternal mortality was reported in both treatment arms. It is unlikely that the study was powered to detect a treatment difference for this outcome.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The study was conducted in patients giving birth by caesarean delivery and therefore, results may not be generalisable to all maternity patients. Also, as the study was conducted in the People's Republic of China there may be some caveats on ethnicity.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The study was conducted in the People's Republic of China, where the delivery of healthcare may not be directly applicable to the Australian healthcare context.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*			
In the intervention group, patients received 10mg/kg TXA infused intravenously over 10 – 20 minutes			

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES4.27 In women giving birth by caesarean delivery, the effect of the routine use of antifibrinolytics (tranexamic acid only) on maternal mortality is uncertain.

Table D4.S Key question: In women giving birth by vaginal delivery, what is the effect of the routine use of antifibrinolytic therapy (tranexamic acid only) on maternal mortality?		Evidence table ref: D4.S
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level II study (Gungorduk 2013, good)	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
No difference was reported between treatment arms (nil maternal mortality in both groups).	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study was conducted in maternity patients giving birth by vaginal delivery. Patients were also included if they had risk factors for PPH. Patients were excluded if they presented with placenta previa, placental abruption, had a caesarean section, uterine scarring, abnormal placentation, history of thromboembolic disease, heart, liver, or renal disorders.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in Turkey, where the delivery of healthcare may not be directly applicable to the Australian healthcare context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		
All patients in the cohort underwent 'active management' of the third stage of labour (prophylactic injection of oxytocin within 2 minutes of birth, early clamping of the umbilical cord, and controlled cord traction following delivery), which may have impacted the overall results. Patients in the intervention group received 1 g TXA administered intravenously at delivery over 5-minutes.		

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES4.28 In women giving birth by vaginal delivery, the effect of the routine use of antifibrinolytic therapy (tranexamic acid only) on maternal mortality is uncertain.

Table D4.T Key question: In women with postpartum haemorrhage after vaginal delivery, what is the effect of antifibrinolytic therapy (tranexamic acid only) on maternal mortality?			Evidence table ref: D4.T
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Includes one Level II study (Ducloy-Bouthors 2011, good)	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
NA	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
Nil maternal mortality was reported in both treatment arms. The authors noted that the study was not powered to detect differences in maternal death.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The study was conducted in women with active, severe PPH after vaginal delivery defined as PPH >800 mL within 2 hours of vaginal delivery. Therefore, results may not be directly generalisable to obstetrics patients with different bleeding severities or clinical conditions.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The study was conducted in France and is therefore reasonably applicable to the Australian healthcare context, provided that patients receive similar adjuvant therapy (in the study, all patients were allowed PRBCs and colloids according to French guidelines; the use of additional procoagulant treatment was permitted in cases of intractable bleeding).	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*			
Patients were administered a loading dose of 4 g TXA in 50 mL normal saline infused over 1 h, then 1 g/h over 6 h.			
EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*			

Component	Rating	Description
1. Evidence base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats
EVIDENCE STATEMENT ES4.29 In women with postpartum haemorrhage after vaginal delivery, the effect of antifibrinolytic therapy (tranexamic acid only) on maternal mortality is uncertain.		

Table D4.U Key question: In women giving birth by caesarean delivery, what is the effect of routine use of antifibrinolytic therapy (tranexamic acid only), on thromboembolic events?			Evidence table ref: D4.U
1. Evidence base (*number of studies, level of evidence and risk of bias in the included studies)*			
Includes four Level II studies (Senturk 2013, good; Xu 2013, fair; Gungorduk 2011, good; Gai 2004, Fair).	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
Nil thromboembolic events were reported in both treatment arms in the studies by Senturk and Gungorduk. In the study by Gai, nil thromboembolic events were reported in the intervention group; results were not reported for the comparator group. In the study by Xu, there was no statistically significant difference between treatment arms for deep vein thrombosis (P=0.38).	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
No difference was shown between treatment arms across all four studies. It is unlikely that the studies were powered to detect a treatment difference for thromboembolic events.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The studies were conducted in women who underwent a caesarean delivery; therefore, the evidence may not be directly generalisable to all maternity patients.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
Two studies were conducted in Turkey and two studies were conducted in the People's Republic of China. Therefore, the delivery of healthcare may not be directly applicable to the Australian healthcare context where treatment protocols and resources may vary.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*			
In three studies, the intervention group received 1 g of TXA administered intravenously over 5 minutes (Senturk, 2013; Gungorduk, 2011; Gai, 2004); whereas in the study by Xu, patients in the intervention group received 10mg/kg TXA infused intravenously over 10–20 minutes			
EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*			

Component	Rating	Description
1. Evidence base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2. Consistency	A	All studies consistent
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats
EVIDENCE STATEMENT ES4.30 In women giving birth by caesarean delivery, the effect of the routine use of antifibrinolytic therapy (tranexamic acid only), on thromboembolic events is uncertain.		

Table D4.V Key question: In women giving birth by vaginal delivery, what is the effect of the routine use of antifibrinolytic therapy (tranexamic acid only) on thromboembolic events?			Evidence table ref: D4.V
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Includes one Level II study (Gungorduk 2013, good)	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
NA	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
Nil thromboembolic events were reported in both treatment arms. However, it is unlikely that the sample size was large enough to detect a treatment difference.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The study was conducted in maternity patients giving birth by vaginal delivery. Patients were also included if they had risk factors for PPH. Patients were excluded if they presented with placenta previa, placental abruption, had a caesarean section, uterine scarring, abnormal placentation, history of thromboembolic disease, heart, liver, or renal disorders.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The study was conducted in Turkey, where the delivery of healthcare may not be directly applicable to the Australian healthcare context.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*			
Patients in the intervention group received 1 g TXA administered intravenously at delivery over 5-minutes.			

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES4.31 In women giving birth by vaginal delivery, the effect of the routine use of antifibrinolytic therapy (tranexamic acid only) on thromboembolic events is uncertain.

Table D4.W Key question: In women with postpartum haemorrhage after vaginal delivery, what is the effect of antifibrinolytic therapy (tranexamic acid only), on thromboembolic events?			Evidence table ref: D4.W
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Includes one Level II study (Ducloy-Bouthors 2011, good)	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
NA	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
There was no statistically significant difference between treatment arms for episodes of deep vein thrombosis in the intention-to-treat analysis (P=0.4) or the per-protocol analysis (P=0.37).	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The study was conducted in women with active, severe PPH after vaginal delivery defined as PPH >800 mL within 2 hours of vaginal delivery. Therefore, results may not be directly generalisable to obstetrics patients with different bleeding severities or clinical conditions.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The study was conducted in France and is therefore reasonably applicable to the Australian healthcare context, provided that patients receive similar adjuvant therapy (in the study, all patients were allowed PRBCs and colloids according to French guidelines; the use of additional procoagulant treatment was permitted in cases of intractable bleeding).	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*			
Patients were administered a loading dose of 4 g TXA in 50 mL normal saline infused over 1 h, then 1 g/h over 6 h.			

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES4.32 In women with postpartum haemorrhage after vaginal delivery, the effect of antifibrinolytic therapy (tranexamic acid only) on thromboembolic events is uncertain.

Table D4.X Key question: In women with placenta problems or unspecified antepartum haemorrhage, what is the effect of antifibrinolytic therapy (tranexamic acid only), on thromboembolic events?			Evidence table ref: D4.X
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Includes one Level III study (Lindoff 1993, poor)	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
NA	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
There was no difference between treatment arms for thromboembolism in the full cohort analysis (P>0.16). There was also no difference overall for thromboembolism (P>0.16) in the subgroup analysis of patients who underwent caesarean section.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The study was conducted in women with placental abruption, placenta praevia or unspecified antepartum haemorrhage, with a subanalysis conducted for caesarean deliveries; therefore, the results may not be generalisable to all maternity patients.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The study was performed in Sweden; therefore, the results can be reasonably applied to the Australian healthcare setting.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The reason for treatment with tranexamic acid in this study was a more severe bleeding complication; therefore, the authors conclude that the study group was presumably more prone to thrombosis. High risk that selection bias affected the results.

The treatment groups differed substantially based on the diagnosis/reason for bleeding (eg. 52.7% in the study group had placental abruption compared to 11.5% in the control group; 29.3% had placenta praevia in the study group compared to 4.8% in the control group).

The standard dose of TXA was 3mg daily, with the mean duration of treatment being 46 days

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES4.33 In women with placenta problems or unspecified antepartum haemorrhage, the effect of antifibrinolytic therapy (tranexamic acid only) on thromboembolic events is uncertain.

Appendix E Quality analyses

One aspect of the 'strength of the evidence' domain in the NHMRC Dimensions of Evidence is study quality. The full quality checklist is based on the quality assessment questions that are included in the NHMRC toolkit, *How to use the evidence: assessment and application of scientific evidence* (NHMRC, 2000). Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.

Each eligible study was assessed against each quality criterion as Y (yes), N (no), NR (not reported) or NA (not applicable). Where applicable, clarification of the criteria or justification for a downgrading of study quality, were provided as comments. Based on the checklist of quality criteria, studies were ultimately graded as good, fair or poor.

As not all quality assessment criteria are applicable to all study types, separate checklists have been applied for systematic reviews, RCTs and cohort studies.

E1 Quality analysis – Question 1

Restrictive versus liberal RBC transfusion

Level II evidence

Study type:				Randomised controlled trial	
Citation:				Koshy, M; Burd, L; Wallace, D; Moawad, A; Baron, J. Prophylactic red-cell transfusions in pregnant patients with sickle cell disease. A randomized cooperative study. New England Journal of Medicine 319 22 (1447- 1452.)	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was assignment of subjects to treatment group randomised?	
✓				• Was the use of randomisation reported?	I
	✓			• Was the method of randomisation reported?	III
		✓		• Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
		✓		• Was a method of allocation concealment reported?	III
		✓		• Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			• Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				• Were baseline patient characteristics and demographics reported?	III
✓				• Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				• Was loss to follow-up reported?	II
			✓	• Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		• Was outcome assessment blinded to treatment allocation?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				• Were the methods used for comparing results between treatment arms appropriate?	III
✓				• If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
✓				• Were subgroup analyses reported?	III-IV
✓				• Were subgroup analyses appropriate?	III-IV

Comments:	An RCT reporting on prophylactic red blood cell transfusions vs red blood transfusions given only if indicated for a medical or obstetric complication. Method of randomisation was not reported, there was no mention of allocation concealment or if outcome assessment was blinded. Baseline characteristics were different for some measures (previous perinatal mortality) bringing into question the method of randomisation. Each randomized group contained only 36 patients, therefore the sensitivity of this study is limited and only large differences could be expected to be statistically significant.	
Quality rating: [Good/Fair/Poor]	Fair.	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

E2 Quality analysis – Question 2

Iron

Level I evidence

			Study type:	Systematic review	
			Citation:	Peña-Rosas JP, De-Regil LM, Dowswell T, Viteri FE. Daily oral iron supplementation during pregnancy. Cochrane Database of Systematic Reviews 2012, Issue 12. Art. No.: CD004736. DOI: 10.1002/14651858.CD004736.pub4.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was an adequate search strategy used?	
✓				• Was a systematic search strategy reported?	I
✓				• Were the databases searched reported?	III
✓				• Was more than one database searched?	III
✓				• Were search terms reported?	IV
✓				• Did the literature search include hand searching?	IV
				B. Were the inclusion criteria appropriate and applied in an unbiased way?	
✓				• Were inclusion/exclusion criteria reported?	II
✓				• Was the inclusion criteria applied in an unbiased way?	III
	✓			• Was only Level II evidence included?	I-IV
				C. Was a quality assessment of included studies undertaken?	
✓				• Was the quality of the studies reported?	III
✓				• Was a clear, pre-determined strategy used to assess study quality?	IV
				D. Were the characteristics and results of the individual studies appropriately summarised?	
✓				• Were the characteristics of the individual studies reported?	II-III
✓				• Were baseline demographic and clinical characteristics reported for patients in the individual studies?	IV
✓				• Were the results of the individual studies reported?	III
				E. Were the methods for pooling the data appropriate?	
✓				• If appropriate, was a meta-analysis conducted?	III-IV
				F. Were the sources of heterogeneity explored?	
✓				• Was a test for heterogeneity applied?	III-IV
✓				• If there was heterogeneity, was this discussed or the reasons explored?	III-IV

Comments:	Level III-1 evidence was included (i.e. quasi-randomised trials). Subgroup differences are explored, with results stratified by gestational age at the start of supplementation and anaemia status at the start of supplementation.	
Quality rating: [Good/Fair/Poor]	Systematic review: Good	
	Included studies: Barton (1994), Batu (1976), Buytaert (1983), Cantlie (1971), Chan (2009), Chanarin (1971), Chisholm (1966), Christian (2003), Cogswell (2003), Corrigan (1936), De Benaze (1989), Eskeland (1997), Falahi (2010), Harvey (2007), Hankin (1963), Hemminki (1991), Holly (1955), Lee (2005), Liu (2000), Makrides (2003), Meier (2003), Menendez (1994), Milman (1991), Paintin (1966), Preziosi (1997), Pritchard (1958), Puolakka (1980), Romslo (1983), Taylor (1982), Tura (1989), Van Eijk (1978), Wallenburg (1983), Wills (1947), Ziaei (2008)	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Study type:				Systematic review	
Citation:				Reveiz L, Gyte GM, Cuervo LG, and Casasbuenas A. (2011) Treatments for iron-deficiency anaemia in pregnancy. *Cochrane database of systematic reviews (Online)*CD003094.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was an adequate search strategy used?	
✓				• Was a systematic search strategy reported?	I
✓				• Were the databases searched reported?	III
✓				• Was more than one database searched?	III
✓				• Were search terms reported?	IV
✓				• Did the literature search include hand searching?	IV
				B. Were the inclusion criteria appropriate and applied in an unbiased way?	
✓				• Were inclusion/exclusion criteria reported?	II
✓				• Was the inclusion criteria applied in an unbiased way?	III
✓				• Was only Level II evidence included?	I-IV
				C. Was a quality assessment of included studies undertaken?	
✓				• Was the quality of the studies reported?	III
✓				• Was a clear, pre-determined strategy used to assess study quality?	IV
				D. Were the characteristics and results of the individual studies appropriately summarised?	
✓				• Were the characteristics of the individual studies reported?	II-III
✓				• Were baseline demographic and clinical characteristics reported for patients in the individual studies?	IV
✓				• Were the results of the individual studies reported?	III
				E. Were the methods for pooling the data appropriate?	
✓				• If appropriate, was a meta-analysis conducted?	III-IV
				F. Were the sources of heterogeneity explored?	
✓				• Was a test for heterogeneity applied?	III-IV
	✓			• If there was heterogeneity, was this discussed or the reasons explored?	III-IV
Comments:				The authors note that the included studies were generally small and methodologically poor, making it difficult to pool data. As such, heterogeneity is not applicable to the majority of the analyses and discussion around this area is minimal.	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: Al (2005), Bayoumeu (2002), Breymann (2001), Digumarthi (2008), Khalafallah (2010), Kumar (2005), Ogunbode (1980), Singh (1998), Suharno (1993), Sun (2010), Wali (2002), Zutschi (2004)	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Level II evidence

Study type:				Randomised controlled trial	
Citation:				Bhandal N and Russell R. (2006) Intravenous versus oral iron therapy for postpartum anaemia. *BJOG: An International Journal of Obstetrics and Gynaecology* 113:1248-1252.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was assignment of subjects to treatment group randomised?	
✓				• Was the use of randomisation reported?	I
✓				• Was the method of randomisation reported?	III
✓				• Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
✓				• Was a method of allocation concealment reported?	III
✓				• Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			• Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				• Were baseline patient characteristics and demographics reported?	III
✓				• Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				• Was loss to follow-up reported?	II
		✓		• Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		• Was outcome assessment blinded to treatment allocation?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				• Were the methods used for comparing results between treatment arms appropriate?	III
			✓	• If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
		✓		• Were subgroup analyses reported?	III-IV
			✓	• Were subgroup analyses appropriate?	III-IV

Comments:	Subjects were randomised using a computer-generated randomisation schedule using opaque, sealed envelopes. The groups did not differ at baseline in characteristics or laboratory data. Only one patient in the study was excluded due to secondary postpartum haemorrhage at home requiring re-admittance for a blood transfusion.	
Quality rating: [Good/Fair/Poor]	Fair	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Study type:				Randomised controlled trial	
Citation:				Breymann C, Gliga F, Bejenariu C, and Strizhova N. (2008) Comparative efficacy and safety of intravenous ferric carboxymaltose in the treatment of postpartum iron deficiency anemia. *International Journal of Gynecology and Obstetrics* 101:67-73.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was assignment of subjects to treatment group randomised?	
✓				• Was the use of randomisation reported?	I
	✓			• Was the method of randomisation reported?	III
			✓	• Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			• Was a method of allocation concealment reported?	III
			✓	• Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			• Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				• Were baseline patient characteristics and demographics reported?	III
✓				• Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				• Was loss to follow-up reported?	II
✓				• Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		• Was outcome assessment blinded to treatment allocation?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				• Were the methods used for comparing results between treatment arms appropriate?	III
		✓		• If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
✓				• Were subgroup analyses reported?	III-IV
			✓	• Were subgroup analyses appropriate?	III-IV
Comments:				The method of randomisation was not reported, nor was any attempt at allocation concealment documented. No differences between the groups were detected at baseline. The authors briefly mention a subgroup analysis which investigated the change in haemoglobin levels among patients with a baseline haemoglobin level of less than 105g/L. However, specific results are not given, with the authors simply stating that the results supported the validity of the main analysis.	
Quality rating: [Good/Fair/Poor]				Poor	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Study type:				Randomised controlled trial	
Citation:				Giannoulis C, Daniilidis A, Tantanasis T, Dinas K, and Tzafettas J. (2009) Intravenous administration of iron sucrose for treating anemia in postpartum women. *Hippokratia* 13:38-40.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was assignment of subjects to treatment group randomised?	
✓				• Was the use of randomisation reported?	I
	✓			• Was the method of randomisation reported?	III
			✓	• Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			• Was a method of allocation concealment reported?	III
			✓	• Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			• Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				• Were baseline patient characteristics and demographics reported?	III
		✓		• Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				• Was loss to follow-up reported?	II
✓				• Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		• Was outcome assessment blinded to treatment allocation?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				• Were the methods used for comparing results between treatment arms appropriate?	III
			✓	• If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
		✓		• Were subgroup analyses reported?	III-IV
			✓	• Were subgroup analyses appropriate?	III-IV

Comments:	The method of randomisation was not reported, nor was any attempt at allocation concealment documented. The before treatment clinical values are presented in broad terms but the study is not explicit about similarity between the groups at baseline. In both study groups, a large number of participants were lost to follow-up, with 34% of the intervention group and 23% of the control group failing to attend follow-up appointments.	
Quality rating: [Good/Fair/Poor]	Poor	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Study type:				Randomised controlled trial	
Citation:				Gupta A, Manaktala U, and Rathore AM. (2013) A randomised controlled trial to compare intravenous iron sucrose and oral iron in treatment of iron deficiency anemia in pregnancy. *Indian Journal of Hematology and Blood Transfusion*1-6.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was assignment of subjects to treatment group randomised?	
✓				• Was the use of randomisation reported?	I
✓				• Was the method of randomisation reported?	III
✓				• Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
✓				• Was a method of allocation concealment reported?	III
✓				• Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			• Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				• Were baseline patient characteristics and demographics reported?	III
✓				• Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				• Was loss to follow-up reported?	II
			✓	• Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		• Was outcome assessment blinded to treatment allocation?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				• Were the methods used for comparing results between treatment arms appropriate?	III
			✓	• If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
		✓		• Were subgroup analyses reported?	III-IV
			✓	• Were subgroup analyses appropriate?	III-IV
Comments:				Subjects were randomised using a randomisation table using opaque, numbered envelopes. Both of the study groups were comparable in terms of socio-demographic, clinical and baseline haematological parameters. No participants were lost to follow-up, nor were any excluded so this did not need to be accounted for in the analysis.	
Quality rating: [Good/Fair/Poor]				Fair	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.

Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Study type:				Randomised controlled trial	
Citation:				Jain G, Palaria U, and Jha SK. (2013) Intravenous iron in postpartum anemia. *Journal of Obstetrics and Gynecology of India* 63:45-48.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was assignment of subjects to treatment group randomised?	
✓				• Was the use of randomisation reported?	I
✓				• Was the method of randomisation reported?	III
✓				• Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			• Was a method of allocation concealment reported?	III
			✓	• Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			• Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				• Were baseline patient characteristics and demographics reported?	III
✓				• Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				• Was loss to follow-up reported?	II
✓				• Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		• Was outcome assessment blinded to treatment allocation?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				• Were the methods used for comparing results between treatment arms appropriate?	III
			✓	• If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
		✓		• Were subgroup analyses reported?	III-IV
			✓	• Were subgroup analyses appropriate?	III-IV
Comments:				Subjects were randomised using a computer-generated randomisation schedule and block randomisation but no attempt at allocation concealment was documented. The baseline characteristics of the women were similar in both study groups.	
Quality rating: [Good/Fair/Poor]				Fair	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Study type:				Randomised controlled trial	
Citation:				Mumtaz A and Farooq F. (2011) Comparison for effects of intravenous versus oral iron therapy for postpartum anemia. *Pakistan Journal of Medical and Health Sciences* 5:116-120.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was assignment of subjects to treatment group randomised?	
✓				• Was the use of randomisation reported?	I
	✓			• Was the method of randomisation reported?	III
			✓	• Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			• Was a method of allocation concealment reported?	III
			✓	• Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			• Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				• Were baseline patient characteristics and demographics reported?	III
		✓		• Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				• Was loss to follow-up reported?	II
		✓		• Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		• Was outcome assessment blinded to treatment allocation?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				• Were the methods used for comparing results between treatment arms appropriate?	III
		✓		• If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
		✓		• Were subgroup analyses reported?	III-IV
			✓	• Were subgroup analyses appropriate?	III-IV
Comments:				The method of randomisation was not reported, nor was any attempt at allocation concealment documented. The before treatment clinical values are presented but the study is not explicit about similarity between the groups at baseline.	
Quality rating: [Good/Fair/Poor]				Poor	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Study type:				Randomised controlled trial	
Citation:				Seid MH, Derman RJ, Baker JB, Banach W, Goldberg C, and Rogers R. (2008) Ferric carboxymaltose injection in the treatment of postpartum iron deficiency anemia: a randomized controlled clinical trial. *American Journal of Obstetrics and Gynecology* 199:435.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was assignment of subjects to treatment group randomised?	
✓				• Was the use of randomisation reported?	I
✓				• Was the method of randomisation reported?	III
✓				• Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			• Was a method of allocation concealment reported?	III
			✓	• Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			• Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				• Were baseline patient characteristics and demographics reported?	III
✓				• Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				• Was loss to follow-up reported?	II
✓				• Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		• Was outcome assessment blinded to treatment allocation?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				• Were the methods used for comparing results between treatment arms appropriate?	III
		✓		• If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
		✓		• Were subgroup analyses reported?	III-IV
			✓	• Were subgroup analyses appropriate?	III-IV
Comments:				Subjects were randomised using a centralised computer randomisation system but no attempt at allocation concealment is reported. There were no significant differences between treatment groups for any demographic or baseline characteristics.	
Quality rating: [Good/Fair/Poor]				Fair	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Study type:				Randomised controlled trial	
Citation:				Van Wyck DB, Martens MG, Seid MH, Baker JB, and Mangione A. (2007) Intravenous ferric carboxymaltose compared with oral iron in the treatment of postpartum anemia: A randomized controlled trial. *Obstetrics and Gynecology* 110:267-278.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was assignment of subjects to treatment group randomised?	
✓				• Was the use of randomisation reported?	I
✓				• Was the method of randomisation reported?	III
✓				• Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			• Was a method of allocation concealment reported?	III
			✓	• Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			• Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				• Were baseline patient characteristics and demographics reported?	III
✓				• Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				• Was loss to follow-up reported?	II
✓				• Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		• Was outcome assessment blinded to treatment allocation?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				• Were the methods used for comparing results between treatment arms appropriate?	III
		✓		• If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
		✓		• Were subgroup analyses reported?	III-IV
			✓	• Were subgroup analyses appropriate?	III-IV
Comments:				Subjects were randomised using a computerised random number generation, blocked randomisation and an interactive voice response system but no attempt at allocation concealment was documented. There were no significant differences at baseline between the groups in demographic descriptors, iron status or severity of anaemia.	
Quality rating: [Good/Fair/Poor]				Fair	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Study type:				Randomised controlled trial	
Citation:				Verma S, Inamdar SA, and Malhotra N. (2011) Intravenous iron therapy versus oral iron in postpartum patients in rural area. *Journal of SAFOG* 3:67-70.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was assignment of subjects to treatment group randomised?	
✓				• Was the use of randomisation reported?	I
	✓			• Was the method of randomisation reported?	III
			✓	• Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			• Was a method of allocation concealment reported?	III
			✓	• Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			• Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				• Were baseline patient characteristics and demographics reported?	III
		✓		• Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
	✓			• Was loss to follow-up reported?	II
			✓	• Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		• Was outcome assessment blinded to treatment allocation?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				• Were the methods used for comparing results between treatment arms appropriate?	III
			✓	• If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
		✓		• Were subgroup analyses reported?	III-IV
			✓	• Were subgroup analyses appropriate?	III-IV
Comments:				The method of randomisation was not reported, nor was any attempt at allocation concealment documented. The before treatment clinical values are presented but the study is not explicit about similarity between the groups at baseline. Loss to follow-up is not reported by the authors.	
Quality rating: [Good/Fair/Poor]				Poor	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Study type:				Randomised controlled trial	
Citation:				Neeru S, Nair N S, Rai L. Iron Sucrose Versus Oral Iron Therapy in Pregnancy Anemia. Indian J Community Med 2012;37:214-8.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was assignment of subjects to treatment group randomised?	
✓				• Was the use of randomisation reported?	I
✓				• Was the method of randomisation reported?	III
✓				• Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			• Was a method of allocation concealment reported?	III
			✓	• Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			• Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				• Were baseline patient characteristics and demographics reported?	III
	✓			• Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				• Was loss to follow-up reported?	II
		✓		• Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		• Was outcome assessment blinded to treatment allocation?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				• Were the methods used for comparing results between treatment arms appropriate?	III
			✓	• If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
	✓			• Were subgroup analyses reported?	III-IV
			✓	• Were subgroup analyses appropriate?	III-IV
Comments:				Subjects were randomised using block randomisation but no reference was made to any attempt at allocation concealment. Baseline demographics were similar at baseline between the groups. However, the intervention group had lower haemoglobin levels, red cell indices and a lower serum iron profile than the control group. The authors dealt with this potential confounder by calculating percentage increases from repeat lab parameters.	
Quality rating: [Good/Fair/Poor]				Poor	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.

Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Study type:				Randomised controlled trial	
Citation:				Westad S, Backe B, Salvesen KA, Nakling J, Okland I, Borthen I, Rognerud Jensen OH, Kolas T, Lokvik B, and Smedvig E. (2008) A 12-week randomised study comparing intravenous iron sucrose versus oral ferrous sulphate for treatment of postpartum anemia. *Acta Obstetricia et Gynecologica Scandinavica* 87:916-923.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was assignment of subjects to treatment group randomised?	
✓				• Was the use of randomisation reported?	I
✓				• Was the method of randomisation reported?	III
✓				• Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			• Was a method of allocation concealment reported?	III
			✓	• Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			• Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				• Were baseline patient characteristics and demographics reported?	III
		✓		• Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				• Was loss to follow-up reported?	II
✓				• Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		• Was outcome assessment blinded to treatment allocation?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				• Were the methods used for comparing results between treatment arms appropriate?	III
		✓		• If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
✓				• Were subgroup analyses reported?	III-IV
✓				• Were subgroup analyses appropriate?	III-IV
Comments:				Subjects were randomised according to the minimisation method, with central randomisation performed via the internet but no attempt at allocation concealment is documented. Baseline characteristics are presented but the study is not explicit about similarity between the groups.	
Quality rating: [Good/Fair/Poor]				Fair	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Study type:				Randomised controlled trial	
Citation:				Deeba S, Purandare SV, and Sathe AV. (2012) Iron deficiency anemia in pregnancy: Intravenous versus oral route. *Journal of Obstetrics and Gynecology of India* 62:317-321.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was assignment of subjects to treatment group randomised?	
✓				• Was the use of randomisation reported?	I
✓				• Was the method of randomisation reported?	III
✓				• Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
✓				• Was a method of allocation concealment reported?	III
✓				• Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			• Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				• Were baseline patient characteristics and demographics reported?	III
✓				• Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				• Was loss to follow-up reported?	II
			✓	• Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		• Was outcome assessment blinded to treatment allocation?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				• Were the methods used for comparing results between treatment arms appropriate?	III
			✓	• If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
		✓		• Were subgroup analyses reported?	III-IV
			✓	• Were subgroup analyses appropriate?	III-IV
Comments:				Subjects were randomised using a computer-generated randomisation schedule using numbered, sealed opaque envelopes. Baseline demographic and clinical characteristics were similar between the groups. No participants were lost to follow-up, nor were there any dropouts so this did not need to be accounted for in the analysis.	
Quality rating: [Good/Fair/Poor]				Fair	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.

Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Study type:				Randomised controlled trial	
Citation:				Bencaiova G, von Mandach U, and Zimmermann R. (2009) Iron prophylaxis in pregnancy: Intravenous route versus oral route. *European Journal of Obstetrics Gynecology and Reproductive Biology* 144:135-139.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was assignment of subjects to treatment group randomised?	
✓				• Was the use of randomisation reported?	I
✓				• Was the method of randomisation reported?	III
✓				• Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
✓				• Was a method of allocation concealment reported?	III
✓				• Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			• Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				• Were baseline patient characteristics and demographics reported?	III
✓				• Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				• Was loss to follow-up reported?	II
✓				• Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		• Was outcome assessment blinded to treatment allocation?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				• Were the methods used for comparing results between treatment arms appropriate?	III
			✓	• If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
✓				• Were subgroup analyses reported?	III-IV
✓				• Were subgroup analyses appropriate?	III-IV
Comments:				Subjects were randomised using a computer-generated randomisation schedule using opaque envelopes. There was no difference between the groups at baseline according to age, gravidity, parity, BMI and blood pressure. Subjects and investigators were not blinded to treatment. Efficacy analysis was on intent-to-treat population. IV prophylaxis was increased to three doses after interim analysis. Subgroup analyses were performed to compare the two different doses of intravenous iron used.	
Quality rating: [Good/Fair/Poor]				Fair	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Study type:				Randomised controlled trial	
Citation:				Froessler B, Cocchiaro C, Saadat-Gilani K, Hodyl N, and Dekker G. (2013) Intravenous iron sucrose versus oral iron ferrous sulfate for antenatal and postpartum iron deficiency anemia: A randomized trial. *Journal of Maternal-Fetal and Neonatal Medicine* 26:654-659.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was assignment of subjects to treatment group randomised?	
✓				• Was the use of randomisation reported?	I
✓				• Was the method of randomisation reported?	III
✓				• Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			• Was a method of allocation concealment reported?	III
			✓	• Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			• Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				• Were baseline patient characteristics and demographics reported?	III
		✓		• Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				• Was loss to follow-up reported?	II
✓				• Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
✓				• Was outcome assessment blinded to treatment allocation?	III
			✓	• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				• Were the methods used for comparing results between treatment arms appropriate?	III
			✓	• If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
		✓		• Were subgroup analyses reported?	III-IV
			✓	• Were subgroup analyses appropriate?	III-IV
Comments:				Subjects were randomised using a telephone service but no reference was made to any attempt at allocation concealment. Data were analysed by a statistician blinded to treatment group. Both age and BMI were similar in the women recruited antenatally and during the postpartum period but the study is not explicit about similarity across the groups at baseline. The authors note that the main limitations of the study were the dropout rate and loss to follow-up.	
Quality rating: [Good/Fair/Poor]				Fair	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Study type:				Randomised controlled trial	
Citation:				Kochhar PK, Kaundal A, and Ghosh P. (2013) Intravenous iron sucrose versus oral iron in treatment of iron deficiency anemia in pregnancy: A randomized clinical trial. *Journal of Obstetrics and Gynaecology Research* 39:504-510.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was assignment of subjects to treatment group randomised?	
✓				• Was the use of randomisation reported?	I
✓				• Was the method of randomisation reported?	III
✓				• Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			• Was a method of allocation concealment reported?	III
			✓	• Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			• Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				• Were baseline patient characteristics and demographics reported?	III
✓				• Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				• Was loss to follow-up reported?	II
✓				• Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		• Was outcome assessment blinded to treatment allocation?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				• Were the methods used for comparing results between treatment arms appropriate?	III
		✓		• If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
		✓		• Were subgroup analyses reported?	III-IV
			✓	• Were subgroup analyses appropriate?	III-IV
Comments:				Subjects were randomised using a randomisation table but no attempt at allocation concealment is reported. The study groups were comparable in terms of demographic, biologic and haematologic parameters at baseline.	
Quality rating: [Good/Fair/Poor]				Fair	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Study type:				Randomised controlled trial	
Citation:				Singh S, Singh S, and Singh PK. (2013) A study to compare the efficacy and safety of intravenous iron sucrose and intramuscular iron sorbitol therapy for anemia during pregnancy. *Journal of Obstetrics and Gynecology of India* 63:18-21.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was assignment of subjects to treatment group randomised?	
✓				• Was the use of randomisation reported?	I
	✓			• Was the method of randomisation reported?	III
			✓	• Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			• Was a method of allocation concealment reported?	III
			✓	• Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			• Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				• Were baseline patient characteristics and demographics reported?	III
✓				• Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
	✓			• Was loss to follow-up reported?	II
			✓	• Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		• Was outcome assessment blinded to treatment allocation?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
		✓		• Were the methods used for comparing results between treatment arms appropriate?	III
			✓	• If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
		✓		• Were subgroup analyses reported?	III-IV
			✓	• Were subgroup analyses appropriate?	III-IV
Comments:				The method of randomisation was not reported, nor was any attempt at allocation concealment documented. Both the groups were comparable for age, parity, socioeconomic status and period of gestation. There is no information on the statistical methods used to analyse the data.	
Quality rating: [Good/Fair/Poor]				Poor	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Study type:				Randomised controlled trial	
Citation:				Hashmi Z, Bashir G, Azeem P, and Shah S. (2006) Effectiveness of intra-venous iron sucrose complex versus intra-muscular iron sorbitol in iron deficiency anemia. *Annals of Pakistan Institute of Medical Sciences* 2:188-191.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was assignment of subjects to treatment group randomised?	
✓				• Was the use of randomisation reported?	I
	✓			• Was the method of randomisation reported?	III
			✓	• Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			• Was a method of allocation concealment reported?	III
			✓	• Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			• Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				• Were baseline patient characteristics and demographics reported?	III
		✓		• Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
	✓			• Was loss to follow-up reported?	II
			✓	• Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		• Was outcome assessment blinded to treatment allocation?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
		✓		• Were the methods used for comparing results between treatment arms appropriate?	III
			✓	• If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
		✓		• Were subgroup analyses reported?	III-IV
			✓	• Were subgroup analyses appropriate?	III-IV
Comments:				The method of randomisation was not reported, nor was any attempt at allocation concealment documented. Baseline characteristics are presented but the study is not explicit about similarity between the groups. There is no information on the statistical methods used to analyse the data. Loss to follow-up was not recorded.	
Quality rating: [Good/Fair/Poor]				Poor	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Level III evidence

Study type:				Case-control study	
Citation:				McCaw-Binns, A., Greenwood, R., Ashley, D., and Golding, J. (1994) Antenatal and perinatal care in Jamaica: Do they reduce perinatal death rates? PAEDIATR.PERINAT.EPIDEMIOL. 8 (SUPPL. 1) 86-97.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was the definition and selection of cases and controls appropriate?	
✓				• Were the cases and controls taken from comparable populations?	III
		✓		• Were the same exclusion criteria used for both cases and controls?	III
		✓		• Was a comparison made between participants and non-participants to establish their similarities or differences?	III
✓				• Were cases clearly defined and differentiated from controls?	III
✓				• Was it clearly established that controls were non-cases?	III
				B. Was the analysis subject to bias?	
		✓		• Were all selected subjects included in the analysis?	III
				C. Was exposure assessment likely to be subject to bias?	
			✓	• Were sufficient measures taken to prevent knowledge of primary exposure influencing case ascertainment?	III
	✓			• Was exposure status measured in a standard, valid, and reliable way?	III
				D. Was outcome assessment likely to be subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III
✓				• Were the main potential confounders identified and taken into account in the design and analysis?	II-III
Comments[b]:				The study was able to obtain data on 94% of all mothers delivering in Jamaica during the defined study period but exclusion criteria are not documented. The authors do not explicitly state that all recruited subjects were included in the final analysis. Exposure status was determined by asking the mothers whether they had taken iron/folic acid during pregnancy but this is unlikely to have influenced case ascertainment.	
Quality rating: [Good/Fair/Poor]				Fair	

Source: Quality criteria were adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra. Rules for assigning quality rating were adapted from SIGN (2008) SIGN 50: a guideline developer's handbook. SIGN, Edinburgh.
a. Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
b. Where applicable, provide clarification for any of the criteria, particularly where it may result in downgrading of the study quality.

Study type:				Cohort study	
Citation:				Titaley, C. R. and Dibley, M. J. (2012) Antenatal iron/folic acid supplements, but not postnatal care, prevents neonatal deaths in Indonesia: Analysis of Indonesia Demographic and Health Surveys 2002/2003-2007 (a retrospective cohort study). BMJ Open 2 (6).	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was the selection of subjects appropriate?	
✓				• Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	• Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				• Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
		✓		• Was loss to follow-up and exclusions from analysis reported?	II
			✓	• Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				• Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		• Was outcome assessment blinded to exposure status?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				• Was follow-up long enough for outcomes to occur?	III
Comments:				Participation in the Indonesia Demographic and Health Survey (IDHS) has an average response rate of 97% but more specific details about response rates in the different groups are not reported. Despite an attempt to consider many potential confounders, the authors note the possibility of residual confounding. Also, information used in the analysis was collected from the mothers, relying on their recollection of supplement use, meaning there is also potential for recall and misclassification bias.	
Quality rating: [Good/Fair/Poor]				Fair	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

ESAs

Level I evidence

Study type:				Systematic review	
Citation:				Dodd J, Dare MR, and Middleton P. (2004) Treatment for women with postpartum iron deficiency anaemia. *Cochrane database of systematic reviews (Online)*CD004222.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was an adequate search strategy used?	
✓				• Was a systematic search strategy reported?	I
✓				• Were the databases searched reported?	III
✓				• Was more than one database searched?	III
✓				• Were search terms reported?	IV
✓				• Did the literature search include hand searching?	IV
				B. Were the inclusion criteria appropriate and applied in an unbiased way?	
✓				• Were inclusion/exclusion criteria reported?	II
✓				• Was the inclusion criteria applied in an unbiased way?	III
✓				• Was only Level II evidence included?	I-IV
				C. Was a quality assessment of included studies undertaken?	
✓				• Was the quality of the studies reported?	III
✓				• Was a clear, pre-determined strategy used to assess study quality?	IV
				D. Were the characteristics and results of the individual studies appropriately summarised?	
✓				• Were the characteristics of the individual studies reported?	II-III
✓				• Were baseline demographic and clinical characteristics reported for patients in the individual studies?	IV
✓				• Were the results of the individual studies reported?	III
				E. Were the methods for pooling the data appropriate?	
✓				• If appropriate, was a meta-analysis conducted?	III-IV
				F. Were the sources of heterogeneity explored?	
✓				• Was a test for heterogeneity applied?	III-IV
			✓	• If there was heterogeneity, was this discussed or the reasons explored?	III-IV
Comments:					
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: Breymann (2000), Breymann (1996), Lebrecht (1995), Makrydimas (1998),	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Study type:	Systematic review	

Citation:				Reveiz L, Gyte GM, Cuervo LG, and Casasbuenas A. (2011) Treatments for iron-deficiency anaemia in pregnancy. *Cochrane database of systematic reviews (Online)*CD003094.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was an adequate search strategy used?	
✓				• Was a systematic search strategy reported?	I
✓				• Were the databases searched reported?	III
✓				• Was more than one database searched?	III
✓				• Were search terms reported?	IV
✓				• Did the literature search include hand searching?	IV
				B. Were the inclusion criteria appropriate and applied in an unbiased way?	
✓				• Were inclusion/exclusion criteria reported?	II
✓				• Was the inclusion criteria applied in an unbiased way?	III
✓				• Was only Level II evidence included?	I-IV
				C. Was a quality assessment of included studies undertaken?	
✓				• Was the quality of the studies reported?	III
✓				• Was a clear, pre-determined strategy used to assess study quality?	IV
				D. Were the characteristics and results of the individual studies appropriately summarised?	
✓				• Were the characteristics of the individual studies reported?	II-III
✓				• Were baseline demographic and clinical characteristics reported for patients in the individual studies?	IV
✓				• Were the results of the individual studies reported?	III
				E. Were the methods for pooling the data appropriate?	
✓				• If appropriate, was a meta-analysis conducted?	III-IV
				F. Were the sources of heterogeneity explored?	
✓				• Was a test for heterogeneity applied?	III-IV
	✓			• If there was heterogeneity, was this discussed or the reasons explored?	III-IV
Comments:				The authors note that the included studies were generally small and methodologically poor, making it difficult to pool data. As such, heterogeneity is not applicable to the majority of the analyses and discussion around this area is minimal.	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: Al (2005), Bayoumeu (2002), Breymann (2001), Digumarthi (2008), Khalafallah (2010), Kumar (2005), Ogunbode (1980), Singh (1998), Suharno (1993), Sun (2010), Wali (2002), Zutschi (2004)	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Level II evidence

Study type:				Randomised controlled trial	
Citation:				Krafft A and Breymann C. (2011) Iron sucrose with and without recombinant erythropoietin for the treatment of severe postpartum anemia: A prospective, randomized, open-label study. *Journal of Obstetrics and Gynaecology Research* 37:119-124.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was assignment of subjects to treatment group randomised?	
✓				• Was the use of randomisation reported?	I
✓				• Was the method of randomisation reported?	III
✓				• Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
✓				• Was a method of allocation concealment reported?	III
✓				• Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			• Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				• Were baseline patient characteristics and demographics reported?	III
✓				• Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
	✓			• Was loss to follow-up reported?	II
			✓	• Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		• Was outcome assessment blinded to treatment allocation?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				• Were the methods used for comparing results between treatment arms appropriate?	III
			✓	• If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
✓				• Were subgroup analyses reported?	III-IV
✓				• Were subgroup analyses appropriate?	III-IV
Comments:				The study was not blinded as those participants in the iron group were not given an erythropoietin placebo.	
Quality rating: [Good/Fair/Poor]				Fair	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Study type:				Randomised controlled trial	
Citation:				Wagstrom E, Akesson A, Van Rooijen M, Larson B, and Bremme K. (2007) Erythropoietin and intravenous iron therapy in postpartum anaemia. *Acta Obstetricia et Gynecologica Scandinavica* 86:957-962.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was assignment of subjects to treatment group randomised?	
✓				• Was the use of randomisation reported?	I
✓				• Was the method of randomisation reported?	III
✓				• Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
✓				• Was a method of allocation concealment reported?	III
✓				• Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			• Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				• Were baseline patient characteristics and demographics reported?	III
✓				• Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				• Was loss to follow-up reported?	II
		✓		• Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		• Was outcome assessment blinded to treatment allocation?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				• Were the methods used for comparing results between treatment arms appropriate?	III
		✓		• If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
	✓			• Were subgroup analyses reported?	III-IV
			✓	• Were subgroup analyses appropriate?	III-IV

Comments:	This was a pilot study. The authors noted that the only statistically significant difference at randomisation was transferring receptor. Age, blood pressure, endogenous erythropoietin levels, haematological indices and markers of iron status or inflammation were similar across the three treatment groups. The ten patients lost to follow-up had a statistically significant lower Hg level (70 g/l) at randomisation than those who completed the study (74 g/l; p<0.01).	
Quality rating: [Good/Fair/Poor]	Fair	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

E3 Quality analysis – Question 3

Fresh frozen plasma

Level III evidence

Study type:				Retrospective cohort study	
Citation:				Reyal F, Sibony O, Oury JF, Luton D, Bang J, Blot P (2004) Criteria for transfusion in severe postpartum hemorrhage: Analysis of practice and risk factors. Eur J Obstet Gynecol Reprod Biol 112(1):61-4.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was the selection of subjects appropriate?	
	✓			• Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	• Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
			✓	• Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				• Was loss to follow-up and exclusions from analysis reported?	II
		✓		• Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				• Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			• Was outcome assessment blinded to exposure status?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
			✓	• Was follow-up long enough for outcomes to occur?	III
Comments:				All patients requiring transfusion had an underlying haemorrhagic complication, whereas not all patients in the control group presented with haemorrhagic risk factors. It is therefore likely that those who received transfusion were more likely to have poorer clinical outcomes. Univariate and multivariate analyses were conducted to account for confounders and risk factors for postpartum haemorrhage; however, these particular outcomes were not relevant to our research question. The retrospective design of the study meant that loss to follow-up was not applicable but all exclusions from analysis were adequately accounted for. Reasons for exclusion of patients from the analysis were adequately described.	
Quality rating: [Good/Fair/Poor]				Fair	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Combination or fixed ratio therapy

Level III evidence

Y	N	NR	NA		
				Study type:	Retrospective cohort study	
				Citation:	Pasquier P, Gayat E, Rackelboom T, La Rosa J, Tashkandi A, Tesniere A, Ravinet J, Vincent JL, Tsatsaris V, Ozier Y, Goffinet F, Mignon A (2013) An observational study of the fresh frozen plasma: Red blood cell ratio in postpartum hemorrhage. Anesth Analg 116(1):155-61.	
Y	N	NR	NA	Quality criteria		Error rating[a]
				A. Was the selection of subjects appropriate?		
	✓			• Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?		II-IV
			✓	• Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?		III
				B. Were all recruited participants included in the analysis?		
			✓	• Does the study report whether all people who were asked to take part did so, in each of the groups being studied?		III
			✓	• Was loss to follow-up and exclusions from analysis reported?		II
			✓	• Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?		III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?		
✓				• Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?		II-IV
				D. Was outcome assessment subject to bias?		
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?		III-IV
	✓			• Was outcome assessment blinded to exposure status?		III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?		III
				E. Was follow-up adequate?		
✓				• Was follow-up long enough for outcomes to occur?		III
				Comments:	Patients groups were selected based on whether or not they received FFP or the amount of FFP administered. Therefore, the study may be prone to selection bias as the decision to transfuse FFP was exclusively under the control of anaesthetists and based on both clinical observation and laboratory coagulation results. Patients who received FFP may have been more likely to experience poorer clinical outcomes than those who did not receive FFP. Loss to follow-up was not applicable due to the retrospective design of the study; however, exclusions from analysis based on eligibility criteria were adequately explained. No prospective measurement of adverse effects associated with transfusion was performed. Because there was no control on treatment allocation in the present study, a propensity score method was used to consider this bias.	
				Quality rating: [Good/Fair/Poor]	Fair	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

E4 Quality analysis – Question 4

Intraoperative cell salvage

Level II evidence

Study type:				Randomised controlled trial	
Citation:				Rainaldi, M. P., Tazzari, P. L., Scagliarini, G., Borghi, B., and Conte, R. (1998) Blood salvage during caesarean section. Br.J.Anaesth. 80 (2) 195-198	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was assignment of subjects to treatment group randomised?	
✓				• Was the use of randomisation reported?	I
	✓			• Was the method of randomisation reported?	III
			✓	• Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			• Was a method of allocation concealment reported?	III
			✓	• Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
		✓		• Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				• Were baseline patient characteristics and demographics reported?	III
✓				• Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
		✓		• Was loss to follow-up reported?	II
			✓	• Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		• Was outcome assessment blinded to treatment allocation?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				• Were the methods used for comparing results between treatment arms appropriate?	III
			✓	• If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
	✓			• Were subgroup analyses reported?	III-IV
			✓	• Were subgroup analyses appropriate?	III-IV
Comments:				The authors report that participants were allocated randomly to the groups but the method of randomisation is not stated. Similarly, no method of allocation concealment has been reported. Baseline demographics were reported, with the two groups similar in age, height and body weight. Loss to follow-up is not reported; no patients are reported to have dropped out of the study at any point. The authors do not state if either the subjects or investigators were blinded in the study, nor whether the outcomes	

	were assessed blind to treatment allocation.	
Quality rating: [Good/Fair/Poor]	Poor	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Level III evidence

			Study type:	Retrospective cohort study	
			Citation:	Malik S, Brooks H, Singhal T (2010) Cell saver use in obstetrics. J Obstet Gynaecol 30(8):826-8.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was the selection of subjects appropriate?	
✓				• Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	• Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
			✓	• Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
			✓	• Was loss to follow-up and exclusions from analysis reported?	II
			✓	• Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
	✓			• Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			• Was outcome assessment blinded to exposure status?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
		✓		• Was follow-up long enough for outcomes to occur?	III
			Comments:	Loss to follow-up and exclusions from analysis were not applicable. No statistical analysis carried out to show significance of differences between treatment groups (patient characteristics or outcomes). Potential important differences existed between the groups at baseline – 27.3% of patients in cell saver treatment group had emergency caesarean, compared to 60.0% in the no cell saver group. This was primarily due to a lack of trained staff out-of-hours for emergency cases, due to financial constraints. Substantial differences also existed between the treatment groups with respect to previous caesarean sections and parity, but statistical significance not reported. Cell salvage was more likely to be used if massive blood loss was anticipated e.g. in multiparous women with a higher risk of obstetric haemorrhage (high risk of selection bias). Blinding was not reported, however outcome assessors are have likely to have had knowledge of the use of cell saver. Follow-up not reported, but assumed to be for duration of hospital stay which would be adequate to measure relevant outcomes	
			Quality rating: [Good/Fair/Poor]	Poor	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Interventional radiology

Level III evidence

			Study type:	Retrospective cohort study	
			Citation:	Ballas J, Hull AD, Saenz C, Warshak CR, Roberts AC, Resnik RR, Moore TR, Ramos GA (2012) Preoperative intravascular balloon catheters and surgical outcomes in pregnancies complicated by placenta accreta: A management paradox. Am J Obstet Gynecol 207(3):216.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was the selection of subjects appropriate?	
✓				• Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
				• Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
			✓	• Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
			✓	• Was loss to follow-up and exclusions from analysis reported?	II
			✓	• Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
	✓			• Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		• Was outcome assessment blinded to exposure status?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				• Was follow-up long enough for outcomes to occur?	III

Comments:	The study was a retrospective cohort study based on data in an ongoing placenta accreta database (lss to follow-up and exclusions from analysis were not applicable). All subjects were identified by their pathologic diagnosis obtained from hysterectomy specimens. No significant differences in maternal characteristics (age, gravidity and parity). Significant difference in the number of patients who had undergone 0 or 2-3 prior caesarean deliveries in the group that had uterine artery balloon (UAB) placed compared with the group that did not. A significantly greater percentage of those with UABs had a predelivery diagnosis of invasive placentation (selection bias). There were also significantly more cases of placenta percreta, as opposed to accreta, diagnosed pathologically in the group that had UABs placed preoperatively (59.3% vs 13.8%; P<0.01). The author's noted that, although UAB may be useful in reducing total blood loss in the setting of a planned caesarean hysterectomy for placenta accreta, the finding may be biased by the strong correlation with prenatal diagnosis and delivery planning at the study institution. In this study there was a high correlation between prenatal diagnosis and placement of UABs, making it difficult to differentiate between the effects of each. A small group of patients (n=17) were diagnosed with accreta prenatally and did not receive UABs. Although they trended towards a higher mean blood loss, the small number and retrospective study design does not allow for adequate comparison of outcomes. Length of follow-up was not reported, but appeared to be while in hospital (i.e. long enough for relevant outcomes to occur).	
Quality rating: [Good/Fair/Poor]	Fair	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Study type:				Retrospective cohort study	
Citation:				Shrivastava V, Nageotte M, Major C, Haydon M, Wing D (2007) Case-control comparison of cesarean hysterectomy with and without prophylactic placement of intravascular balloon catheters for placenta accreta. American Journal of Obstetrics & Gynecology 197(4):402-5.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was the selection of subjects appropriate?	
✓				• Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	• Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				• Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				• Was loss to follow-up and exclusions from analysis reported?	II
			✓	• Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				• Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			• Was outcome assessment blinded to exposure status?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				• Was follow-up long enough for outcomes to occur?	III
Comments:				The retrospective nature of this study means that the outcome assessment was not blinded to exposure status. As outcomes were objective, it is unlikely that measurement bias would have occurred.	
Quality rating: [Good/Fair/Poor]				Fair	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Study type:				Retrospective cohort study	
Citation:				Bodner LJ, Nosher JL, Gribbin C, Siegel RL, Beale S, Scorza W (2006) Balloon-assisted occlusion of the internal iliac arteries in patients with placenta accreta/percreta. Cardiovasc Intervent Radiol 29(3):354-61.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was the selection of subjects appropriate?	
	✓			• Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	• Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
			✓	• Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
			✓	• Was loss to follow-up and exclusions from analysis reported?	II
			✓	• Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
	✓			• Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			• Was outcome assessment blinded to exposure status?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				• Was follow-up long enough for outcomes to occur?	III
Comments:				The two groups were divided by treatment referral patterns and therefore may be subject to selection bias. Diagnosis was made antenatally vs postpartum for intervention vs control. Therefore, those with a more complicated clinical course (diagnosed antenatally) may have been more likely to fall into the intervention group. The two groups were similar for maternal age, gravidity and parity; however, the intervention group had a significantly lower gestational age compared with the control group. It is unlikely that outcome assessment was blinded to exposure status	
Quality rating: [Good/Fair/Poor]				Fair	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Study type:				Prospective cohort study	
Citation:				Levine A, Kuhlman K, Bonn J (1999) Placenta Accreta: Comparison of Cases Managed With and Without Pelvic Artery Balloon Catheters. J Matern Fetal Med 8:173-76.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was the selection of subjects appropriate?	
✓				• Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	• Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			• Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
		✓		• Was loss to follow-up and exclusions from analysis reported?	II
			✓	• Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
	✓			• Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
		✓		• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		• Was outcome assessment blinded to exposure status?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				• Was follow-up long enough for outcomes to occur?	III
Comments:				Baseline characteristics were presented for the overall cohort, not by treatment group so it is hard to determine whether there were significant differences in potential confounders. The sample size was very small and therefore it is unlikely to be powered to detect a treatment difference. Selection bias may be any issue as it is not mentioned whether all people who were asked to take part in the study, did so.	
Quality rating: [Good/Fair/Poor]				Poor	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Recombinant activated factor VII

Level III evidence

Study type:				Retrospective cohort study	
Citation:				Kalina M, Tinkoff G, Fulda G (2011) Massive postpartum hemorrhage: recombinant factor VIIa use is safe but not effective. Del Med J 83(4):109-13.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was the selection of subjects appropriate?	
	✓			• Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
✓				• Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
			✓	• Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
			✓	• Was loss to follow-up and exclusions from analysis reported?	II
			✓	• Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
	✓			• Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		• Was outcome assessment blinded to exposure status?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				• Was follow-up long enough for outcomes to occur?	III
Comments:				The two groups differed on baseline severity of illness (significantly higher APACHE II scores in the study group compared with controls). Exclusions and loss to follow-up were not applicable, as the study was retrospective and included all relevant patient records. Patients chosen to receive intervention also differed from those in the control group as patients only received rFVIIa in circumstances where persistent coagulopathic bleeding existed after the first massive transfusion "pack" was transfused. This was inherent in the massive transfusion protocol at the study institution. High risk that selection bias affected the results.	
Quality rating: [Good/Fair/Poor]				Poor	

rFVIIa, activated recombinant factor VII.

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.

Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Study type:				Retrospective cohort study	
Citation:				Ahonen J, Jokela R, Korttila K (2007) An open non-randomized study of recombinant activated factor VII in major postpartum haemorrhage. Acta Anaesthesiol Scand 51(7):929-36.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was the selection of subjects appropriate?	
✓				• Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	• Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
			✓	• Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
			✓	• Was loss to follow-up and exclusions from analysis reported?	II
			✓	• Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
	✓			• Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		• Was outcome assessment blinded to exposure status?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				• Was follow-up long enough for outcomes to occur?	III
Comments:				Exclusions and loss to follow-up were not applicable, as the study was a retrospective hospital-based cohort study (complete patient characteristic and outcome data was available for all patients). No significant differences in baseline patient characteristics or obstetric data between the treatment groups; however, the relative severity of haemorrhage was not reported and it is likely that the decision to use rFVIIa resulted from a more profound haemorrhage (high risk of selection bias). Follow-up was not explicitly stated but appeared to be while in hospital (i.e. long enough for outcomes to occur).	
Quality rating: [Good/Fair/Poor]				Fair	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Study type:				Retrospective cohort study	
Citation:				Hossain N, Shamsi T, Haider S, Soomro N, Khan NH, Memon GU, Farzana T, Ansari S, Triche EW, Kuczynski E, Lockwood CJ, Paidas MJ (2007) Use of recombinant activated factor VII for massive postpartum hemorrhage. Acta Obstet Gynecol Scand 86(10):1200-6.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was the selection of subjects appropriate?	
✓				• Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
				• Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
			✓	• Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
			✓	• Was loss to follow-up and exclusions from analysis reported?	II
			✓	• Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				• Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			• Was outcome assessment blinded to exposure status?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				• Was follow-up long enough for outcomes to occur?	III
Comments:				No significant differences in most population characteristics (cause of bleeding, type of delivery, surgical intervention, parity and maternal age). Exclusions and loss to follow-up were not applicable, as the study was retrospective and included all relevant patient records. The decision to administer the drug was based solely on the availability of the drug at the time of the woman's haemorrhage (which was unrelated to patient or provider characteristics). Nonetheless, the drug was administered only after other conventional methods failed and women in the rFVIIa group had worse baseline haematological parameters (Hb, PT, aPTT) than those in the comparison group. The differences would tend to attenuate any effects and may, in part, explain the stronger effects of rFVIIa found in the adjusted logistic regression models than in the unadjusted analyses. Follow-up was during hospitalisation and in the postpartum period. This was long enough for outcomes to occur.	
Quality rating: [Good/Fair/Poor]				Fair	

aPTT, activated partial thromboplastin; Hb, haemoglobin; PT, prothrombin; rFVIIa, activated recombinant factor VII.

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.

Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Tranexamic acid

Level II evidence

Study type:				Randomised controlled trial	
Citation:				H.Abdel-Aleem, T. K. Alhusaini M. A. Abdel-Aleem M. Menoufy and A. M. Gu lmezoglu (2013) Effectiveness of tranexamic acid on blood loss in patients undergoing elective cesarean section: randomized clinical trial. J Matern Fetal Neonatal Med 26 (17) 1705-1709	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was assignment of subjects to treatment group randomised?	
✓				• Was the use of randomisation reported?	I
✓				• Was the method of randomisation reported?	III
✓				• Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
✓				• Was a method of allocation concealment reported?	III
✓				• Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			• Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				• Were baseline patient characteristics and demographics reported?	III
	✓			• Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				• Was loss to follow-up reported?	II
			✓	• Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			• Was outcome assessment blinded to treatment allocation?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				• Were the methods used for comparing results between treatment arms appropriate?	III
			✓	• If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
	✓			• Were subgroup analyses reported?	III-IV
			✓	• Were subgroup analyses appropriate?	III-IV
Comments:				Subjects were randomised using computer-generated numbers, with allocations kept inside opaque sealed envelopes. The trial was not double-blinded. The nurses measuring the primary outcome were not blinded to the intervention but the authors state they were unaware of the nature of the intervention. Baseline characteristics differed in three categories between the study groups (BMI, duration of surgery and method of delivery of the placenta). To account for these differences, multivariate regression analysis was conducted to adjust for these potential confounders. Loss to	

	follow-up was reported but there were no losses in the study, nor did any of the participants discontinue the intervention.	
Quality rating: [Good/Fair/Poor]	Fair	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Study type:				Randomised controlled trial	
Citation:				Gungorduk K, Asıcıoğlu O, Yıldırım G, Ark C, Tekirdağ A, Besımoglu B. (2013) Can Intravenous Injection of Tranexamic Acid be Used in Routine Proactice with Active Management of the Third Stage of Labor in Vaginal Delivery? A Randomized Controlled Study. Am J Perinatol 30:407-414.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was assignment of subjects to treatment group randomised?	
✓				• Was the use of randomisation reported?	I
✓				• Was the method of randomisation reported?	III
✓				• Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
✓				• Was a method of allocation concealment reported?	III
✓				• Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
✓				• Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				• Were baseline patient characteristics and demographics reported?	III
✓				• Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				• Was loss to follow-up reported?	II
		✓		• Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
	✓			• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
✓				• Was outcome assessment blinded to treatment allocation?	III
			✓	• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				• Were the methods used for comparing results between treatment arms appropriate?	III
			✓	• If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
	✓			• Were subgroup analyses reported?	III-IV
			✓	• Were subgroup analyses appropriate?	III-IV
Comments:				Measurement of blood loss was subjective however investigators were blinded to treatment allocation and appropriate measures to minimise bias were taken.	

Quality rating: [Good/Fair/Poor]	Good	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Study type:				Randomised controlled trial	
Citation:				Senturk MB, Cakmak Y, Yildiz G, Yildiz P (2013) Tranexamic acid for cesarean section: A double-blind, placebo-controlled, randomized clinical trial. Arch Gynecol Obstet 287:641-645	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was assignment of subjects to treatment group randomised?	
✓				• Was the use of randomisation reported?	I
✓				• Was the method of randomisation reported?	III
✓				• Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
✓				• Was a method of allocation concealment reported?	III
✓				• Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
✓				• Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				• Were baseline patient characteristics and demographics reported?	III
✓				• Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				• Was loss to follow-up reported?	II
✓				• Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
	✓			• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
✓				• Was outcome assessment blinded to treatment allocation?	III
			✓	• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				• Were the methods used for comparing results between treatment arms appropriate?	III
			✓	• If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
	✓			• Were subgroup analyses reported?	III-IV
			✓	• Were subgroup analyses appropriate?	III-IV
Comments:				All outcomes measured were standardised except the process for measuring blood volume loss. The authors acknowledge that the approach used is subjective and difficult to remove amniotic fluid from the measurements. Surrogate measures to indicate bleeding (Hgb, Hct) were appropriate and provide some objective results.	
Quality rating: [Good/Fair/Poor]				Good	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Study type:				Randomised controlled trial	
Citation:				Xu J, Gao W, Ju Y. (2013) Tranexamic acid for the prevention of postpartum haemorrhage after cesarean section: a double-blind randomization trial. Arch Gynecol Obstet 287:463-468.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was assignment of subjects to treatment group randomised?	
✓				• Was the use of randomisation reported?	I
✓				• Was the method of randomisation reported?	III
✓				• Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
✓				• Was a method of allocation concealment reported?	III
✓				• Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
✓				• Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				• Were baseline patient characteristics and demographics reported?	III
✓				• Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
			✓	• Was loss to follow-up reported?	II
			✓	• Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
	✓			• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
✓				• Was outcome assessment blinded to treatment allocation?	III
			✓	• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				• Were the methods used for comparing results between treatment arms appropriate?	III
			✓	• If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
	✓			• Were subgroup analyses reported?	III-IV
			✓	• Were subgroup analyses appropriate?	III-IV

Comments:	The quality rating was downgraded from good to fair based on some methodological concerns. The control group appeared to have a much higher proportion of patients who received transfusion compared to the intervention group and no reasons were provided to explain the difference. The decision to transfused was reportedly based on haemoglobin concentrations, which were very similar between the two groups (p=0.14). As such, the vast difference in transfusion rates between the study groups is not clear.	
Quality rating: [Good/Fair/Poor]	Fair	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Study type:				Randomised controlled trial	
Citation:				Ducloy-Bouthors A-S, Jude B, Duhamel A, Broisin F, Huissoud C, Keita-Meyer H, Mandelbrot L, Tillouche N, Fontaine S, Le Goueff F, Depret-Mosser S, Vallet B, for The EXADELI Study Group and Susen S. (2011) High-dose tranexamic acid reduces blood loss in postpartum haemorrhage. Critical Care 15:R117	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was assignment of subjects to treatment group randomised?	
✓				• Was the use of randomisation reported?	I
✓				• Was the method of randomisation reported?	III
✓				• Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
✓				• Was a method of allocation concealment reported?	III
✓				• Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			• Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				• Were baseline patient characteristics and demographics reported?	III
✓				• Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
			✓	• Was loss to follow-up reported?	II
			✓	• Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
✓				• Was outcome assessment blinded to treatment allocation?	III
			✓	• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				• Were the methods used for comparing results between treatment arms appropriate?	III

✓				• If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
	✓			• Were subgroup analyses reported?	III-IV
			✓	• Were subgroup analyses appropriate?	III-IV
Comments:				Although an open-label study, centralised randomisation and strict data concealment measures were used. After randomisation, administration of the intervention was carried out by the anaesthetist. Obstetricians and midwives were not aware of the treatment allocation so the risk of bias relating to patient management, blood loss measurement, and treatment decisions is low. It is unclear if there was any loos to follow-up.	
Quality rating: [Good/Fair/Poor]				Good	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Study type:				Randomised controlled trial	
Citation:				Gungorduk K, Yıldırım G, Asıcıog˘lu O, Gungorduk OC, Sudolmus S, Ark C. (2011) Efficacy of intravenous tranexamic acid in reducing blood loss after elective cesarean section: A prospective, randomized, double-blind, placebo-controlled study. Am J Perinatol 28:233-240.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was assignment of subjects to treatment group randomised?	
✓				• Was the use of randomisation reported?	I
✓				• Was the method of randomisation reported?	III
✓				• Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
✓				• Was a method of allocation concealment reported?	III
✓				• Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
✓				• Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				• Were baseline patient characteristics and demographics reported?	III
✓				• Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				• Was loss to follow-up reported?	II
✓				• Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			• Was outcome assessment blinded to treatment allocation?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				• Were the methods used for comparing results between treatment arms appropriate?	III
			✓	• If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
	✓			• Were subgroup analyses reported?	III-IV
			✓	• Were subgroup analyses appropriate?	III-IV

Comments:	All outcomes measured were objective and unlikely to be influenced by blinding of assessment (although this is not clearly stated), except the reporting of thromboembolic events (TE). After discharge, women who received the intervention were specifically instructed on the signs and symptoms of a TE, however, there were none reported.	
Quality rating: [Good/Fair/Poor]	Good	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Study type:				Randomised controlled trial	
Citation:				Gai M, Wu L, Su Q, Tatsumoto K. (2004) Clinical observation of blood loss reduced by tranexamic acid during and after caesarian section: a multi-center, randomized trial. Eur J Obstet Gynecol Reprod Biol 112:154-157.	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was assignment of subjects to treatment group randomised?	
✓				• Was the use of randomisation reported?	I
✓				• Was the method of randomisation reported?	III
✓				• Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			• Was a method of allocation concealment reported?	III
			✓	• Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			• Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				• Were baseline patient characteristics and demographics reported?	III
✓				• Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
	✓			• Was loss to follow-up reported?	II
			✓	• Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
	✓			• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		• Was outcome assessment blinded to treatment allocation?	III
	✓			• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				• Were the methods used for comparing results between treatment arms appropriate?	III
			✓	• If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
			✓	• Were subgroup analyses reported?	III-IV
			✓	• Were subgroup analyses appropriate?	III-IV
Comments:				The process for measuring blood volume loss was subjective. The authors do not indicate if the assessment of blood loss was blinded to treatment allocation.	
Quality rating: [Good/Fair/Poor]				Fair	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Level III evidence

Study type:				Retrospective cohort study	
Citation:				Lindoff C, Rybo G, Astedt B. Treatment with tranexamic acid during pregnancy, and the risk of thrombo-embolic complications. Thromb Haemost 1993;70:238-40	
Y	N	NR	NA	Quality criteria	Error rating[a]
				A. Was the selection of subjects appropriate?	
	✓			• Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
		✓		• Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
			✓	• Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
			✓	• Was loss to follow-up and exclusions from analysis reported?	II
			✓	• Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
	✓			• Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		• Was outcome assessment blinded to exposure status?	III
✓				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				• Was follow-up long enough for outcomes to occur?	III
Comments:				Exclusions and loss to follow-up were not applicable, as the study was retrospective and included all relevant patient records. The treatment groups differed substantially based on the diagnosis/reason for bleeding (eg. 52.7% in the study group had abruption placentae compared to 11.5% in the control group; 29.3% had placenta praevia in the study group compared to 4.8% in the control group). Importantly, the reason for treatment with tranexamic acid was a more severe bleeding complication; therefore, this group was presumably more prone to thrombosis. High risk that selection bias affected the results.	
Quality rating: [Good/Fair/Poor]				Poor	

a Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Appendix F Evidence summaries

F1 Evidence summaries – Question 1

Restrictive versus liberal RBC transfusion

Level II evidence

STUDY DETAILS: RCT		
Citation		
Koshy, M; Burd, L; Wallace, D; Moawad, A; Baron, J. Prophylactic red-cell transfusions in pregnant patients with sickle cell disease. A randomized cooperative study. New England Journal of Medicine 1988 319 22 (1447- 1452.)		
Affiliation/Source of funds		
Supported by a grant from the National Institutes of Health.		
Study design	Level of evidence	Location/setting
RCT	Level II	USA / Multicentre Six institutions in Chicago and Johns Hopkins, Baltimore

Intervention	Comparator
Prophylactic red cell blood transfusion Patients received 2 units of packed washed frozen RBCs weekly for three weeks or until the goals of transfusion were reached. The goal of prophylactic transfusion was to maintain the haemoglobin concentration between 6.21 and 6.83mmol per litre (between 10 and 11 g per decilitre) or the haematocrit near 0.33 arbitrary unit (33 %) and to reduce the level of haemoglobin S below 35 % by simple transfusion or partial exchange transfusion.) Two additional units were transfused if the haemoglobin concentration fell below 6.21 mmol per litre. Phlebotomy was performed before partial exchange transfusion. The volume of blood removed depended on the baseline blood count; 500ml was drawn from those who had steady state levels of haemoglobin, and 2 units of packed red cells were transfused. This procedure was repeated weekly until the goals described above were reached.	Restrictive transfusion: Red cell transfusions only for medical or obstetric emergencies. Haematologic indications for transfusion were a haemoglobin concentration below 3.72 mmol per litre (6g per decilitre,) a haematocrit below 0.18 arbitrary unit (18 percent) and a reticulocyte count below 3 percent.

Population characteristics
72 pregnant women with sickle cell anaemia before 28 weeks gestation. Patients were randomised only if they had no complications or had no abortions before the study (spontaneous or elective). Baseline characteristics between randomised groups not significantly different for all outcomes reported but approached significance (P=0.09) for previous perinatal mortality. The use of alcohol before pregnancy was also associated with previous perinatal mortality. The only observational complication in which these two groups differed was the occurrence of multiple pregnancies.

Length of follow-up	Outcomes measured
Patients were entered into the study if they were identified before 28 weeks of gestation, consented to participate, and did not have any disorder that would disqualify them. They were followed until delivery.	Perinatal outcomes in the patient, obstetric complications in the patient, transfusion-related complications in the patients, sickle cell disease-related complications in the patient

INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: An RCT of prophylactic red blood transfusion vs red cell blood transfusion only if indicated for medical or obstetrical complications. Method of randomisation was not reported, there was no mention of allocation concealment or if outcome assessment was blinded. Baseline characteristics were different for some measures (previous perinatal mortality) bringing into question the method of randomisation. Authors report adjusted analysis for multiple gestation and perinatal mortality as baseline characteristics for these measures were notably different between the intervention and comparator groups. The difference in perinatal mortality between pregnancies with multiple fetuses or had previously ended in perinatal death and those pregnancies that did not was significant (P<0.0001).				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	36		36	
Outcome	Intervention (N=36)	Comparator (N=36)	Risk estimate (95% CI)	Statistical significance P-value
Prophylactic RBC transfusion vs selective RBC transfusion				
	n/N (%)	n/N (%)		
Maternal or perinatal mortality				
Perinatal death (%)	6/36 (15%)	2/36 (5%)	NR	No significant difference[a] P=NR
Neonatal death (%)	2/36 (6%)	0	NR	No significant difference[a] P=NR
Stillbirth (%)	4/36 (10%)	2/36 (5%)	NR	No significant difference[a] P=NR
Measures of fetal outcome				
Birth weight (g)	2495	2652	NR	No significant difference[a] P=NR
Gestational age at delivery (wk)	35.8	38.1	NR	Favours selective RBC transfusion P<0.05 [this difference did not remain significant after adjustment for previous perinatal mortality and multiple births]
Premature delivery (<37 wk)	14/36 (39%)	6/36 (17%)	NR	No significant difference[a] P=NR
Transfusion-related SAEs[b]				
Delayed transfusion reaction (no. of patients)	6/36	3/36	NR	No significant difference P=NR
Alloimmunisations (%)	10/36 (29%)	8/36 (21%)	NR	No significant difference P=NR
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to pregnant women with sickle cell anaemia (HbSS) with some caveats				
Applicability				

The study was conducted in the USA between 1979-1986 therefore the evidence is probably applicable to the Australian health care systemwith some caveats
Comments
Patients with sickle-C disease and sickle-beta-thalassaemia were included in the study, but not randomised. Each randomised group contained only 36 patients; therefore, the sensitivity of this study is limited and only large differences could be expected to be statistically significant. Gestational age of the infants was lower in the intervention group than those of the controls, but this difference was not significant after adjustment for previous perinatal mortality and multiple births. Perinatal mortality also approached statistical significance in the intervention group, but was not significant when adjusted for patients with twins or previous perinatal death. There was no difference in the rate of medical and obstetric complications except for pain crisis, which were significantly reduced in the prophylactic transfusion group (P<0.01). Although the rates of alloimmunisation were similar in the prophylactic-transfusion and control group, almost four times as many units of red cells were used in the former group (P<0.01), with no significant benefit in measures of outcome. The authors were unable to detect any improvements in the survival of the mother or fetus that was due to prophylactic transfusion therapy.

Abbreviations: CI, confidence interval; ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

a. with or without adjustment for multiple birth or previous perinatal mortality
b. study did not pre-define transfusion-related SAEs.

F2 Evidence summaries – Question 2

Iron

Level I evidence

<table>
<tr><td colspan="4">STUDY DETAILS: SR/MA</td></tr>
<tr><td colspan="4">Citation</td></tr>
<tr><td colspan="4">Peña-Rosas JP, De-Regil LM, Dowswell T, Viteri FE. Daily oral iron supplementation during pregnancy. Cochrane Database of Systematic Reviews 2012, Issue 12. Art. No.: CD004736. DOI: 10.1002/14651858.CD004736.pub4.</td></tr>
<tr><td colspan="4">Affiliation/Source of funds</td></tr>
<tr><td colspan="4">The authors have no affiliations with any organisation or entity with a direct financial interest in the subject matter of the review. JP Pena-Rosas was the author of an excluded study on iron and folic acid intermittent supplementation. Internal sources of support: Children's Hospital and Oakland Research Institute, USA; Evidence and Programme Guidance Unit, Department of Nutrition for Health and Development, World Health Organization, Switzerland; University of Liverpool, UK. External sources of support: Evidence and Programme Guidance Unit, Department of Nutrition for Health and Development, World Health Organization, Switzerland. T Dowswell is supported by the NIHR NHS Cochrane Collaboration Programme grant scheme award for NHS-prioritised centrally-managed, pregnancy and childbirth systematic reviews, UK.</td></tr>
<tr><td>Study design</td><td>Level of evidence</td><td colspan="2">Location/setting</td></tr>
<tr><td>Systematic review and meta-analysis.
• 60 randomised or quasi-randomised controlled trials were included in the review</td><td>Level I</td><td colspan="2">Predominantly single-setting studies in various countries.
Ireland (Barton, 1994), Myanmar (Batu,1976), Belgium (Buytaert, 1983), Canada (Cantlie, 1971), Hong Kong (Chan, 2009), England (Chanarin, 1971; Chisholm, 1966; Harvey, 2007; Taylor, 1982; Wills, 1947), Nepal (Christian, 2003), USA (Cogswell, 2003; Corrigan, 1936; Holly, 1955; Meier, 2003; Pritchard, 1958), France (De Benaze, 1989), Norway (Eskeland, 1997; Romslo, 1983), Iran (Falahi, 2010; Ziaei, 2008), Australia (Hankin, 1963; Makrides, 2003), Finland (Hemminki, 1991; Puolakka, 1980), South Korea (Lee, 2005), China (Liu, 2000), Gambia (Menendez, 1994), Denmark (Milman, 1991), Scotland (Paintin, 1966), Niger (Preziosi, 1997), Italy (Tura, 1989), Netherlands (Van Eijk, 1978; Wallenburg, 1983)</td></tr>
<tr><td colspan="2">Intervention</td><td colspan="2">Comparator</td></tr>
<tr><td colspan="2">All interventions involved supplementation with daily oral iron
1. Any supplements containing iron
2. Any supplements containing iron and folic acid
3. Iron alone
4. Iron and folic acid
5. Iron and folic acid
6. Iron + other vitamins and minerals
7. Iron + folic acid + other vitamins and minerals
8. Iron + folic acid + other vitamins and minerals
[note: only data for interventions 3 and 4 has been extracted for this review]</td><td colspan="2">1. The same supplement without iron or no treatment/placebo
2. The same supplements without iron nor folic acid, or placebo
3. No treatment/placebo
4. No treatment/placebo
5. Folic acid alone
6. The same other vitamins and minerals (without iron)
7. Folic acid + same vitamins and minerals (without iron)
8. Same vitamins and minerals (without iron + folic acid)</td></tr>
<tr><td colspan="4">Population characteristics</td></tr>
<tr><td colspan="4">Pregnant women of any gestational age and parity</td></tr>
<tr><td>Length of follow-up</td><td colspan="3">Outcomes measured</td></tr>
<tr><td>NA</td><td colspan="3">Primary (infant): birthweight, low birthweight, premature birth, neonatal death, congenital anomalies
Primary (maternal): anaemia at term, iron deficiency at term, iron deficiency anaemia at term, side effects, maternal death, severe anaemia at any time during second or third trimesters, clinical malaria, infection during pregnancy
Secondary (infant): very low birthweight, very premature birth, Hb concentration in the first six months,</td></tr>
</table>

	ferritin concentration in the first six months, development of motor skills, admission to special care unit Secondary (maternal): anaemia at or near term, iron deficiency at or near term, iron deficiency anaemia at or near term, Hb concentration at or near term, Hb concentration within 6 weeks postpartum, high Hb concentrations at any time during second or third trimester, high Hb concentrations at or near term, moderate anaemia at postpartum, maternal severe anaemia at or near term, severe anaemia postpartum, puerperal infection, antepartum haemorrhage, postpartum haemorrhage, transfusion given, diarrhoea, constipation, nausea, heartburn, vomiting, maternal well being/satisfaction, placental abruption, premature rupture of membranes, pre-eclampsia

INTERNAL VALIDITY

Overall quality assessment (descriptive)

Rating: Good

Description: Appropriate search strategies and inclusion criteria used in an unbiased way. Quality assessments clear and pre-determined. Study results clearly reported and summarised. Level III-1 evidence was included (i.e. quasi-randomised trials). Pooling of data was appropriate and tests for heterogeneity applied. Subgroup differences are explored, with results stratified by gestational age at the start of supplementation and anaemia status at the start of supplementation.

RESULTS

Outcome No. trials (No. patients)	Intervention	Comparator	Risk estimate (95% CI)	Statistical significance P-value Heterogeneity P-value (I^2)
Iron alone vs no treatment/placebo				
Transfusion incidence				
	n/N (%)	n/N (%)	Risk ratio	
Transfusion provided 1 trial (N=32) [Hemminki, 1991 removed from analysis]	0/16 (0%)	1/16 (6.3%)	0.33 [0.01, 7.62]	No significant difference P=0.49 Heterogeneity not applicable
2 trials (N=2726) [includes Hemminki, 1991]	27/1352 (2.0%)	47/1374 (3.4%)	0.59 [0.37, 0.94]	Favours iron P=0.025 No significant heterogeneity P=0.72 (I^2=0.0%)
Laboratory measures				
	n/N (%)	n/N (%)	Risk ratio	
Maternal anaemia at term (Hb less than 110 g/L at 37 weeks' gestation or more) 14 trials (N=2136) [c]	142/1131 (12.6%)	345/1005 (34.3%)	0.29 [0.19, 0.47]	Favours iron P < 0.0001 Substantial heterogeneity P < 0.00001 (I^2=80%)
Anaemic at start of supplementation 0 trials (N=0)	0	0	0 [0.00, 0.00]	NA
Non-anaemic at start of supplementation 8 trials (N=1244) [Hemminki, 1991 removed from analysis]	41/673 (6.1%)	157/571 (27.5%)	0.20 [0.10, 0.44]	Favours iron P < 0.0001 Substantial heterogeneity P=0.002 (I^2=70%)
9 trials (N=3938) [includes Hemminki, 1991]	56/2009 (2.8%)	213/1929 (11.0%)	0.23 [0.13, 0.41]	Favours iron P<0.00001 Substantial heterogeneity P=0.004 (I^2=65%)
Unspecified or mixed anaemia status	65/358 (18.2%)	145/334 (43.4%)	0.34 [0.18, 0.64]	Favours iron P=0.00078

5 trials (N=692)				Substantial heterogeneity P=0.002 (I^2=77%)
Maternal anaemia at or near term (Hb less than 110 g/L at 34 weeks' gestation or more) 13 trials (N=1696) [Hemminki, 1991 removed from analysis]	99/908 (10.9%)	247/788 (31.3%)	0.29 [0.18, 0.46]	Favours iron P < 0.00001 Substantial heterogeneity P < 0.0001 (I^2=71%)
14 trials (N=4390) [includes Hemminki, 1991]	114/2244 (5.1%)	303/2146 (14.1%)	0.29 [0.19, 0.45]	Favours iron P<0.00001 Substantial heterogeneity P=0.00002 (I2=72%)
Maternal iron deficiency anaemia at term (Hb less than 110 g/L and at least one additional laboratory indicator at 37 weeks' gestation or more) 6 trials (N=1088)	25/572 (4.4%)	68/516 (13.2%)	0.33 [0.16, 0.69]	Favours iron P=0.0030 Moderate heterogeneity P=0.10 (I^2=49%)
Anaemic at start of supplementation 0 trials (N=0)	0	0	0 [0.00, 0.00]	NA
Non-anaemic at start of supplementation 5 trials (N=968)	25/509 (4.9%)	58/459 (12.6%)	0.39 [0.20, 0.74]	Favours iron P=0.0038 Moderate heterogeneity P=0.17 (I^2=40%)
Unspecified or mixed anaemia status 1 trial (N=120)	0/63 (0.0%)	10/57 (17.5%)	0.04 [0.00, 0.72]	Favours iron P=0.029 Heterogeneity not applicable
Maternal iron deficiency anaemia at or near term (Hb less than 110 g/L and at least one additional laboratory indicator at 34 weeks' gestation or more) 6 trials (N=1088)	25/572 (4.4%)	68/516 (13.2%)	0.33 [0.16, 0.69]	Favours iron P=0.0030 Moderate heterogeneity P=0.10 (I^2=49%)
Moderate anaemia at postpartum (Hb between 80 and less than 110 g/L) 3 trials (N=453)	1/238 (0.4%)	3/215 (1.4%)	0.46 [0.02, 13.91]	No difference P=0.66 Substantial heterogeneity P=0.11 (I^2=60%)
Maternal severe anaemia at any time during second or third trimesters (Hb less than 70 g/L) 7 trials (N=1078)	2/570 (0.4%)	3/508 (0.6%)	0.75 [0.02, 29.10]	No difference P=0.88 Substantial heterogeneity P=0.08 (I^2=67%)
Anaemic at start of supplementation 0 trials (N=0)	0	0	0 [0.00, 0.00]	NA

Non-anaemic at start of supplementation 5 trials (N=816)	2/440 (0.5%)	0/376 (0.0%)	4.98 [0.24, 103.01]	No difference P=0.30 No significant heterogeneity P=1.00 (I^2=0.0%)
Unspecified or mixed anaemia status 2 trials (N=262)	0/130 (0.0%)	3/132 (2.3%)	0.12 [0.01, 2.21]	No difference P=0.15 No significant heterogeneity P=1.00 (I^2=0.0%)
Maternal severe anaemia at or near term (Hb less than 70 g/L at 34 weeks' gestation or more) 7 trials (N=1046)	2/560 (0.4%)	3/486 (0.6%)	0.74 [0.02, 27.81]	No difference P=0.87 Substantial heterogeneity P=0.08 (I^2=66%)
Severe anaemia at postpartum (Hb less than 80 g/L) 7 trials (N=953)	0/511 (0.0%)	24/442 (5.4%)	0.02 [0.00, 0.33]	Favours iron P=0.0062 No significant heterogeneity P=1.00 (I^2=0.0%)
	Mean ± SD (N)	Mean ± SD (N)	Mean difference	
Maternal Hb concentration at or near term (in g/L, at 34 weeks' gestation or more) 16 trials (N=1851)	NR (959)	NR (892)	8.95 [6.37, 11.53]	Favours iron P < 0.00001 Substantial heterogeneity P < 0.00001 (I^2=89%)
Maternal Hb concentration within 6 weeks postpartum (in g/L) 6 trials (N=659)	NR (387)	NR (272)	7.26 [4.78, 9.74]	Favours iron P < 0.00001 Moderate heterogeneity P=0.11 (I^2=44%)
Measures of fetal outcome				
	n/N (%)	n/N (%)	Risk ratio	
Low birthweight (less than 2500 g) 6 trials (N=1136) [Hemminki, 1991 removed from analysis]	25/582 (4.3%)	38/554 (6.9%)	0.63 [0.30, 1.32]	No difference P=0.22 Moderate heterogeneity P=0.12 (i^2=45%)
7 trials (N=3830) [include Hemminki, 1991]	62/1918 (3.2%)	80/1912 (4.2%)	0.71 [0.42, 1.19]	No difference P=0.20 Moderate heterogeneity P=0.15 (I^2=39%)
Anaemic at start of supplementation 0 trials (N=0)	0	0	0 [0.00, 0.00]	NA
Non-anaemic at start of supplementation 5 trials (N=955) [Hemminki, 1991 removed from analysis]	22/489 (4.5%)	33/466 (7.1%)	0.65 [0.25, 1.66]	No difference P=0.36 Substantial heterogeneity P=0.07 (I^2=58%)
6 trials (N=3649) [includes Hemminki, 1991]	59/1825 (3.2%)	75/1824 (4.1%)	0.72 [0.39, 1.32]	No difference P=0.29

				Moderate heterogeneity P=0.09 (I2=50%)
Unspecified or mixed anaemia status 1 trial (N=181)	3/93 (3.2%)	5/88 (5.7%)	0.57 [0.14, 2.31]	No difference P=0.43 Heterogeneity not applicable
Very low birthweight (less than 1500 g) 3 trials (N=697)	2/361 (0.6%)	4/336 (1.2%)	0.55 [0.03, 9.07]	No difference P=0.68 Substantial heterogeneity P=0.14 (I^2=54%)
Premature birth (less than 37 weeks' gestation) 6 trials (N=1713) [Hemminki, 1991 removed from analysis]	57/852 (6.7%)	70/861 (8.1%)	0.82 [0.58, 1.14]	No difference P=0.24 No significant heterogeneity P=0.64 (I^2=0%)
7 trials (N=4407) [include Hemminki, 1991]	97/2188 (4.4%)	127/2219 (5.7%)	0.77 [0.60, 1.00]	Favours iron P=0.048 No significant heterogeneity P=0.73 (I2=0.0%)
Anaemic at start of supplementation 0 trials (N=0)	0	0	0 [0.00, 0.00]	NA
Non-anaemic at start of supplementation 5 trials (N=851) [Hemminki, 1991 removed from analysis]	30/433 (6.9%)	40/418 (9.6%)	0.72 [0.45, 1.13]	No difference P=0.15 No significant heterogeneity P=0.60 (I^2=0%)
6 trials (N=3545) [includes Hemminki, 1991]	70/1769 (4.0%)	97/1776 (5.5%)	0.71 [0.53, 0.97]	Favours iron P=0.028 No significant heterogeneity P=0.76 (I2=0.0%)
Unspecified or mixed anaemia status 1 trial (N=862)	27/419 (6.4%)	30/443 (6.8%)	0.95 [0.58, 1.57]	No difference P=0.85 Heterogeneity not applicable
Very premature birth (less than 34 weeks' gestation) 3 trials (N=690)	3/357 (0.8%)	10/333 (3.0%)	0.32 [0.10, 1.09]	No difference P=0.069 No significant heterogeneity P=0.73 (I^2=0.0%)
	Mean ± SD (N)	Mean ± SD (N)	Mean difference	
Birthweight (in g) 8 trials (N=1259) [Hemminki, 1991 removed from analysis]	NR (668)	NR (5911)	15.81 [-61.14, 92.76]	No difference P=0.69 Moderate heterogeneity P=0.12 (I^2=40%)
Birthweight (in g) 9 trials (N=3953) [includes Hemminki, 1991]	NR (2004)	NR (1949)	16.43 [-37.28, 70.14]	No difference P=0.55 Moderate heterogeneity P=0.17 (I2=31%)
Anaemic at start of supplementation 0 trials (N=0)	0	0	0 [0.00, 0.00]	NA
Non-anaemic at start of supplementation	NR (453)	NR (436)	19.19 [-101.86, 140.25]	No difference P=0.76

6 trials (N=889) [Hemminki, 1991 removed from analysis] 7 trials (N=3583)	 NR (1789)	 NR (1794)	 22.44 [-54.15, 99.03]	Substantial heterogeneity P=0.05 (I^2=54%) No difference P=0.57 Moderate heterogeneity P=0.09 (I2=45%)
Unspecified or mixed anaemia status 2 trials (N=370)	NR (215)	NR (155)	0.90 [-86.32, 88.12]	No difference P=0.98 No significant heterogeneity P=0.49 (I^2=0.0%)
Maternal and perinatal mortality				
	n/N (%)	n/N (%)	Risk ratio	
Maternal death (death while pregnant or within 42 days of termination of pregnancy) 1 trial (N=47)	0/24 (0.0%)	0/23 (0.0%)	0.0 [0.0, 0.0]	No difference P = Not applicable[b] Heterogeneity not applicable
Neonatal death (within 28 days after delivery) 1 trial (N=2694) [includes Hemminki, 1991]	13/1336 (1.0%)	10/1358 (0.7%)	1.32 [0.58, 3.00]	No difference P=0.51 Heterogeneity not applicable
Iron + folic acid vs no treatment/placebo				
Laboratory measures				
	n/N (%)	n/N (%)	Risk ratio	
Maternal anaemia at term (Hb less than 110 g/L at 37 weeks' gestation or more) 3 trials (N=346)	15/208 (7.2%)	39/138 (28.3%)	0.34 [0.21, 0.54]	Favours iron + folic acid P < 0.00001 No significant heterogeneity P=0.48 (I^2=0.0%)
Anaemic at start of supplementation 0 trials (N=0)	0	0	0 [0.00, 0.00]	NA
Non-anaemic at start of supplementation 2 trials (N=280)	5/176 (2.8%)	10/104 (9.6%)	0.24 [0.09, 0.68]	Favours iron + folic acid P=0.0072 No significant heterogeneity P=1.00 (I^2=0.0%)
Unspecified or mixed anaemia status 1 trial (N=66)	10/32 (31.3%)	29/34 (85.3%)	0.37 [0.22, 0.62]	Favours iron + folic acid P=0.00022 Heterogeneity not applicable
Maternal anaemia at or near term (Hb less than 110 g/L at 34 weeks' gestation or more) 3 trials (N=346)	15/208 (7.2%)	39/138 (28.3%)	0.34 [0.21, 0.54]	Favours iron + folic acid P < 0.00001 No significant heterogeneity P=0.48 (I^2=0.0%)
Maternal iron deficiency anaemia at term (Hb less than 110 g/L and at least one additional laboratory indicator at 37 weeks' gestation or more) 1 trial (N=131)	12/111 (10.8%)	5/20 (25.0%)	0.43 [0.17, 1.09]	No difference P=0.077 Heterogeneity not applicable

Maternal iron deficiency anaemia at or near term (Hb less than 110 g/L and at least one additional laboratory indicator at 34 weeks' gestation or more) 1 trial (N=131)	12/111 (10.8%)	5/20 (25.0%)	0.43 [0.17, 1.09]	No difference P=0.077 Heterogeneity not applicable
Moderate anaemia at postpartum (Hb between 80 and less than 110 g/L) 2 trials (N=458)	9/202 (4.5%)	35/256 (13.7%)	0.34 [0.17, 0.69]	Favours iron + folic acid P=0.0028 No significant heterogeneity P=1.00 (I^2=0.0%)
Maternal severe anaemia at any time during second or third trimesters (Hb less than 70 g/L) 4 trials (N=506)	1/238 (0.4%)	15/268 (5.6%)	0.12 [0.02, 0.63]	Favours iron + folic acid P=0.012 No significant heterogeneity P=0.88 (I^2=0.0%)
Maternal severe anaemia at or near term (Hb less than 70 g/L at 34 weeks' gestation or more) 3 trials (N=191)	0/102 (0.0%)	3/89 (3.4%)	0.14 [0.01, 2.63]	No difference P=0.19 No significant heterogeneity P=1.00 (I^2=0.0%)
Severe anaemia at postpartum (Hb less than 80 g/L) 3 trials (N=491)	0/220 (0.0%)	14/271 (5.2%)	0.05 [0.00, 0.76]	Favours iron + folic acid P=0.031 Substantial heterogeneity P < 0.00001 (I^2=100%)
	Mean ± SD (N)	Mean ± SD (N)	Mean difference	
Maternal Hb concentration at or near term (in g/L, at 34 weeks' gestation or more) 3 trials (N=140)	NR (76)	NR (64)	16.13 [12.74, 19.52]	Favours iron + folic acid P < 0.00001 No significant heterogeneity P=0.80 (I^2=0.0%)
Maternal Hb concentration within 6 weeks postpartum (in g/L) 2 trials (N=459)	NR (199)	NR (260)	10.07 [7.33, 12.81]	Favours iron + folic acid P < 0.00001 No significant heterogeneity P=0.91 (I^2=0.0%)
Measures of fetal outcome				
	n/N (%)	n/N (%)	Risk ratio	
Low birthweight (less than 2500 g) 2 trials (N=1311)	220/659 (33.4%)	262/652 (40.2%)	1.07 [0.31, 3.74]	No difference P=0.91 Moderate heterogeneity P=0.24 (I^2=29%)
Very low birthweight (less than 1500 g) 1 trial (N=48)	2/24 (8.3%)	0/24 (0.0%)	5.00 [0.25, 98.96]	No difference P=0.29 Heterogeneity not applicable
Premature birth (less than 37 weeks'	149/768 (19.4%)	140/729 (19.2%)	1.55 [0.40, 6.00]	No difference P=0.53

gestation) 3 trials (N=1497)				Moderate heterogeneity P=0.22 (I^2=34%)
Anaemic at start of supplementation 0 trials (N=0)	0	0	0 [0.00, 0.00]	NA
Non-anaemic at start of supplementation 0 trials (N=0)	0	0	0 [0.00, 0.00]	NA
Unspecified or mixed anaemia status 3 trials (N=1497)	149/768 (19.4%)	140/729 (19.2%)	1.55 [0.40, 6.00]	No difference P=0.53 Moderate heterogeneity P=0.22 (I^2=34%)
Very premature birth (less than 34 weeks' gestation) 2 trials (N=92)	2/48 (4.2%)	0//44 (0.0%)	5.00 [0.25, 98.96]	No difference P=0.29 No significant heterogeneity P=1.00 (I^2=0.0%)
	Mean ± SD (N)	Mean ± SD (N)	Mean difference	
Birthweight (in g) 2 trials (N=1365)	NR (656)	NR (709)	57.73 [7.66, 107.79]	Favours iron + folic acid P=0.024 No significant heterogeneity P=0.31 (I^2=2%)
Maternal and perinatal mortality				
	n/N (%)	n/N (%)	Risk ratio	
Maternal death (death while pregnant or within 42 days of termination of pregnancy) 1 trial (N=131)	0/111 (0.0%)	0/20 (0.0%)	0.0 [0.0, 0.0]	No difference P = Not applicable[b] Heterogeneity not applicable
Neonatal death (within 28 days after delivery) 3 trials (N=1793)	29/849 (3.4%)	40/944 (4.2%)	0.81 [0.51, 1.30]	No difference P=0.39 No significant heterogeneity P=0.48 (I^2=0.0%)
Anaemic at start of supplementation 0 trials (N=0)	0	0	0 [0.00, 0.00]	NA
Non-anaemic at start of supplementation 1 trial (N=97)	1/53 (1.9%)	0/44 (0.0%)	2.50 [0.10, 59.88]	No difference P=0.57 Heterogeneity not applicable
Unspecified or mixed anaemia status 2 trials (N=1696)	28/796 (3.5%)	40/900 (4.4%)	0.79 [0.49, 1.27]	No difference P=0.34 No significant heterogeneity P=1.00 (I^2=0.0%)
EXTERNAL VALIDITY				
Generalisability				
The review is generalisable to pregnant women of any gestational age and parity				
Applicability				
The review is applicable to the Australian context.				
Comments				

Abbreviations: CI, confidence interval; ITT, intention-to-treat; MA, meta-analysis; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review.

[a] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

[b] The review listed the p-value as p<0.00001

[c] Subgroups do not add up to the total for the outcome. The large trial by Hemminki (1991) appears in the subgroup analyses, but not in the overall analysis; whereas, Liu 2000 is included in the overall analysis but not in the groups. The reason for this discrepancy is not clear. According to the subgroup analysis, the results were 121/2367 in the intervention group, 358/2263 in the control group, RR 0.26 [0.16, 0.41], p<0.00001 favouring iron supplement, Heterogeneity p<0.00001, I^2=78%

STUDY DETAILS: SR/MA		
Citation		
Reveiz L, Gyte GM, Cuervo LG, and Casasbuenas A. (2011) Treatments for iron-deficiency anaemia in pregnancy. *Cochrane database of systematic reviews (Online)* CD003094.		
Affiliation/Source of funds		
The authors contributed to this systematic review in a personal capacity and during their spare time. No internal or external sources of support were declared.		
Study design	Level of evidence	Location/setting
Systematic review • 23 randomised controlled trials were included in the review	Level I	Various Turkey (Al, 2005), France (Bayoumeu, 2002), Breymann (2001), Digumarthi (2008), ,), Nigeria (Ogunbode, 1980), China , Sun (2010), India (Kumar, 2005; Zutschi, 2004), Pakistan (Wali 2002), Australia (Khalafallah 2010), Singapore (Singh 1998), Indonesia (Suharno 1993) (including Australia, India, Nigeria, France, Turkey, Malayan, China, United Kingdom, Tanzania, Pakistan)
Intervention	Comparator	
1. Oral iron 2. Intravenous (IV) iron 3. Intramuscular (IM) or intravenous (IV) iron 4. Intravenous (IV) iron 5. Intravenous (IV) iron with recombinant erythropoietin	1. Placebo 2. Placebo 3. Oral iron 4. Intramuscular (IM) iron + oral iron 5. Intravenous (IV) iron	
Population characteristics		
Pregnant women with a diagnosis of anaemia during pregnancy (haemoglobin levels under 11g/dL, or other tests for anaemia as defined by trialists) attributed to iron deficiency.		
Length of follow-up	Outcomes measured	
NA	Primary (women): mortality, morbidity, puerperal sepsis, systematic bacterial infection after delivery, days in intensive care unit, days hospitalised during pregnancy Primary (newborn): mortality, morbidity, days hospitalised, admission to neonatal intensive care unit Secondary (women): preterm labour, premature delivery, pneumonia, postpartum haemorrhage, heart failure, serum ferritin, serum iron, haemoglobin levels, long-term haematological outcomes -maternal side effects: general symptoms, gastrointestinal effects, local symptoms, systemic symptoms Secondary (newborn): low birthweight (less than 2500g), respiratory disease requiring ventilation, small-for-gestational age, cord serum ferritin, cord haemoglobin, other long-term outcomes	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Good Description: Appropriate search strategies and inclusion criteria used in an unbiased way. Quality assessments clear and pre-determined. The authors note that the included studies were generally small and methodologically poor, making it difficult to pool data. As such, heterogeneity is not applicable to the majority of the analyses and discussion around this area is minimal.		

RESULTS				
Outcome No. trials (No. patients)	Intervention	Comparator	Risk estimate (95% CI)	Statistical significance P-value Heterogeneity P-value (I^2)
Oral iron vs placebo				
Laboratory measures				
	n/N (%)	n/N (%)	Risk ratio	
Anaemic during second trimester 1 trial (N=125)	20/63 (31.7%)	52/62 (83.9%)	0.38 [0.26, 0.55]	Favours oral iron P < 0.00001 Heterogeneity not applicable
	Mean ± SD (N)	Mean ± SD (N)	Mean difference	
Haemoglobin levels (g/dL) 2 trials (N=215)	NR (107)	NR (108)	1.34 [0.27, 2.42]	Favours oral iron P=0.014 Substantial heterogeneity P < 0.00001 (I^2=98%)
Ferritin levels (µg/L) I trial (N=125)	3.3 ± 0.5 (63)	2.6 ± 0.5 (62)	0.70 [0.52, 0.88]	Favours oral iron P < 0.00001 Heterogeneity not applicable
Intravenous iron vs placebo (no relevant outcomes)				
Intravenous iron vs oral iron				
Transfusion incidence				
	n/N (%)	n/N (%)	Risk ratio	
Blood transfusion required 3 trials (N=167)	0/84 (0%)	4/83 (4.8%)	0.27 [0.05, 1.59]	No significant difference P=0.15 No significant heterogeneity P=0.97 (I^2=0%)
Laboratory measures				
	n/N (%)	n/N (%)	Risk ratio	
Haemoglobin level > 12g/dL at 30 days 1 trial (N=47)	3/24 (12.5%)	4/23 (17.4%)	0.72 [0.18, 2.87]	No significant difference P=0.64 Heterogeneity not applicable
Haemoglobin level > 11g/dL at birth 1 trial (N=90)	43/45 (95.6%)	28/45 (62.2%)	1.54 [1.21, 1.94]	Favours IV iron P=0.00037 Heterogeneity not applicable
	Mean ± SD (N)	Mean ± SD (N)	Mean difference	
Neonates mean haemoglobin (g/dL) 1 trial (N=47)	15.15 ± 2.1 (24)	15.3 ± 2.17 (23)	-0.15 [-1.37, 1.07]	No significant difference P=0.81 Heterogeneity not applicable
Maternal haemoglobin at birth (g/dL) 1 trial (N=90)	12.01 ± 0.88 (45)	11.26 ± 1.1 (45)	0.75 [0.34, 1.16]	Favours IV iron P=0.00035 Heterogeneity not applicable
Neonates ferritin level (µg/L) 1 trial (N=47)	132 ± 104 (24)	134 ± 107 (23)	-2.00 [-62.36, 58.36]	No significant difference P=0.95 Heterogeneity not applicable

Mean maternal haemoglobin at 4 weeks (g/dL) 3 trials (N=167)	NR (84)	NR (83)	0.44 [0.05, 0.82]	Favours IV iron P=0.027 Moderate heterogeneity P=0.18 (I^2=42%)
Measures of fetal outcome				
	n/N (%)	n/N (%)	Risk ratio	
Preterm labour 1 trial (N=100)	0/50 (0%)	0/50 (0%)	0.0 [0.0, 0.0]	NA
Low birthweight (under 2500g) 1 trial (N=100)	0/50 (0%)	0/50 (0%)	0.0 [0.0, 0.0]	NA
Small-for-gestational age 1 trial (N=100)	8/50 (16%)	5/50 (10%)	1.60 [0.56, 4.56]	No significant difference P=0.38 Heterogeneity not applicable
	Mean ± SD (N)	Mean ± SD (N)	Mean difference	
Neonatal birthweight (g) 3 trials (N=237)	NR (119)	NR (118)	54.29 [-170.11, 278.68]	No significant difference P=0.64 Substantial heterogeneity P=0.07 (I^2=62%)
Maternal and perinatal mortality				
	n/N (%)	n/N (%)	Risk ratio	
Maternal mortality 1 trial (N=100)	0/50 (0%)	0/50 (0%)	0.0 [0.0, 0.0]	NA
Neonatal mortality 2 trials (N=147)	0/74 (0%)	0/73 (0%)	0.0 [0.0, 0.0]	NA
Intravenous iron sucrose with recombinant erythropoietin vs intravenous iron sucrose				
Transfusion incidence				
	n/N (%)	n/N (%)	Risk ratio	
Need transfusion 1 trial (N=40)	0/20 (0%)	0/20 (0%)	0.0 [0.0, 0.0]	NA
Laboratory measures				
	n/N (%)	n/N (%)	Risk ratio	
Haemoglobin < 11g/dL at 4 weeks 1 trial (N=40)	1/20 (5%)	5/20 (25%)	0.20 [0.03, 1.56]	No significant difference P=0.12 Heterogeneity not applicable
Measures of fetal outcome				
	n/N (%)	n/N (%)	Risk ratio	
Birth < 37 weeks 1 trial (N=40)	0/20 (0%)	1/20 (5%)	0.33 [0.01, 7.72]	No significant difference P=0.49 Heterogeneity not applicable
	Mean ± SD (N)	Mean ± SD (N)	Mean difference	
Birthweight (g) 1 trial (N=40)	3332 ± 282 (20)	3462 ± 497 (20)	-130.00 [-380.44, 120.44]	No significant difference P=0.31 Heterogeneity not applicable
Intramuscular iron sorbitol citric acid vs oral iron				

Laboratory measures				
	n/N (%)	n/N (%)	Risk ratio	
Not anaemic at term 1 trial (N=200)	76/100 (76%)	62/100 (62%)	1.23 [1.01, 1.48]	Favours IM iron P=0.035 Heterogeneity not applicable
	Mean ± SD (N)	Mean ± SD (N)	Mean difference	
Mean maternal haemoglobin at birth (g/dL) 1 trial (N=200)	10.5 ± 0.84 (100)	9.96 ± 0.89 (100)	0.54 [0.30, 0.78]	Favours IM iron P=0.000010 Heterogeneity not applicable
Mean maternal haematocrit level at birth (%) 1 trial (N=200)	31.2 ± 2.6 (100)	29.8 ± 2.7 (100)	1.40 [0.67, 2.13]	Favours IM iron P=0.00019 Heterogeneity not applicable
Haematocrit (%) at 4 weeks of treatment 1 trial (N=56) *oral iron 600mg	32.5 ± 2.65 (28)	31.25 ± 2.22 (28)	1.25 [-0.03, 2.53]	No significant difference P=0.056 Heterogeneity not applicable
Haematocrit (%) at 8 weeks of treatment 1 trial (N=59) *oral iron 600mg	35.29 ± 3.6 (31)	32.67 ± 1.3 (28)	2.62 [1.26, 3.98]	Favours IM iron P=0.00015 Heterogeneity not applicable
Haematocrit (%) at 4 weeks of treatment 1 trial (N=56) *oral iron 1200mg	32.5 ± 2.65 (28)	31.25 ± 2.22 (28)	1.25 [-0.03, 2.53]	No significant difference P=0.056 Heterogeneity not applicable
Haematocrit (%) at 8 weeks of treatment 1 trial (N=59) *oral iron 1200mg	35.29 ± 3.6 (31)	32.69 ± 2.53 (28)	2.60 [1.02, 4.18]	Favours IM iron P=0.0012 Heterogeneity not applicable
Intramuscular iron sorbitol citric acid vs oral iron + folic acid				
Laboratory measures				
	n/N (%)	n/N (%)	Risk ratio	
Haemoglobin > 11g/dL at 36 weeks 1 trial (N=150)	42/75 (56%)	51/75 (68%0	0.82 [0.64, 1.06]	No significant difference P=0.13 Heterogeneity not applicable
Haemoglobin > 12g/dL at 36 weeks 1 trial (N=150)	11/75 (14.7%)	21/75 (28%)	0.52 [0.27, 1.01]	No significant difference P=0.053 Heterogeneity not applicable
	Mean ± SD (N)	Mean ± SD (N)	Mean difference	
Mean haemoglobin at 36 weeks (g/dL) 1 trial (N=150)	10.94 ± 0.56 (75)	11.2 ± 0.82 (75)	-0.26 [-0.48, -0.04]	Favours oral iron + folic acid P=0.023 Heterogeneity not applicable
Measures of fetal outcome				
	Mean ± SD (N)	Mean ± SD (N)	Mean difference	
Mean birthweight (g) 1 trial (N=150)	2610 ± 420 (75)	2630 ± 480 (75)	-20.00 [-164.35, 124.35]	No significant difference P=0.79 Heterogeneity not applicable
Intravenous iron sucrose vs intramuscular iron sorbitol + oral iron				

Laboratory measures				
	n/N (%)	n/N (%)	Risk ratio	
Haemoglobin level > 11g/dL at delivery 1 trial (N=40) *IV iron sucrose 500mg	12/15 (80%)	7/25 (28%)	2.86 [1.45, 5.63]	Favours IV iron P=0.0024 Heterogeneity not applicable
Haemoglobin level > 11g/dL at delivery 1 trial (N=45) *IV iron sucrose 200mg	14/20 (70%)	7/25(28%)	2.50 [1.25, 4.99]	Favours IV iron P=0.0093 Heterogeneity not applicable
	Mean ± SD (N)	Mean ± SD (N)	Mean difference	
Maternal haemoglobin level at birth (g/dL) 1 trial (N=40) *IV iron sucrose 500mg	11.8 ± 1.1 (15)	10.2 ± 1.2 (25)	1.60 [0.87, 2.33]	Favours IV iron P=0.000017 Heterogeneity not applicable
Haemoglobin level at delivery (g/dL) 1 trial (N=45) *IV iron sucrose 200mg	11.3 ± 0.9 (20)	10.2 ± 1.2 (25)	1.10 [0.49, 1.71]	Favours IV iron P=0.00044 Heterogeneity not applicable
Intravenous iron + oral iron vs oral iron				
Laboratory measures				
	Mean ± SD (N)	Mean ± SD (N)	Mean difference	
Mean predelivery maternal haemoglobin (g/dL) 1 trial (N=183)	12.66 ± 0.97 (92)	12.18 ± 0.87 (91)	0.48 [0.21, 0.75]	Favours IV iron + oral iron P=0.00042 Heterogeneity not applicable
Mean maternal haemoglobin after delivery (g/dL) 1 trial (N=183)	11.55 ± 1.08 (92)	11.16 ± 1.42 (91)	0.39 [0.02, 0.76]	Favours IV iron + oral iron P=0.037 Heterogeneity not applicable
EXTERNAL VALIDITY				
Generalisability				
The review is applicable to pregnant women with a diagnosis of anaemia (Hg < 11g/dL) attributed to iron deficiency.				
Applicability				
Many of the trials were conducted in low-income countries, which may limit the review's applicability to an Australian context.				
Comments				
The authors note that in general, the included studies were small and methodologically poor, covering a very wide range of differing drugs, doses and routes of administration, making it difficult to pool data. The authors conclude that there is no evidence to suggest that, in otherwise healthy women, the benefits of treatment for mild anaemia in pregnancy will outweigh the adverse effects. There is no evidence that in women with iron deficiency anaemia, improvements in haematological indices translates into clinical improvements.				

Abbreviations: CI, confidence interval; ITT, intention-to-treat; MA, meta-analysis; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review.

[a] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

Level II evidence

STUDY DETAILS: RCT				
Citation				
Bhandal N and Russell R. (2006) Intravenous versus oral iron therapy for postpartum anaemia. *BJOG: An International Journal of Obstetrics and Gynaecology* 113:1248-1252.				
Affiliation/Source of funds				
No source of funds reported. The authors are affiliated with the Department of Anaesthesia, Nuffield Department of Anaesthetics, John Radcliffe Hospital, Oxford, UK.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Single centre, Oxford, UK	
Intervention	Comparator			
Intravenous ferrous sucrose (200mg, two doses given on days 2 and 4)	Oral ferrous sulphate (200mg twice daily for 6 weeks)			
Population characteristics				
Forty-four women with postpartum iron deficiency anaemia (haemoglobin < 9g/dL and ferritin < 15mcg/L at 24-48 hours post-delivery)				
Length of follow-up	Outcomes measured			
40 days	Haemoglobin, haematocrit, red cell indices, ferritin and serum iron levels			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Subjects were randomised using a computer-generated randomisation schedule using opaque, sealed envelopes. The groups did not differ at baseline in characteristics or laboratory data. Only one patient in the study was excluded due to secondary postpartum haemorrhage at home requiring re-admittance for a blood transfusion.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	22		21	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	Intervention (N=22)	Comparator (N=21)	Risk estimate (95% CI)	Statistical significance P-value
IV iron vs oral iron				
Laboratory measures				
	Mean ± SD	Mean ± SD		
Haemoglobin (g/dL) • Day 0 • Day 5 • Day 14 • Day 40	 7.3 ± 0.9 9.9 ± 0.7 11.1 ± 0.6 11.5 ± 1.3	 7.5 ± 0.8 7.9 ± 0.6 9.0 ± 0.4 11.2 ± 1.2	NR	Favours IV iron at days 5 and 14 P < 0.01
Ferritin (µg/L) • Day 0 • Day 5 • Day 14 • Day 40	 13.0 ± 3 48.0 ± 6 37.9 ± 5 42.2 ± 7	 11.0 ± 4 12.0 ± 2 16.0 ± 4 15.0 ± 3	NR	Favours IV iron at days 5, 14 and 40 P < 0.01 (days 5 and 14) P < 0.05 (day 40)

EXTERNAL VALIDITY
Generalisability
The study is generalisable to women with postpartum iron deficiency anaemia.
Applicability
The study was conducted in a single centre in the UK and should be applicable to an Australian context.
Comments
There were no serious adverse events reported in either study group. Compliance was reported as 100% and confirmed using pill counts.

Abbreviations: CI, confidence interval; ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: RCT				
Citation				
Breymann C, Gliga F, Bejenariu C, and Strizhova N. (2008) Comparative efficacy and safety of intravenous ferric carboxymaltose in the treatment of postpartum iron deficiency anemia. *International Journal of Gynecology and Obstetrics* 101:67-73.				
Affiliation/Source of funds				
The study was supported by an unrestricted scientific grant from Vifor international Inc. Switzerland.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Multicentre, Poland, Romania, Russian Federation	
Intervention	Comparator			
Intravenous iron carboxymaltose (up to three weekly doses of 1000mg maximum)	Oral ferrous sulphate (100mg twice daily for 12 weeks)			
Population characteristics				
Three hundred and forty-nine women with postpartum iron deficiency anaemia (haemoglobin ≤ 105g/L).				
Length of follow-up	Outcomes measured			
12 weeks	Haemoglobin, ferritin, transferrin saturation, number and proportion of patients who needed transfusions			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: The method of randomisation was not reported, nor was any attempt at allocation concealment documented. Stratification was by country and severity of anaemia. No differences between the groups were detected at baseline. The authors briefly mention a subgroup analysis which investigated the change in haemoglobin levels among patients with a baseline haemoglobin level of less than 105g/L. However, specific results are not given, with the authors simply stating that the results supported the validity of the main analysis.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	231		118	
Efficacy analysis (ITT)	227		117	
Efficacy analysis (PP)	179		89	
Safety analysis	227		117	
Outcome	Intervention (N=227)	Comparator (N=117)	Risk estimate (95% CI)	Statistical significance P-value
IV iron vs oral iron				
Transfusion incidence				
	n/N (%)	n/N (%)		
Transfusion incidence	1/227 (0.4%)	0 (0%)	NR	P=NR
Laboratory measures				
	n/N (%)	n/N (%)		
Haemoglobin (120-160g/L) • Week 2 • Week 4 • Week 12	95/179 (53.1%) 140/179 (78.2%) 152/179 (84.9%)	42/89 (47.2%) 63/89 (70.8%) 73/89 (82.0%)	NR NR NR	No significant difference (reported in text) P=NR (for all time periods)

Ferritin (50-800µg/L) • Week 2 • Week 4 • Week 12	 127/179 (70.9%) 150/179 (83.8%) 139/179 (77.7%)	 12/89 (13.5%) 15/89 (16.9%) 29/89 (32.6%)	 NR NR NR	Favours IV iron P < 0.0001 (for 2, 4 and 12 weeks)
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to women with postpartum iron deficiency anaemia.				
Applicability				
The study was conducted in multiple countries (Poland, Romania and the Russian Federation) and may be applicable to an Australian context.				
Comments				
The required dose of intravenous iron was calculated for each patient using the modified formula of Ganzoni. There were no treatment-related serious adverse events.				

Abbreviations: CI, confidence interval; ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: RCT				
Citation				
Giannoulis C, Daniilidis A, Tantanasis T, Dinas K, and Tzafettas J. (2009) Intravenous administration of iron sucrose for treating anemia in postpartum women. *Hippokratia* 13:38-40.				
Affiliation/Source of funds				
No source of funds reported. The authors are affiliated with the Second Department of Obstetrics and Gynecology Aristotle University of Thessaloniki, Hippokratio General Hospital.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Single centre, Greece.	
Intervention	Comparator			
IV iron sucrose (total amount 300mg in 3 days)	Oral iron (800mg iron proteinsuccinylate daily for 4 weeks)			
Population characteristics				
One hundred and four postpartum women with severe iron deficiency anaemia (haemoglobin < 8g/dL and ferritin < 10 µg/L).				
Length of follow-up	Outcomes measured			
5 weeks	Haemoglobin, ferritin, SGOT, SGPT blood levels and proteinuria			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: The method of randomisation was not reported, nor was any attempt at allocation concealment documented. The before treatment clinical values are presented in broad terms but the study is not explicit about similarity between the groups at baseline. In both study groups, a large number of participants were lost to follow-up, with 34% of the intervention group and 23% of the control group failing to attend follow-up appointments.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	78		26	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	52		20	
Safety analysis	NR		NR	
Outcome	Intervention (N=78)	Comparator (N=26)	Risk estimate (95% CI)	Statistical significance P-value
IV iron vs oral iron				
Laboratory measures				
	Mean ± SD	Mean ± SD		
Haemoglobin (g/dL) One week after treatment Four weeks after treatment	 8.8 ± NR 12.6 ± NR	 8.1 ± NR 10.3 ± NR	NR	P=NR
Increase in haemoglobin (g/dL)	4.6 ± 0.44	2.3 ± 0.47	NR	Favours IV iron P=0.0001
Ferritin (µg/L) One week after treatment Four weeks after treatment	 38 ± NR 115 ± NR	 19 ± NR 78 ± NR	NR	P=NR

Increase in ferritin (µg/L)	105 ± 11.1	68 ± 9	NR	Favours IV iron P=0.0004
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to women with severe iron deficiency anaemia postpartum.				
Applicability				
The study was conducted in a single centre in Greece and is probably applicable to an Australian context.				
Comments				

Abbreviations: CI, confidence interval; ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: RCT				
Citation				
Gupta A, Manaktala U, and Rathore AM. (2013) A Randomised Controlled Trial to Compare Intravenous Iron Sucrose and Oral Iron in Treatment of Iron Deficiency Anemia in Pregnancy. *Indian Journal of Hematology and Blood Transfusion*1-6.				
Affiliation/Source of funds				
No source of funds reported. The authors are affiliated with Maulana Azad Medical College, New Delhi, India.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Single centre, India	
Intervention	Comparator			
Intravenous iron sucrose (as per calculated dose) + mebendazole (100mg twice daily for 3 days)	Oral ferrous sulphate (200mg thrice daily for 4 weeks) + mebendazole (100mg twice daily for 3 days)			
Population characteristics				
One hundred pregnant women between 24 and 34 weeks gestation with anaemia (haemoglobin 7.0-9.0g/dL and serum ferritin < 15ng/mL)				
Length of follow-up	Outcomes measured			
4 weeks	Haemoglobin, serum ferritin, reticulocyte count rise, side effects and perinatal outcome			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Subjects were randomised using a randomisation table using opaque, numbered envelopes. Both of the study groups were comparable in terms of socio-demographic, clinical and baseline haematological parameters. No participants were lost to follow-up, nor were any excluded so this did not need to be accounted for in the analysis.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	50		50	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	Intervention (N=50)	Comparator (N=50)	Risk estimate (95% CI)	Statistical significance P-value
IV iron + mebendazole vs oral iron + mebendazole				
Transfusion incidence				
	n/N (%)	n/N (%)		
Transfusion incidence	0/50 (0%)	0/50 (0%)	NR	NA
Laboratory measures				
	Mean ± SD	Mean ± SD		
Haemoglobin (g/dL) at • 1 week • 2 weeks • 4 weeks • Delivery	 7.82 ± 0.42 8.39 ± 0.43 9.80 ± 0.46 11.50 ± 0.78	 7.89 ± 0.45 8.11 ± 0.45 9.18 ± 0.55 10.84 ± 1.12	NR	Favours IV iron (at 2 weeks, 4 weeks and delivery) P=0.42 P=0.002 P < 0.0001 P < 0.0001
Serum ferritin (ng/mL) at Week 4	37.45 ± 5.73	13.96 ± 1.88	NR	Favours IV iron P < 0.001

Cord blood haemoglobin in newborns (g/dL)	15.8 ± 0.7	15.6 ± 0.7	NR	No significant difference P=0.106
Serum ferritin in newborns (ng/mL)	155.77 ± 46.34	147.68 ± 39.05	NR	No significant difference P=0.347
Measures of fetal outcome				
	n/N (%)	n/N (%)		
Babies carried to term	45/50 (90%)	44/50 (88%)	NR	P=NR
	Mean ± SD	Mean ± SD		
Period of gestation (weeks)	38.48 ± 1.36	38.31 ± 1.47	NR	No significant difference (reported in text) P=NR
Birthweight (g)	2607 ± 253.28	2568 ± 244.19	NR	No significant difference (reported in text) P=NR
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to pregnant women with anaemia.				
Applicability				
The study was conducted in a single centre in India and may be applicable to an Australian context.				
Comments				
The required dose of intravenous iron was calculated for each patient using a specified formula.				

Abbreviations: CI, confidence interval; ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: RCT				
Citation				
Jain G, Palaria U, and Jha SK. (2013) Intravenous iron in postpartum anemia. *Journal of Obstetrics and Gynecology of India* 63:45-48.				
Affiliation/Source of funds				
No source of funds reported. The authors are affiliated with the Department of Obstetrics and Gynaecology, the Department of Anaesthesia and the Department of Preventative and Social Medicine, Government Medical College, Haldwani, Uttarakhand, India.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Single centre, India	
Intervention	Comparator			
Intravenous iron sucrose (300-600mg in two or three divided doses as per calculated dose)	Oral ferrous fumarate (300mg daily for 14 days)			
Population characteristics				
Forty-six women with postpartum anaemia (haemoglobin < 8g/dL within 48 hours postpartum)				
Length of follow-up	Outcomes measured			
14 days	Haemoglobin, adverse events			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Subjects were randomised using a computer-generated randomisation schedule and block randomisation but no attempt at allocation concealment was documented. The baseline characteristics of were similar in both study groups.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	23		23	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	Intervention (N=23)	Comparator (N=23)	Risk estimate (95% CI)	Statistical significance P-value
IV iron vs oral iron				
Laboratory measures				
	Mean ± SD	Mean ± SD		
Haemoglobin (g/dL) after • Day 7 • Day 14	 8.0 ± 0.4 9.1 ± 0.4	 7.2 ± 0.3 8.0 ± 0.3	NR	Favours IV iron P=0.001 P=0.001
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to women with postpartum anaemia.				
Applicability				
The study was conducted in a single centre in India and may be applicable to an Australian context.				
Comments				
The required dose of intravenous iron was calculated for each patient using a specified formula. No serious adverse events were reported in either study group.				

Abbreviations: CI, confidence interval; ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: RCT				
Citation				
Mumtaz A and Farooq F. (2011) Comparison for effects of intravenous versus oral iron therapy for postpartum anemia. *Pakistan Journal of Medical and Health Sciences* 5:116-120.				
Affiliation/Source of funds				
No source of funds reported. The authors are affiliated with the Obstetrics and Gynaecology Department of Alkhidmat Teaching Hospital Mansoorah Lahore, Pakistan.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Two hospitals in Pakistan	
Intervention	Comparator			
Intravenous ferrous sucrose (two doses of 200mg given on days 2 and 4)	Oral ferrous sulphate (200mg twice daily for 6 weeks)			
Population characteristics				
Eighty women with postpartum iron deficiency anaemia (haemoglobin < 9g/dL and ferritin < 15μg/L) at 24-48 hours post-delivery				
Length of follow-up	Outcomes measured			
40 days	Haemoglobin, haematocrit, red cell indices, serum ferritin and serum iron levels			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: The method of randomisation was not reported, nor was any attempt at allocation concealment documented. The before treatment clinical values are presented but the study is not explicit about similarity between the groups at baseline.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	40		40	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	Intervention (N=40)	Comparator (N=40)	Risk estimate (95% CI)	Statistical significance P-value
IV iron vs oral iron				
Laboratory measures				
	Mean ± SD	Mean ± SD		
Haemoglobin (g/dL) • Day 0 • Day 7 • Day 14 • Day 40	 8.4 ± NR 11.0 ± NR 11.4 ± NR 12.4 ± NR	 7.8 ± NR 8.3 ± NR 9.0 ± NR 11.8 ± NR	NR	No significant difference by day 40 (reported in text) P=NR
Ferritin (μg/L) • Day 0 • Day 7 • Day 14 • Day 40	 9.5 ± NR 46.5 ± NR 40.0 ± NR 43.5 ± NR	 9.7 ± NR 13.0 ± NR 18.0 ± NR 16.7 ± NR	NR	Favours IV iron (at day 7) P=NR
EXTERNAL VALIDITY				
Generalisability				

The study is generalisable to women with postpartum iron deficiency anaemia.
Applicability
The study was conducted in two hospitals in Pakistan and may be applicable to an Australian context.
Comments
Although the trial reports 80 patients participated in the study (with 40 randomised to each study group), the authors also note that originally 86 patients were recruited into the study but due to non-compliance and complications, six patients were excluded from the analysis. No serious adverse effects were reported in either study group.

Abbreviations: CI, confidence interval; ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: RCT				
Citation				
Seid MH, Derman RJ, Baker JB, Banach W, Goldberg C, and Rogers R. (2008) Ferric carboxymaltose injection in the treatment of postpartum iron deficiency anemia: a randomized controlled clinical trial. *American Journal of Obstetrics and Gynecology* 199:435.				
Affiliation/Source of funds				
The authors received research grants from American Regent Inc. to conduct this study and are currently receiving grants to conduct another study with the same product. None of the authors are current or former employees or consultants of American Regent Inc. None report owning stock or stock options in the company. None of the authors report having a financial interest in the product. Doctors Derman and Seid have served on the speaker's bureau for American Regent Inc. in the last year.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Multicentre, USA	
Intervention		Comparator		
Intravenous ferric carboxymaltose (100mg or less repeated weekly to a calculated replacement dose, maximum 2500mg)		Oral ferrous sulphate (325mg thrice daily for 6 weeks)		
Population characteristics				
Two hundred and ninety-one women with postpartum anaemia (ten days or less after delivery with haemoglobin ≤ 10g/dL)				
Length of follow-up		Outcomes measured		
42 days		Haemoglobin, ferritin, haematocrit, serum transferrin saturation and adverse events		
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Subjects were randomised using a centralised computer randomisation system but no attempt at allocation concealment is reported. There were no significant differences between treatment groups for any demographic or baseline characteristics.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	143		148	
Efficacy analysis (ITT)	143		148	
Efficacy analysis (PP)	138		144	
Safety analysis	142		147	
Outcome	Intervention (N=143)	Comparator (N=148)	Risk estimate (95% CI)	Statistical significance P-value
IV iron vs oral iron				
Laboratory measures				
	n/N (%)	n/N (%)		
Subjects achieving correction of anaemia by baseline haemoglobin • ≤8g/dL • 8.1-9.0g/dL • 9.1-10.0g/dL • ≥10.1g/dL	78.9% 90.5% 94.4% 100.0%	43.5% 59.2% 77.3% 88.9%	NR	Favours IV iron (for baseline haemoglobin ≤8g/dL, 8.1-9.0g/dL and 9.1-10.0g/dL P=0.0286 P=0.0008 P=0.0054 P=0.1000
	Mean ± SD	Mean ± SD		

Haemoglobin (g/dL) change from baseline to day 42	4.0 ± 1.06	3.4 ± 1.09	NR	Favours IV iron P < 0.0001
Haematocrit (%) change from baseline to day 42	10.9 ± 3.53	9.5 ± 3.70	NR	Favours IV iron P=0.0014
Ferritin (ng/mL) change from baseline to day 42	225.9 ± 117.96	2.7 ± 20.36	NR	Favours IV iron P < 0.0001
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to women with postpartum anaemia.				
Applicability				
The study was conducted at multiple centres in the USA and should be applicable to an Australian context.				
Comments				
The required dose of intravenous iron was calculated for each patient using a modified Ganzoni formula.				

Abbreviations: CI, confidence interval; ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: RCT				
Citation				
Van Wyck DB, Martens MG, Seid MH, Baker JB, and Mangione A. (2007) Intravenous ferric carboxymaltose compared with oral iron in the treatment of postpartum anemia: A randomized controlled trial. *Obstetrics and Gynecology* 110:267-278.				
Affiliation/Source of funds				
Dr Van Wyck is a consultant and serves as a speaker for American Regent Inc, a division of Luitpold Pharmaceuticals, Shirley, NY. He is also an investigator for a grant supported by American Regent Inc. and serves on the speaker's bureau for Amgen, Thousand Oaks, CA and Ortho Biotech, Bridgewater, NJ. Dr Martens, Dr Baker and Dr Seid have served as research investigators for Luitpold Pharmaceuticals. Dr Martens and Dr Seid also serve on the American Regent speaker's bureau. Dr Mangione is an employee of Luitpold Pharmaceuticals.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Multicentre, USA, Mexico	
Intervention		Comparator		
Intravenous ferric carboxymaltose (≤1000mg repeated weekly to achieve total calculated replacement dose)		Oral ferrous sulfate (325mg thrice daily for 6 weeks)		
Population characteristics				
Three hundred and sixty-one women with postpartum anaemia (within 10 days postpartum, haemoglobin ≤ 10g/dL).				
Length of follow-up		Outcomes measured		
42 days		Haemoglobin, ferritin, transferrin saturation, reticulocyte count or reticulocyte haemoglobin content, number of patients requiring intervention, time to intervention, proportion of patients with improved quality of life and adverse events.		
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Subjects were randomised using a computerised random number generation, blocked randomisation and an interactive voice response system but no attempt at allocation concealment was documented. There were no significant differences at baseline between the groups in demographic descriptors, iron status or severity of anaemia.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	182		179	
Efficacy analysis (ITT)	168		169	
Efficacy analysis (PP)	NR		NR	
Safety analysis	174		178	
Outcome	Intervention (N=182)	Comparator (N=179)	Risk estimate (95% CI)	Statistical significance P-value

IV iron vs oral iron				
Transfusion incidence				
	n/N (%)	n/N (%)		
Transfusion incidence	0/182 (0%)	0/179 (0%)	NR	NA
Laboratory measures				
	Mean ± SD	Mean ± SD		
Subjects achieving haemoglobin ≥ 12.0g/dL by baseline haemoglobin • Overall • <8.1g/dL • 8.1-9.0g/dL • 9.1-10.0g/dL • > 10.0g/dL	~ 90% ± NR ~ 85% ± NR ~ 85% ± NR ~ 95% ± NR ~ 95% ± NR	~ 70% ± NR ~ 45% ± NR ~ 55% ± NR ~ 75% ± NR ~ 90% ± NR	NR	Favours IV iron (for baseline haemoglobin overall, <8.1g/dL, 8.1-9.0g/dL and 9.1-10.0g/dL) P < 0.01 P < 0.05 P < 0.05 P < 0.01 P=NR
Change in haemoglobin (g/dL) • 7 days • 14 days • 28 days • 42 days after initiating treatment	~ 2.25 ± NR ~ 3 ± NR ~ 3.75 ± NR ~ 4.25 ± NR	~ 1.75 ± NR ~ 2.5 ± NR ~ 3 ± NR ~ 3.25 ± NR	NR	Favours IV iron (after 7, 14, 28 and 42 days) P < 0.01 P < 0.001 P < 0.001 P < 0.001
Change in haematocrit (%) • 7 days • 14 days • 28 days • 42 days after initiating treatment	~ 6.5 ± NR ~ 9 ± NR ~ 10.5 ± NR ~ 11 ± NR	~ 5.5 ± NR ~ 7.5 ± NR ~ 9.5 ± NR ~ 9.5 ± NR	NR	Favours IV iron (after 7, 14, 28 and 42 days) P < 0.05 P < 0.001 P < 0.001 P < 0.001
Change in Ferritin (ng/mL) • 7 days • 14 days • 28 days • 42 days after initiating treatment	~ 550 ± NR ~ 550 ± NR ~ 300 ± NR ~ 200 ± NR	~ 0 ± NR ~ 0 ± NR ~ 0 ± NR ~ 0 ± NR	NR	Favours IV iron (after 7, 14, 28 and 42 days) P < 0.001 P < 0.001 P < 0.001 P < 0.001
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to women with postpartum anaemia.				
Applicability				
The study was conducted at multiple centres n the USA and Mexico and may be applicable to an Australian context.				
Comments				
The required dose of intravenous iron was calculated for each patient using the modified Ganzoni formula. No serious drug-related adverse events occurred in either treatment group.				

Abbreviations: CI, confidence interval; ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: RCT				
Citation				
Verma S, Inamdar SA, and Malhotra N. (2011) Intravenous iron therapy versus oral iron in postpartum patients in rural area. *Journal of SAFOG* 3:67-70.				
Affiliation/Source of funds				
No source of funds reported. The authors are affiliated with the Department of Obstetrics and Gynecology, JN Medical College and AVBR Hospital, Wardha, Maharashtra, India.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Single centre, India	
Intervention	Comparator			
Intravenous iron sucrose (three divided doses of 200mg each)	Oral ferrous sulphate (200mg twice daily for one month)			
Population characteristics				
One hundred and fifty women with postpartum iron deficiency anaemia (haemoglobin < 8g/dL) 24 hours after delivery				
Length of follow-up	Outcomes measured			
30 days	Haemoglobin levels, patient satisfaction, quality of life, impact on cost and hospital stay, impact on blood transfusion frequency, impact on stress, depression and cognitive function and impact on breast feeding.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: The method of randomisation was not reported, nor was any attempt at allocation concealment documented. The before treatment clinical values are presented but the study is not explicit about similarity between the groups at baseline. Loss to follow-up is not reported by the authors.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	75		75	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	Intervention (N=75)	Comparator (N=75)	Risk estimate (95% CI)	Statistical significance P-value
IV iron vs oral iron				
Laboratory measures				
	Mean ± SD	Mean ± SD		
Haemoglobin (g/dL) • Day 1 • Day 7 • Day 15 • Day 30	 7.58 ± NR 9.8 ± NR 10.2 ± NR 11.5 ± NR	 7.42 ± NR 7.5 ± NR 8.2 ± NR 10.09 ± NR	NR	Favours IV iron (at day 7) P < 0.05[a]
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to women with postpartum iron deficiency anaemia.				
Applicability				
The study was conducted in a single centre in India and may be applicable to an Australian context.				

Comments
In the intravenous group, two patients suffered serious adverse events (phlebitis and anaphylaxis). The authors note that compliance in the oral iron group was poor in the study, possibly explained by the rural location of the subjects, with the discussion proposing literacy levels and socioeconomic status as relevant factors. No mention of blood transfusion frequency.

Abbreviations: CI, confidence interval; ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.
a. The article reported a significant effect favouring IV iron at day 7, however the data reported in the text does not match that reported in Figure 2. The author was contacted 18 March 2014, but no response received at time of publication.

STUDY DETAILS: RCT				
Citation				
Neeru S, Nair N S, Rai L. Iron Sucrose Versus Oral Iron Therapy in Pregnancy Anemia. Indian J Community Med 2012;37:214-8.				
Affiliation/Source of funds				
No source of funds reported. The authors are affiliated with				
Study design	Level of evidence		Location/setting	
RCT	Level II		Single centre, India	
Intervention	Comparator			
Intravenous iron sucrose (as per calculated dose) followed by ferrous fumarate	Oral ferrous fumarate (300mg)			
Population characteristics				
One hundred pregnant women, from 14 to 36 weeks gestation, with established iron deficiency anaemia (haemoglobin level 6.5-10.9 g/dL and ferritin levels less than 27ng/dL)				
Length of follow-up	Outcomes measured			
One month	Haemoglobin, ferritin, side effects			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: Subjects were randomised using block randomisation but no reference was made to any attempt at allocation concealment. Baseline demographics were similar at baseline between the groups. However, the intervention group had lower haemoglobin levels, red cell indices and a lower serum iron profile than the control group. The authors dealt with this potential confounder by calculating percentage increases from repeat lab parameters.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	50		50	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	45		44	
Safety analysis	NR		NR	
Outcome	Intervention (N=50)	Comparator (N=50)	Risk estimate (95% CI)	Statistical significance P-value
IV iron + oral iron vs oral iron				
Transfusion incidence				
	n/N (%)	n/N (%)		
Blood transfusion	4/50 (8.0%)	NR	NR	P=NR
	n/N (%)	n/N (%)		
Patients achieving target haemoglobin of 11g/dL after one month of treatment	NR (66%)	NR (61%)	NR	No significant different (reported in text) P=NR
Laboratory measures				
	Mean ± SD	Mean ± SD		
Change in haemoglobin (%)	23.62 ± 14.95	14.11 ± 10.66	NR	Favours IV iron + oral iron P=0.001

Change in ferritin (%)	2032.54 ± 1974.43	180.69 ± 308.39	NR	Favours IV iron + oral iron P=0.000
Haemoglobin (g/dL) after treatment	11.24 ± 0.70	11.06 ± 0.63	NR	No significant difference P=0.206 *haemoglobin levels significantly different at baseline between groups
Ferritin after treatment (ng/dL) after treatment	139.93 ± 122.13	27.33 ± 14.96	NR	Favours IV iron + oral iron P=0.000 *ferritin levels significantly different at baseline between groups
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to pregnant women with iron deficiency anaemia.				
Applicability				
The study was conducted in a single centre in India and may be applicable to an Australian context.				
Comments				
The required dose of intravenous iron was calculated for each patient using a specified formula. The authors note that one patient in the intervention group changed to the control group due to giddiness after the first injection of intravenous iron. There were no cases of severe anaphylactic reactions reported in the study.				

Abbreviations: CI, confidence interval; ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: RCT				
Citation				
Westad S, Backe B, Salvesen KA, Nakling J, Okland I, Borthen I, Rognerud Jensen OH, Kolas T, Lokvik B, and Smedvig E. (2008) A 12-week randomised study comparing intravenous iron sucrose versus oral ferrous sulphate for treatment of postpartum anemia. *Acta Obstetricia et Gynecologica Scandinavica* 87:916-923.				
Affiliation/Source of funds				
The authors report no conflicts of interest. This was a researcher initiated trial sponsored by Renapharma AB, the Swedish representative of the manufacturer of iron sucrose. The sponsor had no influence on the conduct of the study nor on analysis of the data, or the writing of this paper.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Multicentre, Norway	
Intervention		Comparator		
Intravenous iron sucrose (600mg, administered as a daily infusion of 200mg) followed by iron sulphate (100mg twice daily from week 5)		Oral iron sulphate (100mg twice daily)		
Population characteristics				
One hundred and twenty-nine women with postpartum haemorrhagic anaemia (haemoglobin 6.5g/100mL-8.5g/100mL and within 48 hours of delivery).				
Length of follow-up		Outcomes measured		
12 weeks		Haemoglobin, ferritin and quality of life		
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Subjects were randomised according to the minimisation method, with central randomisation performed via the internet but no attempt at allocation concealment is documented. Baseline characteristics are presented but the study is not explicit about similarity between the groups.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	58		70	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	45		48	
Safety analysis	NR		NR	
Outcome	Intervention (N=59)	Comparator (N=70)	Risk estimate (95% CI)	Statistical significance P-value
IV iron + oral iron vs oral iron				
Transfusion incidence				
	n/N (%)	n/N (%)		
Transfusion incidence	4/58 (6.9%)	10/70 (14.3%)	NR	No significant difference P=0.18
Laboratory measures				
	Mean ± SD	Mean ± SD		
Haemoglobin (g/L) levels at • Week 4 • Week 8 • Week 12	 ~ 115 ± NR ~ 128 ± NR ~ 130 ± NR (data from graph)	 ~ 115 ± NR ~ 125 ± NR ~ 125 ± NR (data from graph)	NR	No significant difference P=0.89 P=0.13 P=0.11 [reported in text]

Ferritin (µg/L) levels at • Week 4 • Week 8 • Week 12	~ 40 ± NR ~ 32 ± NR ~ 35 ± NR	~ 25 ± NR ~ 30 ± NR ~ 34 ± NR	NR	Favours IV iron + oral iron (at week 4 only) P < 0.001 P=NR P=NR
Haemoglobin (g/100mL) increase after 4 weeks	4.0 ± NR	4.6 ± NR	NR	No significant difference P=0.89
Ferritin (µg/L) increase after 4 weeks	13.7 ± 24.4	4.2 ± 15.5	NR	Favours IV iron P < 0.001
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to women with postpartum anaemia.				
Applicability				
The study was conducted at multiple centres in Norway and should be generalisable to an Australian context.				
Comments				
The authors note that compliance in the oral group was generally poor. A subgroup analysis was carried out, focusing on the 113 patients who did not receive a blood transfusion. At four weeks the mean haemoglobin was not significantly different but after eight and twelve weeks, women in the intravenous group had significantly higher mean haemoglobin levels than those in the oral group (P=0.02). The authors suggest that the different use of blood transfusions may represent a confounder in the study.				

Abbreviations: ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: RCT				
Citation				
Deeba S, Purandare SV, and Sathe AV. (2012) Iron deficiency anemia in pregnancy: Intravenous versus oral route. *Journal of Obstetrics and Gynecology of India* 62:317-321.				
Affiliation/Source of funds				
No source of funds reported. The authors are affiliated with the Department of Obstetrics and Gynecology, K. J. Somaiya Medical College and Research Centre, Somaiya Ayurvihar, Eastern Express Highway, Near Everard Nagar, Sion, Mumbai, India				
Study design	Level of evidence		Location/setting	
RCT	Level II		Single centre, India	
Intervention		Comparator		
Intravenous iron sucrose (as per calculated dose)		Oral ferrous ascorbate (200mg daily with 1.1mg of folic acid)		
Population characteristics				
Two hundred pregnant women between 28 and 37 weeks gestation with established iron deficiency anaemia (haemoglobin levels 6-10g/dL and serum ferritin < 15ng/mL).				
Length of follow-up		Outcomes measured		
Six weeks		Haemoglobin, serum ferritin, adverse events		
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Subjects were randomised using a computer-generated randomisation schedule using numbered, sealed opaque envelopes. Baseline demographic and clinical characteristics were similar between the groups. No participants were lost to follow-up, nor were there any dropouts so this did not need to be accounted for in the analysis.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	100		100	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	Intervention (N=100)	Comparator (N=100)	Risk estimate (95% CI)	Statistical significance P-value
IV iron vs oral iron + folic acid				
Laboratory measures				
	Mean ± SD	Mean ± SD		
Haemoglobin (g/dL) after • 2 weeks • 4 weeks • 6 weeks	 9.63 ± 0.885 10.09 ± 0.8072 10.79 ± 0.8432	 8.5 ± 0.862 9.32 ± 0.8707 9.903 ± 0.8848	NR	Favours IV iron (after 2, 4 and 6 weeks) P=0.000* P=0.000* P=0.000* *All P-values cited as highly significant
Ferritin levels (ng/mL) after • 2 weeks • 4 weeks • 6 weeks	 48.46 ± 16.66 61.05 ± 19.662 86.98 ± 19.939	 16.65 ± 4.87 23.36 ± 8.570 34.78 ± 8.793	NR	Favours IV iron (after 2, 4 and 6 weeks) P=0.000* P=0.000* P=0.000* *All P-values cited as highly significant

EXTERNAL VALIDITY
Generalisability
The study is generalisable to pregnant women with iron deficiency anaemia.
Applicability
The study was conducted in a single centre in India and may be applicable to an Australian context.
Comments
The required dose of intravenous iron was calculated for each patient using a specified formula. There were no serious adverse drug reactions recorded.

Abbreviations: ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: RCT					
Citation					
Bencaiova G, von Mandach U, and Zimmermann R. (2009) Iron prophylaxis in pregnancy: Intravenous route versus oral route. *European Journal of Obstetrics Gynecology and Reproductive Biology* 144:135-139.					
Affiliation/Source of funds					
No source of funds reported. The authors are affiliated with the Department of Obstetrics and Gynaecology, Institute of Obstetric Research, Zurich University Hospital, Switzerland.					
Study design	Level of evidence		Location/setting		
RCT	Level II		Single centre, Switzerland		
Intervention	Comparator				
Intravenous iron sucrose (either two or three 200mg doses) + folic acid given between weeks 20-24, 28-32, and 35-37 of gestation	Oral ferrous sulphate (80mg daily) + folic acid, daily				
Population characteristics					
Two hundred and sixty non-anaemic (haemoglobin ≥ 10.5g/dL) pregnant women between the 15th and 20th week of gestation (single)					
Length of follow-up	Outcomes measured				
NR	Haemoglobin, ferritin levels, gestational age at birth, birthweight, blood loss, transfusion requirements, anaemic treatment requirements in/after pregnancy and length of hospitalisation after delivery				
INTERNAL VALIDITY					
Overall quality assessment (descriptive)					
Rating: Fair Description: Subjects were randomised using a computer-generated randomisation schedule using opaque envelopes. There was no difference between the groups at baseline according to age, gravidity, parity, BMI and blood pressure. Subjects and investigators were not blinded to treatment. Efficacy analysis was on intent-to-treat population. IV prophylaxis was increased to three doses after interim analysis. Subgroup analyses were performed to compare the two different doses of intravenous iron used.					
RESULTS					
Population analysed	Intervention		Comparator		
Randomised	130 (75 received two doses, 55 received three doses)		130		
Efficacy analysis (ITT)	130		130		
Efficacy analysis (PP)	110 (61 received two doses, 49 received three doses)		119		
Safety analysis	NR		NR		
Outcome	Intervention (N=130)		Comparator (N=130)	Risk estimate (95% CI)	Statistical significance P-value
	Two doses	Three doses			

IV iron + folic acid vs oral iron + folic acid					
Transfusion incidence					
	n/N (%)	n/N (%)	n/N (%)		
Transfusion requirement	1/61 (1.6%)	0/49 (0%)	1/119 (0.8%)	NR	No significant difference P=1.00
Laboratory measures					
	Mean ± SD		Mean ± SD		
Haemoglobin before delivery (g/dL)	12.2 ± 0.9		12.4 ± 1.1	NR	No significant difference P=0.110
Haematocrit before delivery (%)	35.2 ± 2.1		35.6 ± 3.1	NR	No significant difference P=0.222
Haemoglobin at day two after delivery (g/dL)	10.6 ± 1.8	11.1 ± 1.3	11.0 ± 1.6	NR	No significant difference P=0.300
	Median (range)		Median (range)		
Ferritin before delivery (µg/L)	50 (4-266)		21 (4-82)	NR	Favours IV iron P < 0.001
Measures of fetal outcome					
	n/N (%)	n/N (%)	n/N (%)		
Gestational age at delivery (< 37 weeks)	1/61 (1.6%)	4/49 (8.2%)	4/119 (3.4%)	NR	No significant difference P=0.741
	Mean ± SD		Mean ± SD		
Birthweight (g)	3325 ± 482	3178 ± 705	3361 ± 567	NR	No significant difference P=0.131
Gestational age at delivery (weeks)	40 ± 2	39 ± 3	40 ± 2	NR	P=0.035
EXTERNAL VALIDITY					
Generalisability					
The study is generalisable to non-anaemic pregnant women.					
Applicability					
The study was conducted in a single centre in Switzerland and should be applicable to an Australian context. Authors note that the dose of elemental iron given (80 mg/day) is lower than that recommended to prevent deficiency of iron (120 mg/day), but was matched to that given in Switzerland for iron prophylaxis (80-100mg iron in a tablet).					
Comments					
There were fourteen cases of serious adverse events in the intravenous iron group and seven cases in the oral iron group but the difference was not statistically significant. The authors concluded there was no clinically significant benefit for the parenteral route in iron prophylaxis of anaemia.					

Abbreviations: CI, confidence interval; ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: RCT				
Citation				
Froessler B, Cocchiaro C, Saadat-Gilani K, Hodyl N, and Dekker G. (2013) Intravenous iron sucrose versus oral iron ferrous sulfate for antenatal and postpartum iron deficiency anemia: A randomized trial. *Journal of Maternal-Fetal and Neonatal Medicine* 26:654-659.				
Affiliation/Source of funds				
The authors report no declarations of interest. The authors are affiliated with the Department of Anaesthesia and Department of Obstetrics and Gynaecology, Lyell McEwin Hospital, Elizabeth Vale, South Australia, Australia, Discipline of Acute Care Medicine and Discipline of Obstetrics and Gynaecology, The University of Adelaide, South Australia, Australia and The Robinson Institute.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Single centre, South Australia, Australia	
Intervention	Comparator			
Intravenous iron sucrose (400mg divided into two 200mg doses) + folic acid 600µg until delivery	Two FGF tablets (ferrous sulfate 250mg with folic acid 600µg) daily until delivery or for six weeks following delivery			
Population characteristics				
Two hundred and seventy-one women (148 pregnant women and 123 women post lower segment caesarean section) with iron deficiency anaemia (haemoglobin < 110g/L and ferritin < 12µg/L).				
Length of follow-up	Outcomes measured			
42 days after delivery	Haemoglobin, ferritin, transfusion of red blood cells and adverse drug reactions.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Subjects were randomised using a telephone service but no reference was made to any attempt at allocation concealment. Data were analysed by a statistician blinded to treatment group. Both age and BMI were similar in the women recruited antenatally and during the postpartum period but the study is not explicit about similarity across the groups at baseline. The authors note that the main limitations of the study were the dropout rate and loss to follow-up.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	137		134	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	100		94	
Safety analysis	NR		NR	
Outcome	Intervention (N=137)	Comparator (N=134)	Risk estimate (95% CI)	Statistical significance P-value
IV iron + folic acid vs oral iron + folic acid				
	n/N (%)	n/N (%)		
Transfusion incidence				
Red blood cell transfusion Antenatal group Postnatal group	 NR (0.8%) NR (0.0%)	 NR (3.0%) NR (2.2%)	NR	No significant difference (reported in text) P=NR
Laboratory measures				
	Median (IQR)	Median (IQR)		

Haemoglobin (g/dL) post-delivery • Day 1 • Day 14 • Day 42	99 (90-108) 119 (112-130) 126 (117-133)	98 (91-108) 122 (113-133) 127 (120-132)	NR	No significant difference at any point P=0.7 P=0.4 P=0.9
Ferritin (µg/L) post-delivery • Day 1 • Day 14 • Day 42	21 (13-38) 71 (26-120) 31 (16-62)	21 (13-33) 38 (20-54) 28 (14-54)	NR	Favours IV iron + folic acid (at day 14) P=0.4 P=0.004 P=0.3
Haemoglobin (g/dL) post-delivery (antenatal cohort) • Day 1 • Day 14 • Day 42	101 (90-113) 128 (117-135) 127 (116-134)	107 (93-115) 129 (122-140) 127 (122-132)	NR	No significant difference at any point P=0.2 P=0.4 P=0.9
Ferritin (µg/L) post-delivery (antenatal cohort) • Day 1 • Day 14 • Day 42	33 (15-52) 39 (22-83) 27 (16-59)	21 (14-33) 40 (16-65) 41 (16-73)	NR	No significant difference at any point P=0.06 P=0.4 P=0.4
Haemoglobin (g/dL) post-delivery (postnatal cohort) • Day 14 • Day 42	115 (107-123) 124 (118-132)	118 (110-127) 127 (120-132)	NR	No significant difference at any point P=0.2 P=0.7
Ferritin (µg/L) post-delivery (postnatal cohort) • Day 14 • Day 42	101 (82-141) 46 (24-64)	37 (24-52) 19 (13-33)	NR	Favours IV iron + folic acid (at days 14 and 42) P < 0.001 P=0.01
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to women with iron deficiency anaemia (both pregnant and postpartum).				
Applicability				
The study was conducted in a single centre in Australia and is directly applicable to the Australian context.				
Comments				
The authors note only one serious adverse event, which was later concluded to be unrelated to the treatment as it had occurred on a previous occasion.				

Abbreviations: CI, confidence interval; ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: RCT				
Citation				
Kochhar PK, Kaundal A, and Ghosh P. (2013) Intravenous iron sucrose versus oral iron in treatment of iron deficiency anemia in pregnancy: A randomized clinical trial. *Journal of Obstetrics and Gynaecology Research* 39:504-510.				
Affiliation/Source of funds				
The authors state there were no potential conflicts of interest, whether of a financial or other nature. No financial arrangements were made with any company/. There were no commercial affiliations. The authors are affiliated with the Department of Obstetrics and Gynaecology, Lady Harding Medical College and Smt. Sucheta Kriplani Hospital and the Department of Obstetrics and Gynaecology, Maulana Azad Medical College and Lok Nayak Hospital, New Delhi, India.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Two hospitals in India	
Intervention		Comparator		
Intravenous iron sucrose (divided doses of 200mg each) + mebendazole (100mg twice daily for three days) and folic acid (5mg daily)		Oral ferrous sulphate (200mg, three times a day for 4 weeks) + mebendazole (100mg twice daily for three days) and folic acid (5mg daily)		
Population characteristics				
One hundred women between 24-34 weeks of gestation, with moderate iron deficiency anaemia (haemoglobin 7.0-9.0g/dL, ferritin level < 15ng/mL).				
Length of follow-up		Outcomes measured		
Four weeks		Haemoglobin, red blood cell indices, reticulocytes, ferritin, side effects and neonatal outcome (gestational age at delivery, birthweight, Apgar score at birth), requirement of blood transfusion.		
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Subjects were randomised using a randomisation table but no attempt at allocation concealment is reported. The study groups were comparable in terms of demographic, biologic and haematologic parameters at baseline.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	50		50	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	49		49	
Safety analysis	NR		NR	
Outcome	Intervention (N=50)	Comparator (N=50)	Risk estimate (95% CI)	Statistical significance P-value
IV iron + mebendazole and folic acid vs oral iron + mebendazole and folic acid				
Transfusion incidence				
	n/N (%)	n/N (%)		
Transfusion incidence	0 (0%)	1/49 (2.0%)	NR	P=NR
Laboratory measures				
	Mean ± SD	Mean ± SD		
Haemoglobin (g/dL) • Day 7 • Day 14 • Day 21 • Day 30	 8.8 ± 0.6 9.7 ± 0.8 10.9 ± 0.8 12.8 ± 1.1	 8.4 ± 0.8 8.9 ± 0.6 9.6 ± 0.9 10.7 ± 0.7	NR	Favours IV iron + mebendazole and folic acid (at days 21 and 30 and at delivery) P=0.009 (at day 21) P=0.002 (at day 30)

• At delivery	13.4 ± 0.9	11.2 ± 0.9		P=0.002 (at delivery)
Ferritin (ng/mL) • Day 7 • Day 30 • At delivery	 36.5 ± 8.7 104 ± 13.4 128.8 ± 15.8	 22.8 ± 9.8 77.6 ± 13.7 94.6 ± 14.2	NR	Favours IV iron + mebendazole and folic acid (at day 30 and at delivery) P=0.005 (at day 30) P=0.001 (at delivery)
Measures of fetal outcome				
	Mean ± SD	Mean ± SD		
Gestational age (weeks)	38 ± 1	37 ± 2	NR	No significant difference P=NR
Birthweight (g)	2870 ± 680	2695 ± 765	NR	No significant difference P=NR
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to pregnant women with moderate iron deficiency anaemia.				
Applicability				
The study was conducted in two hospitals in India and may be applicable to an Australian context.				
Comments				
The authors note that compliance in the oral group was good. The required dose of intravenous iron was calculated for each patient using a specified formula, administered in divided doses.				

Abbreviations: CI, confidence interval; ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: RCT				
Citation				
Singh S, Singh S, and Singh PK. (2013) A study to compare the efficacy and safety of intravenous iron sucrose and intramuscular iron sorbitol therapy for anemia during pregnancy. *Journal of Obstetrics and Gynecology of India* 63:18-21.				
Affiliation/Source of funds				
No source of funds reported. The authors are affiliated with the Department of Obstetrics and Gynaecology and the Department of Ophthalmology, S. N. Medical College, India				
Study design	Level of evidence		Location/setting	
RCT	Level II		Single centre, India	
Intervention	Comparator			
Intravenous iron sucrose (divided into 150mg doses every third day up to calculated dose)	Intramuscular iron sorbitol (as per calculated dose)			
Population characteristics				
One hundred pregnant women of gestational age 14-32 weeks with haemoglobin ≤ 8g/dL.				
Length of follow-up	Outcomes measured			
4 weeks	Haemoglobin and adverse effects			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: The method of randomisation was not reported, nor was any attempt at allocation concealment documented. Both the groups were comparable for age, parity, socioeconomic status and period of gestation. There is no information on the statistical methods used to analyse the data.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	50		50	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	Intervention (N=50)	Comparator (N=50)	Risk estimate (95% CI)	Statistical significance P-value
IV iron vs IM iron				
Laboratory measures				
	n/N (%)	n/N (%)		
Haemoglobin level (g/dL) after 2 weeks • 5-7 • 7.1-9 • 9.1-11 • > 11	 7/50 (14%) 16/50 (32%) 27/50 (54%) -	 12/50 (24%) 33/50 (66%) 5/50 (10%) -	NR	P=NR
Haemoglobin level (g/dL) after 4 weeks • 5-7 • 7.1-9 • 9.1-11 • > 11	 - 9/50 (18%) 39/50 (78%) 2/50 (4%)	 5/50 (10%) 21/50 (42%) 24/50 (48%) -	NR	P=NR
	Mean ± SD	Mean ± SD		

Haemoglobin (g/dL) after • 2 weeks of therapy • 4 weeks of therapy	8.79 ± NR 10.01 ± NR	7.74 ± NR 8.81 ± NR	NR	Favours IV iron P < 0.01 P < 0.01
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to pregnant women with anaemia.				
Applicability				
The study was conducted in a single centre in India and may be applicable to an Australian context.				
Comments				
The required dose of intravenous and intramuscular iron was calculated for each patient using a specified formula. There were no severe adverse effects in either study group.				

Abbreviations: CI, confidence interval; ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: RCT				
Citation				
Hashmi Z, Bashir G, Azeem P, and Shah S. (2006) Effectiveness of intra-venous iron sucrose complex versus intra-muscular iron sorbitol in iron deficiency anemia. *Annals of Pakistan Institute of Medical Sciences* 2:188-191.				
Affiliation/Source of funds				
No source of funds reported. The authors are affiliated with Gomal Medical College and Hashmi Maternity Clinic, Dera Ismail Khan, Pakistan.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Single centre, Pakistan	
Intervention	Comparator			
Intravenous iron sucrose (divided into 200mg doses as per total calculated dose)	Intramuscular iron sorbitol (as recommended for each patient, 75mg daily or alternate days) followed by oral supplements until delivery (75mg)			
Population characteristics				
One hundred women (eighty with gestational age 12-36 weeks from antenatal clinics and twenty after postpartum haemorrhage) presenting with iron deficiency anaemia (haemoglobin < 10g/dL)				
Length of follow-up	Outcomes measured			
Six weeks	Haemoglobin, blood transfusion requirements			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: The method of randomisation was not reported, nor was any attempt at allocation concealment documented. Baseline characteristics are presented but the study is not explicit about similarity between the groups. There is no information on the statistical methods used to analyse the data.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	50		50	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	Intervention (N=50)	Comparator (N=50)	Risk estimate (95% CI)	Statistical significance P-value
IV iron vs IM iron + oral iron				
Transfusion incidence				
	n/N (%)	n/N (%)		
Transfusion incidence	0/50 (0%)	0/50 (0%)	NR	NA
Laboratory measures				
	n/N (%)	n/N (%)		
Target haemoglobin achieved	80%	20%	NR	Favours IV iron P < 0.05
	Mean ± SD	Mean ± SD		
Post therapy haemoglobin (g/dL) at mean interval of 3.6 weeks	9.9 ± 0.7	9.1 ± 0.6	NR	P=NR

Initial rise in haemoglobin (g/dL)	2.6 ± 0.9	1.2 ± 0.8	NR	P=NR
Post therapy final haemoglobin (g/dL)	12.1 ± 0.9	10.1 ± 1.4	NR	P=NR
Final rise of haemoglobin at delivery	4.6 ± 0.3	2.2 ± 0.5	NR	P=NR
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to pregnant women and those with iron deficiency anaemia following postpartum haemorrhage.				
Applicability				
The study was conducted in a single centre in Pakistan and may be applicable to an Australian context.				
Comments				

Abbreviations: CI, confidence interval; ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

Level III evidence

STUDY DETAILS: cohort/case-control				
Citation McCaw-Binns, A., Greenwood, R., Ashley, D., and Golding, J. (1994) Antenatal and perinatal care in Jamaica: Do they reduce perinatal death rates? PAEDIATR.PERINAT.EPIDEMIOL. 8 (SUPPL. 1) 86-97.				
Affiliation/Source of funds				
The study was funded by the International Development Research Centre of Canada. The statistical analyses were supported by the Science and Technology for Development Programme of the Commission of the European Community Contract No. TS2-0041-UK.				
Study design	Level of evidence		Location/setting	
Case-control	Level III-2		Jamaica	
Intervention	Comparator			
Iron	No treatment			
Population characteristics				
94% of all mothers delivering in Jamaica over a two month period in 1986 (September and October) (9919 singleton pregnancies). Data on all stillbirths (weighing 500g or more) and live births dying within seven days of birth occurring in Jamaica over a 12 month period (1 September 1986 to 31 August 1987) was also collected to serve as a control group (1847 singleton perinatal deaths).				
Length of follow-up	Outcomes measured			
12 months (cases) and 2 months (controls)	Perinatal deaths (antepartum fetal deaths (APFD), deaths of live births due to immaturity (IMMAT), deaths from intrapartum asphyxia (IPA) and all perinatal deaths combined (all PND)) compared to babies who survived the first week of life (SURV).			
Method of analysis				
Comparison between the cases and controls (deaths and survivors) used chi-squared tests, with continuity correction for 2 x 2 tables. When appropriate, the Mantel-Haenszel trend test was computed using the statistical software package SPSS. Logistic regression analysis was undertaken in three steps and used the BMDP package. First, the medical factors (medical conditions comprising four care variables) were offered to models already involving the exposure variable. Second, the environmental, social and behavioural variables were taken into consideration and finally, gestation (grouped as < 33, 33-36, 37 + weeks) was taken into account. Effects of commencement of antenatal care, iron supplementation, folic acid, and type of perinatal care were examined, regardless of whether or not the unadjusted relationships were statistically significant.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: The study was able to obtain data on 94% of all mothers delivering in Jamaica during the defined study period but exclusion criteria are not documented. The authors do not explicitly state that all recruited subjects were included in the final analysis. Exposure status was determined by asking the mothers whether they had taken iron/folic acid during pregnancy but this is unlikely to have influenced case ascertainment.				
RESULTS				
Outcome	Intervention (N=6581)	Comparator (N=3197)	Risk estimate 95% CI	Statistical significance, P-value
Iron vs no iron				
Mortality				
	n/N (%)	n/N (%)	Odds ratio (95% CI)	
All perinatal deaths	915/7495 (12.2%)	763/3961 (19.3%)	1.72 [1.55, 1.91]	*Favours iron*[a] P < 0.00001
Adjusted for medical conditions *(N=1341 PND, N=8792 SURV)*	NR	NR	1.52 [1.34, 1.73]	*Favours iron* P < 0.0001

Also adjusted for social, environmental and behavioural variables (N=1009 PND, N=7645 SURV)	NR	NR	1.55 [1.33, 1.81]	*Favours iron* P < 0.0001
Also adjusted for gestational age at delivery (N=1009 PND, N=7645 SURV)	NR	NR	1.26 [1.07, 1.50]	*Favours iron* P < 0.01
Antepartum fetal deaths	265/6846 (3.9%)	237/3434 (6.9%)	1.84 [1.54, 2.20]	*Favours iron*[a] P < 0.00001
Adjusted for medical conditions (N=494 APFD, N=9734 SURV)	NR	NR	1.95 [1.60, 2.37]	*Favours iron* P < 0.0001
Also adjusted for social, environmental and behavioural variables (N=386 APFD, N=8263 SURV)	NR	NR	1.76 [1.38, 2.23]	*Favours iron* P < 0.0001
Also adjusted for gestational at delivery (N=386 APFD, N=8263 SURV)	NR	NR	1.42 [1.09, 1.84]	*Favours iron* P < 0.01
Intrapartum asphyxia deaths	404/6985 (5.8%)	339/3536 (9.6%)	1.73 [1.49, 2.01]	*Favours iron*[a] P < 0.00001
Adjusted for medical conditions (N=595 IPA, N=8792 SURV)	NR	NR	1.40 [1.17, 1.68]	*Favours iron* P < 0.001
Also adjusted for social, environmental and behavioural variables (N=467 IPA, N=7813 SURV)	NR	NR	1.49 [1.21, 1.83]	*Favours iron* P < 0.001
Also adjusted for gestational age at delivery (N=467 IPA, N=7813 SURV)	NR	NR	NR	Not significant P = NR
Deaths from immaturity	149/6730 (2.2%)	143/3340 (4.3%)	1.98 [1.56, 2.49]	*Favours iron*[a] P < 0.00001
Adjusted for medical conditions	NR	NR	NR	Not significant P = NR
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to all pregnant women.				
Applicability				
The study may be applicable to the Australian healthcare context.				
Comments				

The authors noted that most antenatal care is delivered by midwives in Jamaica and that iron is expected to be taken by all pregnant women, but is especially emphasised in women with low haemoglobin levels. In practice, 67% of mothers took iron during pregnancy and this appeared to lower the risk of perinatal death, even after adjustments for medical conditions, social, environmental and behavioural variables and, importantly, gestational age at delivery.

Abbreviations: CI, confidence interval; APFD, antepartum fetal deaths; IPA, Intrapartum asphyxia deaths; ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; SURV, survival.

[a.] OR, 95% CIs and p-values calculated post hoc based on data presented in Appendix 1.

STUDY DETAILS: cohort/case-control				
Citation Titaley, C. R. and Dibley, M. J. (2012) Antenatal iron/folic acid supplements, but not postnatal care, prevents neonatal deaths in Indonesia: Analysis of Indonesia Demographic and Health Surveys 2002/2003-2007 (a retrospective cohort study). BMJ Open 2 (6).				
Affiliation/Source of funds				
No competing interests declared. Christiana Titaley is affiliated with the Center for Health Research, Universitas Indonesia, Depok, Indonesia. Michael Dibley is affiliated with the Sydney School of Public Health, University of Sydney, Sydney, Australia.				
Study design	Level of evidence	Location/setting		
Retrospective cohort	Level III-2	Indonesia		
Intervention	Comparator			
Use of iron/folic acid supplement (any use)	No use of iron/folic acid supplement (never/don't know)			
Population characteristics				
Married women in reproductive age (15-49 years). Survival information from 26 591 most recent live-born infants within the five years prior to each interview (2002 and 2007 Indonesia Demographic and Health Survey (IDHS)) consisting of 12 646 infants from the 2002 IDHS and 13 945 from the 2007 IDHS. Participation in the IDHS has an average response of rate of 97%.				
Length of follow-up	Outcomes measured			
One month (31 days)	Effect of postnatal care on **early neonatal mortality** (deaths in the first week of life, days 1-7) and **all neonatal mortality** (deaths in the first month of life, days 1-31)			
Method of analysis				
Cox regression was used to examine the association between neonatal mortality and the study factors with multivariable analyses used to examine the association between neonatal mortality and the study factors after controlling for covariates. In multivariable analysis, a multistage model using a hierarchical approach was used (16 potential confounders classified into two groups: demographic, socioeconomic status and birthing characteristics, and perinatal healthcare services). At the first stage, community, socioeconomic status, birthing characteristics, year of survey and days of recollection period were entered. At the second stage, use of perinatal healthcare service characteristics (including use of iron/folic acid supplements and postnatal care services) were entered. At both stages, backward elimination was used to remove variables which were not significant ($p > 0.05$). Data were analysed using STATA/MP V.10.00.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Participation in the IDHS has an average response rate of 97% but more specific details about response rates in the different groups are not reported. Despite an attempt to consider many potential confounders, the authors note the possibility of residual confounding. Also, information used in the analysis was collected from the mothers, relying on their recollection of supplement use, meaning there is also potential for recall and misclassification bias. Further, only surviving mothers were included, which might lead to an underestimate of neonatal deaths.				
RESULTS				
Outcome	Intervention (N=17 958)	Comparator (N=7482) [a]	Risk estimate	Statistical significance P-value
Iron+ folic acid vs no iron +folic acid				
Mortality				
	n/N (%)	n/N (%)	Hazard ratio (95% CI)	
Early neonatal mortality [a] (days 1-7 after birth) Unadjusted	107/17 958 (0.6%)	108/7428 (1.45%)	0.48 [0.30, 0.79]	*Favours iron + folic acid* P<0.01
Adjusted model 1[b] (days 1-7 postnatal care)	NR	NR	0.51 [0.31, 0.82]	*Favours iron + folic acid* P=0.01

Adjusted model 2[b] (day 1 postnatal care)	NR	NR	0.49 [0.30, 0.79]	*Favours iron + folic acid* P<0.01
Early neonatal mortality[a] (occurring on the day of delivery, day 1) Adjusted model 2[b] (day 1 postnatal care)	52/17 958 (0.29%)	53/7428 (0.70%)	0.40 [0.21, 0.79]	*Favours iron + folic acid* P=0.01
Early neonatal mortality[c] (occurring after the day of delivery, days 2-7) Adjusted model 2[b] (day 1 postnatal care)	56/17906 (0.31%)	55/7428 (0.73%)	0.54 [0.28, 1.05]	No significant difference P=0.07
All neonatal mortality[a] (days 1-31 after birth) Unadjusted	NR	NR	0.51 [0.33, 0.79]	*Favours iron/folic acid* P < 0.01
Adjusted model 1 (days 1-7 postnatal care)	NR	NR	0.52 [0.33, 0.82]	*Favours iron/folic acid* P=0.01
Adjusted model 2 (day 1 postnatal care)	NR	NR	0.51 [0.32, 0.81]	*Favours iron/folic acid* P=0.01
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to pregnant women.				
Applicability				
The study may be applicable to the Australian healthcare context.				
Comments				
Most common formulation used in Indonesia is iron 60 mg and folic acid 0.25 mg. A mother was classified as using antenatal iron/folic acid if they reported taking tablets for at least one day. Use of iron/folic acid decreased from 69% in 2002/2003 to 67% in 2007. The authors also note poor adherence to the daily supplementation regime (in 2008 only 48% of pregnant women received recommended 90 tablets) and only 66% attended the recommended 4 antenatal visits.				

Abbreviations: CI, confidence interval; ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation..

[a] Data on 3307 cases were missing and were excluded from the analysis
[b] The models were adjusted for duration of recall period at interview, years of survey, type of residence, household wealth index, maternal age at childbirth, presence of complication at delivery, sex of the child, and child size at birth based on mother's subjective assessment
[c] Data on 3290 cases were missing and were excluded from the analysis
[d] The models adjusted for duration of recall period at interview, year of survey, type of residence, household wealth index, maternal age at childbirth, sex of the child, delivery complications, chid size at birth, delivery attendants, and use of iron/folic acid supplements

ESAs

Level I evidence

STUDY DETAILS: SR/MA		
Citation		
Dodd J, Dare MR, and Middleton P. (2004) Treatment for women with postpartum iron deficiency anaemia. *Cochrane database of systematic reviews (Online)* CD004222.		
Affiliation/Source of funds		
Internal sources of support: Department of Obstetrics and Gynaecology, University of Adelaide, Australia. External sources of support: Department of Health and Ageing, Australia. No conflicts of interest were declared.		
Study design	Level of evidence	Location/setting
Systematic review • 6 randomised controlled trials were included in the review.	Level I	Various single centre studies. Location not specified.

Intervention	Comparator
1. Erythropoietin + iron 2. Erythropoietin iv 3. Erythropoietin sc [note: only data for intervention 1 extracted]	1. Iron (oral or IV) 2. Placebo iv 3. Erythropoietin iv

Population characteristics	
Women with a haemoglobin value of less than 12g/dL after delivery up to six weeks after birth	
Length of follow-up	Outcomes measured
NA	Maternal outcomes: use of blood transfusion, fatigue, tolerance for physical load, dyspnoea, tachypnoea, tachycardia, palpitations, orthostatic dizziness, syncope, headache, not breastfeeding (at hospital discharge, six weeks postpartum, six months postpartum), infection up to six weeks postpartum (urinary tract infection requiring treatment, endometritis requiring treatment), psychological wellbeing Use of health resources: length of postnatal hospital stay, readmission to hospital after primary hospital discharge, costs of treatment (for the woman, for the health service) Maternal satisfaction with care: woman satisfied with care Adverse effects of treatment: thromboembolic complications, deep vein thrombosis, pulmonary embolism, anaphylactic reaction, gastrointestinal symptoms (when the treatment is iron supplementation), mild flu-like symptoms, hypertension, hypertensive encephalopathy, seizures, hyperkalaemia or hyperphosphataemia (when the treatment has been erythropoietin), viral infection

INTERNAL VALIDITY
Overall quality assessment (descriptive)
Rating: Good Description: Appropriate search strategies and inclusion criteria used in an unbiased way. Quality assessments clear and pre-determined. Study results clearly reported and summarised. Pooling of data was appropriate and tests for heterogeneity applied.
RESULTS

Outcome No. trials (No. patients)	Intervention	Comparator	Risk estimate (95% CI)	Statistical significance P-value Heterogeneity P-value (I^2)
Erythropoietin + iron vs iron				
Transfusion incidence				
	n/N (%)	n/N (%)	Risk ratio	

Use of blood transfusions 2 trials (N=100)	0/60 (0%)	2/40 (5%)	0.20 [0.01, 3.92)	No significant difference P=0.29 No significant heterogeneity P=1.00 (I^2=0%)
Laboratory measures				
	n/N (%)	n/N (%)	Risk ratio	
Haematocrit > 35% 2 weeks after treatment 1 trial (N=60)	32/40 (80%)	11/20 (55%)	1.45 [0.95, 2.23]	No significant difference P=0.084 Heterogeneity not applicable
	Mean ± SD (N)	Mean ± SD (N)	Mean difference	
Haemoglobin (g/dL) within 2 weeks after treatment 1trial (N=60) *oral or IV iron	10.7 ± 1.1 (30)	11.25 ± 0.55 (30)	-0.55 [-0.99, -0.11]	Favours iron P=0.014 Heterogeneity not applicable
Haemoglobin (g/dL) > 2 weeks to 6 weeks after treatment 1 trial (N=60) *oral or IV iron	12.6 ± 1.6 (30)	12.3 ± 0.8 (30)	0.30 [-0.34, 0.94]	No significant difference P=0.36 Heterogeneity not applicable
	Median (range)	Median (range)	Mean difference	
Haemoglobin (g/dL), days after: • 2 days • 4 days • 14 days • 39 days 1 trial (N=NR) *folate also given to both groups	7.8 (NR) 8.4 (NR) 10.3 (NR) 12.2 (NR)	7.3 (NR) 7.6 (NR) 8.9 (NR) 11.6 (NR)	NR	NR
Haematocrit (median %) , days after: • 2 days • 4 days • 14 days • 39 days 1 trial (N=NR), *folate also given to both groups	25 (NR) 27 (NR) 32 (NR) 37 (NR)	22 (NR) 24 (NR) 27 (NR) 35 (NR)	NR	NR
Thromboembolic events				
	n/N (%)	n/N (%)	Risk ratio	
Thromboembolic complications 2 trials (N=96)	0/64 (0%)	0/32 (0%)	0.0 [0.0, 0.0]	NA
EXTERNAL VALIDITY				
Generalisability				

The review is generalisable to pregnant women with anaemia (Hg <12 g/dL) after delivery and up to six weeks after birth.
Applicability
Applicable to the Australian context
Comments
The authors report that the methodological quality of the included studies is reasonable, little information on clinical outcomes is available with all included studies focusing on haematological indices. This can be seen in the results presented above.

Abbreviations: CI, confidence interval; ITT, intention-to-treat; MA, meta-analysis; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review.

[a] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

STUDY DETAILS: SR/MA				
Citation				
Reveiz L, Gyte GM, Cuervo LG, and Casasbuenas A. (2011) Treatments for iron-deficiency anaemia in pregnancy. *Cochrane database of systematic reviews (Online)* CD003094.				
Affiliation/Source of funds				
The authors contributed to this systematic review in a personal capacity and during their spare time. No internal or external sources of support were declared.				
Study design	Level of evidence	Location/setting		
Systematic review • 23 randomised controlled trials were included in the review	Level I	Various Turkey (Al, 2005), France (Bayoumeu, 2002), Breymann (2001), Digumarthi (2008), ,), Nigeria (Ogunbode, 1980), China , Sun (2010), India (Kumar, 2005; Zutschi, 2004), Pakistan (Wali 2002), Australia (Khalafallah 2010), Singapore (Singh 1998), Indonesia (Suharno 1993) (including Australia, India, Nigeria, France, Turkey, Malayan, China, United Kingdom, Tanzania, Pakistan)		
Intervention	Comparator			
1. Oral iron 2. Intravenous (IV) iron 3. Intramuscular (IM) or intravenous (IV) iron 4. Intravenous (IV) iron 5. Intravenous (IV) iron with recombinant erythropoietin	1. Placebo 2. Placebo 3. Oral iron 4. Intramuscular (IM) iron + oral iron 5. Intravenous (IV) iron			
Population characteristics				
Pregnant women with a diagnosis of anaemia during pregnancy (haemoglobin levels under 11g/dL, or other tests for anaemia as defined by trialists) attributed to iron deficiency.				
Length of follow-up	Outcomes measured			
NA	Primary (women): mortality, morbidity, puerperal sepsis, systematic bacterial infection after delivery, days in intensive care unit, days hospitalised during pregnancy Primary (newborn): mortality, morbidity, days hospitalised, admission to neonatal intensive care unit Secondary (women): preterm labour, premature delivery, pneumonia, postpartum haemorrhage, heart failure, serum ferritin, serum iron, haemoglobin levels, long-term haematological outcomes -maternal side effects: general symptoms, gastrointestinal effects, local symptoms, systemic symptoms Secondary (newborn): low birthweight (less than 2500g), respiratory disease requiring ventilation, small-for-gestational age, cord serum ferritin, cord haemoglobin, other long-term outcomes			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: Appropriate search strategies and inclusion criteria used in an unbiased way. Quality assessments clear and pre-determined. The authors note that the included studies were generally small and methodologically poor, making it difficult to pool data. As such, heterogeneity is not applicable to the majority of the analyses and discussion around this area is minimal.				
RESULTS				
Outcome No. trials (No. patients)	Intervention	Comparator	Risk estimate (95% CI)	Statistical significance P-value Heterogeneity P-value (I^2)
Oral iron vs placebo				
Laboratory measures				

	n/N (%)	n/N (%)	Risk ratio	
Anaemic during second trimester 1 trial (N=125)	20/63 (31.7%)	52/62 (83.9%)	0.38 [0.26, 0.55]	Favours oral iron P < 0.00001 Heterogeneity not applicable
	Mean ± SD (N)	Mean ± SD (N)	Mean difference	
Haemoglobin levels (g/dL) 2 trials (N=215)	NR (107)	NR (108)	1.34 [0.27, 2.42]	Favours oral iron P=0.014 Substantial heterogeneity P < 0.00001 (I^2=98%)
Ferritin levels (µg/L) I trial (N=125)	3.3 ± 0.5 (63)	2.6 ± 0.5 (62)	0.70 [0.52, 0.88]	Favours oral iron P < 0.00001 Heterogeneity not applicable
Intravenous iron vs placebo (no relevant outcomes)				
Intravenous iron vs oral iron				
Transfusion incidence				
	n/N (%)	n/N (%)	Risk ratio	
Blood transfusion required 3 trials (N=167)	0/84 (0%)	4/83 (4.8%)	0.27 [0.05, 1.59]	No significant difference P=0.15 No significant heterogeneity P=0.97 (I^2=0%)
Laboratory measures				
	n/N (%)	n/N (%)	Risk ratio	
Haemoglobin level > 12g/dL at 30 days 1 trial (N=47)	3/24 (12.5%)	4/23 (17.4%)	0.72 [0.18, 2.87]	No significant difference P=0.64 Heterogeneity not applicable
Haemoglobin level > 11g/dL at birth 1 trial (N=90)	43/45 (95.6%)	28/45 (62.2%)	1.54 [1.21, 1.94]	Favours IV iron P=0.00037 Heterogeneity not applicable
	Mean ± SD (N)	Mean ± SD (N)	Mean difference	
Neonates mean haemoglobin (g/dL) 1 trial (N=47)	15.15 ± 2.1 (24)	15.3 ± 2.17 (23)	-0.15 [-1.37, 1.07]	No significant difference P=0.81 Heterogeneity not applicable
Maternal haemoglobin at birth (g/dL) 1 trial (N=90)	12.01 ± 0.88 (45)	11.26 ± 1.1 (45)	0.75 [0.34, 1.16]	Favours IV iron P=0.00035 Heterogeneity not applicable
Neonates ferritin level (µg/L) 1 trial (N=47)	132 ± 104 (24)	134 ± 107 (23)	-2.00 [-62.36, 58.36]	No significant difference P=0.95 Heterogeneity not applicable
Mean maternal haemoglobin at 4 weeks (g/dL) 3 trials (N=167)	NR (84)	NR (83)	0.44 [0.05, 0.82]	Favours IV iron P=0.027 Moderate heterogeneity P=0.18 (I^2=42%)
Measures of fetal outcome				
	n/N (%)	n/N (%)	Risk ratio	
Preterm labour 1 trial (N=100)	0/50 (0%)	0/50 (0%)	0.0 [0.0, 0.0]	NA

Low birthweight (under 2500g) 1 trial (N=100)	0/50 (0%)	0/50 (0%)	0.0 [0.0, 0.0]	NA
Small-for-gestational age 1 trial (N=100)	8/50 (16%)	5/50 (10%)	1.60 [0.56, 4.56]	No significant difference P=0.38 Heterogeneity not applicable
	Mean ± SD (N)	Mean ± SD (N)	Mean difference	
Neonatal birthweight (g) 3 trials (N=237)	NR (119)	NR (118)	54.29 [-170.11, 278.68]	No significant difference P=0.64 Substantial heterogeneity P=0.07 (I^2=62%)
Maternal and perinatal mortality				
	n/N (%)	n/N (%)	Risk ratio	
Maternal mortality 1 trial (N=100)	0/50 (0%)	0/50 (0%)	0.0 [0.0, 0.0]	NA
Neonatal mortality 2 trials (N=147)	0/74 (0%)	0/73 (0%)	0.0 [0.0, 0.0]	NA
Intravenous iron sucrose with recombinant erythropoietin vs intravenous iron sucrose				
Transfusion incidence				
	n/N (%)	n/N (%)	Risk ratio	
Need transfusion 1 trial (N=40)	0/20 (0%)	0/20 (0%)	0.0 [0.0, 0.0]	NA
Laboratory measures				
	n/N (%)	n/N (%)	Risk ratio	
Haemoglobin < 11g/dL at 4 weeks 1 trial (N=40)	1/20 (5%)	5/20 (25%)	0.20 [0.03, 1.56]	No significant difference P=0.12 Heterogeneity not applicable
Measures of fetal outcome				
	n/N (%)	n/N (%)	Risk ratio	
Birth < 37 weeks 1 trial (N=40)	0/20 (0%)	1/20 (5%)	0.33 [0.01, 7.72]	No significant difference P=0.49 Heterogeneity not applicable
	Mean ± SD (N)	Mean ± SD (N)	Mean difference	
Birthweight (g) 1 trial (N=40)	3332 ± 282 (20)	3462 ± 497 (20)	-130.00 [-380.44, 120.44]	No significant difference P=0.31 Heterogeneity not applicable
Intramuscular iron sorbitol citric acid vs oral iron				
Laboratory measures				
	n/N (%)	n/N (%)	Risk ratio	
Not anaemic at term 1 trial (N=200)	76/100 (76%)	62/100 (62%)	1.23 [1.01, 1.48]	Favours IM iron P=0.035 Heterogeneity not applicable
	Mean ± SD (N)	Mean ± SD (N)	Mean difference	
Mean maternal haemoglobin at birth (g/dL) 1 trial (N=200)	10.5 ± 0.84 (100)	9.96 ± 0.89 (100)	0.54 [0.30, 0.78]	Favours IM iron P=0.000010 Heterogeneity not applicable

Mean maternal haematocrit level at birth (%) 1 trial (N=200)	31.2 ± 2.6 (100)	29.8 ± 2.7 (100)	1.40 [0.67, 2.13]	Favours IM iron P=0.00019 Heterogeneity not applicable
Haematocrit (%) at 4 weeks of treatment 1 trial (N=56) *oral iron 600mg	32.5 ± 2.65 (28)	31.25 ± 2.22 (28)	1.25 [-0.03, 2.53]	No significant difference P=0.056 Heterogeneity not applicable
Haematocrit (%) at 8 weeks of treatment 1 trial (N=59) *oral iron 600mg	35.29 ± 3.6 (31)	32.67 ± 1.3 (28)	2.62 [1.26, 3.98]	Favours IM iron P=0.00015 Heterogeneity not applicable
Haematocrit (%) at 4 weeks of treatment 1 trial (N=56) *oral iron 1200mg	32.5 ± 2.65 (28)	31.25 ± 2.22 (28)	1.25 [-0.03, 2.53]	No significant difference P=0.056 Heterogeneity not applicable
Haematocrit (%) at 8 weeks of treatment 1 trial (N=59) *oral iron 1200mg	35.29 ± 3.6 (31)	32.69 ± 2.53 (28)	2.60 [1.02, 4.18]	Favours IM iron P=0.0012 Heterogeneity not applicable
Intramuscular iron sorbitol citric acid vs oral iron + folic acid				
Laboratory measures				
	n/N (%)	n/N (%)	Risk ratio	
Haemoglobin > 11g/dL at 36 weeks 1 trial (N=150)	42/75 (56%)	51/75 (68%0	0.82 [0.64, 1.06]	No significant difference P=0.13 Heterogeneity not applicable
Haemoglobin > 12g/dL at 36 weeks 1 trial (N=150)	11/75 (14.7%)	21/75 (28%)	0.52 [0.27, 1.01]	No significant difference P=0.053 Heterogeneity not applicable
	Mean ± SD (N)	Mean ± SD (N)	Mean difference	
Mean haemoglobin at 36 weeks (g/dL) 1 trial (N=150)	10.94 ± 0.56 (75)	11.2 ± 0.82 (75)	-0.26 [-0.48, -0.04]	Favours oral iron + folic acid P=0.023 Heterogeneity not applicable
Measures of fetal outcome				
	Mean ± SD (N)	Mean ± SD (N)	Mean difference	
Mean birthweight (g) 1 trial (N=150)	2610 ± 420 (75)	2630 ± 480 (75)	-20.00 [-164.35, 124.35]	No significant difference P=0.79 Heterogeneity not applicable
Intravenous iron sucrose vs intramuscular iron sorbitol + oral iron				
Laboratory measures				
	n/N (%)	n/N (%)	Risk ratio	
Haemoglobin level > 11g/dL at delivery 1 trial (N=40) *IV iron sucrose 500mg	12/15 (80%)	7/25 (28%)	2.86 [1.45, 5.63]	Favours IV iron P=0.0024 Heterogeneity not applicable

Haemoglobin level > 11g/dL at delivery 1 trial (N=45) *IV iron sucrose 200mg	14/20 (70%)	7/25(28%)	2.50 [1.25, 4.99]	Favours IV iron P=0.0093 Heterogeneity not applicable
	Mean ± SD (N)	Mean ± SD (N)	Mean difference	
Maternal haemoglobin level at birth (g/dL) 1 trial (N=40) *IV iron sucrose 500mg	11.8 ± 1.1 (15)	10.2 ± 1.2 (25)	1.60 [0.87, 2.33]	Favours IV iron P=0.000017 Heterogeneity not applicable
Haemoglobin level at delivery (g/dL) 1 trial (N=45) *IV iron sucrose 200mg	11.3 ± 0.9 (20)	10.2 ± 1.2 (25)	1.10 [0.49, 1.71]	Favours IV iron P=0.00044 Heterogeneity not applicable
Intravenous iron + oral iron vs oral iron				
Laboratory measures				
	Mean ± SD (N)	Mean ± SD (N)	Mean difference	
Mean predelivery maternal haemoglobin (g/dL) 1 trial (N=183)	12.66 ± 0.97 (92)	12.18 ± 0.87 (91)	0.48 [0.21, 0.75]	Favours IV iron + oral iron P=0.00042 Heterogeneity not applicable
Mean maternal haemoglobin after delivery (g/dL) 1 trial (N=183)	11.55 ± 1.08 (92)	11.16 ± 1.42 (91)	0.39 [0.02, 0.76]	Favours IV iron + oral iron P=0.037 Heterogeneity not applicable
EXTERNAL VALIDITY				
Generalisability				
The review is applicable to pregnant women with a diagnosis of anaemia (Hg < 11g/dL) attributed to iron deficiency.				
Applicability				
Many of the trials were conducted in low-income countries, which may limit the review's applicability to an Australian context.				
Comments				
The authors note that in general, the included studies were small and methodologically poor, covering a very wide range of differing drugs, doses and routes of administration, making it difficult to pool data. The authors conclude that there is no evidence to suggest that, in otherwise healthy women, the benefits of treatment for mild anaemia in pregnancy will outweigh the adverse effects. There is no evidence that in women with iron deficiency anaemia, improvements in haematological indices translates into clinical improvements.				

Abbreviations: CI, confidence interval; ITT, intention-to-treat; MA, meta-analysis; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review.

[a] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

Level II evidence

STUDY DETAILS: RCT				
Citation				
Krafft A and Breymann C. (2011) Iron sucrose with and without recombinant erythropoietin for the treatment of severe postpartum anemia: A prospective, randomized, open-label study. *Journal of Obstetrics and Gynaecology Research* 37:119-124.				
Affiliation/Source of funds				
No source of funds reported. The authors are affiliated with the Feto-maternal Hematology Group, Division of Obstetrics, Department of Obstetrics and Gynecology, University Hospital, Zurich, Switzerland.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Switzerland, single centre study	
Intervention	Comparator			
1. 10,000U iv rhEPO plus 200 mg iv iron sucrose	200mg iv iron sucrose			
Population characteristics				
40 postpartum women with severe postpartum anaemia (haemoglobin < 8.5g/dL). The inclusion criteria were: prepartal haemoglobin > 10.0g/dL, severe postpartum anaemia, defined by haemoglobin < 8.5g/dL 24-48 hours after delivery.				
Length of follow-up	Outcomes measured			
15 days	Haematocrit, haemoglobin, red cell indices, percentage of hypochromic red cells, reticulocyte count, serum ferritin, transferrin saturation, soluble transferrin receptor concentration, C-reactive protein, folic acid concentration, vitamin B12, erythropoietin levels and interleukin 6.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Subjects were randomised using random number tables using sealed envelopes; the study was not blinded (participants in the iron group were not given an erythropoietin placebo and investigator blinding not reported); patient baseline characteristics were similar between treatment groups.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	20		20	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	Intervention (N=20)	Comparator (N=20)	Risk estimate (95% CI)	Statistical significance P-value
Recombinant human erythropoietin + iron sucrose vs iron sucrose				
Transfusion incidence				
	n/N (%)	n/N (%)	• Risk Ratio	
Transfusion incidence	0	0	0 [0.0, 0.0]	NA
Laboratory measures				
	Mean ± SD	Mean ± SD		

Haemoglobin increase (g/dL) after: • 4 days • 8 days • 15 days	 1.0 ± 0.2 2.4 ± 0.2 3.9 ± 0.1	 0.5 ± 0.1 1.9 ± 0.1 3.0 ± 0.1	 NR NR NR	Favours iv rhEPO + iron P < 0.05 (for all time periods)
Haemoglobin (g/dL) • Baseline • End of treatment	 7.1 ± 1.1 10.7 ± 1.2	 7.5 ± 0.7 10.5 ± 0.7	 NR NR	No significant difference P=NR
Haematocrit (%) • Baseline • End of treatment	 21.4 ± 3.3 33.4 ± 3.5	 22.8 ± 2.2 32.9 ± 1.9	NR NR	No significant difference P=NR
Ferritin (µg/L) • Baseline • End of treatment	 46 ± 73 187 ± 89	 32 ± 37 221 ± 102	 NR NR	No significant difference P=NR
Thromboembolic events				
	n/N (%)	n/N (%)	Risk Ratio	
Thromboembolic complications	0	0	0 [0.0, 0.0]	NA
EXTERNAL VALIDITY				
Generalisability				
The study is applicable to women with severe postpartum anaemia (<8.5 g/dL)				
Applicability				
The study was conducted in a single centre in Switzerland and should be applicable to an Australian context.				
Comments				
Authors note no serious adverse events in either group.				

Abbreviations: CI, confidence interval; Hg, haemoglobin; ITT, intention-to-treat; iv, intravenous; PP, per-protocol; rhEPO, recombinant human erythropoietin; RCT, randomised controlled trial; sc, subcutaneous; SD, standard deviation.

STUDY DETAILS: RCT					
Citation					
Wagstrom E, Akesson A, Van Rooijen M, Larson B, and Bremme K. (2007) Erythropoietin and intravenous iron therapy in postpartum anaemia. *Acta Obstetricia et Gynecologica Scandinavica* 86:957-962.					
Affiliation/Source of funds					
Funding Roche AB, Stockholm, Sweden and The Swedish Research Council, Karolinska Institutet.					
Study design		Level of evidence		Location/setting	
RCT		Level II		Two hospitals in Stockholm, Sweden	
Intervention			Comparator		
1. 10 000 U rhEPO plus iv iron 2. 20,000 U rhEPO plus iv iron			IV iron		
Population characteristics					
60 women in the postpartum period. The criteria for randomisation were haemoglobin ≤ 80g/L within 72 hours after delivery and > 18 years of age.					
Length of follow-up			Outcomes measured		
14 days			Haemoglobin, haematocrit, platelets, C-reactive protein, serum ferritin, serum iron, total iron binding capacity, soluble transferrin receptor and erythropoietin.		
INTERNAL VALIDITY					
Overall quality assessment (descriptive)					
Rating: Fair Description: Subjects were randomised using random number tables using sealed envelopes; the study was not blinded (participants in the iron group were not given an erythropoietin placebo and investigator blinding not reported); the only statistically significant difference at randomisation was transferring receptor. Age, blood pressure, endogenous erythropoietin levels, haematological indices and markers of iron status or inflammation were similar across the three treatment groups. Ten patients lost to follow-up					
RESULTS					
Population analysed	Intervention (10 000 rhEPO + IV iron)		Intervention (20 000 rhEPO + IV iron)	Comparator (IV iron)	
Randomised	20		20	20	
Efficacy analysis (ITT)	NR		NR	NR	
Efficacy analysis (PP)	19		15	16	
Safety analysis	NR		NR	NR	
Outcome	Intervention (N=20)	Intervention (N=20)	Comparator (N=20)	Risk estimate (95% CI)	Statistical significance P-value

Recombinant human erythropoietin sc + iv iron sucrose vs iv iron sucrose					
Laboratory measures					
	Mean ± SD	Mean ± SD	Mean ± SD		
Haemoglobin (g/L) [a] • Day 0 • Day 3 • Day 7 • Day 14	75 ± 5.1 ~ 81 ± NR ~ 94 ± NR ~ 102 ± NR	75 ± 4.6 ~ 79 ± NR ~ 92 ± NR ~ 102 ± NR	73 ± 4.7 ~ 77 ± NR ~ 90 ± NR ~ 102 ± NR	NR	No significant difference between the treatment groups P=0.589 [favours all three treatment groups P < 0.001]
Ferritin (µg/L) • Day 0 • Day 3 • Day 7 • Day 14	45 ± 32.7 ~ 270 ± NR ~ 240 ± NR ~ 110 ± NR	51 ± 50.0 ~ 260 ± NR ~ 230 ± NR ~ 110 ± NR	26 ± 19.9 ~ 240 ± NR ~ 210 ± NR ~ 110 ± NR	NR	No significant difference between the treatment groups P=0.646 Concentration increased from day 0 to day 3 p < 0.001 after which it decreased but was still higher than at randomisation (p < 0.001)
EXTERNAL VALIDITY					
Generalisability					
The study is applicable to women with severe postpartum haemorrhage (Hg ≤ 80 g/L)					
Applicability					
The study was conducted in two hospitals in Sweden and should be applicable to an Australian context.					
Comments					
This was a pilot study. According to post hoc power calculations more than 800 patients are needed to achieve a statistically significant difference between groups. The ten patients lost to follow-up had a statistically significant lower Hg level (70 g/l) at randomisation than those who completed the study (74 g/l; p<0.01). The loss to follow-up was not considered unexpected by the authors. Authors conclude that 'iv iron can be useful in the treatment of postpartum anaemia as a complement to oral iron therapy and that rhEPO provides no additional benefit'.					

Abbreviations: CI, confidence interval; Hg, haemoglobin; ITT, intention-to-treat; iv, intravenous; PP, per-protocol; RCT, randomised controlled trial; rh EPO, recombinant human erythropoietin; sc, subcutaneous; SD, standard deviation.

[a] approximate data (~) obtained from figures.

F3 Evidence summaries – Question 3

Fresh frozen plasma

Level III evidence

STUDY DETAILS: Retrospective cohort study		
Citation		
Reyal F, Sibony O, Oury JF, Luton D, Bang J, Blot P (2004) Criteria for transfusion in severe postpartum hemorrhage: Analysis of practice and risk factors. Eur J Obstet Gynecol Reprod Biol 112(1):61-4.		
Affiliation/Source of funds		
Hopital Robert Debre, 48 Boulevard Serurier, 75019 Paris, France		
Study design	Level of evidence	Location/setting
Retrospective cohort study	Level III-2	Single teaching hospital/France
Intervention	Comparator	
Transfusion immediately postpartum (n=44). Out of 44 patients who received transfusion, 24 received fresh frozen plasma (FFP). • 5 patients received FFP only • 19 patients received red blood cells and FFP • 20 patients received red blood cells only	No transfusion (n=19,138)	
Population characteristics		
19,182 women who gave birth between 1 January 1992 and 31 December 1998 at the maternity ward of the Robert Debre University Teaching Hospital in Paris. • Records were retrospectively reviewed • Exclusion criteria were: elective termination of pregnancy, delivery before 24 weeks of amenorrhea, transfusion in the absence of haemorrhage. Transfusion 44 women who had singleton or multiple pregnancy, delivery >24 weeks of amenorrhea, transfusion of red blood cells and/or FFP in the 21 days following delivery in the presence of a haemorrhagic complication. • Haemoglobin (mean, (SD)): 5.8 g/dl (1.76) • All 44 patients had at least one proposed haemorrhagic risk factor (n (%)): caesarean section 26 (59%); premature birth 16 (36%), grand multiparity 12 (27%), forceps delivery 11 (25%), vascular disease 10 (23%), scarred uterus 9 (20%), multiple pregnancies 7 (16%), placenta previa and/or accreta 6 (14%), maternal thrombopenia 4 (9%), birth weight above 4000 g 1 (2%). No transfusion 19,138 women who had singleton or multiple pregnancy, delivery >24 weeks of amenorrhea and did not receive transfusion • Age (mean (SD)): 30.2 (4.8) years; parity (mean (SD)): 1.8 (1.14) • Singleton pregnancies (n (%)): 18,610 (97.2%); twin pregnancies (n (%)): 478 (2.5%); triplet pregnancies (n (%)): 51 (0.3%) • 8048 patients presented no haemorrhagic risk factor (42%) • 11,090 had at least one proposed haemorrhagic risk factor (n (%)): forceps delivery 4523 (24%), grand multiparity 3813 (20%), caesarean section 2248 (12%), scarred uterus 1612 (9%), premature birth 1503 (8%), birth weight above 4000 g 1277 (7%), hyperthermia during labour 960 (5%), maternal thrombopenia 815 (4%), vascular disease 780 (4%), placenta previa/accreta 154 (0.8%)		
Length of follow-up	Outcomes measured	
NA	Postpartum haemorrhage (PPH) and transfusion risk factors, complications[a], transfusion volume[b]	
Method of analysis		
For PPH/transfusion risk factors, categorical variables were analysed by chi-square test or Fisher exact test. Odds ratios are reported with 95% CI. A P-value of 0.05 or less was considered to indicate statistical significance.		

INTERNAL VALIDITY			
Overall quality assessment (descriptive)			
Rating: Fair Description: Patients requiring transfusion had an underlying haemorrhagic complication, whereas not all patients in the control group presented with haemorrhagic risk factors; therefore, it is likely that those who received transfusion were more likely to have poorer clinical outcomes. Univariate and multivariate analyses were conducted to account for confounders and risk factors for postpartum haemorrhage; however, these particular outcomes are not relevant to the current research question. Also, the retrospective design of the study meant that loss to follow-up was not applicable but all exclusions from analysis were adequately accounted for. Reasons for exclusion of patients from the analysis were adequately described.			
RESULTS			
Outcome	Intervention (N=44)	Comparator (N=19138)	Statistical significance P-value
Transfusion (including fresh frozen plasma) vs no transfusion			
	n/N (%)	n/N (%)	
Maternal mortality	0/44 (0%)	NR	P=NR
EXTERNAL VALIDITY			
Generalisability			
The study was conducted in women who had singleton or multiple pregnancy and delivery >24 weeks since amenorrhea. However, cases were also selected based on having a haemorrhagic complication and all patients were from a medical unit located in a paediatrics hospital with a neonatal intensive care unit and significant prenatal diagnosis activity; therefore the authors claim that the patients compose a high risk population. Results may not be directly generalisable to all obstetrics/maternity patients.			
Applicability			
The study was conducted in France, where the level of healthcare is likely comparable to that in Australia. However, review of hospital records in the study was conducted from 1 January 1992 to 31 December 1998; therefore, current practice may have changed since this time.			
Comments			
Not all patients in the intervention arm received fresh frozen plasma (24 out of 44) and some of these patients also received concomitant red blood cells in addition to fresh frozen plasma (19 out of 24).			

Abbreviations: CI, confidence interval; FFP, fresh frozen plasma; SD, standard deviation.

a The authors reported 3patients in the intervention group underwent hysterectomy, however they did not disclose if patients received FFP and/or red blood cells.

b. One to 18 units of FFP was administered to the 24 patients who received FFP. The authors did not disclose the volume of FFP received by patients who received FFP only versus those who received FFB plus RBC.

Combination or fixed ratio therapy

Level III evidence

STUDY DETAILS: Retrospective cohort study		
Citation		
Pasquier P, Gayat E, Rackelboom T, La Rosa J, Tashkandi A, Tesniere A, Ravinet J, Vincent JL, Tsatsaris V, Ozier Y, Goffinet F, Mignon A (2013) An observational study of the fresh frozen plasma: Red blood cell ratio in postpartum hemorrhage. Anesth Analg 116(1):155-61.		
Affiliation/Source of funds		
From the Département d'Anesthésie-Réanimation, Hôpital d'Instruction des Armées Bégin, Saint-Mandé; Département d'Anesthésie-Réanimation, Hôpital Lariboisiere, Assistance Publique—Hôpitaux de Paris, Université Paris Diderot, Paris; Département d'Anesthésie-Réanimation and Maternité Port-Royal, Hôpital Cochin, Assistance Publique—Hôpitaux de Paris, Université Paris Descartes, Paris, France; and Department of Intensive Care, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium. The authors declare no conflicts of interest.		
Study design	Level of evidence	Location/setting
Retrospective cohort study	Level III-2	Tertiary university maternity unit/ France
Intervention	Comparator	
• FFP (n=41) • High FFP:RBC ratio (n=NR)	• No FFP (n=101) • Low FFP:RBC ratio (n=NR)	
Patients were transfused according to the severity of bleeding as stated in the European guidelines for Trauma (2010). The decision to transfuse FFP was at the discretion of the anaesthesiologist. During the study period, no antifibrinolytic drugs, such as tranexamic acid, were used; nor fibrinogen concentrate administered.		
Population characteristics		
142 women diagnosed with severe postpartum haemorrhage (>500 mL) during a 4-year period (2006–2009) • Patients were included in the study if they had delivered after 24 weeks gestation, were treated with sulprostone and required transfusion with red blood cells within 6 hours of delivery • Patients were then stratified according to the need for additional interventions to control bleeding • Leading cause of postpartum haemorrhage was uterine atony (61%) followed by abnormal placentation (26%) • Population characteristics not presented separately for fresh frozen plasma versus no fresh frozen plasma treatment groups		
Length of follow-up	Outcomes measured	
NA	Primary outcome: requirement for additional intervention to control bleeding Other outcomes: transfusion volume, haematological laboratory measures, FFP:RBC ratio over time, complications of severe postpartum haemorrhage	
Method of analysis		
Propensity scoring was used to assess the effect of a high FFP:RBC ratio on bleeding control. The inverse probability of treatment weighting (IPTW) technique was used, where exposed and unexposed individuals are weighted to represent the population. The variables included in the propensity score model were the total number of RBCs transfused, the lowest values of fibrinogen concentration and platelet counts, the longest prothrombin time, and the year of inclusion. The effect of a high FFP:RBC ratio in the weighted sample was then assessed using a generalised linear model.		

INTERNAL VALIDITY			
Overall quality assessment (descriptive)			
Rating: Fair Description: The study may be prone to selection bias as the decision to transfuse FFP was exclusively under the control of anaesthetists and based on both clinical observation and laboratory coagulation results. Patients groups were selected based on whether or not they received FFP and the also amount of FFP. Therefore, patients who received FFP may have been more likely to experience poorer clinical outcomes than those who did not receive FFP. Loss to follow-up was not applicable due to the retrospective design of the study; however, exclusions from analysis based on eligibility criteria were adequately explained. No prospective measurement of adverse effects associated with transfusion was performed. Because there was no control on treatment allocation in the present study, a propensity score method was used to consider this bias.			
RESULTS			
FFP vs no FFP			
Outcome	Intervention (N=41)	Comparator (N=101)	Statistical significance P-value
Maternal mortality			
	n/N (%)	n/N (%)	
Maternal mortality	0	0	P=NR
Transfusion requirements			
	Mean ± SD	Mean ± SD	
Volume of RBC (units)	6.8 ± 5.3	2.7 ± 1.2	*Favours no FFP* P<0.001
Volume of FFP (units)	4.3 ± 2.5	NA	NA
Volume of platelets (units)	0.49 ± 0.98	0.01 ± 0.1	*Favours no FFP* P<0.001
	Median [IQR]	Median [IQR]	
Volume of RBC (units)	2 [4.5]	2 [1]	P=NR
Volume of FFP (units)	3 [4]	NA	NA
Volume of platelets (units)	0 [1]	0 [0]	P=NR
Additional interventions to control bleeding			
	n/N (%)	n/N (%)	
Requirement for at least one additional procedure	23/41 (56)	29/101 (29)	P=NR
Embolisation	10/41 (24)	24/101 (24)	P=NR
Arterial ligation	8/41 (20)	4/101 (4)	P=NR
Hysterectomy	13/41 (32)	3/101 (3)	P=NR
Secondary outcomes			
Laboratory measures			
	Mean ± SD	Mean ± SD	
Nadir platelets (giga/L)	88 ± 52	158 ± 79	*Favours no FFP* P=0.001
Longest prothrombin time (s)	21.7 ± 7.2	14.9 ± 2.2	*Favours no FFP* P<0.001
Nadir fibrinogen (g/L)	1.1 ± 0.8	2.7 ± 1.1	*Favours no FFP* P<0.001

High[b] FFP:RBC ratio vs low[c] FFP:RBC ratio			
Outcome	Intervention (N=NR)	Comparator (N=NR)	Statistical significance P-value
Transfusion requirements (in patients who received FFP)			
	Mean ± SD	Mean ± SD	
Volume of RBC (units), unweighted	5.5 ± 3.1	12.7 ± 9.0	No significant difference P=0.08
Volume of RBC (units), weighted	5.9 ± 3.3	8.5 ± 6.5	No significant difference P=0.19
Additional interventions to control bleeding (in patients who received FFP)			
	n/N (%)	n/N (%)	
Overall	NR	NR	*Favours high FFP:RBC ratio* OR (95%CI): 1.58 (1.19-2.10) P=0.003
Secondary outcomes			
Laboratory measures			
	Mean ± SD	Mean ± SD	
Nadir platelets (giga/L), unweighted	91 ± 49	57 ± 33	No significant difference P=0.04
Nadir platelets (giga/L), weighted	87 ± 49	73 ± 28	No significant difference P=0.29
Nadir fibrinogen (g/L), unweighted	1.2 ± 0.9	1.1 ± 0.4	No significant difference P=0.57
Nadir fibrinogen (g/L), weighted	1.2 ± 0.4	1.2 ± 0.9	No significant difference P=0.75
Longest prothrombin time (s), unweighted	18.0 ± 2.6	18.4 ± 2.9	No significant difference P=0.72
Longest prothrombin time (s), weighted	18.0 ± 2.6	17.4 ± 2.5	No significant difference P=0.52
EXTERNAL VALIDITY			
Generalisability			
The study was conducted in women with severe postpartum haemorrhage and therefore may not be generalisable to all maternity patients or all women with postpartum haemorrhage.			
Applicability			
The study was performed in France; therefore the results are likely to be applicable to the Australian healthcare setting due to comparable availability of resources.			
Comments			
The authors acknowledge that the retrospective nature of the study make it more prone to severity bias. Decisions regarding the failure of conservative therapy and the need for additional interventions to control bleeding may vary among centres or caregivers. Use of third-line advanced treatments may also depend on the availability of equipment or expertise in different centres. No prospective measurement of adverse effects associated with transfusion was performed; therefore it cannot be excluded that adverse effects may be more common with increased use of FFP. Still, major events were likely to be registered in the medical files or electronic medical records, and the authors noted that no meaningful complications from blood transfusions or maternal deaths were recorded.			

Abbreviations: CI, confidence interval; FFP, fresh frozen plasma; OR, odds ratio; RBC, red blood cell; SD, standard deviation.
a A total of 52 patients (37%) required at least one additional intervention (embolisation and/or arterial ligation and/or hysterectomy). Bleeding control was obtained with sulprostone only in the remaining 90 patients (63%).
b Defined as > 1 U of FFP for every 2 U of packed RBCs
c Defined as ≤ 1 U of FFP for every 2 U of packed RBCs

F4 Evidence summaries – Question 4

Intraoperative cell salvage

Level II evidence

STUDY DETAILS: RCT				
Citation				
Rainaldi, M. P., Tazzari, P. L., Scagliarini, G., Borghi, B., and Conte, R. (1998) Blood salvage during caesarean section. Br.J.Anaesth. 80 (2) 195-198				
Affiliation/Source of funds				
No source of funds reported. The authors are affiliated with the Anaesthesia and Intensive Care Maternity Unit, Service of Immunohaematology, First Obstetrics Clinic and Anaesthesia and Intensive Care, Bologna, Italy.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Italy, hospital	
Intervention		Comparator		
Intraoperative cell salvage		No intraoperative cell salvage		
Population characteristics				
68 women undergoing caesarean section.				
Length of follow-up		Outcomes measured		
NR		Use of homologous blood transfusions, haemoglobin concentrations, duration of hospital stay.		
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: The authors report that participants were allocated randomly to the groups but the method of randomisation is not stated. Similarly, no method of allocation concealment has been reported. Baseline demographics were reported, with the two groups similar in age, height and body weight. Loss to follow-up is not reported; no patients are reported to have dropped out of the study at any point. The authors do not state if either the subjects or investigators were blinded in the study, nor whether the outcomes were assessed blind to treatment allocation.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	34		34	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	Intervention (N=34)	Comparator (N=34)	Risk estimate (95% CI)	Statistical significance P-value
Intraoperative cell salvage vs no intraoperative cell salvage				
	n/N (%)	n/N (%)		
Homologous RBC transfusion	1/34 (2.9%)	8/34 (23.5%)	NR	*Favours intraoperative cell salvage* P=0.01
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to women undergoing a caesarean section.				
Applicability				

The study results are applicable to the Australian setting with few caveats. The study was conducted in Italy.
Comments
The authors provide guidelines for the procedure and conclude that intraoperative cell salvage may be associated with a better outcome and shorter hospital stay.

Abbreviations: CI, confidence interval; ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

Level III evidence

STUDY DETAILS: Retrospective cohort study		
Citation		
Malik S, Brooks H, Singhal T (2010) Cell saver use in obstetrics. J Obstet Gynaecol 30(8):826-8.		
Affiliation/Source of funds		
Department of Obstetrics and Gynaecology and Anaesthesia, Leicester General Hospital, UK. The authors report no conflicts of interest.		
Study design	Level of evidence	Location/setting
Retrospective cohort study	Level III-2	Hospital maternity unit; UK
Intervention	Comparator	
Cell saver/intraoperative cell salvage (n=77)	No cell saver/intraoperative cell salvage (n=70)	
Population characteristics		
147 obstetric patients who underwent elective or emergency caesarean section between July 2005 and August 2008. All participants were (i) patients with placenta previa or (ii) Jehovah's Witnesses Intraoperative cell salvage (IOCS): 77 women who underwent IOCS during caesarean section • Age (mean, range): 32 (18-44); Previous caesarean sections (mean, range): 2.2 (0-4); Type of delivery (n,%): elective n=56 (72.7%), emergency: n=21 (27.3%) No IOCS: 70 women who underwent caesarean section without IOCS • Age (mean, range): 34 (23-42); Previous caesarean sections (mean, range): 0.9 (0-3); Type of delivery (n,%): elective n=28 (40.0%), emergency: n=42 (60.0%)		
Length of follow-up	Outcomes measured	
NR	Blood loss, salvaged blood, homologous blood transfusion, adverse events	
Method of analysis		
NA		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Poor Description: Retrospective cohort study – loss to follow-up and exclusions from analysis were not applicable. No statistical analysis carried out to show significance of differences between treatment groups (patient characteristics or outcomes). Potential important differences existed between the groups at baseline – 27.3% of patients in cell saver treatment group had emergency caesarean, compared to 60.0% in the no cell saver group. This was primarily due to a lack of trained staff out-of-hours for emergency cases (due to financial constraints). Substantial differences also existed between the treatment groups with respect to previous caesarean sections and parity, but statistical significance not reported. Cell salvage was more likely to be used if massive blood loss was anticipated e.g. in multiparous women with a higher risk of obstetric haemorrhage (high risk of selection bias). Blinding was not reported, however outcome assessors are likely to have had knowledge of the use of cell saver. Follow-up not reported, but assumed to be for duration of hospital stay. This may not be an adequate enough period to detect thromboembolic outcomes.		
RESULTS		

Outcome	Intervention (N=77)	Comparator (N=70)	Statistical significance P-value
IOCS vs no IOCS			
Thromboembolic events			
	n/N (%)	n/N (%)	
Thromboembolism	0/77 (0%)	NR	NA
Additional interventions to control bleeding			
	n/N (%)	n/N (%)	

Return to theatre	0/77 (0%)	NR	NA
Transfusion			
	Total units	Total units	
Homologous blood transfusion (units per treatment arm)	31	29	NR
EXTERNAL VALIDITY			
Generalisability			
The study was performed in women who are Jehovah's Witnesses or who had placenta previa. Therefore, the results may not be generalisable to all maternity patients.			
Applicability			
Study performed in the UK; therefore, the results should be applicable to the Australian setting. The study institution had a limited number of staff trained in cell salvage (particularly out-of-hours). The amount of blood salvaged from patients in the study was proportionally small compared with blood loss, reflecting the way blood was salvaged. Due to the low amount of blood salvaged (mean: 95.5 ml; median: 0 ml; range: 0-1,800 ml) and the low amount of blood processed and re-transfused (13 units), the results (particularly for the homologous blood transfusion outcome in the IOCS treatment arm) may not be generalisable to other populations that have more trained staff in cell salvage, greater resources, or better techniques to salvage more blood. Also, the cell salvage system used in the study included a double suction method. Collection into the cell salvage collection chamber did not start until after delivery of the baby and placenta. Only blood directly collected by suction from the surgical field was salvaged. All processed blood was transfused via a 'Leukogard' filter.			
Comments			

Abbreviations: CI, confidence interval; CS, caesarean section; IOCS, intraoperative cell salvage; ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

Interventional radiology

Level III evidence

<table>
<tr><td colspan="3">STUDY DETAILS: Retrospective cohort study</td></tr>
<tr><td colspan="3">Citation</td></tr>
<tr><td colspan="3">Ballas J, Hull AD, Saenz C, Warshak CR, Roberts AC, Resnik RR, Moore TR, Ramos GA (2012) Preoperative intravascular balloon catheters and surgical outcomes in pregnancies complicated by placenta accreta: A management paradox. Am J Obstet Gynecol 207(3):216.</td></tr>
<tr><td colspan="3">Affiliation/Source of funds</td></tr>
<tr><td colspan="3">The Divisions of Maternal-Fetal Medicine and Gynecologic Oncology, Department of Reproductive Medicine, and the Division of Interventional Radiology, Department of Radiology, University of California, San Diego, CA and the Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Cincinnati Health Center, Cincinnati, OH. The authors report no conflict of interest.</td></tr>
<tr><td>Study design</td><td>Level of evidence</td><td>Location/setting</td></tr>
<tr><td>Retrospective cohort study</td><td>Level III-2</td><td>Data collected from hospitals and compiled in database at the University of California, San Diego, US</td></tr>
<tr><td colspan="2">Intervention</td><td>Comparator</td></tr>
<tr><td colspan="2">Uterine artery balloon (UAB) catheters (n=59)[a] placed in the proximal internal iliac artery</td><td>No UAB catheters (n=58)</td></tr>
<tr><td colspan="3">Population characteristics</td></tr>
<tr><td colspan="3">117 patients with pathology-proven placenta accreta/percreta that underwent caesarean hysterectomy between 1990 – 2011
UAB: 59 women with pathology-proven accreta/percreta that had UABs placed preoperatively
• Age (mean ± SD): 32.6 ± 5.8; Prior caesarean sections: 0 (n=1, 1.7%), 1 (n=19, 32.2%), 2 or 3 (n=32, 54.2%), 4 (n=7, 11.9%); Final pathology: accreta (n=24, 40.7%), percreta (n=35, 59.3%)
• 30/59 (50.8%) had balloons inflated intraoperatively; 29 of the 30 had balloons inflated once excessive bleeding (haemorrhage) was encountered
No UAB: 58 women with pathology-proven accreta/percreta that did not have UABs
• Age (mean ± SD): 33.2 ± 6.3; Prior caesarean sections: 0 (n=15, 25.9%), 1 (n=19, 32.8%), 2 or 3 (n=19, 32.8%), 4 (n=5, 8.6%); Final pathology: accreta (n=50, 86.2%), percreta (n=8, 13.8%)</td></tr>
<tr><td colspan="2">Length of follow-up</td><td>Outcomes measured</td></tr>
<tr><td colspan="2">NR</td><td>Primary outcomes: estimated blood loss (EBL)[b], the need for transfusion of blood products[c], the number of units of blood products transfused, operative time.
Other outcomes: complications related to the balloon catheters</td></tr>
<tr><td colspan="3">Method of analysis</td></tr>
<tr><td colspan="3">Data that were not normally distributed were log transformed for analysis using parametric statistical tests and retransformed for presentation. Continuous variables were analysed using Student t-test, whereas categorical outcomes were analysed using χ^2 or Fisher exact tests. All analyses were performed using SPSS Statistical Software (version 16.0) and significance was considered at P<0.05.</td></tr>
</table>

INTERNAL VALIDITY

Overall quality assessment (descriptive)

Rating: Fair

Description: The study was a retrospective cohort study based on data in an ongoing placenta accreta database. All subjects were identified by their pathologic diagnosis obtained from hysterectomy specimens. No significant differences in maternal characteristics (age, gravidity and parity). Significant difference in the number of patients who had undergone 0 or 2-3 prior caesarean deliveries in the group that had UAB placed compared with the group that did not.

A significantly greater percentage of those with UABs had a predelivery diagnosis of invasive placentation (selection bias). There were also significantly more cases of placenta percreta, as opposed to accreta, diagnosed pathologically in the group that had UABs placed preoperatively (59.3% vs 13.8%; P<0.01). The author's noted that, although UAB may be useful in reducing total blood loss in the setting of a planned caesarean hysterectomy for placenta accreta, the finding may be biased by the strong correlation with prenatal diagnosis and delivery planning at the study institution. In this study there was a high correlation between prenatal diagnosis and placement of UABs, making it difficult to differentiate between the effects of each. A small group of patients (n=17) were diagnosed with accreta prenatally and did not receive UABs. Although they trended towards a higher mean blood loss, the small number and retrospective study design does not allow for adequate comparison of outcomes. Length of follow-up was not reported, but appeared to be while in hospital (i.e. long enough for relevant outcomes to occur).

RESULTS

Outcome	Intervention (N=59)	Comparator (N=58)	Statistical significance P-value
UAB vs No UAB			
	n/N (%)	n/N (%)	
Need for transfusion (includes PRBC, FFP and platelets)	46/59 (78%)	46/58 (79%)	*No significant difference* P=0.37
Massive transfusion (≥6 units PRBCs)	18/59 (31%)	30/58 (52%)	*Favours UAB* P=0.03
	Mean ± SD	Mean ± SD	
PRBC transfused (units)	4.7 ± 2.1	5.9 ± 1.7	*No significant difference* P=0.14
FFP transfused (units)	3.9 ± 2.1	5.2 ± 2.3	*No significant difference* P=0.17
Platelets transfused (units)	2.1 ± 2.1	2.1 ± 1.9	*No significant difference* P=0.89
UAB (Subgroup 1: balloons inflated intraoperatively) vs UAB (Subgroup 2: balloon not inflated)			
	Subgroup 1 (n=30)	Subgroup 2 (n=29)	
	n/N (%)	n/N (%)	
Need for transfusion	28/30 (93.3%)	18/29 (62.1%)	*Favours group with uninflated UAB* P=0.005
	Mean	Mean	
PRBC transfused (units)	5.7	3.4	*Favours group with uninflated UAB* P=0.02

EXTERNAL VALIDITY

Generalisability

The study was conducted in women with placenta accreta or one of its variants (i.e. percreta) and therefore may not be generalisable to all maternity patients. Effectiveness of the UAB in reducing blood loss/need for transfusion and other clinical outcomes may vary significantly according to how the UAB is utilised intraoperatively (eg. whether the balloon is inflated automatically with fetal delivery or only inflated when indicated with the onset of significant haemorrhage).Overall, generalising the study results is complicated by the "highly variable nature of prenatal diagnosis, delivery planning, operating room protocols, and intraoperative goals such as uterine preservation and attempted removal of the placenta".

Applicability

The study was performed in the US; therefore the results should be applicable to the Australian setting. At the study institution, in the setting of a prenatally diagnosed accreta, a planned delivery via caesarean hysterectomy at 34-35 weeks is coordinated between perinatologists, gynecology-oncologists, neonatologists, and main operating room staff. In addition, interventional radiology is consulted for the placement of UABs on the morning of surgery.
Comments
Author's conclusion: preoperative placement of UABs is relative safe and is associated with a reduced EBL and fewer massive transfusions compared with a group without UABs. "In our primary analysis, the placement of UABs decreases the overall surgical morbidity in our population, as measured by decreased mean estimated blood loss, fewer cases with EBL of more than 2500mL, and fewer massive transfusions despite a substantially higher rate of placenta percreta in the group that received UABs. However, a subanalysis comparing the group that had their UABs inflated intraoperatively shows significantly higher mean EBL and amount of PRBCs transfused". In 29 of the 30 cases in the study (whose UAB was inflated), haemorrhage was the indication for inflating balloons, and in 1 case they were inflated at the time of hysterectomy, thus precluding analysis of the effect of differential timing of UAB inflation.

Abbreviations: CI, confidence interval; EBL, estimated blood loss; FFP, fresh frozen plasma; ITT, intention-to-treat; PP, per-protocol; PRBC, packed red blood cells; RCT, randomised controlled trial; SD, standard deviation; UAB, uterine artery balloon.

a in all but three cases, balloon catheters were placed via the common femoral arteries. In the first three cases, vascular access was achieved via axillary/high brachial arteries.

b EBL was further dichotomised into cases with EBL ≤ or > 2500mL.

c Amount of PRBCs transfused was further dichotomised into cases requiring ≤ or > 6 units of PRBCs (massive transfusion).

STUDY DETAILS: Retrospective cohort study		
Citation		
Shrivastava V, Nageotte M, Major C, Haydon M, Wing D (2007) Case-control comparison of cesarean hysterectomy with and without prophylactic placement of intravascular balloon catheters for placenta accreta. American Journal of Obstetrics & Gynecology 197(4):402-5.		
Affiliation/Source of funds		
Divisions of Maternal-Fetal Medicine, Departments of Obstetrics and Gynecology, Irvine Medical Center, University of California, Orange, CA (Drs Shrivastava, Major, Haydon, and Wing), and Long Beach Memorial Medical Center/Miller's Children's Hospital, Long Beach, CA (Dr Nageotte).		
Study design	Level of evidence	Location/setting
Retrospective cohort study	Level III-2	USA, hospital databases and billing records from two medical facilities
Intervention	Comparator	
Occlusive balloon catheterisation (anterior division of the internal iliac artery) prior to caesarean hysterectomy	No occlusive balloon catheterisation prior to caesarean hysterectomy	
Population characteristics		
69 women who underwent caesarean hysterectomy for presumed placenta accreta or one of its variants, based on pre-specified diagnoses and procedure codes from hospital databases and billing records from 1995 to 2006. Subjects were excluded if they had caesarean hysterectomy performed for other indications such as uterine atony, cervical dysplasia, cervical cancer or uterine rupture. Iliac balloon catheterisation[a]: 19 women who had preoperative balloon catheterisation. 5/19 (26%) had four or more previous caesareans. • Age (mean ± SD): 33 ± 4.7; race (Caucasian) [n (%)]: 7 (37%); gestational age (mean ± SD): 35.3 ± 1.8 • Placental pathology [n (%)]: accreta 13 (68%); increta 4 (21%); percreta 2 (11%) No iliac balloon catheterisation: 50 women who did not have occlusive balloon catheterisation. 3/50 (6%) had four or more previous caesareans. • Age (mean ± SD): 34 ± 6.4; race (Caucasian) [n (%)]: 13 (26%); gestational age (mean ± SD): 33.6 ± 4.8 • Placental pathology [n (%)]: accreta 36 (72%); increta 8 (16%); percreta 6 (12%)		
Length of follow-up	Outcomes measured	
NA	Primary outcomes: estimated blood loss, transfused blood products, operative time, postoperative hospital days Secondary outcomes: development of DIC, febrile morbidity, postoperative ileus, wound complications, need for reoperation	
Method of analysis		
Statistical analysis for the primary outcomes was performed using the Mann-Whitney U test. The association between interventions and discrete variables in the secondary outcomes were analysed using the Fisher exact test. Significance was considered at a probability value of less than .05. A sensitivity analysis was performed to examine the effect of removing those cases in which hysterectomy was performed emergently for intraoperatively diagnosed placenta accreta (which may have skewed the comparator group towards having more blood loss).		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: The method of diagnosis of placenta accreta or its subtypes varied considerably between the groups which may have introduced selection bias such that occlusive balloon catheters were placed in subjects with findings of more severe disease. The retrospective nature of this study means that the outcome assessment was not blinded to exposure status. However, as outcomes were objective, it is unlikely that measurement bias would have occurred. There was no significant difference between the study groups for potential confounders with the exception of ethnicity (more Caucasians in the intervention group) and number of prior caesarean deliveries (intervention group had greater proportion with four or more prior caesareans).		

RESULTS			
Outcome	Intervention (N= 19)	Comparator (N= 50)	Statistical significance P-value
Iliac balloon catheterisation vs no iliac balloon catheterisation			
Transfusion			
	Median (range)	Median (range)	
Transfusion volume, blood products (units)	10 (0-43)	6.5 (0-50)	No significant difference P=0.60
Transfusion volume, blood products excluding intraoperatively diagnosed cases (units)	10 (0-43)	8 (0-54)	No significant difference P=0.81
Thromboembolic events			
	n/N (%)	n/N (%)	
Thrombosis	2/19 (10.5%)[b]	NR	NR
Additional interventions to control bleeding			
	n/N (%)	n/N (%)	
Need for reoperation[c]	4/19 (21%)	6/50 (12%)	P=NR
EXTERNAL VALIDITY			
Generalisability			
The study was conducted in women who underwent caesarean hysterectomy for presumed placenta accreta or one of its variants (increta or precreta) and therefore may not be generalisable to all obstetrics patients. Around 90% of patients in the study had placenta accreta or increta and the results may therefore not be generalisable to patients with the more complicated variant, placenta percreta.			
Applicability			
Although the patients were from medical facilities in the USA, the majority of patients in the cohort were Hispanic. Therefore, the results may be applied in the Australian context but with some caveats on ethnicity and require access to healthcare facilities where interventional radiology is available.			
Comments			
The study was unable to demonstrate any difference in transfusion requirements or need for reoperation in patients receiving prophylactic intravascular balloon catheters.			

Abbreviations: CI, confidence interval; DIC, disseminated intravascular coagulation; SD, standard deviation.
a After delivery of the infant, the balloon catheters were inflated in all subjects and a supracervical or total hysterectomy was performed. The balloons were usually deflated intraoperatively to assure that haemostasis was achieved after the uterus had been removed.
b One patient had an internal iliac artery thrombosis; one had a femoral artery thrombosis.
c The authors did not specify what this entailed or for what purpose (i.e. may not have been specifically to control bleeding).

STUDY DETAILS: Retrospective cohort study		
Citation		
Bodner LJ, Nosher JL, Gribbin C, Siegel RL, Beale S, Scorza W (2006) Balloon-assisted occlusion of the internal iliac arteries in patients with placenta accreta/percreta. Cardiovasc Intervent Radiol 29(3):354-61.		
Affiliation/Source of funds		
Department of Radiology, UMDNJ–Robert Wood Johnson Medical School, Medical Education Building, Room 404, P.O. Box 19, New Brunswick, NJ 08903-0019, USA; Department of Radiology, St. Peters University Hospital, 254 Easton Avenue, New Brunswick, NJ 08903, USA; Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, Saint Peters University Hospital, 254 Easton Avenue, New Brunswick, NJ 08903, USA		
Study design	Level of evidence	Location/setting
Retrospective cohort study	Level III-2	USA/single centre teaching hospital
Intervention	Comparator	
Balloon occlusion (bilateral) of the anterior division of the internal iliac artery prior to scheduled caesarean followed by transcatheter embolisation with Gelfoam pledgets after delivery	No balloon occlusion prior to scheduled caesarean or embolisation after delivery	
Population characteristics		
28 women with a diagnosis of placenta accreta/percreta at a university teaching hospital between June 2000 and December 2002 • Records were retrospectively reviewed • Placenta previa was detected in all 28 patients in the second or third trimester • All patients were scheduled for caesarean section and possible hysterectomy Balloon occlusion and transcatheter embolisation 6 women with an antenatal diagnosis of placenta acreta/percreta • Age (mean): 35.3 years; gestational age (mean): 32.5 weeks No balloon occlusion or transcatheter embolisation 22 women with a postpartum diagnosis of placenta acreta/percreta • Age (mean): 35.3 years; gestational age (mean): 36.5 weeks		
Length of follow-up	Outcomes measured	
NA	Days in the intensive care unit after delivery, total hospital days, volume of transfused blood products, volume of fluid replacement intraoperatively, operating room time, estimated blood loss, postoperative morbidity and mortality	
Method of analysis		
A two-sample, one-tailed Student's t-test was performed		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: The two groups were divided by treatment referral patterns and therefore may be subject to selection bias. The referral bias meant that patients with a prenatal diagnosis of placenta accreta and especially those with a more complicated prenatal course, fell into the embolisation group (reflected in a significantly higher number of days in hospital, p=0.007). The study groups were also significantly different in terms of gestational age at delivery (p=0.019). It is unlikely that the outcome assessment was blinded to exposure status. Given the small sample size, it is also unlikely that the number of participants was large enough to detect a treatment difference.		

RESULTS			
Outcome	Intervention (N=6)	Comparator (N=22)	Statistical significance P-value
Balloon occlusion and embolisation vs no balloon occlusion or embolisation			
Transfusion			
	Mean	Mean	
Volume of blood transfused (units, packed red blood cells)	6.5	6.3	No significant difference P=0.47
Maternal mortality			
	n/N (%)	n/N (%)	
Maternal mortality	0/6 (0%)	0/22 (0%)	P=NR
Additional interventions to control bleeding			
	n/N (%)	n/N (%)	
Overall	6/6 (100%)	22/22 (100%)	P=NR
Hysterectomy	5/6 (83%)[a]	22/22 (100%)	P=NR
Uterine artery ligation	0/6 (0%)	5/22 (23%)	P=NR
Thromboembolic events			
	n/N (%)	n/N (%)	
Myocardial infarction	NR	1/22 (5%)	P=NR
Perinatal mortality			
	n/N (%)	n/N (%)	
Fetal mortality	0/6 (0%)	0/22 (0%)	P=NR
EXTERNAL VALIDITY			
Generalisability			
This study was conducted in patients with placenta accreta/percreta. Therefore, results may not be generalisable to all maternity patients.			
Applicability			
The study was conducted in the USA, where the level of healthcare is likely comparable to that in Australia. For example, it is likely that a diagnosis of placenta previa would also result in a scheduled caesarean section in Australia, as was the case for all 28 patients in the study. As such, the findings are likely applicable but require access to healthcare facilities with interventional radiology. Specific trends relating to intraoperative strategies/protocols may vary between countries or hospitals and warrant consideration. In the study, occlusion balloons were inflated at the time of cord clamping and the results may therefore not be applicable in situations where different strategies with respect to the intraoperative utilisation/timing of occlusion balloon inflation have been adopted. In the present study, balloon occlusion preceded embolisation based on the belief that balloon occlusion would allow temporary control of haemorrhage.			
Comments			
The authors conclude that the findings of the study do not support the contention that, in patients with placenta accreta/percreta, prophylactic temporary balloon occlusion and embolisation prior to hysterectomy diminishes intraoperative blood loss. Given the small sample size, it is unlikely that the number of patients in the study was large enough to detect a treatment difference They also stated that they found "no convincing difference between the two groups" and suggested that it was "not possible to recommend prophylactic embolisation of the anterior division of the uterine arteries prior to caesarean hysterectomy for placenta accreta".			

Abbreviations: CI, confidence interval; SD, standard deviation.

a One patient's bleeding was adequately controlled by prophylactic balloon occlusion and embolisation; therefore, the patient did not undergo a hysterectomy and instead had uterine curettage.

STUDY DETAILS: Prospective cohort study			
Citation			
Levine A, Kuhlman K, Bonn J (1999) Placenta Accreta: Comparison of Cases Managed With and Without Pelvic Artery Balloon Catheters. J Matern Fetal Med 8:173-76.			
Affiliation/Source of funds			
Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania Department of Radiology, Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania			
Study design	Level of evidence	Location/setting	
Prospective cohort study	Level III-2	USA/single hospital	
Intervention	Comparator		
Pelvic artery balloon catheterisation (catheters were placed in the internal iliac arteries n=7, its anterior division n=1, or the uterine arteries n=2).	No pelvic artery balloon catheterisation		
Population characteristics			
9 patients seen at the hospital between January 1994 and August 1997. The age range for the total cohort was 28-38 years. Eight out of nine patients included in the study had a history of at least one prior caesarean delivery. Pelvic artery balloon catheterisation[a]: 5 women with antenatal sonographic diagnosis of placenta accreta No pelvic artery balloon catheterisation: 4 women who were delivered by caesarean hysterectomy for unsuspected placenta accreta			
Length of follow-up	Outcomes measured		
NR	Estimated blood loss, transfusion requirements, complications, length of hospital stay		
Method of analysis			
Statistical analysis were performed using the Mann-Whitney U test			
INTERNAL VALIDITY			
Overall quality assessment (descriptive)			
Rating: Poor Description: The sample size (N=9) was very small and limited the ability to detect any treatment difference. Baseline characteristics were not reported by treatment group; therefore it was difficult to judge whether confounding may have been an issue. Selection bias may be an issue, as it is unclear whether all people who were asked to participate actually took part in the study.			
RESULTS			
Outcome	Intervention (N=5)	Comparator (N=4)	Statistical significance P-value
Pelvic artery catheterisation vs no catheterisation			
Transfusion			
	n/N (%)	n/N (%)	
Transfusion incidence (packed red blood cells)	4/5 (80%)	4/4 (100%)	P=NR
Transfusion incidence (fresh frozen plasma)	1/5 (20%)	0/4 (0%)	P=NR
Transfusion incidence (platelets)	1/5 (20%)	0/4 (0%)	P=NR

	Mean	Mean	
Transfusion dose in transfused patients (units, packed red blood cells)	5.5	4.0	No significant difference P=NS
Transfusion dose in transfused patients (units, fresh frozen plasma)	10	0	P=NR
Transfusion dose in transfused patients (units, platelets)	2	0	P=NR
Perinatal mortality			
	n/N (%)	n/N (%)	
Neonatal mortality	0/5 (0%)	0/4 (0%)	P=NR
Additional interventions to control bleeding			
	n/N (%)	n/N (%)	
Hysterectomy[b]	4/5 (80%)[c]	4/4 (100%)	P=NR
Pelvic artery embolisation	0/5 (0%)	1/4 (25%)	P=NR
EXTERNAL VALIDITY			
Generalisability			
The study was conducted in women with placenta accreta or one of its variants (percreta, increta) and therefore may not be generalisable to all maternity patients.			
Applicability			
Study performed in the USA; therefore the results should be applicable to the Australian setting. Requires access to facilities where interventional radiology is available.			
Comments			
The study found that the use of pelvic artery balloon occlusion catheters in patients requiring caesarean hysterectomy for placenta accreta did not improve surgical outcomes compared with patients managed without balloons. However, these preliminary findings are based on a very small number of patients; therefore, it is unlikely that the study was adequately powered to detect any treatment difference.			

Abbreviations: CI, confidence interval; SD, standard deviation.
a Balloons were inflated after the infant was delivered and the cord clamped. The balloons were deflated at the end of the case, and the catheters removed after documenting haemostasis.
b Delivery by caesarean hysterectomy was a requirement for being included in the comparator group.
c One patient had partial accreta and required only a caesarean section.

Recombinant activated factor VII

Level III evidence

STUDY DETAILS: Retrospective cohort study			
Citation			
Kalina M, Tinkoff G, Fulda G (2011) Massive postpartum hemorrhage: recombinant factor VIIa use is safe but not effective. Del Med J 83(4):109-13.			
Affiliation/Source of funds			
Department of Surgery, Christiana Care Health System; Newark, DE, USA			
Study design	Level of evidence	Location/setting	
Retrospective cohort study	Level III-2	Level One trauma centre; USA	
Intervention	Comparator		
rFVIIa, NovoSeven® (n=8) • Dose ranged between 50 µg/kg and 100 µg/kg • No patient received more than one dose	No rFVIIa (n=19)		
All patients also received a massive transfusion, six units of packed red blood cells, via a massive transfusion protocol[b].			
Population characteristics			
27 obstetric patients with massive PPH[a] • Based on patient records from December 2003 to October 2006 • Age (mean ± SD): 32.5 ± 5.1 years (no significant difference between groups) • Study group had an APACHE II score of 25.8 ± 8.6 (significantly higher than the control group, P=0.009)			
Length of follow-up	Outcomes measured		
NR	Blood product administration, rates of PE, DVT, MI, hysterectomy, and mortality (maternal and fetal), surgical site infection, uterine artery embolisation		
Method of analysis			
Continuous variables within groups were analysed with paired *t-test*, and independent *t-test* between groups. Categorical variables were compared via χ^2 or Fishers Exact test and significance was denoted by a p≤0.05			
INTERNAL VALIDITY			
Overall quality assessment (descriptive)			
Rating: Poor Description: The two groups differed on baseline severity of illness (significantly higher APACHE II scores in the study group compared with controls). Exclusions and loss to follow-up were not applicable, as the study was retrospective and included all relevant patient records. The findings were based on a small number of patients; therefore it is unlikely that the study was adequately powered to detect any treatment difference on some outcomes. Patients chosen to receive intervention also differed from those in the control group as patients only received rFVIIa in circumstances where persistent coagulopathic bleeding existed after the first massive transfusion "pack" was transfused. This was inherent in the massive transfusion protocol at the study institution. High risk that selection bias affected the results.			
RESULTS			
Outcome	Intervention (N=8)	Comparator (N=19)	Statistical significance P-value
rFVIIa vs no rFVIIa			
Transfusion			
	Mean ± SD	Mean ± SD	
Transfused PRBC (units)	19.1 ± 7.8	10.58 ± 5.2	*Favours no rFVIIa* P=0.004

Transfused cryoprecipitate (units)	2.6 ± 0.8	1.0 ± 1.0	*Favours no rFVIIa* P<0.001
Transfused FFP (units)[c]	7.7 ± NR	4.9 ± NR	*No significant difference* P=NR
Transfused platelets (units)[c]	5.0 ± NR	2.0 ± NR	*No significant difference* P=NR
Maternal mortality			
	n/N (%)	n/N (%)	
Maternal mortality	0/8 (0%)	0/19 (0%)	*No significant difference* P=NR
Additional interventions to control bleeding			
	n/N (%)	n/N (%)	
Hysterectomy	6/7 (85.7%)	11/19 (57.9%)	*No significant difference* P=0.357
Uterine artery embolisation	2/7 (28.6%)	2/19 (10.5%)	*No significant difference* P=0.29
Thromboembolic events			
	n/N (%)	n/N (%)	
DVT	0/8 (0%)	0/19 (0%)	*No significant difference* P=NR
PE	0/8 (0%)	0/19 (0%)	*No significant difference* P=NR
MI	0/8 (0%)	0/19 (0%)	*No significant difference* P=NR
Secondary outcomes			
	n/N (%)	n/N (%)	
Fetal mortality	0/8 (0%)	2/19 (10.5%)	*No significant difference* P=0.39
EXTERNAL VALIDITY			
Generalisability			
The results were based on a very small sample size and are affected by patient selection bias. Therefore, they may not be applicable to the general population of maternity patients with PPH.			
Applicability			
Study performed in the USA; therefore, the results should be applicable to the Australian setting.			
Comments			
The authors conclude that rFVIIa use in massive postpartum haemorrhage is safe, "but we found no efficacy in decreasing required blood product transfusions". "Our study suggests that the benefit derived from a massive transfusion protocol instituted once the patient suffers a massive postpartum haemorrhage may have a similar if not greater influence than the use of recombinant Factor VIIa". "Surgical site infections in this study were likely attributable to the emergent nature of the procedure and surgical technique".			

Abbreviations: CI, confidence interval; APACHE, Acute Physiology and Chronic Health Evaluation; DVT, deep vein thrombosis; FFP, fresh frozen plasma; MI, myocardial infarction; NR, not reported; PE, pulmonary embolism; PP, per-protocol; PPH, postpartum haemorrhage; PRBC, packed red blood cells; rFVIIa, activated recombinant factor VII; SD, standard deviation.

a In this study, massive PPH referred to any patient who received six or more units of transfused PRBCs within the first 24 hours.

b According to the massive transfusion protocol at the study institution, a "massive transfusion pack" is administered to patients who sustain a massive haemorrhage. The pack includes six units of PRBCs, four units of FFP, ten units of cryoprecipitate, and one packet of plateletpharesis for transfusion. Recombinant Factor VIIa is administered in accordance with the massive transfusion protocol in circumstances where persistent coagulopathic bleeding exists only after the first "pack" is transfused.

c Publication did not provide numerical values – read from graph

STUDY DETAILS: Retrospective cohort study			
Citation			
Ahonen J, Jokela R, Korttila K (2007) An open non-randomized study of recombinant activated factor VII in major postpartum haemorrhage. Acta Anaesthesiol Scand 51(7):929-36.			
Affiliation/Source of funds			
Department of Anaesthesia and Intensive Care, Helsinki University Hospital, Finland. Source of funds not reported			
Study design	Level of evidence	Location/setting	
Retrospective cohort study	Level III-2	Tertiary referral hospital for high risk pregnancies; Finland	
Intervention		Comparator	
rFVIIa, NovoSeven® (n=26) Dose (mean ± SD (range)): 100 µg/kg ± 14 (73-122)		No rFVIIa (n=22)	
Population characteristics			
48 obstetric patients with major PPH Main cause of bleeding: • Uterine or birth canal tear (n=16); abnormal placentation (n=6); atony (n=17); removal of retained placenta/fragments (n=9) rFVIIa: 26 women who received rFVIIa for the treatment of major PPH • Age (mean ± SD): 33 ± 4; Weeks of gestation (mean ± SD): 38 ± 3; Haemoglobin level (mean ± SD; range): 86 g/l ± 14 (range: 51-109 g/l) • 8 patients (30.8%) underwent peripartum hysterectomy before rFVIIa was administered No rFVIIa: 22 women who were treated as a result of major PPH during the same time period but without the use of rFVIIa • Age (mean ± SD): 33 ± 4; Weeks of gestation (mean ± SD): 38 ± 4 • 6 patients (27.3%) underwent peripartum hysterectomy			
Length of follow-up		Outcomes measured	
NR		Haemoglobin, platelet count, TT, PT, APTT, thrombin time, fibrinogen, AT3, FV, FVIII, D-dimer, bleeding before rFVIIa, total bleeding, RBC, platelets, FFP, fibrinogen concentrate	
Method of analysis			
Data compared using the chi-square and the two-sample, two-tailed Student's t-test assuming unequal variances			
INTERNAL VALIDITY			
Overall quality assessment (descriptive)			
Rating: Fair Description: Exclusions and loss to follow-up were not applicable, as the study was a retrospective hospital-based cohort study (complete patient characteristic and outcome data was available for all patients). No significant differences in baseline patient characteristics or obstetric data between the treatment groups; however, the relative severity of haemorrhage was not reported and it is likely that the decision to use rFVIIa resulted from a more profound haemorrhage (high risk of selection bias). Follow-up was not explicitly stated but appeared to be while in hospital (i.e. long enough for outcomes to occur).			
RESULTS			
Outcome	Intervention (N=26)	Comparator (N=22)	Statistical significance P-value[a]
rFVIIa vs no rFVIIa			
Transfusion incidence			
	Mean ± SD (range)	Mean ± SD (range)	
RBC (units)	20 ± 8 (7-39)	13 ± 6 (6-26)	*Favours no rFVIIa* P=0.003
Platelets (units)	23 ± 12 (8-54)	14 ± 10 (8-48)	*Favours no rFVIIa*

			P=0.014
FFP (units)	12 ± 6 (4-22)	10 ± 5 (4-18)	*No significant difference* P=0.074
	n/N (%)	n/N (%)	
Fibrinogen concentrate	15/26 (57.7%)	5/22 (22.7%)	*Favours no rFVIIa* P=0.014
Additional interventions to control bleeding			
	n/N (%)	n/N (%)	
'Good'[b] response to rFVIIa	17/26 (65.4%)	NA	NA
'Moderate'[c] response to rFVIIa	3/26 (11.5%)	NA	NA
'Poor'[d] response to rFVIIa	6/26 (23.1%)	NA	NA
Thromboembolic events			
Pulmonary embolism	1	NR	NA

EXTERNAL VALIDITY

Generalisability

The study was conducted in women with massive PPH and therefore may not be generalisable to all maternity patients or all women with PPH. In addition, the following population characteristics or study conditions were present that may limit the generalisability of the results:

- all fluids and blood products were administered using one to two Hot LineTM devices (Smiths Medical MD Inc., St Paul, MA, USA)
- all patients actively warmed using a forced air warmer
- in most women, the laboratory values at the time of rFVIIa administration were in accordance with the targets provided in guidelines presented by the authors of the study (Haemoglobin: 70 g/l; TT: 40% (international normalised ratio <1.5); APTT <1.5 x upper normal range; platelets 50 x 109/l; fibrinogen 1.0 g/l (fibrinogen concentrate and/or FFP)
- the blood gas analysis did not reveal severe acidosis or low ionized calcium at the time of rFVIIa administration

Applicability

Study performed in Finland; therefore, the results should be applicable to the Australian setting. According to Guidelines for the use of rFVIIa in major PPH at the study institution, the use of rFVIIa should be considered when the patient has lost about 1.5 times her blood volume.

Comments

The authors stated that "the number of patients is far too small to make any conclusion about the possible association between laboratory parameters and the response to rFVIIa administration"

"rFVIIa should not be used to compensate for an inadequate replacement therapy, and it is unlikely that it could work optimally if there is a lack of the basic and final components of the coagulation cascade. Early and effective administration of RBC, fibrinogen concentrate, FFP and platelets as well as the control of uterine atony [uterine massage and oxytocin, misoprostole, methylergometrine and sulprostone] are the cornerstone of any massive PPH. These manoeuvres are essential before considering the administration of rFVIIa".

"In conclusion, in case of ongoing bleeding, every effort should be made to reveal a localized bleeding which should be managed by surgery or selective arterial embolisation".

"These results or the case reports published recently do not give any evidence to extend the use of rFVIIa into less severe cases of PPH or into its prophylactic use. This policy would result in a profound increase in the overall costs of the treatment".

Abbreviations: APTT, activated partial thromboplastin time; AT3, antithrombin-3; CI, confidence interval; D-dimer, fibrin degradation products; FFP, fresh frozen plasma; FV, factor V; FVIII, factor VIII; NR, not reported; PP, per-protocol; PPH, postpartum haemorrhage; PT, prothrombin time; RBC, red blood cells; rFVIIa, recombinant activated factor VII; SD, standard deviation; TT, thromboplastin time.

a P < 0.05 was considered to be statistically significant

b when bleeding after administration was 1000 ml or less and no additional interventions were needed or only vaginal lacerations were sutured

c when bleeding was more than 1000 ml but no additional surgical or radiological interventions were required

d when cessation of the bleeding necessitated a subsequent selective arterial embolisation or surgical interventions (laparotomy for hemostasis and/or arterial ligation)

e 17 hours after the administration of rFVIIa and cessation of bleeding

STUDY DETAILS: Retrospective cohort study		
Citation		
Hossain N, Shamsi T, Haider S, Soomro N, Khan NH, Memon GU, Farzana T, Ansari S, Triche EW, Kuczynski E, Lockwood CJ, Paidas MJ (2007) Use of recombinant activated factor VII for massive postpartum hemorrhage. Acta Obstet Gynecol Scand 86(10):1200-6.		
Affiliation/Source of funds		
Connecticut, USA: Yale University School of Medicine (Yale Women and Children's Center for Blood Disorders, Yale Center for Perinatal, Pediatric & Environmental Epidemiology, Department of Obstetrics, Gynecology and Reproductive Sciences) Karachi, Pakistan: Bismillah Taqee Institute of Health Sciences & Blood Disorders, Civil Hospital Karachi, Dow University of Health Sciences		
Study design	Level of evidence	Location/setting
Retrospective cohort study	Level III-2	Pakistan/ single centre (Department of Obstetrics and Gynaecology and Surgical Intensive Care Unit of Civil Hospital Karachi)
Intervention		Comparator
rFVIIa (n=18) Dose: • 8 patients received a single dose of 3.6 mg • 7 patients received a single dose of 4.8 mg • 3 patients received two doses of 2.4 mg (3 hours apart)		No rFVIIa (n=16)
Both groups of women were also treated according to standard protocol for the management of PPH, which could include medical and surgical measures, such as use of uterotonic agents, prostaglandins, internal iliac ligation and hysterectomy		
Population characteristics		
34 patients with massive PPH (defined as blood loss >1,500 ml) from March 2005 to October 2006. rFVIIa: 18 women with massive PPH who received rFVIIa (when rFVIIa was available at the hospital and all conventional medical and surgical methods failed to stop bleeding) • Age (median, 25th-75th percentile): 29.0 (26.0 – 32.0) • Baseline haemoglobin: ≥ 60 g/l (n=6, 33.3%); < 60 g/l (n=12 (66.7%) • Baseline PT (median, 25th-75th percentile): 23.0 (17.2 – 39.0) • Baseline aPTT (median, 25th-75th percentile): 50.0 (38.0 – 73.0) No rFVIIa: 16 women with massive PPH who did not receive rFVIIa (i.e. treated with conventional medical and surgical methods only due to limited availability of rFVIIa at the hospital) • Age (median, 25th-75th percentile): 28.5 (25.5 – 30.0) • Baseline haemoglobin: ≥ 60 g/l (n=11, 73.3%); < 60 g/l (n=4 (26.7%) • Baseline PT (median, 25th-75th percentile): 18.0 (14.0 – 21.0) • Baseline aPTT (median, 25th-75th percentile): 38.0 (31.0 – 44.0)		
Length of follow-up	Outcomes measured	
During hospitalisation and in the postpartum period	Maternal mortality, correction of coagulation profile (PT time, aPTT time), transfusion of blood products, preservation of fertility (hysterectomy), adverse drug events	
Method of analysis		
Unadjusted associations between treatment group and baseline parameters were assessed using χ^2 tests for categorical variables and Kruskal-Wallis non-parametric tests for continuous variables. Among the patients treated with rFVIIa, pre- and post- changes in aPTT and PT levels after administration of the drug were examined by calculating change scores for each variable, and testing their significance using the Wilcoxon signed rank test. Unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated from logistic regression models. A final adjusted model was chosen using a backward elimination strategy. Potential confounders remained in the final model if they were independent risk factors for maternal mortality or if their removal resulted in a ≥ 10% change in the treatment group parameter estimate.		

INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: No significant differences in most population characteristics (cause of bleeding, type of delivery, surgical intervention, parity and maternal age). Exclusions and loss to follow-up were not applicable, as the study was retrospective and included all relevant patient records. The decision to administer the drug was based solely on the availability of the drug at the time of the woman's haemorrhage (which was unrelated to patient or provider characteristics). Nonetheless, the drug was administered only after other conventional methods failed and women in the rFVIIa group had worse baseline haematological parameters (Hb, PT, aPTT) than those in the comparison group. The differences would tend to attenuate any effects and may, in part, explain the stronger effects of rFVIIa found in the adjusted logistic regression models than in the unadjusted analyses. Follow-up was during hospitalisation and in the postpartum period. This was long enough for outcomes to occur.				
RESULTS				
Outcome	Intervention (N=18)	Comparator (N=16)	Risk estimate OR [95% CI]	Statistical significance P-value
rFVIIa vs no rFVIIa				
Transfusion				
	Mean ± SD	Mean ± SD		
Units of PRBC transfused	4.0 ± 4.46	9.61 ± 6.7	NR	*Favours rFVIIa* P=0.007
Maternal mortality				
	n/N (%)	n/N (%)		
Maternal mortality[a]	5/18 (28%)[c]	8/16 (50%)	0.29 [0.06, 1.26]	*No significant difference* P=0.09
Maternal mortality[b]	5/18 (28%)	8/16 (50%)	0.04 [0.002, 0.83][d]	*Favours rFVIIa* P=NR
Thromboembolic events				
	n/N (%)	n/N (%)		
Thrombosis	0/18 (0%)	0/16 (0%)	NR	*No significant difference* P=NR
Myocardial infarction	0/18 (0%)	0/16 (0%)	NR	*No significant difference* P=NR
Additional inteventions to control bleeding				
	n/N (%)	n/N (%)		
Total hysterectomy	11/18 (61.1%)	6/16 (37.5%)	NR	*No significant difference* P=NR
EXTERNAL VALIDITY				
Generalisability				
The study was conducted in women with massive PPH and therefore may not be generalisable to all maternity patients or all women with PPH. Generalisability may also be limited by the fact that the study institute did not have the facilities for arterial embolisation and none of the patients were receiving any other anticoagulant therapy.				
Applicability				
Study performed in Pakistan; therefore the results may have limited applicability to the Australian setting due to vastly different availability of resources.				
Comments				
Potential confounders included causes of bleeding, type of delivery, gestational age at delivery, maternal age, baseline PT, baseline aPTT, and baseline haemoglobin "Publication bias towards successful off-label use of new therapies would favour those for which the drug was found to have an affect"				

"Our results support that timely administration of rFVIIa in women with massive PPH improves outcome…. Though there are no clear guidelines on the time of administration of rFVIIa, the consensus opinion is that it should be given before the onset of coagulopathy due to massive transfusion". "Based on our experience, we recommend administering rFVIIa early in order to avoid dilutional coagulopathy". "In conclusion, our observations provide strong evidence for the use of rFVIIa in massive PPH that is unresponsive to conventional haemostatic measures".

Abbreviations: aPTT, activated partial thromboplastin; CI, confidence interval; NR, not reported; OR, odds ratio; PP, per-protocol; PPH, postpartum haemorrhage; PRBC, packed red blood cells; PT, prothrombin; rFVIIa, activated recombinant factor VII.

a In the unadjusted analysis

b In the final adjusted model (adjusted for haemoglobin at delivery and aPTT)

c The results section reported that "22% in the rFVIIa group died" which corresponds to 4/18; however, the discussion states that there were "5 deaths in our treatment group" which corresponds to 28%. The latter results have been reported, as the discussion goes on to explain the specific cause of death of five participants, making it the more reliable information.

d In the final adjusted model (accounting for baseline haemoglobin and aPTT), rFVIIa treatment significantly decreased the likelihood of death by 96%

Tranexamic acid

Level II evidence

STUDY DETAILS: RCT		
Citation		
Abdel-Aleem H., Alhusaini T. K., Abdel-Aleem M. A., Menoufy M., and Gulmezoglu A. M. (2013) Effectiveness of tranexamic acid on blood loss in patients undergoing elective caesarean section: randomized clinical trial. J Matern Fetal Neonatal Med 26 (17) 1705-1709		
Affiliation/Source of funds		
The authors report no declarations of interest. The authors are affiliated with the Department of Obstetrics and Gynecology, Women's Health Centre, Assiut, Egypt and UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research, WHO, Geneva, Switzerland.		
Study design	Level of evidence	Location/setting
RCT	Level II	Egypt, university hospital
Intervention	Comparator	
Tranexamic acid (1g, given slowly intravenously over 10 minutes before operation commenced) + oxytocin (5IU IV bolus and 20IU IV infusion)	No tranexamic acid + oxytocin (5IU IV bolus and 20IU intravenous infusion)	
Population characteristics		
740 pregnant women with singleton fetus at ≥ 37 weeks gestation who underwent an elective caesarean section. Patients were excluded if they had: history of medical disorders, preeclampsia, antepartum haemorrhage, history of thromboembolic disorders, polyhydramnios, macrosomia, history of sensitivity to tranexamic acid and patients taking anticoagulant therapy.		
Length of follow-up	Outcomes measured	
Two hours postoperative	Primary Mean blood loss (mL) (during operation and for two hours after operation) Secondary Incidence of postpartum haemorrhage, cases with postpartum blood loss ≥ 500mL and ≥ 1000mL, the use of additional uterotonics, use of additional surgical intervention to control postpartum haemorrhage, the incidence of mild side effects, mean change in haematocrit value, mean change in haemoglobin value, number of hospital admission days, serious adverse events (such as thromboembolic events), admission to ICU and state of the patient at discharge	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: Subjects were randomised using computer-generated numbers, with allocations kept inside opaque sealed envelopes. The trial was not double-blinded. The nurses measuring the primary outcome were not blinded to the intervention but the authors state they were unaware of the nature of the intervention. Baseline characteristics differed in three categories between the study groups (BMI, duration of surgery and method of delivery of the placenta). To account for these differences, multivariate regression analysis was conducted to adjust for these potential confounders. Loss to follow-up was reported but there were no losses in the study, nor did any of the participants discontinue the intervention.		
RESULTS		

Population analysed	Intervention	Comparator
Randomised	373	367
Efficacy analysis (ITT)	373	367
Efficacy analysis (PP)	NR	NR

Safety analysis	NR		NR	
Outcome	Intervention (N=373)	Comparator (N=367)	Risk estimate (95% CI)	Statistical significance P-value
Tranexamic acid vs no tranexamic acid				
	n/N (%)	n/N (%)		
Additional surgical interventions to control postpartum haemorrhage	0	0	NR	NR
Serious adverse side effects (e.g. thromboembolism)	0	0	NR	NR
Deaths prior to discharge	0	0	NR	NR
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to pregnant women undergoing an elective caesarean.				
Applicability				
The study results are probably applicable to the Australian setting with some caveats. The study was conducted in Egypt.				
Comments				
All participants received oxytocin (5IU IV bolus and 20IU intravenous infusion) according to hospital policy and judgement of the surgeon. As indicated above, three baseline characteristics differed between the study groups; BMI, caesarean section duration and manual delivery of the placenta. However, the authors state that the differences in results between the groups are larger than could be explained by these baseline differences. They conclude that tranexamic acid significantly reduced the amount of blood loss during and after caesarean section but that the trial was not powered to assess safety, particularly thromboembolic complications.				

Abbreviations: CI, confidence interval; ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: RCT		
Citation		
Gungorduk K, Asıcıoğlu O, Yıldırım G, Ark C, Tekirdağ A, Besımoglu B. (2013) Can Intravenous Injection of Tranexamic Acid be Used in Routine Proactice with Active Management of the Third Stage of Labor in Vaginal Delivery? A Randomized Controlled Study. Am J Perinatol 30:407-414.		
Affiliation/Source of funds		
Mardin Women and Children Hospital, Mardin, Turkey; Department of Obstetrics and Gynecology, Kanuni Sultan Süleyman Teaching Hospital, Istanbul, Turkey The study did not receive pharmaceutical company support.		
Study design	Level of evidence	Location/setting
RCT	Level II	Turkey/Single teaching hospital
Intervention	Comparator	
Tranexamic acid 1 g/10 mL TXA diluted in 20 mL 5% glucose administered intravenously at delivery over 5-minutes	Placebo 30 mL of 5% glucose administered intravenously at delivery over 5-minutes	
Population characteristics		
454 women in labour with gestational age between 34 and 42 weeks, a live fetus, cephalic presentation, and expected vaginal birth. Patients were also included if they had risk factors for PPH such as multiple gestation, polyhydramnios, estimated fetal weight ≥ 4500 g, grand multiparity (5 or more), preeclampsia, or previous PPH. Patients were excluded if they presented with placenta previa, placental abruption, had a CS, uterine scarring, abnormal placentation, history of thromboembolic disease, heart, liver, or renal disorders excluded. TXA group 228 women in labour (220 available for analysis) • Age (mean ± SD): 27.9 ± 4.9 years • Gestational age (mean ± SD): 38.6 ± 1.4 weeks • Preoperative Hg (mean ± SD): 11.3 ± 1.1 g/L Control group 226 women in labour (219 available for analysis) • Age (mean ± SD): 27.6 ± 4.8 years • Gestational age (mean ± SD): 39.0 ± 2.7 weeks • Preoperative Hg (mean ± SD): 11.2 ± 1.0 g/L		
Length of follow-up	Outcomes measured	
24 h after surgery and at 3 weeks post-delivery	Primary: Volume of blood loss Other: Incidence of PPH (>500 mL), incidence of severe PPH (≥1000 mL), need for blood transfusion, need for additional uterotonic agents (200 μg IV methylergometrine, 20 IU oxytocin in 500 mL Ringers lactate and/or 800 μg misoprostol), side effects of TXA, PT, active PTT, CBC, liver and renal function tests,	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Good Description: A randomised, double-blind, placebo-controlled study. Simple randomisation using random number tables performed by pharmacy staff that took no further part in the study. Participants and investigators were blinded to the treatment allocation until discharge. Blood loss measurement was subjective (weight of sheet, materials used). After discharge, women who received TXA were specifically instructed on signs and symptoms of thromboembolic events. No significant difference in patient characteristics (age, weight, preoperative laboratory measures, or obstetric interventions) was observed between treatment groups. All patients and infants included in the analysis (modified ITT) for each group were available for follow-up.		
RESULTS		
Population analysed	Intervention	Comparator
Randomised	226	228

Efficacy analysis (modified[a] ITT)	219		220	
Safety analysis	219		220	
Outcome	Intervention (N=219)	Comparator (N=220)	Risk estimate (95% CI)	Statistical significance P-value
TXA vs Placebo				
	n/N (%)	n/N (%)		
Requirement for blood transfusion	1 (0.5%)	3 (1.4%)	RR: 3.01 (0.31 – 28.74)	No significant difference P=0.37
Maternal mortality	0	0	-	-
Additional interventions to control bleeding: surgical interventions	0	0	NR	NR
Thromboembolic events	0	0	-	-
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to women giving birth by vaginal delivery, including those at risk of PPH.				
Applicability				
The study results are probably applicable to the Australian setting.				
Comments				
The authors conclude that use of TXA with standard active management of the third stage of labour significantly reduces postpartum blood loss and results in fewer cases of PPH. The sample size was not sufficient to detect thromboembolic events, or the need for blood transfusion.				

Abbreviations: CI, confidence interval; CS, caesarean section; ITT, intention-to-treat; PPH, postpartum haemorrhage; RCT, randomised controlled trial; SD, standard deviation.

a The authors state that data were analysed on an ITT basis. A modified ITT analysis was reported, which did not include those who were excluded following randomisation due to: caesarean delivery, delivery in bed and chorioamnionitis

STUDY DETAILS: RCT		
Citation		
Senturk MB, Cakmak Y, Yildiz G, Yildiz P (2013) Tranexamic acid for cesarean section: A double-blind, placebo-controlled, randomized clinical trial. Arch Gynecol Obstet 287:641-645.		
Affiliation/Source of funds		
Department of Obstetrics and Gynaecology, Batman Women Health and Children's Hospital, Batman, Turkey; Department of Obstetrics and Gynaecology, Bucak State Hospital, Bucak, Turkey The authors state no conflict of interest / Ministry of Health paid the cost of drugs.		
Study design	Level of evidence	Location/setting
RCT	Level II	Turkey / Hospital setting
Intervention	Comparator	
Tranexamic Acid (TXA) Four ampules equal to 20 cc and 1 g of TXA administered intravenously over 5 minutes before anaesthesia and 10 minutes before incision.	Placebo 20 cc 5% dextrose solution administered intravenously over 5 minutes before anaesthesia and 10 minutes before incision.	
All patients received 20 IU oxytocin IV in bolus form after removal of placenta.		
Population characteristics		
223 healthy women with normal pregnancy undergoing elective and urgent caesarean section. Patients were excluded if they had a high body mass index, venous thromboembolism, uterine myoma, active liver or kidney diseases, polyhydramnios and overweight fetus, allergies to TXA or other drugs (especially NSAID), or patients receiving antithrombotics. TXA group 101 women undergoing elective or urgent caesarean section • Age (mean ± SD): 30.2 ± 6.83 years • Gaviditiy (mean ± SD): 3.98 ± 2.57 • Preoperative Hg (mean ± SD): 11.66 ± 1.02 g/dL Placebo group 122 women undergoing elective or urgent caesarean section • Age (mean ± SD): 29.22 ± 6.93 years • Gaviditiy (mean ± SD): 3.78 ± 2.19 • Preoperative Hg (mean ± SD): 11.86 ± 1.32 g/dL		
Length of follow-up	Outcomes measured	
Laboratory measures taken 2 h prior to surgery and 8 h after CS. 2 weeks after operation	Primary Blood loss volume, Hg, Hct values, RBC counts, Other Liver and kidney function tests, side effects of TXA (nausea, vomiting, venous thrombosis)	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Good Description: A double-blind, placebo-controlled, randomised clinical trial in a single hospital unit, assessing efficacy of IV TXA to reduce intrapartum and postpartum bleeding. Patients were randomised using random number tables. No statistical difference was observed in age, gravidity, weight, systolic and diastolic blood pressure and mean operation duration between the two groups. No differences were observed between the two groups for serum AST, urea and creatinine values before surgery. The measures for ALT (U/l) were higher in the study group (12.85 ± 8.26 vs 10.86 ± 6.64, $p = 0.047$). Appears to be no loss to follow-up, but not specified. No drug allergies or serious GI side effects were observed in patients who received TXA, and neither patient nor baby developed a venous thromboembolism. The need for blood transfusion or any additional interventions to control bleeding were deemed not necessary for patients in either group. Use of oxytocin in all patients may confound the results.		

RESULTS				
Population analysed	Intervention		Comparator	
Randomised	101		122	
Efficacy analysis (ITT)	101		122	
Efficacy analysis (PP)	NR		NR	
Safety analysis	101		122	
Outcome	Intervention (N=101)	Comparator (N=122)	Risk estimate (95% CI)	Significance P-value
TXA vs Placebo				
	n/N (%)	n/N (%)		
Transfusion incidence	None required	None required	NR	NR
Additional interventions to control bleeding (hysterectomy, artery ligation, additional uterotonic agents)	None required	None required	NR	NR
Thromboembolic events	None observed	None observed	NR	NR
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to healthy women giving birth by caesarean section.				
Applicability				
The study results are probably applicable to the Australian setting.				
Comments				
The authors conclude that that TXA is effective in reducing intrapartum and postpartum bleeding in patients giving birth by caesarean section.				

Abbreviations: CI, confidence interval; Hct, Haematocrit; Hgb, Haemoglobin; I TT, intention-to-treat; NSAID, non-steroidal anti-inflammatory drugs; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; SD, standard deviation; TXA, tranexamic acid.

STUDY DETAILS: RCT		
Citation		
Xu J, Gao W, Ju Y. (2013) Tranexamic acid for the prevention of postpartum hemorrhage after cesarean section: a double-blind randomization trial. Arch Gynecol Obstet 287:463-468.		
Affiliation/Source of funds		
Department of Anesthesiology, Daqing Oilfield General Hospital, Daqing, PRC; Department of Anesthesiology, The Second Affiliated Hospital, Harbin Medical University, Harbin, PRC; Department of Intensive Care Unit, The Third Affiliated Hospital, Harbin Medical University, Harbin, PRC. The authors declare no conflicts of interest.		
Study design	Level of evidence	Location/setting
RCT	Level II	PRC/hospital setting
Intervention	Comparator	
Tranexamic acid (TXA) 10mg/kg TXA 200 ml normal saline infused intravenously over 10 – 20 minutes before anaesthesia	Placebo 200 ml normal saline infused intravenously over 10 – 20 minutes before anaesthesia	
After delivery, all patients were given 10 units of oxytocin in normal saline by iv drip over 30 minutes and 0.4mg of iv methylergometrine. Transfusion of packed RBCs occurred if Hg concentration reached 8.0 g/dL and FFP if blood loss exceeded 2500 mL.		
Population characteristics		
176 primipara women aged 22 – 34 years with a singleton pregnancy scheduled to undergo caesarean section. Patients were excluded if they were <18 years, allergic to TXA, had multiple pregnancies, macrosomia, or polyhydramnios, or had severe complications involving the heart, liver, kidney, or brain, or blood disorders, or known hemostatic abnormalities. TXA group 88 primipara women scheduled to undergo caesarean section • Age (mean ± SD): 26.7 ± 3.7 • Gestational age (mean ± SD): 38.7 ± 1.0 • Preoperative Hg level (mean ± SD): 12.4 ± 1.3 Placebo group 88 primipara women scheduled to undergo caesarean section (86 included in analysis) • Age (mean ± SD): 27.1 ± 4.1 • Gestational age (mean ± SD): 38.8 ± 1.1 • Preoperative Hg level (mean ± SD): 12.6 ± 1.2		
Length of follow-up	Outcomes measured	
After placental delivery and at 2 h after birth.	Primary volume of blood loss Other blood pressure, heart rate, respiratory rate, PT, PTT, serum haemoglobin, platelet count, incidence of PPH, side effects of treatment.	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: A double-blind, placebo-controlled, randomised clinical trial. Patients were randomised using a computer-generated, random sequence. Intervention solutions were prepared by an anaesthetist who was not involved in patient management or assessment. Measurement of blood loss was subjective and involved calculated weight of materials used (gauze, pads, sanitary towels etc.). Treatment groups were similar with respect to age, race, gestational age and other preoperative measures. The authors do not report full data on the incidence of blood transfusion and there were some concerns about the higher proportion of patients who received transfusion compared with the intervention group and no reasons were provided to explain the difference. The study was not sufficiently powered to address safety or mortality.		
RESULTS		
Population analysed	Intervention	Comparator
Randomised	88	88

Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	88		86	
Safety analysis	88		86	
Outcome	Intervention (N=88)	Comparator (N=86)	Risk estimate (95% CI)	Statistical significance *P*-value
Tranexamic acid vs Placebo				
	n/N (%)	n/N (%)		
Infusion of packed RBC	8/88 (9%)	19/86 (22%)	NR	NR
Maternal mortality	0	0	NR	NR
Deep vein thrombosis	2/88	2/86	NR	No significant difference *P*=0.38
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to women giving birth by caesarean section.				
Applicability				
The study results are probably applicable to the Australian setting with some caveats.				
Comments				
The authors conclude treatment with TXA 20 minutes prior to anaesthesia in women undergoing elective caesarean section is effective in reducing postoperative blood loss, and that observed side effects are mild and transient.				

Abbreviations: CI, confidence interval; FFP, fresh frozen plasma; Hg, haemoglobin; ITT, intention-to-treat; IV, intravenous; NR, not reported; PP, per-protocol; PPH, postpartum haemorrhage; PRC, People's Republic of China; RCT, randomised controlled trial; SD, standard deviation; TXA, tranexamic acid.

STUDY DETAILS: RCT		
Citation		
Ducloy-Bouthors A-S, Jude B, Duhamel A, Broisin F, Huissoud C, Keita-Meyer H, Mandelbrot L, Tillouche N, Fontaine S, Le Goueff F, Depret-Mosser S, Vallet B, for The EXADELI Study Group and Susen S. (2011) High-dose tranexamic acid reduces blood loss in postpartum haemorrhage. Critical Care 15:R117		
Affiliation/Source of funds		
CHU Lille, Lille France; Université Lille Nord de France, Lille, France; Hôpital de la Croix Rousse, Hôpitaux civils de Lyon, Lyon, France; CHU Louis Mourier, Assistance Publique des Hôpitaux de Paris, Colombes, France; Université Paris 7 - Diderot, Paris, France; Maternité Monaco, centre hospitalier, Valenciennes, France; Maternité Paul Gellée, centre hospitalier, Roubaix, France. The study was funded and monitored by the French Ministry of Health in the "Programme Hospitalier de Recherche Clinique"		
Study design	Level of evidence	Location/setting
RCT	Level II	France/Multicentre obstetrics setting (5 tertiary care centres and 3 secondary obstetric units)
Intervention	Comparator	
TXA Loading dose of 4 g in 50 mL normal saline infused over 1 h, then 1 g/h over 6 h.	No TXA	
Packed RBC and colloids could be used according to French guidelines and the use of additional procoagulant treatments was permitted only in cases involving intractable bleeding. Vascular loading was as follows: crystalloid Ringer's lactate solution (500 mL) and the gelatin plasma expander Gelofusine 4% (500 mL) for the first bleeding litre, then an infusion of gelatin was administered to compensate for blood loss (vol/vol). When blood loss exceeded 2,500 mL, loading was partially supported by an infusion of fresh frozen plasma (FFP). Infusion of PRBCs was indicated when the patient's haemoglobin level was <8 g/dL. The use of additional procoagulant treatment (FFP, platelets and fibrinogen concentrate) was not permitted before 2h after inclusion. Intractable bleeding was defined as PPH >2,500 mL or blood flow >500 mL/30 minutes. Postpartum thromboprophylaxis was carried out with low-molecular-weight heparin 50 IU/kg/day in the patients in severe condition in both groups from day 1 until the inflammatory syndrome disappeared.		
Population characteristics		
154 women with PPH >800 mL within 2 hours of vaginal delivery were deemed eligible for inclusion. Two did not give consent; therefore, a total of 152 women were randomised. All pregnant women receiving prenatal care in third trimester were invited to participate in the study. Patients with PPH >500 mL after vaginal delivery were managed according to the following: bladder catheter, manual removal of retained placenta, genital tract examination, uterine exploration, and administration of oxytocin (30 U/30 min). If these procedures failed sulprostone was administered (500 μg in 1 h). Patients were excluded if they were less than 18 years, presence of known haemostatic abnormalities, history of thrombosis or epilepsy, or had CS. TXA group 78 women with PPH >800 mL within 2 hours of vaginal delivery • Age (mean ± SD): 29 ± 4 years • Gestational age (mean ± SD): 39.5 ± 2 weeks • Atony-related PPH (*n*): 54 Control group 74 women with PPH >800 mL within 2 hours of vaginal delivery • Age (mean ± SD): 28 ± 5 years • Gestational age (mean ± SD): 39.5 ± 1.8 weeks • Atony-related PPH (*n*): 50		

Length of follow-up	Outcomes measured
Blood volume loss measured at 30 min, 2 h, and 6 h. Transfusion of packed RBC at 6 h and at day 42.	Primary Efficacy of TXA in reducing blood loss in PPH. Secondary Effect of TXA on duration of bleeding, anaemia, need for invasive procedures (hysterectomy, surgical artery ligatures, embolisation), need for transfusion, late postpartum curettage, and general outcome (intensive care unit stay, use of any vasopressors, dyspnoea, renal and multiple organ failure), side effects of TXA.

INTERNAL VALIDITY

Overall quality assessment (descriptive)

Rating: Good

Description: Prospective, open-label, multicentre, randomised, controlled trial. Patients were randomised using computer-generated random number sequence. Investigators analysing the data were blinded to treatment allocation. Measurement of blood loss was achieved through the use of specially designed graduated collection pouches. There was no significant difference between treatment groups with respect to patient characteristics (age, weight, obstetric history and delivery interventions) and measures used to manage PPH. The study was not powered to address safety issues, but the authors observe that the only side effects recorded were mild and reversible. Results relating to risk of thrombosis may be confounded by the administration of thromboprophylaxis as recommended for PPH inflammatory syndrome.

RESULTS

Population analysed	Intervention		Comparator	
Randomised	78		74	
Efficacy analysis (ITT)	77		74	
Efficacy analysis (PP)	72		72	
Safety analysis	NR		NR	
Outcome	Intervention (ITT: N=77 PP: N=72)	Comparator (ITT: N=74 PP: N=72)	Risk estimate (95% CI)	Statistical significance P-value
TXA vs No TXA				
	n/N (%)	n/N (%)		
Transfusion volume or incidence				
PRBC transfusion before 6 h	ITT10/77 (13%) PP 7/72 (10%)	ITT 13/74 (18%) PP 12/72 (17%)	NR	No significant difference P=0.17 P=0.65
PRBC transfusion total through day 42	ITT13/77 (17%) PP 9/72 (13%)	ITT 20/74 (27%) PP 20/72 (28%)	NR	No significant difference P=0.33 P=0.16
PRBC Units administered before 6 h	ITT 22[a] PP 18	ITT 38[a] PP 32[a]	NR	No significant difference P=0.27[a] P=0.44[a]
PRBC Units administered total through day 42	ITT 28 PP 24	ITT 62 PP 56[a]	NR	Favours TXA P<0.001 P<0.001
Additional procoagulant treatment (fibrinogen, FFP)	1/72 (1.4%)	7/72 (9.7%)	NR	Favours TXA P=0.001
Maternal mortality				
Maternal mortality	0	0	NR	P=NR

Additional interventions to control bleeding:				
Arterial embolisation	ITT 5/77 (6.5%) PP 4/72 (5.5%)	ITT 5/74 (6.8%) PP 5/72 (6.9%)	NR	No significant difference P=0.94 P=0.73
Surgical arterial ligature or hysterectomy	ITT 0 PP 0	ITT 2/74 (2.7%) PP 2/72 (2.8%)	NR	No significant difference P=0.24 P=0.5
Late postpartum curettage (after day 7)	ITT 1/77 (1.3%) PP 1/72 (1.4%)	ITT 2/74 (2.7%) PP 2/72 (2.8%)	NR	No significant difference P=1.0 P=1.0
Thromboembolic events				
Deep vein thrombosis	ITT 2/77 (3%) PP 2/72 (3%)	ITT 1/74 (1%) PP 1/72 (1%)	NR	No significant difference P=0.4 P=0.37
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to women with active, severe PPH after vaginal delivery.				
Applicability				
The study results are probably applicable to the Australian setting.				
Comments				
The authors conclude that TXA administered to women with overt PPH significantly decreases blood loss, bleeding duration, and results in fewer additional procoagulant treatments. The need for PRBC transfusion is also reduced in the TXA group. In addition, the authors noted that the study was not powered to detect differences in maternal death or number of invasive procedures (which are ultimately the goals of maternity treatment) and "the power of the study does not allow for a definite conclusion regarding the risk of thrombosis" related to TXA.				

Abbreviations: CI, confidence interval; ITT, intention-to-treat; PP, per-protocol; PRBC, packed red blood cell; RCT, randomised controlled trial; SD, standard deviation; TXA, tranexamic acid.

a The value specified differs from the published data. The author was contacted to clarify data and has acknowledged and corrected the error.

STUDY DETAILS: RCT		
Citation		
Gungorduk K, Yıldırım G, Asıcıoğlu O, Gungorduk OC, Sudolmus S, Ark C. (2011) Efficacy of Intravenous Tranexamic Acid in Reducing Blood Loss after Elective Cesarean Section: A Prospective, Randomized, Double-Blind, Placebo-Controlled Study. Am J Perinatol 28:233-240.		
Affiliation/Source of funds		
Department of Obstetrics and Gynecology, Mardin Women and Children Hospital, Mardin; Department of Obstetrics and Gynecology, Istanbul Bakirkoy Women and Children Hospital, Istanbul, Turkey. Source of funds not reported		
Study design	Level of evidence	Location/setting
RCT	II	Turkey /Single teaching hospital

Intervention	Comparator
Tranexamic acid (TXA) 1 g/10 mL diluted with 20 mL of 5% glucose administered intravenously over a 5-minute period and 10 minutes prior to incision	Placebo 30 mL 5% glucose administered intravenously over a 5-minute period and 10 minutes prior to incision
After delivery, all patients received 5 IU IV bolus of oxytocin, then 30 IU oxytocin in 500 mL lactated Ringer's solution infused at a rate of 125 mL/h and 1 g cefazolin diluted in 20 mL normal saline administered over a 5-minute period.	
Population characteristics	
660 women undergoing elective caesarean section after 38 weeks estimated gestational age. Patients with increased risk of PPH such as anaemia (Hg <7 g%), multiple gestation, antepartum haemorrhage (placenta previa, placental abruption), abnormal placentation (accreta, increta, percreta), uterine fibroids, polyhydramnios, history of uterine atony and postpartum bleeding, current of previous history of significant disease (e.g. heart, liver or renal disease) were excluded. TXA group 330 women undergoing elective caesarean section after 38 weeks estimated gestational age • Age (mean ± SD): 26.3 ± 3.5 years • Gestational age (mean ± SD) 38.7 ± 0.6 weeks • Preoperative Hg (mean ± SD): 11.4 ± 0.8 g/L Placebo group 330 women undergoing elective caesarean section after 38 weeks estimated gestational age • Age(mean ± SD): 26.6 ± 3.6 years • Gestational age (mean ± SD): 38.8 ± 0.6 weeks • Preoperative Hg (mean ± SD): 11.3 ± 0.6 g/L	
Length of follow-up	Outcomes measured
Immediately after placental delivery, and 1 and 2 hours after birth Side effects measured 2nd day after birth and 3 and 6 weeks after surgery	Primary estimated blood loss during CS calculated via difference in haematocrit values Other vital signs (heart rate, blood pressure, respiratory rate), laboratory measures (prothrombin time, active prothrombin time, CBC, liver and renal function tests), need for additional uterotonic agents (e.g. oxytocin, prostaglandin F2α), excessive bleeding (estimated blood loss >1000 mL), need for blood transfusion, TXA side effects, thromboembolic events, duration of hospital stay, neonatal outcomes

INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: A double-blind, placebo-controlled, randomised clinical trial in a large teaching hospital. Patients were randomised using a random number table by staff who took no further part in the study. Providers and patients were blinded to the intervention. Treatment groups were similar with respect to maternal demographics, indications for caesarean delivery, and other preoperative measures. Maternal and neonatal outcomes did not differ significantly between treatment groups. The authors report no loss to follow-up. The study was too small to assess parameters such as thromboembolic events, or maternal/perinatal mortality. The study was also limited by the exclusion of women at high risk for PPH.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	330		330	
Efficacy analysis (ITT)	330		330	
Efficacy analysis (PP)	330		330	
Safety analysis	330		330	
Outcome	Intervention (N=330)	Comparator (N=330)	Risk estimate (95% CI)	Significance *P*-value
Tranexamic acid vs Placebo				
	n/N (%)	n/N (%)		
Packed RBC transfusion	2/330 (0.6%)	7/330 (2.1%)	RR 3.5 (0.7-16.7)	No significant difference *P*=0.17
Volume of packed RBC transfusion in transfused patients (units)	Mean: 1.5[a]	Mean: 1.6[b]		
Additional interventions to control bleeding: surgical procedures (B-lynch suture, uterine artery ligation, hysterectomy)	0	0	-	-
Thromboembolic events (DVT, myocardial infarction, stroke, renal failure, pulmonary embolism)	0	0	-	-
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to women giving birth by caesarean section with low risk of PPH.				
Applicability				
The study results are probably applicable to the Australian setting.				
Comments				
The authors conclude TXA is safe and significantly reduces bleeding, blood loss, and the need for use of additional uterotonic agents in women undergoing elective caesarean section.				

Abbreviations: CI, confidence interval; CBC, complete blood count; Hg, Haemoglobin; ITT, intention-to-treat; PP, per-protocol; PPH, postpartum haemorrhage, RBC, red blood cell; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation; TXA, tranexamic acid; TE, thromboembolic events.
a Calculated post hoc: One patient received 1 unit and one patient received 2 units
b Calculated post hoc: Four patients received 1 unit, two patients received 2 units, one patient received 3 units

STUDY DETAILS: RCT		
Citation		
Gai M, Wu L, Su Q, Tatsumoto K. (2004) Clinical observation of blood loss reduced by tranexamic acid during and after caesarian section: a multi-center, randomized trial. Eur J Obstet Gynecol Reprod Biol 112:154-157.		
Affiliation/Source of funds		
Department of Obstetrics and Gynecology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China; Beijing Gynecological and Obstetrical Hospital, Beijing, China; Shanghai International Peace Maternity & Child Health Hospital, Shanghai, China; International Medical Communications Department, Daiichi Pharmaceutical Co. Ltd., Tokyo, Japan Source of funds not reported.		
Study design	Level of evidence	Location/setting
RCT	Level II	PRC/Multicentre hospital setting
Intervention	Comparator	
Tranexamic acid (TXA) 1 g/10 mL TXA diluted with 20 mL 5% glucose administered intravenously over 5 minutes and 10 minutes before incision	No TXA	
After delivery, all patients received 10 U oxytocin IV drip and 20 U oxytocin into intrauterine wall		
Population characteristics		
180 primipara women with singleton delivered by caesarean section. Patients were excluded if they had a blood disorder, severe medical or surgical complications involving the heart, liver, kidneys, or brain, allergy to TXA, history of thromboembolic disorders, abnormal placenta, severe pregnancy complications, multiple pregnancies, or complications with myoma. TXA group 91 term primipara women undergoing caesarean section • Age (mean ± SD): 29.71 ± 4.18 • Gestational age (mean ± SD): 38.80 ± 1.11 Control group 89 term primipara women undergoing caesarean section • Age (mean ± SD): 29.75 ± 4.01 • Gestational age (mean ± SD): 38.67 ± 1.03		
Length of follow-up	Outcomes measured	
After placental delivery and at 1 and 2 h after birth Postoperative laboratory measures taken on 3rd day after birth	Efficacy: volume of blood loss, incidence of PPH (bleeding > 400 mL within 2h after birth) Safety: vital signs (HR, RR, BP), Side effects of TXA including general and local site reactions, laboratory measures (CBC, urinalysis, liver function, kidney function, prothrombin time and activity) Other: uterine contractility, placental separation, neonatal manifestations	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: Prospective, randomised, case-controlled clinical trial. Study was not blinded. Patients were randomised using a consecutive numbered chart. Treatment groups were similar with respect to age, race, gestational age and other preoperative measures. Authors report no statistical difference in obstetrics measures/indications for CS between the two groups, but data not provided. Measurement of blood loss was subjective and involved calculated weight of materials used (gauze, pads, sanitary towels etc.). No significant difference in neonatal outcomes observed (mean birth weight, Apgar score). Authors do not report on whether or not transfusions were required or if additional interventions to control bleeding were administered.		
RESULTS		
Population analysed	Intervention	Comparator
Randomised	NR	NR

Efficacy analysis (ITT)	91		89	
Efficacy analysis (PP)	NR		NR	
Safety analysis	91		89	
Outcome	Intervention (N=91)	Comparator (N=89)	Risk estimate (95% CI)	Statistical significance P-value
TXA vs No TXA				
	n/N (%)	n/N (%)		
Thromboembolic events	None observed	NR		
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to healthy women giving birth by caesarean section. The results may not be generalisable to all maternity patients (e.g. those with placenta problems).				
Applicability				
The study results are probably applicable to the Australian setting.				
Comments				
The authors conclude that TXA significantly reduces bleeding and the incidence of PPH in the period between placental delivery to 2 h postpartum and report significant side effects following the administration of TXA in the study group.				

Abbreviations: CI, confidence interval; BP, blood pressure; CBC, complete blood count; HR, heart rate; ITT, intention-to-treat; IV, intravenous; PP, per-protocol; PPH, postpartum haemorrhage; PRC, People's Republic of China; RCT, randomised controlled trial; RR, respiratory rate; SD, standard deviation; TXA, tranexamic acid.

Level III evidence

STUDY DETAILS: Retrospective cohort study		
Citation		
Lindoff C, Rybo G, Astedt B. Treatment with tranexamic acid during pregnancy, and the risk of thrombo-embolic complications. Thromb Haemost 1993;70:238-40		
Affiliation/Source of funds		
Department of Obstetrics and Gynaecology, University of Lund, University Hospital, Lund, Sweden; University of Gothenburg, Eastern Hospital, Gothenburg, Sweden. The work was supported by the Medical Faculty of the Universities of Lund and Gothenburg, and by the Swedish Medical Research Council (Grant No. 04523).		
Study design	Level of evidence	Location/setting
Retrospective cohort study	Level III-2	Two hospitals; Lund and Gothenburg, Sweden
Intervention	Comparator	
Tranexamic acid (n=256) • Treatment continued until delivery • Mean duration of treatment: 46 days • Standard dose: 3g daily	No tranexamic acid (n=1,846)	
Population characteristics		
2,102 obstetric patients with placental abruption, placenta praevia or unspecified antepartum haemorrhage • The 2,102 patients with various bleeding disorders during pregnancy were identified from a larger group of 53,452 patients (i.e. all of the deliveries performed at the two study hospitals between 1979 and 1988). mic acid group: 256 women who received tranexamic acid • 169 (66.0%) out of 256 were delivered by caesarean section • 135 (52.7%) out of 256 were diagnosed with placental abruption; 75 (29.3%) with placenta praevia; 46 (18.0%) with unspecified antepartum haemorrhage • 104 (40.6%) out of 256 were treated for 1-3 days; 46 (18.0%) for 3-7 days; 106 (41.4%) for >7 days xamic acid group: 1,846 women who did not receive tranexamic acid • 443 (24.0%) out of 1,846 were delivered by caesarean section • 212 (11.5%) out of 1,846 were diagnosed with placental abruption; 89 (4.8%) with placenta praevia; 1,545 (83.7%) with unspecified antepartum haemorrhage		
Length of follow-up	Outcomes measured	
NR	Complications during pregnancy and labour, arterial and venous thromboembolic complications	
Method of analysis		
Results were analysed using odds ratios with 95% confidence limits and p-values. Odd ratios for the occurrence of thrombo-embolism were calculated both for the group of patients with bleeding disorders (n=2,102) and the subgroup of patients delivered by caesarean section (n=612).		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Poor Description: The treatment groups differed substantially based on the diagnosis/reason for bleeding (eg. 52.7% in the study group had placental abruption compared to 11.5% in the control group; 29.3% had placenta praevia in the study group compared to 4.8% in the control group). Importantly, the reason for treatment with tranexamic acid was a more severe bleeding complication; therefore, the authors conclude that the study group was presumably more prone to thrombosis. High risk that selection bias affected the results.		

RESULTS				
Tranexamic acid vs No tranexamic acid				
Outcome	Intervention (N=256)	Comparator (N=1,846)	Risk estimate OR [95% CI]	Statistical significance P-value
Thromboembolic events				
	n/N (%)	n/N (%)		
Thromboembolism	2/256 (0.78%)[a]	4/1846 (0.22%)	3.6 [0.7-17.8]	*No significant difference* P>0.16
Subanalysis: Tranexamic acid vs No tranexamic acid in patients delivered by caesarean section				
Outcome	Intervention (N=169)	Comparator (N=443)	Risk estimate OR [95% CI]	Statistical significance P-value
Thromboembolic events				
	n/N (%)	n/N (%)		
Thromboembolism	1/169 (0.59%)	4/443 (0.90%)	0.65 [0.1-5.8]	*No significant difference* P>0.16
PE	1/169 (0.59%)	1/443 (0.23%)	NR	
DVT	NR	3/443 (0.68%)	NR	
EXTERNAL VALIDITY				
Generalisability				
The study was conducted in women with placental abruption, placenta praevia or unspecified antepartum haemorrhage, with a subanalysis conducted for caesarean deliveries; therefore, the results may not be generalisable to all maternity patients.				
Applicability				
Study performed in Sweden; therefore, the results should be applicable to the Australian setting.				
Comments				
The authors conclude that the the administration of AMCA to a risk group with complicated pregnancies frequently delivered by Caesarean section has elicited no conclusive evidence of any thrombogenic effect of AMCA, and there would seem to be no reason to alter the indications for AMCA treatment or the recommended dosages.				

Abbreviations: AMCA, tranexamic acid; CI, confidence interval; DVT, deep vein thrombosis; OR, odds ratio; PE, pulmonary embolism; PP, per-protocol; SD, standard deviation.

a Both were pulmonary embolisms, one occurred after 61 days of treatment with tranexamic acid (delivered via emergency caesarean section) and the other after 15 days of treatment (delivered vaginally).