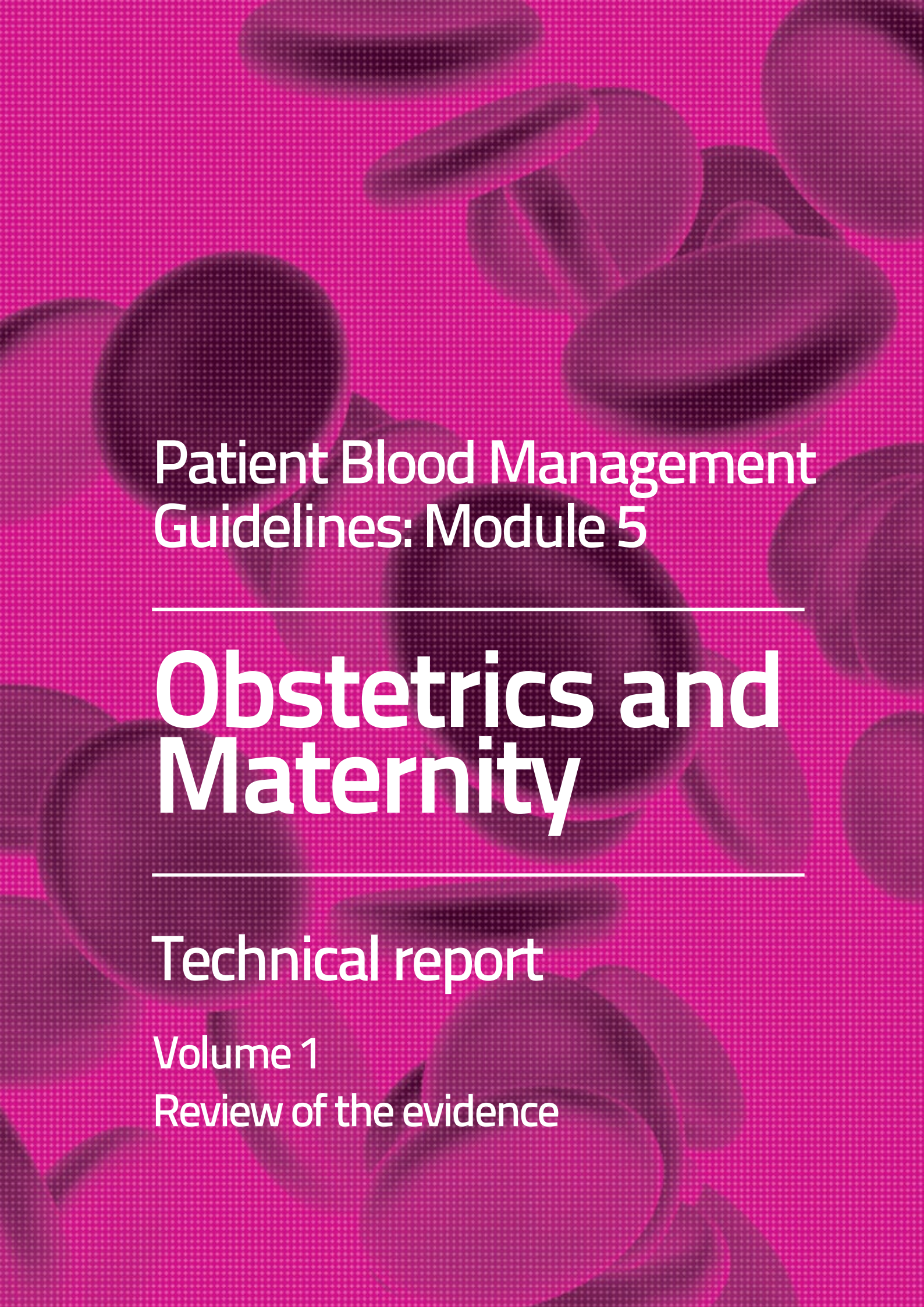

Patient Blood Management Guidelines: Module 5

Obstetrics and Maternity

Technical report

Volume 1
Review of the evidence

Note

This volume presents the main body of evidence found by a systematic literature review on obstetric and maternity patient blood management. Volume 2 presents the related appendixes (Appendix A to Appendix F). These two volumes cover all research questions developed for this topic.

Contents

Tables

Abbreviations and acronyms

APACHE	acute physiology and chronic health evaluation
APH	antepartum haemorrhage
APTT	activated partial thromboplastin time
ASBT	Australasian Society of Blood Transfusion
CI	confidence interval
CADTH	Canadian Agency for Drugs and Technologies in Health
CRG	Consumer/Clinical Reference Group
ES	evidence statement
ESA	erythropoiesis stimulating agent
EWG	Expert Working Group
FFP	fresh frozen plasma
Hb	haemoglobin
HTA	health technology assessment
ICU	intensive care unit
IM	intramuscular
INR	international normalisation ratio
IR	interventional radiology
IV	intravenous
MD	mean difference
MTP	massive transfusion protocol
NBA	National Blood Authority
NHMRC	National Health and Medical Research Council
NICE	National Institute for Health and Clinical Excellence (UK)
NR	not reported
OR	odds ratio
PBM	patient blood management
PICO	population, intervention, comparator, outcome
POC	point of care
PPH	postpartum haemorrhage

PRBC	packed red blood cells
PT	prothrombin time
R	recommendation
RCT	randomised controlled trial
RBC	red blood cells
rFVIIa	recombinant activated factor VII
RR	relative risk
SD	standard deviation
TACO	transfusion-related circulatory volume overload
TGA	Therapeutic Goods Administration
TRALI	transfusion-related acute lung injury
TTP	thrombocytopenic purpura
TXA	tranexamic acid
UAB	uterine artery balloon
WHO	World Health Organization

1 Introduction

This document presents the methods and results relating to the findings from a systematic literature review on obstetric and maternity patient blood management. It is the first volume of a technical report produced as part of the development process for the *Patient blood management guidelines: Module 5 – Obstetrics and Maternity* – the fifth in a series of six modules that focus on evidence-based patient blood management and will replace the 2001 National Health and Medical Research Council/Australasian Society of Blood Transfusion (NHMRC/ASBT) *Clinical practice guidelines on the use of blood components*.[1] The six modules of the guidelines are being developed in three phases, as shown in **Table 1.1**.

Table 1.1 Phases of development of guideline modules

Phase	Modules
I	Critical bleeding/massive transfusion
	Perioperative
II	Medical
	Critical care
III	Obstetrics and Maternity
	Paediatric/neonatal

This volume covers all the research questions. Volume 2 of the technical report presents the related appendixes.

The document Patient blood management guidelines: *Module 5 – Obstetrics and Maternity* gives information on:

- governance arrangements for the guidelines
- committee memberships and affiliations
- the background research team.

2 Methods

2.1 Research question development

An Expert Working Group (EWG) met for the first time in July 2008. At this meeting members were provided with a comprehensive analysis of existing guidelines relevant to the clinical areas of focus. An independent systematic review expert provided a detailed presentation on framing clinical questions for systematic review. EWG members self-nominated to participate in relevant areas of clinical focus for each module. This action formed the basis for the establishment of a Consumer/Clinical Reference Group (CRG) for each module.

Following the July 2008 meeting, members of each CRG generated questions to be considered for inclusion in their respective guidelines. Before the next meeting, CRG members discussed first-draft questions, and acknowledged that question content would influence consideration of expanding CRG memberships to ensure relevant clinical and consumer representation. CRG members agreed that it would be appropriate to circulate draft questions to relevant clinical colleges and societies for input and feedback at an early stage and before inclusion in a statement of requirement for a systematic reviewer.

The EWG met in September 2008 to further develop and prioritise the proposed questions. During the development of research questions, it became apparent that several questions would be relevant for systematic review for all modules (Phases I to III). These became known as generic questions; six of these were ultimately developed.

Another two workshop meetings were held in November 2008. All EWG members attended these meetings, where questions were further prioritised, combined and refined. In January 2009, a meeting of the CRG Chairs finalised questions that were subsequently provided to systematic reviewers.

This process resulted in *generic* (i.e. relevant to all six modules in the series) and *specific* (i.e. specific to each module) foreground questions for systematic review and questions for background research. The background questions were to be addressed through general research undertaken by registrars supervised by CRG members. Background questions were designed to provide general information for the guidelines and to assist in providing generalised clinical practice tips. They were intended to capture information that was considered to fall outside the scope of the foreground questions addressed by the systematic literature review. Foreground and background questions were further refined through consultation among the systematic reviewers and technical writer, the CRG, the National Blood Authority (NBA) and the independent systematic review expert.

Research questions were developed for all but the critical care module. The requirement for this module was not identified until after the initial systematic review for Phase I had commenced.

Intervention questions were intended to determine the effects on patient outcomes of various strategies that can be used in patient blood management. The aetiology question was designed to determine whether the risk factor anaemia causes adverse outcomes. The prognostic question was concerned with clinical information that predicts outcomes.

2.1.1 Foreground research questions

Research questions to be investigated in the obstetrics and maternity module were reviewed or developed by the CRG at a face-to-face workshop held on 18–19 February 2013. Generic research questions and a specific research question were developed and refined at the

workshop, and were then further refined via email correspondence and during teleconferences held between February and 7 June 2013.

There are four foreground research questions for this module. Questions 1–3 are generic questions (relevant to all six modules of these guidelines), whereas Question 4 is specific to this module:

- *Question 1* – In maternity patients, what is the effect of red blood cell (RBC) transfusion on patient outcomes? (Interventional question)
- *Question 2* – In maternity patients, what is the effect of non-transfusion interventions to increase haemoglobin (Hb) concentration on morbidity, mortality and need for RBC blood transfusion? (Interventional question)
- *Question 3* – In maternity patients, what is the effect of fresh frozen plasma (FFP), cryoprecipitate, fibrinogen concentrate, and/or platelet transfusion on patient outcomes? (Interventional question)
- *Question 4* – In maternity patients, what is the effect of non-obstetric strategies that aim to minimise maternal blood loss in the peripartum period on transfusion and clinical outcomes? (Interventional question)

The term 'maternity' was chosen to describe to the patient population of interest throughout the module and technical reports (instead of 'obstetric'). This is because 'maternity' refers to pregnant women, and women at the time of childbirth and in the recuperative period following birth, whereas 'obstetrics' refers to the branch of medicine that deals with the care of women during pregnancy and childbirth. It can be argued that because the majority of pregnant women are not sick, they are not patients. However, for ease of reading and clarity, the CRG agreed to use the term 'women' where possible and the term 'maternity patients' rather than the more cumbersome 'women who use maternity services' or 'pregnant and postpartum women' throughout. This also prevents limiting the guideline to obstetric care. An exception is 'women with major obstetric haemorrhage' as this is a specific sub-group of patients that needed to be defined. The terms in the evidence statements reflect the populations identified in the underlying evidence.

Further, the term 'neonate' was used to reflect the evidence when referring to the newborn. This is because 'neonate' refers to a defined period of time up to 28 days following birth, whereas 'newborn' has no scientific definition.

Two questions were excluded from the Phase II and Phase III modules because they were not interventional questions; hence, clinical recommendations could not easily be made. The first was an aetiological question (Is anaemia an independent risk factor for adverse outcomes?) and the other was a prognostic question (At what international normalised ratio (INR) (or prothrombin time [PT]/partial thromboplastin time [APTT]) for FFP, fibrinogen level for cryoprecipitate, platelet count for platelets concentrates should patients be transfused to avoid risks of significant adverse events?).

One further question (What is the effect of rFVIIa [prophylaxis or treatment] on morbidity, mortality and transfusion rate?) was not covered in the Phase II modules because it had already been covered in Phase I. This question was excluded as a separate question from the Phase III modules, but rFVIIa was included as an intervention within the specific question (i.e. Question 4).

Details of research question criteria are presented in **Appendix 1** of this volume.

2.1.2 Background research questions

The background research questions developed for maternity patient blood management were:

- Is anaemia an independent risk factor for adverse pregnancy outcomes? What recommendations should be made for the detection, diagnosis and management of anaemia during pregnancy?
- What guidance can be given regarding transfusion support for maternity services?
- What obstetric-specific factors should be considered in adapting and/or modifying a massive transfusion protocol?
- What guidance can be provided to assist in the care of maternity patients for whom transfusion is not acceptable?

2.1.3 Aboriginal and Torres Strait Islander populations

Prevalence of anaemia in Aboriginal and Torres Strait Islander populations is known to be higher than in the general Australian population.[2] The electronic search terms did not specifically search for or limit retrieval of articles to studies that addressed socioeconomic, Aboriginal or Torres Strait Islander subgroups. However, in accordance with NHMRC guideline development requirements, the reviewers were required to isolate any papers addressing these populations for specific consideration by the CRG. No papers were identified that addressed these populations specifically.

2.2 Literature searches

NHMRC standards and procedures require that clinical practice guidelines be based on systematic identification and synthesis of the best available scientific evidence.[3] Systematic reviews were conducted for all generic and specific research questions, using a stepped process in which the highest level body of evidence was assessed before lower levels of evidence were considered. If there was sufficient Level I evidence to address all primary outcomes of a research question (as specified in the population, intervention, comparator, outcome [PICO] criteria), Level II and III evidence was not assessed. However, the literature search was updated to identify any Level II studies published since the search date of the key Level I evidence. If no relevant Level I evidence was available for a particular research question, a literature search was conducted to identify Level II studies, and if no studies were identified, the process was repeated for lower level evidence (if specified in the PICO criteria). For primary outcomes not addressed in higher level evidence, a search of lower level evidence was conducted for those particular outcomes only.

Three main strategies were used to identify all potentially relevant literature: electronic database searching, manual searching, and literature recommended by expert members of the CRG.

2.2.1 Electronic databases

The systematic reviewers carried out searches using the following primary databases:

- EMBASE and Medline via the EMBASE.com interface
- Cochrane Library Database: a database of systematic reviews, other reviews, clinical trials, methods studies, technology assessments, economic evaluations and Cochrane Groups.

Search strategies for all primary databases were developed in consultation with a specialist search strategist. All strategies were based on the PICO criteria developed for the research

questions (**Appendix 1** in this volume). Full details of all search strategies, including the search dates, for the primary databases are presented in **Appendix A** (Volume 2).

Additional secondary databases searched included Health Technology Assessment (HTA) agency websites (e.g. NICE in the UK, CADTH in Canada), guideline websites and databases (e.g. Guidelines International Network, National Guidelines Clearing House), clinical trial registries (e.g. Current Controlled Trials MetaRegister) and PreMedline (accessed via the PubMed interface and limited to 12 months from the search date).

Each secondary database was searched by a single reviewer using simple search strategies (based on those developed for the primary databases) and articles that met the inclusion criteria identified. Searches of the secondary databases occurred on 13 and 14 June 2013.

2.2.2 Manual searching of reference lists

Members of the systematic review/technical writing group manually hand-searched reference lists included in relevant articles identified by the systematic literature search. This strategy identified some additional articles that were not found in electronic database searches. Additional articles found by manual searching are indicated in the literature search results presented in **Appendix C** (Volume 2).

2.2.3 Expert sources

Articles recommended by CRG members were considered for inclusion, provided the articles met the criteria for inclusion.

2.2.4 Background question research

Research for background questions was undertaken by registrars under the supervision of CRG members. These questions were not researched by applying systematic review processes. Registrars were advised to use sources ranging from medical textbooks, grey literature, published scientific and review articles (identified through PubMed, EMBASE or Cochrane databases), series yearbooks and other relevant medical literature. Because the intention was to identify relevant information that could inform best practice, background research was not limited to evidence or general information only applicable to Australia and New Zealand.

2.2.5 Issues relevant to Aboriginal and Torres Strait Islander peoples and culturally and linguistically diverse communities

The focus of the systematic review was on physiological parameters surrounding the decision to transfuse. As such, there were no distinct physiological issues relevant to Aboriginal and Torres Strait Islander peoples, and culturally and linguistically diverse communities.

The greater prevalence of certain conditions (e.g. anaemia and chronic kidney disease) in some Indigenous Australian communities has a socioeconomic, not physiological, basis. No socioeconomic literature pertaining to Australia's Aboriginal and Torres Strait Islander peoples was identified in the literature searches for any research question.

2.2.6 Cost effectiveness

A specific literature search for economic evidence was not conducted. It was intended that the technical report would incorporate an appraisal of any relevant economic evidence if identified in the literature searches; however, no such evidence was found.

2.3 Inclusion and exclusion criteria

Inclusion criteria were determined from the PICO criteria that formed the basis of the systematically reviewed research questions (**Appendix 1** in this volume). Studies reporting at least one of the primary outcomes were eligible for inclusion if they also satisfied the correct intervention and comparator criteria. Studies that did not meet one or more of these criteria were excluded.

Additional reasons for excluding studies were:

- non-human studies
- non-English language studies
- non-systematic reviews, editorials, opinion pieces and letters
- case series, pre–post or post studies
- research or systematic review protocols not defined.

Titles and abstracts of every record retrieved by searching the primary and secondary databases were reviewed, and full articles were retrieved for further assessment where the articles were considered to meet the inclusion criteria. Articles that could not be included or excluded on the basis of information in the title or abstract were retrieved as full text before a final decision was made on inclusion or exclusion.

One reviewer from the evidence review team screened the titles and abstracts (where available) for all citations retrieved by the literature search. A second reviewer then performed quality checks on a random subset of excluded citations. All citations listed for inclusion for full text review were independently assessed by a second reviewer. Any disagreements were resolved by a third reviewer.

Articles reporting on the basis of the following study designs were considered for inclusion when PICO criteria were met:

- systematic reviews of randomised controlled trials (RCTs) and/or cohort studies
- RCTs or pseudo-RCTs
- cohort studies
- case–control studies

Studies that initially met inclusion criteria but were later excluded are documented, with reasons for their exclusion, in **Appendix B** (Volume 2). Examples of reasons for exclusion in this circumstance include different systematic reviews reporting the same primary studies (in which case, the highest quality systematic review reporting the best available data was used), and inadequate data reporting.

2.4 Classification and assessment of evidence

Studies identified for inclusion from the literature search were classified according to the NHMRC levels of evidence hierarchy (**Table 2.1**). To ensure that modules were based on the best available evidence, studies of higher levels of evidence (Levels I or II) were included in preference to those presenting lower levels of evidence (Levels III or IV). This was to minimise the potential for bias in the evidence base for each systematically reviewed question. However, lower level studies were reviewed where evidence was not available in higher level studies for any of the primary outcomes.

Studies identified from the systematic literature review were assessed according to NHMRC dimensions of evidence (**Table 2.2**).[4] There are three main domains: strength of the evidence, size of the effect, and relevance of the evidence. The first domain was derived directly from the literature identified for a particular intervention, aetiology or prognostic study. The other two domains were determined in consultation with the CRG as part of the study assessment process during the review of the evidence considered for module development. An aspect of the strength of the evidence domain is the level of evidence of the study, which was determined as described above using the NHMRC levels of evidence hierarchy outlined in **Table 2.1**.

Table 2.1 NHMRC evidence hierarchy: designations of levels of evidence according to type of research question

Level	Intervention[a]	Prognosis	Aetiology[b]
I[c]	A systematic review of Level II studies	A systematic review of Level II studies	A systematic review of Level II studies
II	A randomised controlled trial	A prospective cohort study[d]	A prospective cohort study
III–1	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)	All or none[e]	All or none[e]
III–2	A comparative study with concurrent controls: • non-randomised, experimental trial[f] • cohort study • case–control study • interrupted time series with a control group	Analysis of prognostic factors among persons in a single arm of a randomised controlled trial	A retrospective cohort study
III–3	A comparative study without concurrent controls: • historical control study • two or more single arm study[g] • interrupted time series without a parallel control group	A retrospective cohort study	A case–control study
IV	Case series with either post-test or pre-test/post-test outcomes	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series

Source: NHMRC (2009)[4]

[a] Definitions of these study designs are provided on pages 7–8, *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000)[5]

[b] If it is possible and ethical to determine a causal relationship using experimental evidence, then the 'intervention' hierarchy of evidence should be used. If it is only possible or ethical to determine a causal relationship using observational evidence (e.g. groups cannot be allocated to a potential harmful exposure, such as nuclear radiation), then the 'aetiology' hierarchy of evidence should be utilised.

[c] A systematic review will only be assigned a level of evidence as high as the studies it contains, except where those studies contain Level II evidence. Systematic reviews of Level II evidence provide more data than the individual studies, and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review quality should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome or result, as different studies (and study designs) might contribute to each different outcome.

[d] At study inception, the cohort is either non-diseased or all at the same stage of the disease. A randomised controlled trial with persons either non-diseased or at the same stage of the disease in both arms of the trial would also meet the criterion for this level of evidence.

[e] All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of smallpox after large-scale vaccination.

[f] This also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (i.e. utilise A vs. B and B vs. C to determine A vs. C).

[g] Comparing single arm studies i.e. case series from two studies. This would also include unadjusted indirect comparisons (i.e. utilise A vs. B and B vs. C to determine A vs. C, without statistical adjustment for B).

Table 2.2 NHMRC dimensions of evidence

Dimension	Definition
Strength of evidence	
Level	Each included study is assessed according to its place in the research hierarchy. This illustrates the potential of each included study to adequately answer a particular research question and indicates the degree to which design has minimised the impact of bias on the results
Quality	Included studies are critically appraised for methodological quality. Each study is assessed according to the potential that bias, confounding and/or chance has influenced the results
Statistical precision	Primary outcomes of included studies are assessed to establish whether the effect is real, rather than due to chance. Using a level of significance such as a *p*-value and/or confidence interval, the precision of the estimate of the effect is evaluated. This considers the degree of certainty regarding the existence of a true effect
Size of effect	The clinical importance of the findings of each study is assessed. This concept refers to the measure of effect or point estimate reported in the results of each study (e.g. mean difference, relative risk). For meta-analysis pooled measures of effect are assessed. Size of effect refers to the distance of the point estimate from its null value and also the values included in the corresponding 95% confidence interval. Size of effect indicates the clinical impact a particular factor or intervention will have on a patient and is considered in the context of patient relevant clinical differences
Relevance of evidence	The translation of research evidence to clinical practice is addressed by this dimension. It is regarded as potentially the most subjective of the evidence assessments. There are two questions concerning the appropriateness of outcomes and relevance of study questions: Are the outcomes measured in the study relevant to patients? How closely do the elements of the study research question match with those of the clinical question being considered?

Source: NHMRC (2009)[4]

2.4.1 Quality appraisal

The methodological quality of the included studies was assessed using the criteria presented in **Appendix 2** of this volume.[5] Quality assessment criteria varied according to whether included studies were systematic reviews, RCTs, cohort studies or case–control studies. No weighting of quality criteria was applied, but studies that met all criteria, or all but one, were considered to be of good quality with a low risk of bias. Quality assessments of included studies for all systematically reviewed research questions are presented in **Appendix E** (Volume 2).

2.4.2 Data extraction

Data and information were extracted into evidence summary tables according to the inclusion criteria. Evidence summary tables were based on NHMRC requirements for externally developed guidelines.[6] All articles retrieved for full text review were initially screened, critically appraised, and data extracted by one evidence reviewer. A second reviewer independently checked and reviewed all articles, data extractions, and quality assessments. Any disagreements were resolved by a third reviewer.

Extracted data and information included general study details (citation, study design, evidence level, country and setting); characteristics of study participants; details of interventions and comparators; details of study validity, both internal (e.g. allocation and blinding) and external (applicability and generalisability); and results for outcomes specified in the inclusion criteria. Where relevant studies were identified, extracted data and information were used to construct study characteristics and results tables of included evidence for each systematically reviewed research question. Evidence summary tables for all included studies are presented in **Appendix F** (Volume 2).

2.5 Assessment of the body of evidence and formulation of recommendations

The body of evidence for each module recommendation was graded in accordance with the NHMRC framework for developing evidence-based recommendations.[4] Assessment of the body of evidence considers the dimensions of evidence of studies relevant to that recommendation (**Table 2.2**). A modified NHMRC evidence statement form was used with each clinical research question considered in the development of the guidelines (see **Appendix 3** of this volume). That is, a separate form was used for consolidation of the evidence (evidence statement form) and the development of recommendations (recommendation form). The decision to separate out the two components of the NHMRC evidence statement form was due to the inevitability of several evidence statement forms leading to only one recommendation. Also, the current NHMRC evidence statement form does not provide a space to capture the actual wording of evidence statements.

Before the evidence statement form was completed, included studies were critically appraised and relevant data were summarised, as described. This information was required to formulate each recommendation and determine the overall grade of the body of evidence supporting each recommendation.

The key findings from included studies were summarised as evidence statements for each systematically reviewed research question. Where required, separate evidence statements were developed for different patient populations and outcomes. CRG input helped to ensure that the size of effects and relevance of evidence were considered when developing evidence statements. Where no evidence or insufficient relevant evidence was identified, this was explained in the evidence statement.

Completed evidence statement forms and recommendation forms for each research question are presented in **Appendix D** (Volume 2).

2.5.1 Use of the modified NHMRC evidence statement form

The modified NHMRC evidence statement form was applied in five steps.

Step 1 Rating each of the five components

To inform grading of recommendations, the body of evidence underpinning each evidence statement was assessed. Five key components were rated (**Table 2.3**). The first two components – evidence base and consistency – were derived directly from the literature identified for each research question. During review of identified evidence, CRG guidance was also required to assess the clinical impact, generalisability and applicability of included studies.

For each evidence statement, the five components presented in **Table 2.3** were rated according to the matrix shown in **Table 2.4**. This grading system was designed to accommodate variation in the body of evidence. For example, a large number of studies with minimal bias may be included, but have limited applicability to the Australian health-care context. Alternatively, a body of evidence may consist of a small number of trials with a moderate risk of bias, but have a significant clinical impact and high applicability to the Australian health-care context. Rating results were entered into the modified NHMRC evidence statement form, together with any additional explanatory information relevant to each component. The results section for each research question includes the body-of-evidence matrix-rating assessment for each evidence statement.

Table 2.3 Components of the evidence statement

Component	Definition
Evidence base	
Quantity	Reflects the number of studies included as the evidence base. Also takes into account the number of patients in relation to frequency of the outcomes measured (i.e. study statistical power). Meta-analysis can be used to combine results of studies to increase the power and statistical precision of effect estimates.
Level	Reflects the best study type for the specific type of research question (intervention, prognosis). Level I evidence would be the best evidence to answer each question.
Quality	Reflects how well studies were designed and conducted in order to eliminate bias.
Consistency	Assesses whether findings are consistent across included studies, including a range of study populations and study designs. Meta-analysis of randomised studies should present statistical analysis of heterogeneity that demonstrates little statistical difference between studies. Presentation of an I^2 statistic illustrates the extent of heterogeneity between studies. Clinical heterogeneity between studies should also be explored.
Clinical impact	Measures the potential benefit from application of the guidelines to a population. Several factors need to be considered when estimating clinical impact, including relevance of the evidence to the clinical question; statistical precision and size of the effect; relevance of the effect to patients compared with other management options or none. Other relevant factors are the duration of therapy required to achieve the effect, and the balance of risks and benefits (taking into account the size of the patient population).
Generalisability	Addresses how well the subjects and settings of included studies match those of the recommendation. Population issues that could affect recommendations include sex, age, ethnicity, and baseline risk or level of care (e.g. community or hospital setting). This is an important consideration when evidence comes from randomised controlled trials, where setting and entry requirements are generally narrow and therefore may not be representative of all patients to whom the recommendation may be applied in practice. In this circumstance broader-based population studies may be useful for confirming evidence from randomised controlled trials.
Applicability	Addresses whether the evidence base is relevant to the Australian health-care setting in general or to more local settings for specific recommendations (e.g. rural areas or cities). Factors that will affect the applicability of study findings include organisational factors (e.g. availability of trained staff, specialised equipment and resources) and cultural factors (e.g. attitudes to health issues, including those that may affect compliance with guidelines recommendations).

Source: NHMRC (2009)[4]

Table 2.4 Body-of-evidence matrix

Component	A	B	C	D
	Excellent	**Good**	**Satisfactory**	**Poor**
Evidence base	Several Level I or II studies with low risk of bias	One or two Level II studies with low risk of bias or a systematic review/multiple Level III studies with low risk of bias	Level III studies with low risk of bias, or Level I or II studies with moderate risk of bias	Level IV studies, or Level I to III studies with high risk of bias
Consistency	All studies consistent	Most studies consistent and inconsistency can be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population/s studied in body of evidence are the same as the target population for the guidelines	Population/s studied in the body of evidence are similar to the target population for the guidelines	Population/s studied in the body of evidence are different to the target population but it is clinically sensible to apply this evidence to the target population for the guidelines	Population/s studied in the body of evidence are different to the target population, and hard to judge whether it is sensible to generalise to the target population for the guidelines
Applicability	Directly applicable to the Australian health-care context	Applicable to Australian health-care context with a few caveats	Probably applicable to Australian health-care context with some caveats	Not applicable to Australian health-care context

Source: NHMRC (2009)[4]

A rating of 'NA' was attributed for consistency when only one study was included.

Step 2 Preparation of an evidence statement matrix

An evidence statement matrix was completed to summarise the synthesis of the evidence relating to the evidence statement or statements for each research question. This summary presented ratings for the five components of the body-of-evidence matrix assessed for each evidence statement. Multiple statements were required where the evidence differed in population subgroups, or where differences in an intervention (e.g. dose/mode of administration) could lead to different results. Other relevant issues and dissenting opinions were recorded if required.

In practice, Steps 1 and 2 to complete the modified NHMRC evidence statement forms were conducted concurrently for each evidence statement.

Step 3 Formulation of a recommendation based on the body of evidence

Step 3 involved formulating the wording of the recommendation. This wording was intended to reflect the strength of the body evidence; that is, where the evidence base was regarded as poor or unreliable, words such as 'must' or 'should' were not used. The wording of recommendations was developed in conjunction with the CRG during meetings to review the evidence base for research questions.

Step 4 Determination of the grade for the recommendation

The overall grade for each recommendation was determined from a summary of the rating for each component of the body of evidence. Definitions of the NHMRC grades of recommendations are presented in **Table 2.5**. In accordance with the NHMRC framework, recommendations were not graded A or B unless the evidence base and consistency of evidence were both rated A or B (unless only one study was included, and consistency was rated 'NA' – in this situation the quality, size and strength of the evidence base was relied upon to grade the recommendation). The grading of recommendations was determined in conjunction with the CRG.

Developed recommendations were entered into the recommendation forms, and the corresponding evidence statement forms were noted, along with the overall grade determined in this step (**Appendix D**, Volume 2).

Table 2.5 Definitions of NHMRC grades for recommendations

Grade	Definition
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendations must be applied with caution

Source: NHMRC (2009)[4]

Step 5 Implementation of guidelines recommendations

The NHMRC framework directs that guidelines implementation should be considered at the same time as recommendations are formulated. The recommendation form contains questions related to the implementation of each module (**Appendix 4** in this volume). These are:

- Will this recommendation result in changes in usual care?
- Are there any resource implications associated with implementing this recommendation?
- Will the implementation of this recommendation require changes in the way care is currently organised?
- Is the guidelines development group aware of any barriers to the implementation of this recommendation?

This section of the recommendation form was completed in consultation with the CRG when each recommendation was formulated and graded. Implementation issues are recorded in the recommendation forms presented in **Appendix D** (Volume 2).

2.5.2 Practice points

Practice points were developed by the CRG through a facilitated group discussion and consensus process (**Appendix 4** in this volume) in the following circumstances:

- where the underpinning evidence would have led to a Grade D evidence-based recommendation
- where the CRG developed evidence-based recommendations graded C and above, but considered that additional information was required to guide clinical practice (wherever possible, this guidance was sourced from other evidence-based guidelines assessed to be of high quality)

- where insufficient evidence was identified to support the development of an evidence-based recommendation.

The preferred term for this type of recommendation is a 'consensus-based recommendation'.[7] However, to be consistent with the first four modules of the patient blood management guidelines and to avoid confusion, the term 'practice point' will continue to be used for the final two modules. The new terminology will be adopted across all six modules at the first review.

Recommendations, practice points and expert opinion points were formulated, discussed, and agreed by the CRG at face-to-face meetings. No major debate or dissenting viewpoints about the evidence occurred.

2.6 Limitations of the review methodology

This review used a structured approach to reviewing the literature. However, as with all study types can be subject bias. Reporting biases are a particular problem related to systematic reviews and include publication bias (small, negative trials tend not to be published), time-lag bias (delayed publication of negative findings), multiple publication bias (positive results published and counted multiple times), language bias (significant results tend to be published in English language journals) and outcome reporting bias (selective reporting of favourable outcomes).

Some of these biases are potentially present in these reviews. For example, only data published in peer-reviewed journals were included. Unpublished material was not included as such material typically has insufficient information upon which to base quality assessment, and it has not been subject to the peer-review process. In addition, the search was limited to English language publications only, so language bias is also a potential problem. Outcome reporting bias and inclusion criteria bias are unlikely as the methodology used in the review and the scope of the review was defined in advance.

3 Findings of systematic review

This chapter provides the findings of the systematic review, based on the four questions listed in Chapter 2.

3.1 Question 1

Question 1 (Interventional)

In maternity patients, what is the effect of RBC (allogeneic) transfusion on patient outcomes?

RBC, red blood cell

3.1.1 RBC transfusion

Evidence statements – red blood cell transfusion		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES1.1	In maternity patients, the effect of RBC transfusion on maternal and perinatal mortality, functional and performance status, and measures of fetal outcome is unknown (no evidence).	NA	NA	NA	NA	NA
ES1.2	In pregnant women with sickle cell disease, the effect of prophylactic RBC transfusion on maternal and perinatal mortality is uncertain (See evidence matrix D1.A in Volume 2 of the technical report)	√	NA	NA	√√√	√
ES1.3	In pregnant women with sickle cell disease, the effect of prophylactic RBC transfusion on measures of fetal outcome is uncertain (See evidence matrix D1.B in Volume 2 of the technical report)	√	NA	NA	√√√	√
ES1.4	In pregnant women with sickle cell disease, the effect of RBC transfusion on functional and performance status is unknown (no evidence)	NA	NA	NA	NA	NA

ES, evidence statement; RBC, red blood cell
√√√=A; √√=B; √=C; X=D; NA, not applicable

Practice points – RBC transfusion Note: refer to background question 3	
PP1	Major blood loss can develop rapidly around the time of giving birth in the absence of haemodynamic compromise; hence, close monitoring of all women, and early recognition and rapid response are critical.
PP2	In maternity patients requiring massive transfusion, the use of RBC and other blood components may be life-saving. However, in non-maternity patients, transfusion of RBC and other blood components is independently associated with increased morbidity and mortality.
PP3	In maternity patients with critical bleeding, a structured approach to patient care that includes escalation procedures, and timely and appropriate use of RBC and other blood components (e.g. an MTP) may reduce the risk of morbidity and mortality.
PP4	In maternity patients who are not actively bleeding, RBC transfusion should not be dictated by a Hb concentration alone, but should also be based on assessment of the patient's clinical status (e.g. the risk of further haemorrhage). Most maternity patients are otherwise healthy and can generally tolerate moderate degrees of anaemia while medical therapies take effect.
PP5	In maternity patients who are not actively bleeding, non-transfusion therapies, including iron, should be considered as part of the treatment of anaemia. (see recommendations R2 and R3 and practice points PP9 to PP14)
PP6	In maternity patients who are not actively bleeding, where transfusion is indicated, a single unit of RBC, followed by clinical reassessment to determine the need for further transfusion, is appropriate. This reassessment will also guide the decision on whether to retest the Hb level.
PP7	In maternity patients, the risk of RBC alloimmunisation and potential clinical impact should be considered when balancing the risks and benefits of RBC transfusion.
PP8	Direct evidence of the efficacy of RBC transfusion for treatment of anaemia is not available in maternity patients. Evidence from other patient groups and CRG consensus suggests that, with a: • Hb concentration >90 g/L, RBC transfusion is usually inappropriate. • Hb concentration of 70–90 g/L, RBC transfusion is not associated with reduced mortality. The decision to transfuse patients (with a single unit followed by reassessment) should be based on the need to relieve clinical signs and symptoms of anaemia, the availability of other therapies for the treatment of anaemia, the expected timeframe to giving birth and the presence of risk factors for haemorrhage. • Hb concentration <70 g/L, RBC transfusion may be associated with reduced mortality and may be appropriate. However, transfusion may not be required in well−compensated patients or where other specific therapy is available.

ARDs, acute respiratory distress syndrome; CRG, Clinical/Consumer Reference Group; Hb, haemoglobin; MTP, massive transfusion protocol; PP, practice point; R, recommendation; RBC, red blood cell

Evidence gaps and areas of future research – RBC transfusion
• In maternity patients, there is a lack of evidence on the Hb and ferritin levels that are associated with optimal maternal and fetal outcomes. • In anaemic maternity patients who are not actively bleeding, there is a lack of evidence of the effect of transfusion on patient-centred outcomes (including mortality, morbidity, and functional and performance status) In bleeding maternity patients, there is a lack of evidence of the effect of transfusion on patient-centred outcomes (including mortality, morbidity, postnatal recovery, quality of life, functional status, breastfeeding and psychological health). • What is the place of an MTP in the management of obstetric haemorrhage?
Hb, Haemoglobin; MTP, massive transfusion protocol

Methods

Two comparisons were assessed in this review: transfusion versus no transfusion (or alternative transfusion dose); and restrictive transfusion versus liberal transfusion in maternity patients.

Because this is an intervention question, the levels of evidence are as follows:

- Level I – a systematic review of two or more Level II studies
- Level II – an RCT
- Level III–1 – a pseudo-RCT
- Level III–2 – a comparative study with concurrent controls (including non-randomised, experimental trials, cohort studies, case-control studies and interrupted time series with a control group)
- Level III–3 – a comparative study without concurrent controls (including historical control studies, two or more single arm studies, interrupted time series without a parallel control group)
- Level IV – case series with either post-test or pre-test/post-test outcomes.

For the purposes of this review, a systematic review of Level III–2 or Level III–3 evidence was classified as Level III evidence.

For this question, the only evidence considered was Level III–2 or higher, published after 1985. In addition, for Level III evidence, the only studies considered were those that included at least 100 subjects.

One study was identified for this population from the systematic review and hand searching process (see **Appendix C**, Volume 2).

The literature search identified no literature pertaining to Australia's Aboriginal and Torres Strait Islander peoples relevant to this research question.

Summary of evidence

Level I evidence

The literature search identified no systematic reviews that examined the effect of RBC transfusion in maternity patients and reported primary outcomes relevant to our research question (see **Section 4.1**).

Level II evidence

The literature search identified one RCT (Koshy et al 1988)[8] that assessed the effect of prophylactic RBC transfusion in pregnant women with sickle cell disease. The characteristics of this study are summarised in **Table 3.1**.The study by Koshy et al (1998)[8] was a multicentre trial (conducted in the USA over a 7-year period from 1979 to 1986) that assessed the effect of prophylactic RBC transfusion in pregnant women with sickle cell disease. The trial included 36 women who received prophylactic RBC transfusion at the beginning of their pregnancy care, compared with 36 women who received RBC transfusion only if indicated for medical or obstetric complications. The outcomes measured included perinatal outcomes, and complications related to obstetrics, transfusion or sickle cell disease.

Table 3.1 Prophylactic RBC transfusion versus restricted RBC transfusion – characteristics and quality of Level II evidence

Study	Study type *Study quality*	Population N	Intervention N	Comparator N	Outcomes
Koshy 1988[8]	RCT *Fair*	Pregnant sickle cell women (HbSS) N = 72	Prophylactic transfusions of frozen red cells N = 36	Red cell transfusions for medical or obstetrics emergencies N = 36	Perinatal mortality Fetal outcomes Transfusion-related SAEs.

Abbreviations: HbSS, haemoglobin SS genotype; RCT, randomised controlled trial; SAE, serious adverse event

Level III evidence

The literature search did not identify any Level III–1 or Level III–2 studies that examined the effect of RBC transfusion in maternity patients.

Results

Maternal and perinatal mortality

Pregnant women with sickle cell disease

Koshy et al (1988)[8] 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. **Table 3.2** provides a summary of these results.

Table 3.2 Prophylactic RBC transfusion versus restrictive RBC transfusion in pregnant women with sickle cell anaemia – maternal and perinatal mortality

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention (N) vs comparator (N)	Outcome	Results			
						Prophylactic RBC transfusion N/N (%)	Restrictive RBC transfusion N/N (%)	Risk estimate (95% CI)	*Statistical significance* P-value
LEVEL II EVIDENCE									
Koshy 1988[8] Level II *Fair*	RCT N = 72	Pregnant women with sickle cell anaemia (HbSS)	Chicago, USA	Prophylactic transfusions of frozen red cells (N = 36) vs RBC transfusions for medical or obstetrics emergencies (N = 36)	Maternal mortality	0/36	0/36	NR	No significant difference. P= NR
					Stillbirth (%)	4/36 (10)	2/36 (5)	NR	No significant difference. P = NR
					Neonatal death (%)	2/36 (6)	0	NR	No significant difference. P = NR
					Perinatal death (%)	6/36 (15)	2/36 (5)	NR	No significant difference. P = NR
					There were no significant differences between the two randomised groups, with or without adjustment for multiple birth or previous perinatal mortality. Baseline characteristics between randomised groups were not significantly different for all outcomes reported but approached statistical significance (P=0.09) for previous perinatal mortality. 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).				

Abbreviations: CI, confidence interval; HbSS, haemoglobin SS genotype; NR, not reported; RCT, randomised controlled trial; RBC, red blood cell

Functional and performance status

No studies were identified that reported the effect of RBC transfusion on measures of functional and performance status (e.g. postnatal depression, breastfeeding rates).

Measures of fetal outcome

Pregnant women with sickle cell disease

One study was identified that reported on measures of fetal outcomes (birth weight, gestation, preterm birth). **Table 3.3** summarises these results.

Koshy et al (1988)[8] reported no significant difference between treatment groups for birth weight or preterm birth. A statistically significant difference ($P<0.05$) favouring restrictive RBC transfusion was reported for gestational age at birth; however, this difference did not remain significant after adjustment for previous perinatal mortality and multiple birth.

Table 3.3 Prophylactic RBC transfusion versus restrictive RBC transfusion in pregnant women with sickle cell anaemia – measures of fetal outcome

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Prophylactic RBC transfusion Mean N/N (%)	Restrictive RBC transfusion Mean N/N (%)	Risk estimate (95% CI)	*Statistical significance* P-value
LEVEL II EVIDENCE									
Koshy 1988[8] Level II *Fair*	RCT N = 72	Pregnant sickle cell women (HbSS)	Chicago, USA	Prophylactic transfusions of frozen red cells (N = 36) vs RBC transfusions for medical or obstetrics emergencies (N = 36)	Birth weight Mean (g)	2495	2652	NR	No significant difference P=NR
					Gestation (weeks)	35.8	38.1	NR	*Favours restrictive RBC transfusion* P = 0.05
						Difference between the two randomised groups did not remain significant after adjustment for previous perinatal mortality and multiple births [a]			
					Preterm birth (%)	3/36 (8)	3/36 (8)	NR	No significant difference P = NR

Abbreviations: CI, confidence interval; HbSS, haemoglobin SS genotype; NR, not reported; RCT, randomised controlled trial; RBC, red blood cell

[a] Baseline characteristics between randomised groups were not significantly different for all outcomes reported but approached statistical significance (P=0.09) for previous perinatal mortality. 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)

Secondary outcomes

Transfusion-related SAEs

One study was identified that reported on transfusion-related SAEs (**Table 3.4**). Koshy et al (1988) reported no significant difference between treatment groups for delayed transfusion reactions (6/36 vs 3/36; RR 2.0; 95% CI 0.54, 7.39) or alloimmunisations (10/36 vs 8/36; RR 1.25; 95% CI 0.56, 2.80). However, as this evidence has not strictly undergone the systematic review process (secondary outcomes were extracted from studies that reported one or more primary outcomes); this outcome should be interpreted with caution.

Thromboembolic events

No studies were identified that reported on the effect of RBC transfusion on thromboembolic events in maternity patients. However, as this evidence has not strictly undergone the systematic review process (secondary outcomes were extracted from studies that reported one or more primary outcomes); this should be interpreted with caution.

Table 3.4 Prophylactic RBC transfusion versus restrictive RBC transfusion in pregnant women with sickle cell anaemia – secondary outcomes

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Prophylactic RBC transfusion Mean N/N (%)	Restrictive RBC transfusion Mean N/N (%)	Risk estimate (95% CI)	*Statistical significance* P-value
LEVEL II EVIDENCE									
Koshy 1988[8] Level II *Fair*	RCT N = 72	Pregnant sickle cell women (HbSS)	Chicago, USA	Prophylactic transfusions of frozen red cells (N = 36) vs RBC transfusions for medical or obstetrics emergencies (N = 36)	Delayed transfusion reaction	6/36 (16.7)	3/36 (8.3)	RR	No significant difference P=NR
					Alloimmunisations	10/36 (29)	8/36 (21)	NR	No significant difference P=NR

Abbreviations: CI, confidence interval; HbSS, haemoglobin SS genotype; NR, not reported; RCT, randomised controlled trial; RBC, red blood cell

3.2 Question 2

Question 2 (Interventional)

In maternity patients, what is the effect of non-transfusion interventions to increase Hb concentration on morbidity, mortality and need for RBC blood transfusion?

Hb, haemoglobin; RBC, red blood cell

3.2.1 Oral and/or parenteral iron

Evidence statements – oral and/or parenteral iron (transfusion incidence)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES2.1	In pregnant women, the effect of routine oral iron compared to no treatment or placebo on transfusion incidence is uncertain (See evidence matrix D2.E in Volume 2 of the technical report)	√	NA	NA	√√	√
ES2.2	In pregnant women, the effect of oral iron plus folic acid compared to no treatment or placebo on transfusion incidence is unknown (no evidence)	NA	NA	NA	NA	NA
ES2.3	In maternity patients with iron deficiency anaemia, the effect of IV iron compared to oral iron on transfusion incidence is uncertain (See evidence matrix D2.F in Volume 2 of the technical report)	√	√√√	NA	√√	√
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 (See evidence matrix D2.G in Volume 2 of the technical report)	√	√√√	NA	√√	√
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 (See evidence matrix D2.H in Volume 2 of the technical report)	√	√√√	NA	√√√	√√
ES2.6	In pregnant women with iron deficiency anaemia, the effect of IM iron compared to oral iron on transfusion incidence is unknown (no evidence)	NA	NA	NA	NA	NA
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 (See evidence matrix D2.I in Volume 2 of the technical report)	X	NA	NA	√√√	√

ES, evidence statement; IM, intramuscular; IV, intravenous
√√√=A; √√=B; √=C; X=D; NA, not applicable

Evidence statements – oral and/or parenteral iron (laboratory measures)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES2.8	In pregnant women, oral iron reduces maternal anaemia (Hb <110 g/L) at 34 weeks gestation or more compared to no treatment or placebo (See evidence matrix D2.J in Volume 2 of the technical report)	√√√	√√	√	√	√
ES2.9	In pregnant women, oral iron reduces maternal iron deficiency anaemia (Hb <110 g/L) at 34 weeks gestation or more compared to no treatment or placebo (See evidence matrix D2.J in Volume 2 of the technical report)	√√√	√√	√	√	√
ES2.10	In pregnant women, the effect of oral iron compared to no treatment or placebo on postpartum anaemia (Hb <110 g/L) is uncertain (See evidence matrix D2.J in Volume 2 of the technical report)	√√√	X	NA	√√	√
ES2.11	In pregnant women with iron-deficiency anaemia, oral iron improves laboratory values (Hb and serum ferritin) and reduces anaemia (Hb <110 g/L) compared to no treatment or placebo (See evidence matrix D2.K in Volume 2 of the technical report)	√	√√√	√	√	√
ES2.12	In pregnant women, oral iron plus folic acid reduces maternal anaemia (Hb <110 g/L) at 34 weeks gestation or more compared to no treatment or placebo (See evidence matrix D2.L in Volume 2 of the technical report)	√√√	√√	√	√√√	√
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 (See evidence matrix D2.L in Volume 2 of the technical report)	√	NA	NA	√√√	√
ES2.14	In pregnant women, oral iron plus folic acid reduces moderate anaemia postpartum (Hb between 80 g/L and 110 g/L) compared to no treatment or placebo (See evidence matrix D2.L in Volume 2 of the technical report)	X	√√	NA	√√	X
ES2.15	In pregnant women, the effect of oral iron plus folic acid compared to no treatment or placebo on severe anaemia (Hb <80 g/L) is uncertain (See evidence matrix D2.L in Volume 2 of the technical report)	√	√√	NA	√√	X
ES2.16	In maternity patients with iron deficiency anaemia, IV iron may lead to more rapid correction of laboratory measures (Hb and ferritin) than oral iron; however, at completion of therapy Hb levels were similar in both groups but ferritin continued to be higher with IV iron (See evidence matrix D2.M in Volume 2 of the technical report)	√	√√	√	√√	√

Evidence statements – oral and/or parenteral iron (laboratory measures)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES2.17	In maternity patients with anaemia, the superiority of IV iron plus oral iron compared to oral iron alone in increasing Hb or ferritin levels is uncertain (See evidence matrix D2.N in Volume 2 of the technical report)	√	√√	√	√√	√√
ES2.18	In maternity patients with iron deficiency anaemia, IV iron is more effective at increasing Hb and ferritin levels than oral iron plus folic acid (See evidence matrix D2.O in Volume 2 of the technical report)	√	NA	√	√√√	√
ES2.19	In non-anaemic pregnant women, prophylactic IV iron plus folic acid compared to oral iron plus folic acid does not improve Hb levels but does increase ferritin level before delivery (See evidence matrix D2.P in Volume 2 of the technical report)	√	NA	X	√√√	√√
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 Hb and ferritin levels (See evidence matrix D2.P in Volume 2 of the technical report)	√	√√	√	√√√	√√
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 Hb levels but was more effective in increasing ferritin levels (See evidence matrix D2.P in Volume 2 of the technical report)	√	NA	X	√√√	√√ √
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 (See evidence matrix D2.T in Volume 2 of the technical report)	X	NA	X	√√√	X
ES2.23	In pregnant women with iron deficiency anaemia, IM iron may increase maternal Hb and haematocrit compared to oral iron (See evidence matrix D2.S in Volume 2 of the technical report)	X	√√√	X	√√√	√
ES2.24	In pregnant women with iron deficiency anaemia, IV iron is more effective than IM iron in increasing Hb levels (See evidence matrix D2.Q in Volume 2 of the technical report)	X	NA	√	√√√	√
ES2.25	In pregnant women with iron deficiency anaemia, IV iron increases Hb levels more than IM iron plus oral iron (See evidence matrix D2.R in Volume 2 of the technical report)	X	√√√	√	√√√	√
ES, evidence statement; Hb, haemoglobin; IM, intramuscular; IV, intravenous √√√=A; √√=B; √=C; X=D; NA, not applicable						

Evidence statements – oral and/or parenteral iron (measures of fetal outcome)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
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 (See evidence matrix D2.U in Volume 2 of the technical report)	√√	√√√	NA	√√√	√√
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 birth weight, incidence of preterm birth and small-for-gestational age) is uncertain (See evidence matrix D2.V in Volume 2 of the technical report)	√√	√	NA	√	X
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 (See evidence matrix D2.W in Volume 2 of the technical report)	√	√√√	NA	√√	√
ES2.29	In non-anaemic pregnant women, the effect of prophylactic IV iron plus folic acid compared to oral iron plus folic acid on measures of fetal outcomes is uncertain (See evidence matrix D2.X in Volume 2 of the technical report)	√	NA	NA	√√√	√√
ES2.30	In pregnant women with iron deficiency anaemia, the effect of IV iron plus folic acid compared to oral iron plus folic acid on measures of fetal outcomes is uncertain (See evidence matrix D2.X in Volume 2 of the technical report)	√	NA	NA	√√√	√√
ES2.31	In pregnant women, the effect of IV iron plus oral iron compared to oral iron on fetal outcomes is unknown (no evidence)	NA	NA	NA	NA	NA
ES2.32	In pregnant women, the effect of IV iron compared to IM iron on measures of fetal outcomes is unknown (no evidence)	NA	NA	NA	NA	NA
ES2.33	In pregnant women with iron deficiency anaemia, the effect of IM iron compared to oral iron on measures of fetal outcome is unknown (no evidence)	NA	NA	NA	NA	NA
ES2.34	In pregnant women with iron deficiency anaemia, the effect of IM iron compared to iron plus folic acid on birth weight is uncertain (See evidence matrix D2.Y in Volume 2 of the technical report)	X	NA	NA	√√√	X

ES, evidence statement; RBC, red blood cell
√√√=A; √√=B; √=C; X=D; NA, not applicable

Evidence statements – oral and/or parenteral iron (mortality)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES2.35	In pregnant women, the effect of oral iron compared to no treatment or placebo on maternal mortality is uncertain (See evidence matrix D2.Z in Volume 2 of the technical report)	√	NA	NA	√√√	√√
ES2.36	In pregnant women, the effect of oral iron compared to no treatment or placebo on perinatal and neonatal mortality is uncertain (See evidence matrix D2.Z in Volume 2 of the technical report)	√	NA	√	√	√
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 (See evidence matrix D2.AA in Volume 2 of the technical report)	√	√	NA	√	√
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 (See evidence matrix D2.AB in Volume 2 of the technical report)	√√	√√√	NA	√√	√√
ES2.39	In pregnant women, the effect of IV iron plus oral iron compared to oral iron alone on maternal and perinatal mortality is unknown (no evidence)	NA	NA	NA	NA	NA
ES2.40	In pregnant women, the effect of IV iron compared to IM iron on maternal and perinatal mortality is unknown (no evidence)	NA	NA	NA	NA	NA
ES2.41	In pregnant women with iron deficiency anaemia, the effect of IM iron compared to oral iron on perinatal mortality is unknown (no evidence)	NA	NA	NA	NA	NA
ES2.42	In maternity patients, the effect of IM iron compared to oral iron plus folic acid on maternal and perinatal mortality is unknown (no evidence)	NA	NA	NA	NA	NA
ES, evidence statement; RBC, red blood cell √√√=A; √√=B; √=C; X=D; NA, not applicable						

Recommendations – oral and/or parenteral iron	
R1 (Grade C)	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*[9]
R2 (Grade C)	The administration of iron to pregnant women with iron deficiency anaemia is recommended; IV iron is preferred when rapid restoration of Hb and iron stores is required.
R3 (Grade C)	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*[9]
Hb, haemoglobin; IV, IV iron; R, recommendation	

Practice points – oral and/or parenteral iron	
PP9	In maternity patients with iron deficiency anaemia, a therapeutic dose of elemental iron (100–200 mg daily) should be prescribed, and the response to therapy monitored. If the response to oral iron is inadequate, IV iron should be used.
PP10	In maternity patients with iron deficiency without anaemia, a low dose of elemental iron (e.g. 20-80 mg daily) may be considered, and may be better tolerated than higher doses.
PP11	In maternity patients requiring iron, IV iron is preferred when oral iron is poorly tolerated (affecting compliance), or absorption is likely to be impaired.
PP12	When IV iron is prescribed, calculation of the dose should take into consideration the iron deficit.
PP13	The routine use of IM iron is not advised where alternatives are available.
IM, intramuscular; IV, intravenous; PP, practice point	

Evidence gaps and areas of future research – oral and/or parenteral iron
• There is a lack of evidence on what degree of anaemia is clinically relevant in maternity patients and what is the clinically relevant degree of anaemia that equates to 'optimisation' of Hb? • There is need for further research investigating the impact of routine iron supplementation in pregnancy and in iron deficiency anaemia. Studies should focus on patient-centred outcomes (in addition to laboratory measures) and should also report on compliance. • When and how frequently should iron stores be assessed during pregnancy? • Does giving birth affect hepcidin levels and iron absorption? • In women with moderate to severe postpartum anaemia what is the comparative efficacy of IV iron versus RBC transfusion on short and long-term patient outcomes.
Hb, Haemoglobin; IV, intravenous

Background

Anaemia during pregnancy is a risk factor for transfusion and there is evidence of an association with adverse maternal and perinatal outcomes. The majority of cases of anaemia are due to red cell iron deficiency associated with depleted iron stores and inadequate iron intake. Iron is required for expansion of maternal red cell mass as well as the red cell mass of the fetal and placental circulation. Still, there are potential clinical hazards of iron supplementation in already iron replete women and there is a risk of elevated Hb in non-anaemic women.

Methods

The systematic review examined the evidence for the use of oral and/or parenteral (IV or IM) iron therapy in maternity patients. All modes of administration of iron were eligible for inclusion, as were any active head-to-head comparisons (i.e. oral vs parenteral). Studies examining the role of micronutrient supplementation on maternal and perinatal outcomes, and those comparing different doses of iron or comparing daily iron with intermittent use were determined by the CRG to be out of scope for this review.

Because this is an intervention question, the levels of evidence are as detailed in **Section 3.1.1**. For the purposes of this review, a systematic review of Level III–2 or Level III–3 evidence was classified as Level III evidence.

For this question, the only evidence considered was Level III–2 or higher, published after 1970. In addition, for Level III evidence, it was intended that the only studies considered were those that included at least 100 subjects. A search of lower level evidence was only conducted for primary outcomes not addressed in higher level evidence (see **Section 2.2**).

There were two Level I studies,[10,11] 17 subsequently published Level II studies,[12-28] and two Level III studies[29,30] (see **Appendix C**, Volume 2) identified in the systematic review and hand searching process that evaluated the use of oral and/or parenteral iron in maternity patients and reported primary outcomes relevant to our research question (see **Section 4.1**).

The literature search identified no literature pertaining to Australia's Aboriginal and Torres Strait Islander peoples relevant to this research question.

Summary of the evidence

Level I evidence

There were two Level I studies that were identified as being the highest quality and most recent comprehensive reviews that evaluated the use of iron in maternity patients.[10,11] The main characteristics of these reviews are summarised in **Table 3.5**.

Pena-Rosas et al (2012)[10] included 60 randomised or quasi-RCTS with data from 27 402 subjects that evaluated the use of daily oral iron supplements in pregnant women of any gestational age and parity. The authors examined the effects of oral iron on transfusion incidence, laboratory measures, fetal outcomes and mortality and included trials conducted in a variety of countries. Eight comparisons were included in the review by Pena-Rosas et al (2012)[10] assessing daily oral iron, either alone or in conjunction with folic acid, or with other vitamins and minerals as a public health intervention; however, only two comparisons (oral iron or oral iron plus folic acid compared with no treatment or placebo) were considered relevant for inclusion in this review. The other comparisons were confounded such that the effects of oral iron or oral iron plus folic acid alone could not be determined.

One RCT was removed from the analysis reported by Pena-Rosas et al (2012)[10] due to concerns about the control group, as defined by the research protocol for this systematic review. Hemminki et al (1991)[31] randomised participants to one of two treatment groups: either a routine iron group or a selective iron group. Pregnant women in the selective iron group were provided with iron supplementation if they met specified clinical conditions (haematocrit <0.30, Hb <100 g/L), which changed after 33 weeks of gestation (haematocrit <0.31, Hb <105 g/dL). Hemminki et al (1991)[31] was not originally included in the analysis by Pena-Rosas et al (2012).[10] However, this decision was reversed following correspondence from the authors of the trial, who argued for its inclusion based on the design and size of the study. The CRG felt that the lack of a valid comparator (i.e. no treatment/placebo) necessitated the removal of Hemminki et al (1991),[31] in agreement with the original assessment made by Pena-Rosas et al (2012).[10] This is reflected in the data presented in the relevant analyses for all outcomes.

Reveiz et al (2011)[11] included 23 RCTs with data from 3198 subjects and incorporated several comparisons that included oral iron, IV iron and IM iron. The review was focused on a specific subset of the population: pregnant women with a diagnosis of anaemia and Hb levels less than 11 g/dL (or other tests for anaemia as defined by trialists) and examined the effects on transfusion incidence, laboratory measures, fetal outcomes and mortality.

Table 3.5 Oral and/or parenteral iron – characteristics and quality of Level I evidence

Study	Study type *Study quality*	Population N	Comparison	Outcomes
Pena-Rosas et al (2012)[10]	Systematic review *Good*	Pregnant women of any gestational age and parity N = 27 402	Iron vs no treatment or placebo Iron + folic acid vs no treatment or placebo	Transfusion incidence Laboratory measures Measures of fetal outcome Mortality
Reveiz et al (2011)[11]	Systematic review *Good*	Pregnant women with a diagnosis of anaemia (Hb levels under 11 g/dL, or other tests for anaemia as defined by trialists) attributed to iron deficiency N = 3198	Oral iron vs placebo IV iron vs oral iron IV iron + oral iron vs oral iron IV iron vs IM iron + oral iron IM iron vs oral iron IM iron vs oral iron + folic acid	Transfusion incidence Laboratory measures Measures of fetal outcome Mortality

Abbreviations: IM, intramuscular; IV, intravenous

Level II evidence

The systematic review by Pena-Rosas et al (2012)[10] was considered to provide sufficient evidence for the use of daily oral iron in pregnant women of any gestation age or parity, therefore no further search for Level II evidence for oral iron was performed.

The systematic review by Reveiz et al (2011)[11] was updated to identify more recent Level II evidence that examined the use of parenteral iron (IV or IM) in maternity patients. Level II studies identified in our literature search that were published after the literature search date conducted in the Reveiz et al (2011)[11] systematic review were identified. Seventeen RCTs were retrieved during this process that evaluated the use of parenteral iron in maternity patients.[12-28] The main characteristics of these RCTs are summarised in **Table 3.6**.

IV iron versus oral iron

Nine RCTs compared IV iron with oral iron. Three of these included postpartum women with anaemia,[20,24,26] four included postpartum women with iron deficiency anaemia,[13,14,22,27] one included postpartum women with severe iron deficiency anaemia,[17] and one RCT was in pregnant women with anaemia.[18] The study by Gupta et al (2013)[18] also administered mebendazole, for the treatment of worms, to both groups. These trials were conducted in a variety of countries, with three run in single-centres in India,[18,20,27] one in a single centre in the United Kingdom,[13] one in a single centre in Greece,[17] one in multiple sites in Pakistan,[22] one in multiple centres across the USA,[24] one in multiple centres across the USA and Mexico[26] and one in multiple centres across Poland, Romania and the Russian Federation.[14]

IV iron plus oral iron versus oral iron

Two RCTs compared IV iron and oral iron to oral iron alone. One of these included pregnant women with established iron deficiency anaemia in a single centre in India,[23] whereas the other included postpartum women with haemorrhage anaemia across multiple sites in Norway.[28]

IV iron versus oral iron and folic acid

One RCT compared IV iron with oral iron and folic acid and included pregnant women with established iron deficiency anaemia in a single centre in India.[15]

IV iron plus folic acid versus oral iron plus folic acid

Three RCTS compared IV iron and folic acid with oral iron and folic acid. One included non-anaemic pregnant women,[12] one included pregnant women with moderate iron deficiency anaemia,[21] and one included both pregnant and postpartum women with iron deficiency anaemia.[16] One trial was conducted in a single centre in Switzerland,[12] one in a single centre in Australia,[16] and one in multiple sites in India.[21] The study by Kochhar et al (2013)[21] also administered mebendazole to both groups.

The dose of elemental iron (80 mg/day) given in the study by Bencaiova (2009)[12] 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).

IV iron versus IM iron

One RCT compared IV iron with IM iron and included pregnant women with anaemia in a single centre in India.[25]

IV iron versus IM iron plus oral iron

One RCT compared IV iron with IM iron and oral iron and included both pregnant and postpartum women with iron deficiency anaemia in a single centre in Pakistan.[19]

A number of issues arose when evaluating the effect of iron on morbidity, mortality and the need for RBC transfusion. There were questions around the definitions of anaemia used, doses of iron and routes of administration, compliance with therapy, side effects of treatment, under-powering and applicability to the Australian health-care setting. The recommendations and conclusions of this systematic review reflect these concerns.

The studies examined the effect of iron in different subsets of the maternity population. Some studies included all pregnant women, of any gestational age and parity, whereas others only included pregnant or postpartum women with a specified degree of anaemia. Definitions of anaemia varied between studies, with varying cut-offs for Hb and ferritin values determining inclusion into the studies. The CRG raised concerns over these apparent inconsistencies and the difficulty in applying the results to practice.

The included studies administered different doses of iron using different modes of administration and there was a high level of variation in the doses of iron given to participants in the studies. For example, Seid et al (2008)[24] and Van Wyck et al (2007)[26] administered 325 mg ferrous sulphate thrice daily to subjects in the oral iron groups, whereas subject in the study by Bencaiova et al (2009)[12] received 80 mg ferrous sulphate once daily.

Similar discrepancies were observed with IV iron. Froessler et al (2013)[16] and Mumtaz et al (2011)[22] each gave participants a total of 400 mg IV iron sucrose, whereas other studies calculated the iron deficit for each patient and treated accordingly. Gupta et al (2013)[18] took this approach, recording the range of iron sucrose administered to patients as 737.6 mg to 1095.2 mg. Some of the studies concurrently treated patients for worms with mebendazole, including Gupta et al (2013)[18] and Kochhar et al (2013).[21]

Table 3.6 Parenteral iron – characteristics and quality of Level II evidence

Study	Study type *Study quality*	Population N	Comparison	Outcomes
IV iron vs oral iron				
Bhandal et al (2006)[13]	RCT *Fair*	Women with postpartum iron deficiency anaemia (Hb <9 g/dL and ferritin <15mc g/L at 24–48 hours post-birth) N = 44	IV iron vs oral iron	Laboratory measures
Breymann et al (2008)[14]	RCT *Poor*	Women with postpartum iron deficiency anaemia (Hb ≤105 g/L) N = 349	IV iron vs oral iron	Transfusion incidence Laboratory measures
Giannoulis et al (2009)[17]	RCT *Poor*	Postpartum women with severe iron deficiency anaemia (Hb <8 g/dL and ferritin <10µg/L) N = 104	IV iron vs oral iron	Laboratory measures
Gupta et al (2013)[18]	RCT *Fair*	Pregnant women between 24 and 34 weeks gestation with anaemia (Hb 7.0–9.0 g/dL and serum ferritin <15ng/mL) N = 100	IV iron vs oral iron	Transfusion incidence Laboratory measures Measures of fetal outcome
Jain et al (2013)[20]	RCT *Fair*	Women with postpartum anaemia (Hb <8 g/dL within 48 hours postpartum) N = 46	IV iron vs oral iron	Laboratory measures
Mumtaz et al (2011)[22]	RCT *Poor*	Women with postpartum iron deficiency anaemia (Hb <9 g/dL and ferritin <15µg/L) at 24–48 hours post-birth N = 80	IV iron vs oral iron	Laboratory measures
Seid et al (2008)[24]	RCT *Fair*	Women with postpartum anaemia (10 days or less after birth with Hb ≤10 g/L) N = 291	IV iron vs oral iron	Laboratory measures
Van Wyck et al (2007)[26]	RCT *Fair*	Women with postpartum anaemia (within 10 days postpartum, Hb ≤10 g/dL) N = 361	IV iron vs oral iron	Transfusion incidence Laboratory measures
Verma et al (2011)[27]	RCT *Poor*	Women with postpartum iron deficiency anaemia (Hb <8 g/dL) 24 hours after birth N = 150	IV iron vs oral iron	Laboratory measures
IV iron plus oral iron vs oral iron				
Neeru et al (2012)[23]	RCT *Poor*	Pregnant women, from 14 to 36 weeks gestation, with established iron deficiency anaemia (Hb 6.5–10.9 g/dL and ferritin levels <27n g/dL) N = 100	IV iron + oral iron vs oral iron	Transfusion incidence Laboratory measures
Westad et	RCT	Women with postpartum	IV iron + oral	Transfusion incidence

al (2008)[28]	*Fair*	haemorrhage anaemia (Hb 6.5/100mL–8.5 g/mL and within 48 hours of birth) N = 129	iron vs oral iron	Laboratory measures
IV iron vs oral iron plus folic acid				
Deeba et al (2012)[15]	RCT *Fair*	Pregnant women between 28 and 37 weeks gestation with established iron deficiency anaemia (Hb levels 6–10 g/dL and serum ferritin <15n g/mL) N = 200	IV iron vs oral iron + folic acid	Laboratory measures
IV iron plus folic acid vs oral iron plus folic acid				
Bencaiova et al (2009)[12]	RCT *Fair*	Non-anaemic (Hb ≥10.5 g/dL) pregnant women between the 15th and 20th week of gestation N = 260	IV iron + folic acid vs oral iron + folic acid	Transfusion incidence Laboratory measures Measures of fetal outcome
Froessler et al (2013) [16]	RCT *Fair*	Women (148 pregnant and 123 post lower segment caesarean section) with iron deficiency anaemia (Hb <110 g/L and ferritin <12µg/L) N = 271	IV iron + folic acid vs oral iron + folic acid	Transfusion incidence Laboratory measures
Kochhar et al (2013)[21]	RCT *Fair*	Women between 24–34 weeks of gestation, with moderate iron deficiency anaemia (Hb 7.0–9.0 g/dL, ferritin level <15n g/mL) N = 100	IV iron + folic acid vs oral iron + folic acid	Transfusion incidence Laboratory measures Measures of fetal outcome
IV iron vs IM iron				
Singh et al (2013)[25]	RCT *Poor*	Pregnant women of gestational age 14–32 weeks with Hb ≤8 g/dL N = 100	IV iron vs IM iron	Laboratory measures
IV iron vs IM iron plus oral iron				
Hashmi et al (2006) [19]	RCT *Poor*	Women (80 with gestational age 12–36 weeks from antenatal clinics and 20 after postpartum haemorrhage) with iron deficiency anaemia (Hb <10 g/dL) N = 100	IV iron vs IM iron + oral iron	Transfusion incidence Laboratory measures

Abbreviations: Hb, haemoglobin; IM, intramuscular; IV, intravenous; RCT, randomised controlled trial

Level III evidence

The Level III evidence that evaluated the use of iron in maternity patients was screened to identify those studies that reported on the outcome of mortality. The main characteristics of the two studies[29,30] identified during this process are summarised in **Table 3.7**.

The study by McCaw-Binns et al (1994)[29,30] was a case-control study conducted in Jamaica between 1986 and 1987. It compared 9919 singleton pregnancies delivered in a two month period and surviving the early neonatal period, to 1847 singleton perinatal deaths occurring over a twelve month period. The mothers were asked whether they had taken any iron or folic acid supplements during the course of the pregnancy. The main outcome was perinatal death, and included antepartum fetal deaths, deaths from of live births due to immaturity and deaths from intrapartum asphyxia. Logistic regression analysis was undertaken in three steps comprising all medical factors previously shown to be independently related to each type of perinatal death. 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. The authors note that iron is expected to be taken by all pregnant women in Jamaica, but it is especially emphasised in women with low haemoglobin levels. It is therefore possible that there is some selection bias in this study. In practice, 67% of mothers were reported to take iron during their pregnancy but compliance was not assessed and baseline haemoglobin levels were not reported.

Titaley et al (2012)[28] conducted a retrospective cohort study using data from the Indonesia Demographic and Health Survey (IDHS) of 2002 and 2007. Women of reproductive age (15-49 years) completed the survey, which included information on the 26 591 most recent live-born infants within the five years prior to each survey. Early neonatal mortality (in the first week of life) and all neonatal mortality (in the first month of life) were examined. Again, participating women were asked to recall their use of iron and folic acid supplements during their pregnancy.

Table 3.7 Oral and/or parenteral iron – characteristics and quality of Level II evidence

Study	Study type *Study quality*	Population N	Comparison	Outcomes
McCaw-Binns et al (1994)[29,30]	Case-control study *Fair*	Pregnant women delivering over a defined time period N=11 766	Iron vs no treatment	Mortality (perinatal)
Titaley et al (2012)[28]	Retrospective cohort study *Fair*	Ever married women in reproductive age (15-49 years) N=26 591	Iron/folic acid vs no treatment	Mortality

Results

Transfusion incidence

Transfusion incidence was assessed in a number of treatment comparisons with evidence available for the following: oral iron versus no treatment or placebo, IV iron versus oral iron, IV iron with oral iron versus oral iron, IV iron with folic acid versus oral iron with folic acid and IV iron versus IM iron with oral iron. There was no significant difference between treatment arms for any comparison reporting transfusion requirements; however, the individual studies were small and often underpowered to detect a significant difference in transfusion incidence or volume. It was not possible to pool results because of the heterogeneity of patient populations and interventions assessed.

The systematic review did not identify any evidence relating to oral iron with folic acid versus placebo, IV iron versus oral iron with folic acid, IV iron versus IM iron, IM iron versus oral iron, or IM iron versus oral iron with folic acid.

Oral iron versus no treatment or placebo

The Level I study by Pena-Rosas et al (2012)[10] included one RCT that compared oral iron to no treatment among pregnant women of any age and parity and reported on transfusion incidence (**Table 3.8**). Pena-Rosas (2012)[10] included one additional trial (Hemminki et al, 1991)[31] that compared routine oral iron with selective oral iron, which was removed for this review. There was no significant difference in the number of transfusions provided between the treatment groups (1 trial; 0/16 (0%) vs 1/16 (6.3%); RR 0.33; 95% CI 0.01, 7.62).

Intravenous iron versus oral iron

The Level I study by Reveiz et al (2011)[11] identified three studies that compared IV iron with oral iron among pregnant women with iron deficiency anaemia (**Table 3.9**). Reveiz et al (2011)[11] found no significant difference between treatment groups in the number of blood transfusions required in pregnant women with iron deficiency anaemia (3 trials; 0/84 (0%) vs 4/83 (4.8%); RR 0.27; 95% CI 0.05, 1.59).

A further three Level II studies published after the Reveiz et al (2011)[11] review were identified that examined the effect of IV iron on transfusion incidence in various maternity populations (**Table 3.9**). Gupta et al (2013)[18] recorded no events in either study group comparing IV iron to oral iron in pregnant women with anaemia; as did Van Wyck et al (2007)[26] in a population of postpartum women with anaemia. Similar results were reported by Breymann et al (2008)[14] who investigated the same comparison in women with postpartum iron deficiency anaemia: 1/227 (0.4%) vs 0 (0%).

Intravenous iron plus oral iron versus oral iron

Two RCTs compared IV iron with oral iron to oral iron alone (**Table 3.10**), reporting no significant differences between treatment groups. Neeru et al (2012)[23] focused on pregnant women with iron deficiency anaemia, but only provided the number of blood transfusions required in the intervention group, whereas Westad et al (2008)[28] found no difference in transfusion incidence in women with postpartum anaemia: 4/58 (6.9%) vs 10/70 (14.3%).

Intravenous iron plus folic acid versus oral iron plus folic acid

Three RCTs compared IV iron with folic acid to oral iron with folic acid (**Table 3.11**), reporting no significant differences in transfusion requirements. The first two studies focused on pregnant women and the incidence of transfusion in a non-anaemic population – 1/61 (1.6%) or 0/49 (0%) vs 1/119 (0.8%) – using two different doses of IV iron,[12] and one with moderate iron deficiency anaemia – 0 (0%) vs 1/49 (2.0%).[21] The third study[16] presented results for both antenatal and postnatal cohorts, with no differences in either population.

Intravenous iron versus intramuscular iron plus oral iron

Hashmi et al (2006)[19] compared IV iron with IM and oral iron (**Table 3.12**), among a mixed maternity population reporting no transfusions in either study group – 0/50 (0%) vs 0/50 (0%).

Table 3.8 Oral iron versus placebo – transfusion incidence

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Iron N/N (%) Mean ±SD	Placebo N/N (%) Mean ±SD	Risk estimate (95% CI) Mean difference	*Statistical significance* P-value
LEVEL I EVIDENCE									
DURING PREGNANCY									
Pena-Rosas et al (2012)[10] Level I *Good*	Systematic review of 60 RCTs and quasi-RCTs identified 1 trial (Puolakka 1980)[32] with an unclear risk of bias [a] N = 32	Pregnant women of any gestational age and parity	Finland	Oral iron vs no treatment/placebo	Transfusion provided	0/16 (0%)	1/16 (6.3%)	0.33 [0.01, 7.62]	No significant difference P=0.49 Heterogeneity not applicable

Abbreviations: CI, confidence interval; SD, standard deviation

[a] Pena-Rosas (2012) included one additional trial (Hemminki et al, 1991)[31] that compared routine oral iron with selective oral iron, which was removed for this review.

Table 3.9 Intravenous iron versus oral iron – transfusion incidence

Study Level of evidence Quality	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						IV iron N/N (%) Mean ±SD	Oral iron N/N (%) Mean ±SD	Risk estimate (95% CI) Mean difference	*Statistical significance* P-value
LEVEL I EVIDENCE									
DURING PREGNANCY									
Reveiz et al (2011)[11] Level I *Good*	Systematic review of 23 RCTs included 2 trials (Al 2005, Bayoumeu 2002),[33,34] each with an unclear risk of bias and 1 trial (Digumarthi 2008),[35] with a high/unclear risk of bias N = 167	Pregnant women with a diagnosis of anaemia (Hb levels under 11 g/dL, or other tests for anaemia as defined by trialists) attributed to iron deficiency	Turkey, France	IV iron vs oral iron	Blood transfusion required	0/84 (0.0%)	4/83 (4.8%)	0.27 [0.05, 1.59]	No significant difference P=0.15 No significant heterogeneity I^2=0%
LEVEL II EVIDENCE									
DURING PREGNANCY									
Gupta et al (2013)[18] Level II *Fair*	1 RCT N = 100	Pregnant women between 24 and 34 weeks gestation with anaemia (Hb 7.0–9.0 g/dL and serum ferritin <15n g/mL)	Single centre, India	IV iron sucrose (as per calculated dose) + mebendazole (100 mg twice daily for 3 days) vs oral ferrous sulphate (200 mg thrice daily for 4 weeks) + mebendazole (100 mg twice daily for 3 days)	Transfusion incidence	0/50 (0%)	0/50 (0%)	NR	NA
POSTPARTUM									
Breymann et al (2008)[14] Level II *Poor*	1 RCT N = 349	Women with postpartum iron deficiency anaemia (Hb ≤105 g/L)	Multicentre, Poland, Romania, Russian Federation	IV iron carboxymaltose (up to three weekly doses of 1000 mg maximum) vs oral ferrous sulphate (100 mg twice daily for 12 weeks)	Transfusion incidence	1/227 (0.4%)	0/117 (0%)	NR	NR

Study Level of evidence Quality	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						IV iron N/N (%) Mean ±SD	Oral iron N/N (%) Mean ±SD	Risk estimate (95% CI) Mean difference	*Statistical significance* P-value
Van Wyck et al (2007)[26] Level II *Fair*	1 RCT N = 361	Women with postpartum anaemia (within 10 days postpartum, Hb ≤10 g/dL)	Multicentre, USA, Mexico	Intravenous ferric carboxymaltose (≤1000 mg repeated weekly to achieve total calculated replacement dose) vs oral ferrous sulphate (325 mg thrice daily for 6 weeks)	Transfusion incidence	0/182 (0%)	0/179 (0%)	NR	NA

Abbreviations: CI, confidence interval; Hb, haemoglobin; IV, intravenous; NR, not reported; RCT, randomised controlled trial; SD, standard deviation

Table 3.10 Intravenous iron + oral iron versus oral iron – transfusion incidence

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						IV iron + oral iron N/N (%) Mean ±SD	Oral iron N/N (%) Mean ±SD	Risk estimate (95% CI) Mean difference	*Statistical significance* P-value
LEVEL II EVIDENCE									
DURING PREGNANCY									
Neeru et al (2012)[23] Level II *Poor*	1 RCT N = 100	One hundred pregnant women, from 14 to 36 weeks gestation, with established iron deficiency anaemia (Hb 6.5–10.9 g/dL and ferritin levels <27n g/dL)	Single centre, India	IV iron sucrose (as per calculated dose) followed by ferrous fumarate vs oral ferrous fumarate (300 mg)	Blood transfusion	4/50 (8.0%)	NR	NR	P=NR
POSTPARTUM									
Westad et al (2008)[28] Level II *Fair*	1 RCT N = 129	Women with postpartum haemorrhage anaemia (Hb 6.5/100mL–8.5 g/mL and within 48 hours of birth)	Multicentre, Norway	IV iron sucrose (600 mg, administered as a daily infusion of 200 mg) followed by iron sulphate (100 mg twice daily from week 5) vs oral iron sulphate (100 mg twice daily)	Transfusion incidence	4/58 (6.9%)	10/70 (14.3%)	NR	No significant difference P=0.18

Abbreviations: CI, confidence interval; Hb, haemoglobin; IV, intravenous; NR, not reported; RCT, randomised controlled trial; SD, standard deviation

Table 3.11 Intravenous iron + folic acid versus oral iron + folic acid – transfusion incidence

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results				
						IV iron + folic acid N/N (%)		Oral iron + folic acid N/N (%)	Risk estimate (95% CI)	*Statistical significance* P-value
LEVEL II EVIDENCE										
DURING PREGNANCY										
Bencaiova et al (2009)[12] Level II *Fair*	1 RCT N = 260	Non-anaemic (Hb ≥10.5 g/dL) pregnant women between the 15th and 20th week of gestation	Single centre, Switzerland	IV iron sucrose (either two doses of 200 mg or three doses of 200 mg) + folic acid vs oral ferrous sulphate (80 mg daily) + folic acid	Transfusion requirement	1/61 (1.6%) *two doses	0/49 (0%) *three doses	1/119 (0.8%)	NR	No significant difference P=1.00
Kochhar et al (2013)[21] Level II *Fair*	1 RCT N = 100	Women between 24–34 weeks of gestation, with moderate iron deficiency anaemia (Hb 7.0–9.0 g/dL, ferritin level <15n g/mL)	Two hospitals in India	IV iron sucrose (divided doses of 200 mg each) + mebendazole (100 mg twice daily for 3 days) and folic acid (5 mg daily) vs oral ferrous sulphate (200 mg, three times a day for 4 weeks) + mebendazole (100 mg twice daily for 3 days) and folic acid (5 mg daily)	Transfusion incidence	0/49 (0%)		1/49 (2.0%)	NR	P=NR
Froessler et al (2013)[16] Level II *Fair*	1 RCT N = 271	Women (148 pregnant and 123 post lower segment caesarean section) with iron deficiency anaemia (Hb <110 g/L and ferritin <12µg/L)	Single centre, South Australia, Australia	IV iron sucrose (400 mg divided into two 200 mg doses) + folic acid 600 µg until birth vs two FGF tablets (ferrous sulphate 250 mg with folic acid 600 µg) daily until birth or for 6 weeks following birth	RBC transfusion Antenatal group	NR (0.8%)		NR (3.0%)	NR	No significant difference (reported in text) P=NR

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						IV iron + folic acid N/N (%)	Oral iron + folic acid N/N (%)	Risk estimate (95% CI)	*Statistical significance* P-value
POSTPARTUM									
Froessler et al (2013)[16] Level II *Fair*	1 RCT N = 271	Women (148 pregnant and 123 post lower segment caesarean section) with iron deficiency anaemia (Hb <110 g/L and ferritin <12µg/L)	Single centre, South Australia, Australia	IV iron sucrose (400 mg divided into two 200 mg doses) + folic acid 600 µg until birth vs two FGF tablets (ferrous sulphate 250 mg with folic acid 600 µg) daily until birth or for 6 weeks following birth	RBC transfusion Postnatal group	0/62 (0.0%)	1/45 (2.2%)	NR	No significant difference (reported in text) P=NR

Abbreviations: CI, confidence interval; Hb, haemoglobin; IV, intravenous; NR, not reported; RBC, red blood cell; RCT, randomised controlled trial; SD, standard deviation

Table 3.12 Intravenous iron versus intramuscular iron + oral iron – transfusion incidence

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						IV iron N/N (%)	IM iron + oral iron N/N (%)	Risk estimate (95% CI)	*Statistical significance* P-value
LEVEL II EVIDENCE									
MIXED POPULATION (DURING PREGNANCY AND POSTPARTUM)									
Hashmi et al (2006)[19] Level II *Poor*	1 RCT N = 100	Women (80 with gestational age 12–36 weeks from antenatal clinics and 20 after postpartum haemorrhage) with iron deficiency anaemia (Hb <10 g/dL)	Single centre, Pakistan	IV iron sucrose (divided into 200 mg doses as per total calculated dose) vs IM iron sorbitol (as recommended for each patient, 75 mg daily or alternate days) followed by oral supplements until birth (75 mg)	Transfusion incidence	0/50 (0%)	0/50 (0%)	NR	NA

Abbreviations: CI, confidence interval; Hb, haemoglobin; IM, intramuscular; IV, intravenous; NR, not reported; RCT, randomised controlled trial

Laboratory measures

Laboratory measures were assessed in all identified treatment comparisons. Evidence was available for iron versus no treatment or placebo, oral iron with folic acid versus no treatment or placebo, IV iron versus oral iron, IV iron with oral iron versus oral iron, IV iron versus oral iron with folic acid, IV iron with folic acid versus oral iron with folic acid, IV iron versus IM iron, IV iron versus IM iron with oral iron, IM iron versus oral iron, and IM iron versus oral iron with folic acid.

As discussed previously, there were a number of concerns about the evidence examining iron in maternity patients, making assessment of the effectiveness of this intervention difficult. One point of difference in the included studies specific to laboratory measure was the timing of measurements, with some studies not measuring laboratory values until week 2 of the trial and others beginning at day 5 or 7. As noted in the evidence statements, the overall trend indicated that IV iron may lead to a more rapid restoration of laboratory measures than oral iron, but this difference was often not maintained upon completion of the studies. Some studies may not have captured this initial difference by delaying the timing of measurements.

Oral iron versus no treatment or placebo

The Level I study by Pena-Rosas et al (2012)[10] included 14 trials that compared oral iron to no treatment or placebo (**Table 3.13**) and reported a significant difference favouring oral iron in pregnant women for several laboratory measures. Pena-Rosas (2012) included one additional trial (Hemminki et al, 1991)[31] that compared routine oral iron with selective oral iron, which was removed from the relevant analyses for this review.

Maternal anaemia at term (Hb <110 g/L at 37 weeks gestation or more) was presented as an overall analysis (14 trials; 142/1131 (12.6%) vs 345/1005 (34.3%); RR 0.29; 95% CI 0.19, 0.47) and as subgroup analyses based on the anaemia status of the participating mothers (anaemic at start of supplementation, non-anaemic at start of supplementation, or mixed/unspecified anaemia status). The result favoured oral iron over no treatment or placebo for the latter two subgroup analyses (there were no trials identified for mothers with anaemia at start of supplementation).

Similarly, maternal iron deficiency anaemia at term (Hb <110 g/L and at least one additional laboratory indicator at 37 weeks gestation or more) produced a significant result in the overall analysis (6 trials; 25/572 (4.4%) vs 68/516 (13.2%); RR 0.33; 95% CI 0.16, 0.69), as well as the subgroup analysis by anaemia status. Pena-Rosas et al (2012)[10] also reported a significant effect favouring oral iron for maternal Hb at or near term (g/L, 34 weeks gestation or more) (16 trials; MD: 8.95; 95% CI 6.37, 11.53) and within 6 weeks postpartum (g/L) (6 trials; MD: 7.26; 95% CI 4.78, 9.74).

The Level I study by Reveiz et al (2011)[11] included two studies that compared oral iron and placebo in pregnant women with iron deficiency anaemia and demonstrated significantly higher Hb (g/dL) (2 trials; MD: 1.34; 95% CI 0.27, 2.42) and ferritin levels (µg/L) (1 trial; 3.3 ±0.5 vs 2.6 ±0.5; MD: 0.70; 95% CI 0.52, 0.88) when treated with oral iron.

Oral iron plus folic acid versus no treatment or placebo

The Level I study by Pena-Rosas et al (2012)[10] included five studies that compared oral iron and folic acid to no treatment or placebo (**Table 3.14**), and reported similar laboratory measures. Maternal anaemia at term (Hb <110 g/L at 37 weeks gestation or more) was presented as an overall analysis (3 trials; 15/208 (7.2%) vs 39/138 (28.3%); RR 0.34; 95% CI 0.21, 0.54) and a subgroup analysis by baseline anaemia status, with both results favouring oral iron and folic acid in pregnant women. A significant difference was also observed for maternal Hb within 6 weeks postpartum (g/L) (2 trials; MD: 10.07; 95% CI 7.33, 12.81), which favoured oral iron and folic acid. However, there was no significant difference in maternal iron deficiency anaemia at term

(Hb <110 g/L and at least one additional laboratory indicator at 37 weeks gestation or more) (1 trial; 12/111 (10.8%) vs 5/20 (25.0%); RR 0.43; 95% CI 0.17, 1.09).

Intravenous iron versus oral iron

As shown in **Table 3.15**, the Level I study by Reveiz et al (2011)[11] included three trials that compared IV iron to oral iron in pregnant women with iron deficiency anaemia, reporting significant differences in maternal Hb at birth (g/dL) (1 trial; 12.01 ±0.88 vs 11.26 ±1.1; MD: 0.75; 95% CI 0.34, 1.16) and maternal Hb at 4 weeks (g/dL) (3 trials; MD: 0.44; 95% CI 0.05, 0.82), favouring IV iron.

A further nine Level II studies published after the review by Reveiz et al (2011)[11] investigated IV iron and oral iron in different maternity populations. Gupta et al (2013)[18] focused on pregnant women with anaemia, and demonstrated significantly higher Hb (g/dL) levels at 2 weeks (8.39 ±0.43 vs 8.11 ±0.45), 4 weeks (9.80 ±0.46 vs 9.18 ±0.55), at birth (11.50 ±0.78 vs 10.84 ±1.12) and ferritin levels (ng/mL) at 4 weeks (37.45 ±5.73 vs 13.96 ±1.88) in the group given IV iron.

The remaining eight Level II studies examined the effect of IV iron in postpartum women with anaemia. Bhandal et al (2006)[13] reported significant differences in Hb (g/dL) at days 5 (9.9 ±0.7 vs 7.9 ±0.6) and 14 (11.1 ±0.6 vs 9.0 ±0.4) and ferritin (µg/L) at days 5 (48.0 ±6 vs 12.0 ±2), 14 (37.9 ±5 vs 16.0 ±4) and 40 (42.2 ±7 vs 15.0 ±3). Breymann et al (2008)[14] did not find any difference in the number of subjects falling within a specified Hb target range but did for the ferritin target range, with the results favouring IV iron at 2 (127/179 (70.9%) vs 12/89 (13.5%), 4 (150/179 (83.8%) vs 15/89 (16.9%) and 12 weeks (139/179 (77.7%) vs 29/89 (32.6%).

Giannoulis et al (2009)[17] reported Hb increase (g/dL) (4.6 ±0.44 vs 2.3 ±0.47) and ferritin increase (µg/L) (105 ±11 vs 68 ±9), with both measures favouring IV iron. Similarly, Mumtaz et al (2011)[22] measured participant's Hb and ferritin over the course of the trial, noting significant differences between the groups. However, this difference was only apparent at day 7 for both Hb (g/dL) (11.0 vs 8.3) and ferritin (µg/L) (46.5 vs 13.0); with the authors noting that the difference in Hb was no longer significant by day 40 of the trial.

Jain et al (2013)[20] only reported Hb values (g/dL) after 7 (8.0 ±0.4 vs 7.2 ±0.3) and 14 days (9.1 ±0.4 vs 8.0 ±0.3), with both time points favouring IV iron. Similarly, Verma et al (2011)[27] found a significantly higher Hb (g/dL) at day 7 (9.8 vs 7.5), but this significance was not maintained.

Seid et al (2008)[24] and Van Wyck et al (2007)[26] reported on Hb, ferritin and haematocrit changes over the course of each study. Seid et al (2008)[24] measured the change from baseline to day 42 in Hb (g/dL) (4.0 ±1.06 vs 3.4 ±1.09), ferritin (ng/mL) (225.9 ±117.96 vs 2.7 ±20.36) and haematocrit (%) (10.9 ±3.53 vs 9.5 ±3.70), demonstrating significant results for each laboratory measure favouring IV iron. Van Wyck et al (2007)[26] also reported changes in Hb, ferritin and haematocrit, with results presented for 7, 14, 28 and 42 days from baseline. The differences between the groups at each time point were also significant.

Intravenous iron plus oral iron versus oral iron

Reveiz et al (2011)[11] included one trial that compared IV iron with oral iron to oral iron alone in pregnant women with iron deficiency anaemia (**Table 3.16**). The review reported results that favoured IV iron with oral iron for pre-birth maternal Hb (g/dL) (12.66 ±0.97 vs 12.18 ±0.87; MD 0.48; 95% CI 0.21, 0.75) and maternal Hb after birth (g/dL) (11.55 ±1.08 vs 11.16 ±1.42; MD 0.39; 95% CI 0.02, 0.76).

Two additional Level II studies published after the review by Reveiz et al (2011)[11] also examined the effect of IV iron with oral iron on laboratory measures. One study by Neeru et al (2012)[23] was also in pregnant women with iron deficiency anaemia, that reported significantly larger

percentage changes in Hb (23.62 ±14.95 vs 14.11 ±10.66) and ferritin (2032.54 ±1974.43 vs 180.69 ±308.39), that favoured IV iron with oral iron.

Westad et al (2008)[28] examined the effect of IV iron plus oral iron in women with postpartum anaemia and did not find a significant difference in Hb increase (g/dL) after 4 weeks (4.0 vs 4.6) but did for ferritin (µg/L) after 4 weeks (13.7 ±24.4 vs 4.2 ±15.5), favouring IV iron with oral iron compared with oral iron alone.

Intravenous iron versus oral iron plus folic acid

One Level II study by Deeba et al (2012)[15] compared IV iron with oral iron and folic acid (**Table 3.17**) in pregnant women with iron deficiency anaemia, measuring Hb (g/dL) after 2 (9.63 ±0.89 vs 8.5 ±0.86), 4 (10.09 ±0.81 vs 9.32 ±0.87) and 6 weeks (10.79 ±0.84 vs 9.90 ±0.88), as well as ferritin (ng/mL) after 2 (48.46 ±16.66 vs 16.65 ±4.87), 4 (61.05 ±19.66 vs 23.36 ±8.57) and 6 weeks (86.98 ±19.94 vs 34.78 ±8.79). All results were noted as highly significant and favoured IV iron.

Intravenous iron plus folic acid versus oral iron plus folic acid

Three Level II studies compared IV iron with folic acid to oral iron with folic acid (**Table 3.18**). Bencaiova et al (2009)[12] included non-anaemic pregnant women, demonstrating significantly higher ferritin (µg/L) levels before birth (50 (4–266) vs 21 (4–82)) in the IV iron and folic acid group but not in Hb or haematocrit levels before birth. Kochhar et al (2013)[21] examined pregnant women with moderate iron deficiency, again demonstrating significant differences favouring IV iron with folic acid for Hb (g/dL) at day 30 (12.8 ±1.1 vs 10.7 ±0.7) and birth (13.4 ±0.9 vs 11.2 ±0.9) and ferritin (ng/mL) at day 30 (104 ±13.4 vs 77.6 ±13.7) and birth (128.8 ±15.8 vs 94.6 ±14.2). Froessler et al (2013)[16] included a mixed maternity population, reporting no significant differences in Hb (g/dL) post-birth at any time point but did report significantly higher ferritin (µg/L) post-birth (71 (26–120) vs 38 (20–54)) in the IV iron and folic acid group. However, this difference was only significant at day 14, not at any other time point post-birth.

Intravenous iron versus intramuscular iron

The Level II study by Singh et al (2013)[25] focused on pregnant women with anaemia, comparing IV iron with IM iron (**Table 3.19**). After two (8.79 vs 7.74) and four (10.01 vs 8.81) weeks of treatment, Hb (g/dL) levels were significantly higher in the IV iron group.

Intravenous iron versus intramuscular iron plus oral iron

Reveiz et al (2011)[11] reported significantly higher maternal Hb levels (g/dL) at birth (1 trial; 11.8 ±1.1 vs 10.2 ±1.2; MD 1.60; 95% CI 0.87, 2.33) and at birth (1 trial; 11.3 ±0.9 vs 10.2 ±1.2; MD 1.10; 95% CI 0.49, 1.71) in the IV group when comparing IV iron to IM iron with oral iron among pregnant women with anaemia (**Table 3.20**). The Level II study by Hashmi et al (2006)[19] included a mixed maternity population, with a significantly greater percentage of participants achieving target Hb in the IV iron group (80%) than the IM iron and oral iron group (20%).

Intramuscular iron versus oral iron

Reveiz et al (2011)[11] identified two RCTs that compared IM iron to oral iron in pregnant women with anaemia (**Table 3.21**). Maternal Hb at birth (g/dL) was significantly higher in the intramuscular group (1 trial; 10.5 ±0.84 vs 9.96 ±0.89; MD 0.54; 95% CI 0.30, 0.78), as was haematocrit at birth (1 trial; 31.2 ±2.6 vs 29.8 ±2.7; MD 1.40; 95% CI 0.67, 2.13). Although haematocrit at 8 weeks was not significantly different between the groups, the results at 4 weeks favoured IM iron over oral iron (1 trial; 32.5 ±2.65 vs 31.25 ±2.22; MD 1.25; 95% CI –0.03, 2.53).

Intramuscular iron versus oral iron plus folic acid

Reveiz et al (2011)[11] compared IM iron with oral iron and folic acid (**Table 3.22**), reporting a significant difference in Hb at 36 weeks (g/dL) (1 trial; 10.94 ±0.56 vs 11.2 ±0.82; MD –0.26; 95% CI –0.48, –0.04), which favoured oral iron and folic acid in pregnant women with anaemia.

Table 3.13 Oral iron versus placebo – laboratory measures

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population *Subgroup analysis*	Setting Location	Intervention vs comparator	Outcome	Results			
						Iron N/N (%) Mean ±SD	Placebo N/N (%) Mean ±SD	Risk estimate (95% CI) MD	*Statistical significance* P-value
LEVEL I EVIDENCE									
DURING PREGNANCY									
Pena-Rosas et al (2012)[10] Level I *Good*	Systematic review of 60 RCTs and quasi-RCTs 14 trials[a] N = 2136	Pregnant women of any gestational age and parity	Norway, Denmark, Finland, England, USA, France, Australia, Myanmar, China, Niger	Iron vs no treatment/placebo	Maternal anaemia at term (Hb <110 g/L at 37 weeks gestation or more)	142/1131 (12.6%)	345/1005 (34.3%)	0.29 [0.19, 0.47]	*Favours oral iron* P <0.0001 Substantial heterogeneity I^2=80%
		Anaemic at start of supplementation *0 trials* *N = 0*	NA			0	0	0.0 [0.0, 0.0]	NA
		Non-anaemic at start of supplementation *8 trials*[b] *N = 1244*	England, USA, France, Norway,			41/673 (6.1%)	157/571 (27.5%)	0.20 [0.10, 0.44]	*Favours oral iron* P <0.0001 Substantial heterogeneity I^2=70%
		Unspecified or mixed anaemia status *5 trials* *N = 692*	Myanmar, England, Denmark, Niger, USA			65/358 (18.2%)	145/334 (43.4%)	0.34 [0.18, 0.64]	*Favours oral iron* P=0.00078 Substantial heterogeneity I^2=77%
	Systematic review of 60 RCTs and quasi-RCTs 13 trials[b] N = 1696	Pregnant women of any gestational age and parity	Norway, Denmark, Finland, England, USA, France, Australia, Myanmar, Niger	Iron vs no treatment/placebo	Maternal anaemia at or near term (Hb <110 g/L at 34 weeks gestation or more)	99/908 (10.9%)	247/788 (31.3%)	0.29 [0.18, 0.46]	*Favours oral iron* P <0.00001 Substantial heterogeneity I^2=71%
	Systematic review of 60 RCTs and quasi-RCTs 6 trials	Pregnant women of any gestational age and parity	Iran, Norway, Denmark, Australia, USA, Italy	Iron vs no treatment/placebo	Maternal iron deficiency anaemia at term (Hb <110 g/L and at least one additional laboratory	25/572 (4.4%)	68/516 (13.2%)	0.33 [0.16, 0.69]	*Favours oral iron* P=0.0030 Moderate heterogeneity I^2=49%

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population *Subgroup analysis*	Setting Location	Intervention vs comparator	Outcome	Results			
						Iron N/N (%) Mean ±SD	Placebo N/N (%) Mean ±SD	Risk estimate (95% CI) MD	*Statistical significance* P-value
	N = 1088	*Anaemic at start of supplementation* *0 trials* *N = 0*	NA		indicator at 37 weeks gestation or more)	0	0	0.0 [0.0, 0.0]	NA
		Non-anaemic at start of supplementation *5 trials* *N = 968*	USA, Norway, Iran, Australia, Italy			25/509 (4.9%)	58/459 (12.6%)	0.39 [0.20, 0.74]	*Favours oral iron* P=0.0038 Moderate heterogeneity I^2=40%
		Unspecified or mixed anaemia status *1 trial* *N = 120*	Denmark			0/63 (0.0%)	10/57 (17.5%)	0.04 [0.00,0.72]	*Favours oral iron* P=0.029
	Systematic review of 60 RCTs and quasi-RCTs 6 trials N = 1088	Pregnant women of any gestational age and parity	Iran, Norway, Denmark, Australia, USA, Italy	Iron vs no treatment/placebo	Maternal iron deficiency anaemia at or near term (Hb <110 g/L and at least one additional laboratory indicator at 34 weeks gestation or more)	25/572 (4.4%)	68/516 (13.2%)	0.33 [0.16, 0.69]	*Favours oral iron* P=0.0030 Moderate heterogeneity I^2=49%
	Systematic review of 60 RCTs and quasi-RCTs 7 trials N = 1078	Pregnant women of any gestational age and parity	USA, England, Norway, Denmark, Australia, Myanmar	Iron vs no treatment/placebo	Maternal severe anaemia at any time during second or third trimesters (Hb <70 g/L)	2/570 (0.4%)	3/508 (0.6%)	0.75 [0.02, 29.10]	No significant difference P=0.88 Substantial heterogeneity I^2=67%
		Anaemic at start of supplementation *0 trials* *N = 0*	NA			0	0	0.0 [0.0, 0.0]	NA
		Non-anaemic at start of supplementation *5 trials* *N = 816*	USA, Norway, England, Australia			2/440 (0.5%)	0/376 (0.0%)	4.98 [0.24, 103.31]	No significant difference P=0.30 No significant heterogeneity I^2=0%

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population *Subgroup analysis*	Setting Location	Intervention vs comparator	Outcome	Results			
						Iron N/N (%) Mean ±SD	Placebo N/N (%) Mean ±SD	Risk estimate (95% CI) MD	*Statistical significance* P-value
		Unspecified or mixed anaemia status *2 trials* *N = 262*	Myanmar, Denmark			0/130 (0.0%)	3/132 (2.3%)	0.12 [0.01, 2.21]	No significant difference P=0.15 No significant heterogeneity I^2=0%
	Systematic review of 60 RCTs and quasi-RCTs 7 trials N = 1046	Pregnant women of any gestational age and parity	Myanmar, USA, Norway, Australia, Denmark, Norway	Iron vs no treatment/placebo	Maternal severe anaemia at or near term (Hb <70 g/L at 34 weeks gestation or more)	2/560 (0.4%)	3/486 (0.6%)	0.74 [0.02, 27.81]	No significant difference P=0.87 Substantial heterogeneity I^2=66%
	Systematic review of 60 RCTs and quasi-RCTs 3 trials (Batu 1976, Eskeland 1997),[36,37] each with unclear risk of bias and (Makrides 2003),[38] with low/unclear risk of bias N = 453	Pregnant women of any gestational age and parity	Myanmar, Norway, Australia	Iron vs no treatment/placebo	Moderate anaemia at postpartum (Hb between 80 and 110 g/L)	1/238 (0.4%)	3/215 (1.4%)	0.46 [0.02, 13.91]	No significant difference P=0.66 Substantial heterogeneity I^2=60%
	Systematic review of 60 RCTs and quasi-RCTs 7 trials N = 953	Pregnant women of any gestational age and parity	Myanmar, USA, Norway, Australia, Denmark, Finland	Iron vs no treatment/placebo	Severe anaemia at postpartum (Hb <80 g/L)	0/511 (0.0%)	24/442 (5.4%)	0.02 [0.00, 0.33]	*Favours oral iron* P=0.0062 No significant heterogeneity I^2=0%
	Systematic review of 60 RCTs and quasi-RCTs 16 trials N = 1851	Pregnant women of any gestational age and parity	Netherlands, Finland, Belgium, Canada, Myanmar, Norway, France, England, USA, Iran, Australia, Denmark, Italy	Iron vs no treatment/placebo	Maternal Hb concentration at or near term (g/L, at 34 weeks gestation or more)	NR	NR	8.95 [6.37, 11.53]	*Favours oral iron* P <0.00001 Substantial heterogeneity I^2=89%

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population *Subgroup analysis*	Setting Location	Intervention vs comparator	Outcome	Results			
						Iron N/N (%) Mean ±SD	Placebo N/N (%) Mean ±SD	Risk estimate (95% CI) MD	*Statistical significance* P-value
	Systematic review of 60 RCTs and quasi-RCTs 6 trials N = 659	Pregnant women of any gestational age and parity	Canada, Gambia, Australia, South Korea, England, Denmark	Iron vs no treatment/placebo	Maternal Hb concentration within 6 weeks postpartum (g/L)	NR	NR	7.26 [4.78, 9.74]	*Favours oral iron* P <0.00001 Moderate heterogeneity I^2=44%
Reveiz et al (2011)[11] Level I *Good*	Systematic review of 23 RCTs 1 trial (Suharno 1993),[39] with low/unclear risk of bias N = 125	Pregnant women with a diagnosis of anaemia (Hb levels under 11 g/dL, or other tests for anaemia as defined by trialists) attributed to iron deficiency	Indonesia	Oral iron vs placebo	Anaemic during second trimester	20/63 (31.7%)	52/62 (83.9%)	0.38 [0.26, 0.55]	*Favours oral iron* P <0.00001
	Systematic review of 23 RCTs 2 trials (Suharno 1993),[39] with low/unclear risk of bias and (Sun 2010),[40] with unclear risk of bias N = 215	Pregnant women with a diagnosis of anaemia (Hb levels under 11 g/dL, or other tests for anaemia as defined by trialists) attributed to iron deficiency	Indonesia, China	Oral iron vs placebo	Hb levels (g/dL)	NR	NR	1.34 [0.27, 2.42]	*Favours oral iron* P=0.014 Substantial heterogeneity I^2=98%
	Systematic review of 23 RCTs 1 trial (Suharno 1993),[39] with low/unclear risk of bias N = 125	Pregnant women with a diagnosis of anaemia (Hb levels under 11 g/dL, or other tests for anaemia as defined by trialists) attributed to iron deficiency	Indonesia	Oral iron vs placebo	Ferritin levels (µg/L)	3.3 ±0.5	2.6 ±0.5	0.70 [0.52, 0.88]	*Favours oral iron* P <0.00001

Abbreviations: CI, confidence interval; Hb, haemoglobin; MD, mean difference; NR, not reported; RCT, randomised controlled trial

[a] Total number of trials does not add up to subgroups. The large trial by Hemminki (1991)[31] appeared in the subgroup analyses, but not in the overall analysis; whereas, Liu 2000 is included in the overall analysis but not in the subgroups. The reason for this discrepancy is not clear.

[b] Pena-Rosas (2012)[10] included one additional trial (Hemminki et al, 1991)[31] that compared routine oral iron with selective oral iron, which was removed for this review.

Table 3.14 Oral iron + folic acid versus placebo – laboratory measures

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population *Subgroup analysis*	Setting Location	Intervention vs comparator	Outcome	Results			
						Iron + folic acid N/N (%) Mean ±SD	Placebo N/N (%) Mean ±SD	Risk estimate (95% CI) MD	*Statistical significance* P-value
LEVEL I EVIDENCE									
DURING PREGNANCY									
Pena-Rosas et al (2012)[10] Level I *Good*	Systematic review of 60 RCTs and quasi-RCTs 3 trials (Barton 1994, Chisholm 1966),[41,42] each with low/unclear risk of bias and (Batu 1976),[36] with unclear risk of bias N = 346	Pregnant women of any gestational age and parity	Ireland, Myanmar, England	Iron + folic acid vs no treatment/placebo	Maternal anaemia at term (Hb <110 g/L at 37 weeks gestation or more)	15/208 (7.2%)	39/138 (28.3%)	0.34 [0.21, 0.54]	*Favours iron + folic acid* P <0.00001 No significant heterogeneity I^2=0%
		Anaemic at start of supplementation *0 trials* *N = 0*	NA			0	0	0.0 [0.0, 0.0]	NA
		Non-anaemic at start of supplementation *2 trials* *N = 280*	Ireland, England			5/176 (2.8%)	10/104 (9.6%)	0.24 [0.09, 0.68]	*Favours iron + folic acid* P=0.0072 No significant heterogeneity I^2=0%
		Unspecified or mixed anaemia status at start of supplementation *1 trial* *N = 66*	Myanmar			10/32 (31.3%)	29/34 (85.3%)	0.37 [0.22, 0.62]	*Favours iron + folic acid* P=0.00022
	Systematic review of 60 RCTs and quasi-RCTs 3 trials (Barton 1994, Chisholm 1966),[41,42] each with low/unclear risk of bias and (Batu 1976),[36] with unclear risk of bias N = 346	Pregnant women of any gestational age and parity	Ireland, Myanmar, England	Iron + folic acid vs no treatment/placebo	Maternal anaemia at or near term (Hb <110 g/L at 34 weeks gestation or more)	15/208 (7.2%)	39/138 (28.3%)	0.34 [0.21, 0.54]	*Favours iron + folic acid* P <0.00001 No significant heterogeneity I^2=0%

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population *Subgroup analysis*	Setting Location	Intervention vs comparator	Outcome	Results			
						Iron + folic acid N/N (%) Mean ±SD	Placebo N/N (%) Mean ±SD	Risk estimate (95% CI) MD	*Statistical significance* P-value
	Systematic review of 60 RCTs and quasi-RCTs 1 trial (Lee 2005),[43] with unclear risk of bias N = 131	Pregnant women of any gestational age and parity	South Korea	Iron + folic acid vs no treatment/placebo	Maternal iron deficiency anaemia at term (Hb <110 g/L and at least one additional laboratory indicator at 37 weeks gestation or more)	12/111 (10.8%)	5/20 (25.0%)	0.43 [0.17, 1.09]	No significant difference P=0.077
					Maternal iron deficiency anaemia at term (Hb <110 g/L and at least one additional laboratory indicator at 34 weeks gestation or more)	12/111 (10.8%)	5/20 (25.0%)	0.43 [0.17, 1.09]	No significant difference P=0.077
	Systematic review of 60 RCTs and quasi-RCTs 2 trials (Christian 2003, Lee 2005),[43,44] each with unclear risk of bias N = 458	Pregnant women of any gestational age and parity	Nepal, South Korea	Iron + folic acid vs no treatment/placebo	Moderate anaemia at postpartum (Hb between 80 and 110 g/L)	9/202 (4.5%)	35/256 (13.7%)	0.34 [0.17, 0.69]	*Favours iron + folic acid* P=0.0028 No significant heterogeneity I^2=0%
	Systematic review of 60 RCTs and quasi-RCTs 4 trials N = 506	Pregnant women of any gestational age and parity	Ireland, Myanmar, Nepal, South Korea	Iron + folic acid vs no treatment/placebo	Maternal severe anaemia at any time during second or third trimesters (Hb <70 g/L)	1/238 (0.4%)	15/268 (5.6%)	0.12 [0.02, 0.63]	*Favours iron + folic acid* P=0.012 No significant heterogeneity I^2=0%
	Systematic review of 60 RCTs and quasi-RCTs 3 trials (Barton 1994),[41] with low/unclear risk of bias and (Batu 1976, Lee 2005),[36,43] each with unclear risk of bias N = 191	Pregnant women of any gestational age and parity	Ireland, Myanmar, South Korea	Iron + folic acid vs no treatment/placebo	Maternal severe anaemia at or near term (Hb <70 g/L at 34 weeks gestation or more)	0/102 (0.0%)	3/89 (3.4%)	0.14 [0.01, 2.63]	No significant difference P=0.19 No significant heterogeneity I^2=0%

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population *Subgroup analysis*	Setting Location	Intervention vs comparator	Outcome	Results			
						Iron + folic acid N/N (%) Mean ±SD	Placebo N/N (%) Mean ±SD	Risk estimate (95% CI) MD	*Statistical significance* P-value
	Systematic review of 60 RCTs and quasi-RCTs 3 trials (Batu 1976, Christian 2003, Lee 2005),[36,43,44] each with unclear risk of bias N = 491	Pregnant women of any gestational age and parity	Myanmar, Nepal, South Korea	Iron + folic acid vs no treatment/placebo	Severe anaemia at postpartum (Hb <80 g/L)	0/220 (0.0%)	14/271 (5.2%)	0.05 [0.00, 0.76]	*Favours iron + folic acid* P=0.031 Substantial heterogeneity I^2=100%
	Systematic review of 60 RCTs and quasi-RCTs 3 trials (Barton 1994),[41] with low/unclear risk of bias and (Batu 1976, Taylor 1982),[36,45] each with unclear risk of bias N = 140	Pregnant women of any gestational age and parity	Ireland, Myanmar, England	Iron + folic acid vs no treatment/placebo	Maternal mean Hb concentration at or near term (g/L, at 34 weeks gestation or more)	NR	NR	16.13 [12.74, 19.52]	*Favours iron + folic acid* P <0.00001 No significant heterogeneity I^2=0%
	Systematic review of 60 RCTs and quasi-RCTs 2 trials (Christian 2003, Taylor 1982),[44,45] each with unclear risk of bias N = 459	Pregnant women of any gestational age and parity	Nepal, England	Iron + folic acid vs no treatment/placebo	Maternal Hb concentration within 6 weeks postpartum (g/L)	NR	NR	10.07 [7.33, 12.81]	*Favours iron + folic acid* P <0.00001 No significant heterogeneity I^2=0%

Abbreviations: CI, confidence interval; Hb, haemoglobin; IV, intravenous; MD, mean difference; NR, not reported; RCT, randomised controlled trial; SD, standard deviation

Table 3.15 Intravenous iron versus oral iron – laboratory measures

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						IV iron N/N (%) Mean ±SD	Oral iron N/N (%) Mean ±SD	Risk estimate (95% CI) MD	*Statistical significance* P-value
LEVEL I EVIDENCE									
DURING PREGNANCY									
Reveiz et al (2011)[11] Level I *Good*	Systematic review of 23 RCTs 1 trial (Bayoumeu 2002),[34] with unclear risk of bias N = 47	Pregnant women with a diagnosis of anaemia (Hb levels under 11 g/dL, or other tests for anaemia as defined by trialists) attributed to iron deficiency	France	IV iron vs oral iron	Hb >12 g/dL at 30 days	3/24 (12.5%)	4/23 (17.4%)	0.72 [0.18, 2.87]	No significant difference P=0.64
	Systematic review of 23 RCTs 1 trial (Al 2005),[33] with unclear risk of bias N = 90	Pregnant women with a diagnosis of anaemia (Hb levels under 11 g/dL, or other tests for anaemia as defined by trialists) attributed to iron deficiency	Turkey	IV iron vs oral iron	Hb >11 g/dL at birth	43/45 (95.6%)	28/45 (62.2%)	1.54 [1.21, 1.94]	*Favours IV iron* P=0.00037
	Systematic review of 23 RCTs 1 trial (Al 2005), with unclear risk of bias N = 90	Pregnant women with a diagnosis of anaemia (Hb levels under 11 g/dL, or other tests for anaemia as defined by trialists) attributed to iron deficiency	Turkey	IV iron vs oral iron	Maternal Hb at birth (g/dL)	12.01 ±0.88	11.26 ±1.1	MD 0.75 [0.34, 1.16]	*Favours IV iron* P=0.00035
	Systematic review of 23 RCTs 3 trials (Al 2005, Bayoumeu 2002),[33,34] each with unclear risk of bias and (Digumarthi 2008),[35] with high/unclear risk of bias N = 167	Pregnant women with a diagnosis of anaemia (Hb levels under 11 g/dL, or other tests for anaemia as defined by trialists) attributed to iron deficiency	Turkey, France	IV iron vs oral iron	Mean maternal Hb at 4 weeks (g/dL)	NR	NR	MD 0.44 [0.05, 0.82]	*Favours IV iron* P=0.027 Moderate heterogeneity I^2=42%

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						IV iron N/N (%) Mean ±SD	Oral iron N/N (%) Mean ±SD	Risk estimate (95% CI) MD	*Statistical significance* P-value
LEVEL II EVIDENCE									
DURING PREGNANCY									
Gupta et al (2013)[18] Level II *Fair*	1 RCT N = 100	Pregnant women between 24 and 34 weeks gestation with anaemia (Hb 7.0–9.0 g/dL and serum ferritin <15n g/mL)	Single centre, India	IV iron sucrose (as per calculated dose) + mebendazole (100 mg twice daily for 3 days) vs oral ferrous sulphate (200 mg thrice daily for 4 weeks) + mebendazole (100 mg twice daily for 3 days)	Hb (g/dL) at: 1 week 2 weeks 4 weeks Birth	 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 NR NR NR	*Favours IV iron* (at 2 weeks, 4 weeks and birth) 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
POSTPARTUM									
Bhandal et al (2006)[13] Level II *Fair*	1 RCT N = 44	Women with postpartum iron deficiency anaemia (Hb <9 g/dL and ferritin <15mc g/L at 24–48 hours post-birth)	Single centre, Oxford, UK	IV ferrous sucrose (200 mg, two doses given on days 2 and 4) vs oral ferrous sulphate (200 mg twice daily for 6 weeks)	Hb (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)
Breymann et al (2008)[14] Level II *Poor*	1 RCT N = 349	Women with postpartum iron deficiency anaemia (Hb ≤105 g/L)	Multicentre, Poland, Romania, Russian Federation	IV iron carboxymaltose (up to three weekly doses of 1000 mg maximum) vs oral ferrous sulphate (100 mg twice daily for 12 weeks)	Hb (120–160 g/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)

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						IV iron N/N (%) Mean ±SD	Oral iron N/N (%) Mean ±SD	Risk estimate (95% CI) MD	*Statistical significance* P-value
Giannoulis et al (2009)[17] Level II *Poor*	1 RCT N = 104	Postpartum women with severe iron deficiency anaemia (Hb <8 g/dL and ferritin <10µg/L)	Single centre, Greece	IV iron sucrose (total amount 300 mg in 3 days) vs oral iron (800 mg iron proteinsuccinylate daily for 4 weeks)	Hb (g/dL) 1 week after treatment 4 weeks after treatment	 8.8 ±NR 12.6 ±NR	 8.1 ±NR 10.3 ±NR	 NR	P=NR
					Increase in Hb (g/dL)	4.6 ±0.44	2.3 ±0.47	NR	*Favours IV iron* P=0.0001
					Ferritin (µg/L) 1 week after treatment 4 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
Jain et al (2013)[20] Level II *Fair*	1 RCT N = 46	Women with postpartum anaemia (Hb <8 g/dL within 48 hours postpartum)	Single centre, India	IV iron sucrose (300–600 mg in two or three divided doses as per calculated dose) vs oral ferrous fumarate (300 mg daily for 14 days)	Hb (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
Mumtaz et al (2011)[22] Level II *Poor*	1 RCT N = 80	Women with postpartum iron deficiency anaemia (Hb <9 g/dL and ferritin <15µg/L) at 24–48 hours post-birth	Two hospitals in Pakistan	IV ferrous sucrose (two doses of 200 mg given on days 2 and 4) vs oral ferrous sulphate (200 mg twice daily for 6 weeks)	Hb (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	*Favours IV iron* (at day 7) P=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

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						IV iron N/N (%) Mean ±SD	Oral iron N/N (%) Mean ±SD	Risk estimate (95% CI) MD	*Statistical significance* P-value
Seid et al (2008)[24] Level II *Fair*	1 RCT N = 291	Women with postpartum anaemia (10 days or less after birth with Hb ≤10 g/L)	Multicentre, USA	IV ferric carboxymaltose (100 mg or less repeated weekly to a calculated replacement dose, maximum 2500 mg) vs oral ferrous sulphate (325 mg thrice daily for 6 weeks)	Subjects achieving correction of anaemia by baseline Hb ≤8 g/dL 8.1–9.0 g/dL 9.1–10.0 g/dL ≥10.1 g/dL	 78.9% 90.5% 94.4% 100.0%	 43.5% 59.2% 77.3% 88.9%	NR	*Favours IV iron* (for baseline Hb ≤8 g/dL, 8.1–9.0 g/dL and 9.1–10.0 g/dL P=0.0286 P=0.0008 P=0.0054 P=0.1000
					Hb (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
Van Wyck et al (2007)[26] Level II *Fair*	1 RCT N = 361	Women with postpartum anaemia (within 10 days postpartum, Hb ≤10 g/dL)	Multicentre, USA, Mexico	IV ferric carboxymaltose (≤1000 mg repeated weekly to achieve total calculated replacement dose) vs oral ferrous sulphate (325 mg thrice daily for 6 weeks)	Subjects achieving Hb ≥12.0 g/dL by baseline Hb: Overall <8.1 g/dL 8.1–9.0 g/dL 9.1–10.0 g/dL >10.0 g/dL	(from graph) ~ 90% ±NR ~ 85% ±NR ~ 85% ±NR ~ 95% ±NR ~ 95% ±NR	(from graph) ~ 70% ±NR ~ 45% ±NR ~ 55% ±NR ~ 75% ±NR ~ 90% ±NR	NR	*Favours IV iron* (for baseline Hb overall, <8.1 g/dL, 8.1–9.0 g/dL and 9.1–10.0 g/dL) P <0.01 P <0.05 P <0.05 P <0.01 P=NR
					Change in Hb (g/dL) 7 days 14 days 28 days 42 days after initiating treatment	 ~ 2.25 ±NR ~ 3 ±NR ~ 3.75 ±NR ~ 4.25 ±NR (data shown in graph)	 ~ 1.75 ±NR ~ 2.5 ±NR ~ 3 ±NR ~ 3.25 ±NR (data shown in graph)	NR	*Favours IV iron* (after 7, 14, 28 and 42 days) P <0.01 P <0.001 P <0.001 P <0.001

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						IV iron N/N (%) Mean ±SD	Oral iron N/N (%) Mean ±SD	Risk estimate (95% CI) MD	*Statistical significance* P-value
					Change in haematocrit (%) 7 days 14 days 28 days 42 days after initiating treatment	~ 6.5 ±NR ~ 9 ±NR ~ 10.5 ±NR ~ 11 ±NR (data shown in graph)	~ 5.5 ±NR ~ 7.5 ±NR ~ 9.5 ±NR ~ 9.5 ±NR (data shown in graph)	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 (data shown in graph)	~ 0 ±NR ~ 0 ±NR ~ 0 ±NR ~ 0 ±NR (data shown in graph)	NR	*Favours IV iron* (after 7, 14, 28 and 42 days) P <0.001 P <0.001 P <0.001 P <0.001
Verma et al (2011)[27] Level II *Poor*	1 RCT N = 150	Women with postpartum iron deficiency anaemia (Hb <8 g/dL) 24 hours after birth	Single centre, India	IV iron sucrose (three divided doses of 200 mg each) vs oral ferrous sulphate (200 mg twice daily for one month)	Hb (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

Abbreviations: CI, confidence interval; Hb, haemoglobin; IV, intravenous; MD, mean difference; NR, not reported; RCT, randomised controlled trial; SD, standard deviation

Table 3.16 Intravenous iron + oral iron versus oral iron – laboratory measures

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						IV iron + oral iron N/N (%) Mean ±SD	Oral iron N/N (%) Mean ±SD	Risk estimate (95% CI) Mean difference	*Statistical significance* P-value
LEVEL I EVIDENCE									
DURING PREGNANCY									
Reveiz et al (2011)[11] Level I *Good*	Systematic review of 23 RCTs 1 trial (Khalafallah 2010),[46] with low/unclear risk of bias N = 183	Pregnant women with a diagnosis of anaemia (Hb levels under 11 g/dL, or other tests for anaemia as defined by trialists) attributed to iron deficiency	Australia	IV iron + oral iron vs oral iron	Mean pre-birth maternal Hb (g/dL)	12.66 ±0.97	12.18 ±0.87	MD 0.48 [0.21, 0.75]	*Favours IV iron + oral iron* P=0.00042
	Systematic review of 23 RCTs 1 trial (Khalafallah 2010),[46] with low/unclear risk of bias N = 183	Pregnant women with a diagnosis of anaemia (Hb levels under 11 g/dL, or other tests for anaemia as defined by trialists) attributed to iron deficiency	Australia	IV iron + oral iron vs oral iron	Mean maternal Hb after birth (g/dL)	11.55 ±1.08	11.16 ±1.42	MD 0.39 [0.02, 0.76]	*Favours IV iron + oral iron* P=0.037
LEVEL II EVIDENCE									
DURING PREGNANCY									
Neeru et al (2012)[23] Level II *Poor*	1 RCT N = 100	One hundred pregnant women, from 14 to 36 weeks gestation, with established iron deficiency anaemia (Hb 6.5–10.9 g/dL and ferritin levels <27n g/dL)	Single centre, India	IV iron sucrose (as per calculated dose) followed by ferrous fumarate vs oral ferrous fumarate (300 mg)	Patients achieving target Hb of 11 g/dL after one month of treatment	NR (66%)	NR (61%)	NR	No significant difference (reported in text) P=NR
					Change in Hb (%)	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

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						IV iron + oral iron N/N (%) Mean ±SD	Oral iron N/N (%) Mean ±SD	Risk estimate (95% CI) Mean difference	*Statistical significance* P-value
					Hb (g/dL) after treatment	11.24 ±0.70	11.06 ±0.63	NR	No significant difference P=0.206 *Hb 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
POSTPARTUM									
Westad et al (2008)[28] Level II *Fair*	1 RCT N = 129	Women with postpartum haemorrhage anaemia (Hb 6.5/100mL–8.5 g/mL and within 48 hours of birth)	Multicentre, Norway	IV iron sucrose (600 mg, administered as a daily infusion of 200 mg) followed by iron sulphate (100 mg twice daily from week 5) vs oral iron sulphate (100 mg twice daily)	Hb (g/L) levels at: Week 4 Week 8 Week 12	~ 115 ±NR ~ 128 ±NR ~ 130 ±NR (from graph)	~ 115 ±NR ~ 125 ±NR ~ 125 ±NR (from graph)	NR	No significant difference P=0.89 P=0.13 P=0.11
					Ferritin (µg/L) levels: Week 4 Week 8 Week 12	~ 40 ±NR ~ 32 ±NR ~ 35 ±NR (from graph)	~ 25 ±NR ~ 30 ±NR ~ 34 ±NR (from graph)	NR	*Favours IV iron + oral iron* (at week 4 only) P <0.001 P=NR P=NR
					Hb (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 + oral iron* P <0.001

Abbreviations: CI, confidence interval; Hb, haemoglobin; IV, intravenous; NR, not reported; RCT, randomised controlled trial; SD, standard deviation

Table 3.17 Intravenous iron versus oral iron + folic acid – laboratory measures

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results IV iron N/N (%) Mean ±SD	Oral iron + folic acid N/N (%) Mean ±SD	Risk estimate (95% CI)	*Statistical significance* P-value
LEVEL II EVIDENCE									
DURING PREGNANCY									
Deeba et al (2012)[15] Level II *Fair*	1 RCT N = 200	Pregnant women between 28 and 37 weeks gestation with established iron deficiency anaemia (Hb levels 6–10 g/dL and serum ferritin <15n g/mL)	Single centre, India	IV iron sucrose (as per calculated dose) vs oral ferrous ascorbate (200 mg daily with 1.1 mg of folic acid)	Hb (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 + oral 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 + oral iron* (after 2, 4 and 6 weeks) P=0.000* P=0.000* P=0.000* *All p-values cited as highly significant

Abbreviations: CI, confidence interval; Hb, haemoglobin; IV, intravenous; NR, not reported; RCT, randomised controlled trial; SD, standard deviation

Table 3.18 Intravenous iron + folic acid versus oral iron + folic acid – laboratory measures

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						IV iron + folic acid N/N (%) Mean ±SD Median (range/IQR)	Oral iron + folic acid N/N (%) Mean ±SD Median (range/IQR)	Risk estimate (95% CI)	*Statistical significance* P-value
LEVEL II EVIDENCE									
DURING PREGNANCY									
Bencaiova et al (2009)[12] Level II Fair	1 RCT N = 260	Non-anaemic (Hb ≥10.5 g/dL) pregnant women between the 15th and 20th week of gestation	Single centre, Switzerland	IV iron sucrose (either two doses of 200 mg or three doses of 200 mg) + folic acid vs oral ferrous sulphate (80 mg daily) + folic acid	Hb before birth (g/dL)	12.2 ±0.9	12.4 ±1.1	NR	No significant difference P=0.110
					Haematocrit before birth (%)	35.2 ±2.1	35.6 ±3.1	NR	No significant difference P=0.222
					Hb at day two after birth (g/dL)	10.6 ±1.8 *two doses 11.1 ±1.3 *three doses	11.0 ±1.6	NR	No significant difference P=0.300
					Ferritin before birth (µg/L)	50 (4–266) *range	21 (4–82) *range	NR	*Favours IV iron + folic acid* P <0.001
Kochhar et al (2013)[21] Level II Fair	1 RCT N = 100	Women between 24–34 weeks of gestation, with moderate iron deficiency anaemia (Hb 7.0–9.0 g/dL, ferritin level <15n g/mL)	Two hospitals in India	IV iron sucrose (divided doses of 200 mg each) + mebendazole (100 mg twice daily for 3 days) and folic acid (5 mg daily) vs oral ferrous sulphate (200 mg, three times a day for 4 weeks) + mebendazole (100 mg twice daily for 3 days) and folic acid (5 mg daily)	Hb (g/dL) Day 7 Day 14 Day 21 Day 30 At birth	 8.8 ±0.6 9.7 ±0.8 10.9 ±0.8 12.8 ±1.1 13.4 ±0.9	 8.4 ±0.8 8.9 ±0.6 9.6 ±0.9 10.7 ±0.7 11.2 ±0.9	NR	*Favours IV iron + folic acid* (at days 21 and 30 and at birth) P=0.009 (at day 21) P=0.002 (at day 30) P=0.002 (at birth)
					Ferritin (ng/mL) Day 7 Day 30 At birth	 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 + folic acid* (at day 30 and at birth) P=0.005 (at day 30) P=0.001 (at birth)

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						IV iron + folic acid N/N (%) Mean ±SD Median (range/IQR)	Oral iron + folic acid N/N (%) Mean ±SD Median (range/IQR)	Risk estimate (95% CI)	*Statistical significance* P-value
Froessler et al (2013)[16] Level II Fair	1 RCT N = 271	Women (148 pregnant and 123 post lower segment caesarean section) with iron deficiency anaemia (Hb <110 g/L and ferritin <12µg/L)	Single centre, South Australia, Australia	IV iron sucrose (400 mg divided into two 200 mg doses) + folic acid 600µg until birth vs two FGF tablets (ferrous sulphate 250 mg with folic acid 600µg) daily until birth or for 6 weeks following birth	Hb (g/dL) post-birth (antenatal cohort) Day 1 Day 14 Day 42	101 (90–113) 128 (117–135) 127 (116–134) *IQR	107 (93–115) 129 (122–140) 127 (122–132) *IQR	NR	No significant difference at any point P=0.2 P=0.4 P=0.9
					Ferritin (µg/L) post-birth (antenatal cohort) Day 1 Day 14 Day 42	33 (15–52) 39 (22–83) 27 (16–59) *IQR	21 (14–33) 40 (16–65) 41 (16–73) *IQR	NR	No significant difference at any point P=0.06 P=0.4 P=0.4
POSTPARTUM									
Froessler et al (2013)[16] Level II Fair	1 RCT N = 271	Women (148 pregnant and 123 post lower segment caesarean section) with iron deficiency anaemia (Hb <110 g/L and ferritin <12µg/L)	Single centre, South Australia, Australia	IV iron sucrose (400 mg divided into two 200 mg doses) + folic acid 600µg until birth vs two FGF tablets (ferrous sulphate 250 mg with folic acid 600µg) daily until birth or for 6 weeks following birth	Hb (g/dL) post-birth (postnatal cohort) Day 14 Day 42	115 (107–123) 124 (118–132) *IQR	118 (110–127) 127 (120–132) *IQR	NR	No significant difference at any point P=0.2 P=0.7
					Ferritin (µg/L) post-birth (postnatal cohort) Day 14 Day 42	101 (82–141) 46 (24–64) *IQR	37 (24–52) 19 (13–33) *IQR	NR	*Favours IV iron + folic acid* (at days 14 and 42) P <0.001 P=0.01
MIXED POPULATION (DURING PREGNANCY AND POSTPARTUM)									
Froessler et al (2013)[16] Level II Fair	1 RCT N = 271	Women (148 pregnant and 123 post lower segment caesarean section) with iron	Single centre, South Australia, Australia	IV iron sucrose (400 mg divided into two 200 mg doses) + folic acid 600µg until birth vs two FGF tablets (ferrous sulphate 250 mg with	Hb (g/dL) post-birth Day 1 Day 14 Day 42	99 (90–108) 119 (112–130) 126 (117–133) *IQR	98 (91–108) 122 (113–133) 127 (120–132) *IQR	NR	No significant difference at any point P=0.7 P=0.4 P=0.9

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						IV iron + folic acid **N/N (%)** **Mean ±SD** **Median (range/IQR)**	**Oral iron + folic acid** **N/N (%)** **Mean ±SD** **Median (range/IQR)**	**Risk estimate (95% CI)**	***Statistical significance*** **P-value**
		deficiency anaemia (Hb <110 g/L and ferritin <12µg/L)		folic acid 600µg) daily until birth or for 6 weeks following birth	Ferritin (µg/L) post-birth Day 1 Day 14 Day 42	21 (13–38) 71 (26–120) 31 (16–62) *IQR	21 (13–33) 38 (20–54) 28 (14–54) *IQR	NR	*Favours IV iron + folic acid* (at day 14) P=0.4 P=0.004 P=0.3

Abbreviations: CI, confidence interval; Hb, haemoglobin; IV, intravenous; NR, not reported; RCT, randomised controlled trial; SD, standard deviation

Table 3.19 Intravenous iron versus intramuscular iron – laboratory measures

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						IV iron N/N (%) Mean ±SD	IM iron N/N (%) Mean ±SD	Risk estimate (95% CI) Mean difference	*Statistical significance* P-value
LEVEL II EVIDENCE									
DURING PREGNANCY									
Singh et al (2013)[25] Level II *Poor*	1 RCT N = 100	Pregnant women of gestational age 14–32 weeks with Hb ≤8 g/dL	Single centre, India	IV iron sucrose (divided into 150 mg doses every third day up to calculated dose) vs IM iron sorbitol (as per calculated dose)	Hb (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
					Hb (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
					Hb (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

Abbreviations: CI, confidence interval; Hb, haemoglobin; IM, intramuscular; IV, intravenous; NR, not reported; RCT, randomised controlled trial; SD, standard deviation

Table 3.20 Intravenous iron versus intramuscular iron + oral iron – laboratory measures

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						IV iron N/N (%) Mean ±SD	IM iron plus oral iron N/N (%) Mean ±SD	Risk estimate (95% CI) Mean difference	*Statistical significance* P-value
LEVEL I EVIDENCE									
DURING PREGNANCY									
Reveiz et al (2011)[11] Level I *Good*	Systematic review of 23 RCTs 1 trial (Wali, 2002),[47] with high/unclear risk of bias N = 40	Pregnant women with a diagnosis of anaemia (Hb levels under 11 g/dL, or other tests for anaemia as defined by trialists) attributed to iron deficiency	Pakistan	IV iron sucrose vs IM iron sorbitol + oral iron *IV iron sucrose 500 mg	Hb >11 g/dL at birth	12/15 (80.0%)	7/25 (28.0%)	2.86 [1.45, 5.63]	*Favours IV iron* P=0.0024
					Maternal Hb (g/dL) at birth	11.8 ±1.1	10.2 ±1.2	1.60 [0.87, 2.33]	*Favours IV iron* P=0.000017
	Systematic review of 23 RCTs 1 trial (Wali 2002),[47] with high/unclear risk of bias N = 45	Pregnant women with a diagnosis of anaemia (Hb levels under 11 g/dL, or other tests for anaemia as defined by trialists) attributed to iron deficiency	Pakistan	IV iron sucrose vs IM iron sorbitol + oral iron *IV iron sucrose 200 mg	Hb >11 g/dL at birth	14/20 (70.0%)	7/25 (28.0%)	2.50 [1.25, 4.99]	*Favours IV iron* P=0.0093
					Maternal Hb (g/dL) at birth	11.3 ±0.9	10.2 ±1.2	1.10 [0.49, 1.71]	*Favours IV iron* P=0.00044
LEVEL II EVIDENCE									
MIXED POPULATION (DURING PREGNANCY AND POSTPARTUM)									
Hashmi et al (2006)[19] Level II *Poor*	1 RCT N = 100	Women (80 with gestational age 12–36 weeks from antenatal clinics and 20 after postpartum haemorrhage) with iron deficiency anaemia (Hb <10 g/dL)	Single centre, Pakistan	IV iron sucrose (divided into 200 mg doses as per total calculated dose) vs IM iron sorbitol (as recommended for each patient, 75 mg daily or alternate days) followed by oral supplements until birth (75 mg)	Target Hb achieved	80%	20%	NR	*Favours IV iron* P <0.05
					Post therapy Hb (g/dL) at mean interval of 3.6 weeks	9.9 ±0.7	9.1 ±0.6	NR	P=NR
					Initial rise in Hb (g/dL)	2.6 ±0.9	1.2 ±0.8	NR	P=NR
					Post therapy final Hb (g/dL)	12.1 ±0.9	10.1 ±1.4	NR	P=NR
					Final rise of Hb at birth	4.6 ±0.3	2.2 ±0.5	NR	P=NR

Abbreviations: CI, confidence interval; Hb, haemoglobin; IM, intramuscular; IV, intravenous; NR, not reported; RCT, randomised controlled trial; SD, standard deviation

Table 3.21 Intramuscular iron versus oral iron – laboratory measures

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						IM iron N/N (%) Mean ±SD	Oral iron N/N (%) Mean ±SD	Risk estimate (95% CI) Mean difference	*Statistical significance* P-value
LEVEL I EVIDENCE									
Reveiz et al (2011)[11] Level I *Good*	Systematic review of 23 RCTs 1 trial (Zutschi 2004),[48] with unclear risk of bias N = 200	Pregnant women with a diagnosis of anaemia (Hb levels under 11 g/dL, or other tests for anaemia as defined by trialists) attributed to iron deficiency	India	IM iron sorbitol citric acid vs oral iron	Not anaemic at term	76/100 (76.0%)	62/100 (62.0%)	1.23 [1.01, 1.48]	*Favours IM iron* P=0.035
					Mean maternal Hb at birth (g/dL)	10.5 ±0.84	9.96 ±0.89	0.54 [0.30, 0.78]	*Favours IM iron* P=0.000010
					Mean maternal haematocrit (%) at birth	31.2 ±2.6	29.8 ±2.7	1.40 [0.67, 2.13]	*Favours IM iron* P=0.00019
	Systematic review of 23 RCTs 1 trial (Ogunbode 1980),[49] with low/unclear risk of bias N = 56 at 4 weeks N = 59 at 8 weeks	Pregnant women with a diagnosis of anaemia (Hb levels under 11 g/dL, or other tests for anaemia as defined by trialists) attributed to iron deficiency	Nigeria	IM iron sorbitol citric acid vs oral iron[a] *oral iron 600 mg	Haematocrit (%): 4 weeks 8 weeks	32.5 ±2.65 35.29 ±3.6	31.25 ±2.22 32.67 ±1.3	1.25 [–0.03, 2.53] 2.62 [1.26, 3.98]	No significant difference at 4 weeks P=0.056 *Favours IM iron* (at 8 weeks) P=0.00015
	Systematic review of 23 RCTs 1 trial (Ogunbode 1980),[49] with low/unclear risk of bias N = 56 at 4 weeks N = 59 at 8 weeks	Pregnant women with a diagnosis of anaemia (Hb levels under 11 g/dL, or other tests for anaemia as defined by trialists) attributed to iron deficiency	Nigeria	IM iron sorbitol citric acid vs oral iron[a] *oral iron 1200 mg	Haematocrit (%): 4 weeks 8 weeks	32.5 ±2.65 35.29 ±3.6	31.25 ±2.22 32.69 ±2.53	1.25 [–0.03, 2.53] 2.60 [1.02, 4.18]	No significant difference (at 4 weeks) P=0.056 *Favours IM iron* (at 8 weeks) P=0.0012

Abbreviations: CI, confidence interval; Hb, haemoglobin; IM, intramuscular; NR, not reported; RCT, randomised controlled trial; SD, standard deviation

[a] All participants received 5 mg of folic acid and 25 mg of pyrimethamine once weekly

Table 3.22 Intramuscular iron versus oral iron + folic acid – laboratory measures

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						IM iron N/N (%) Mean ±SD	Oral iron + folic acid N/N (%) Mean ±SD	Risk estimate (95% CI) Mean difference	*Statistical significance* P-value
LEVEL I EVIDENCE									
DURING PREGNANCY									
Reveiz et al (2011)[11] Level I *Good*	Systematic review of 23 RCTs 1 trial (Kumar, 2005),[50] with high/unclear risk of bias N = 150	Pregnant women with a diagnosis of anaemia (Hb levels under 11 g/dL, or other tests for anaemia as defined by trialists) attributed to iron deficiency	India	IM iron sorbitol citric acid vs oral iron + folic acid	Hb >11 g/dL at 36 weeks	42/75 (56.0%)	51/75 (68.0%)	0.82 [0.64, 1.06]	No significant difference P=0.13
					Hb >12 g/dL at 36 weeks	11/75 (14.7%)	21/75 (28.0%)	0.52 [0.27, 1.01]	No significant difference P=0.053
					Mean Hb at 36 weeks (g/dL)	10.94 ±0.56	11.2 ±0.82	–0.26 [–0.48, –0.04]	*Favours oral iron + folic acid* P=0.023

Abbreviations: CI, confidence interval; Hb, haemoglobin; IM, intramuscular; NR, not reported; RCT, randomised controlled trial; SD, standard deviation

Measures of fetal outcome

Measures of fetal outcomes were assessed by multiple treatment comparisons with evidence available for iron versus no treatment or placebo, oral iron with folic acid versus no treatment or placebo, IV iron versus oral iron, IV iron with folic acid versus oral iron with folic acid and IM iron versus oral iron with folic acid.

The systematic review did not identify any evidence relating to IV iron with oral iron versus oral iron, IV iron versus oral iron with folic acid, IV iron versus IM iron, IV iron versus IM iron with oral iron or IM iron versus oral iron.

Oral iron versus no treatment or placebo

The Level I study by Pena-Rosas et al (2012)[10] included six trials that compared oral iron to no treatment or placebo in pregnant women of any age and parity, and found no significant differences across a range of fetal outcomes (**Table 3.23**). One additional trial (Hemminki et al, 1991)[31] was included by Pena-Rosas (2012) that compared routine oral iron with selective oral iron, which was removed for this review.

Pena-Rosas et al (2012) examined the incidence of low birth weight (<2500 g) (6 trials; 25/582 (4.3%) vs 38/554 (6.9%); RR 0.63; 95% CI 0.30, 1.32) and premature birth (<37 weeks gestation) in pregnant women (6 trials; 57/582 (6.7%) vs 70/861 (8.1%); RR 0.82; 95% CI 0.58, 1.14), as well as birth weight (g) (8 trials; MD 15.81; 95% CI –61.14, 92.76). Based on the anaemia status of the participating mothers, a subgroup analysis was performed for these outcomes but this additional assessment did not yield any significant results. This study also reported on the incidence of very low birth weight (<1500 g) (3 trials; 2/361 (0.6%) vs 4/336 (1.2%); RR 0.55; 95% CI 0.03, 9.07), again not a statistically significant result.

Oral iron plus folic acid versus no treatment or placebo

The Level I study by Pena-Rosas et al (2012)[10] also compared oral iron and folic acid to no treatment or placebo in pregnant women of any age and parity (**Table 3.24**), and reported similar fetal outcomes. However, there was a significant difference favouring oral iron and folic acid for birth weight (g) (2 trials; MD 57.73; 95% CI 7.66, 107.79).There was no difference in the incidence of low birth weight (<2500 g) (2 trials; 220/659 (33.4%) vs 262/652 (40.2%); RR 1.07; 95% CI 0.31, 3.74), or very low birth weight among pregnant women (<1500 g) (1 trial; 2/24 (8.3%) vs 0/24 (0%); RR 5.00; 95% CI 0.25, 98.96). Premature birth (<37 weeks gestation) was presented as an overall analysis (149/768 (19.4%) vs 140/729 (19.2%); RR 1.55; 95% CI 0.40, 6.00), as well as a subgroup analysis by anaemia status, with neither evaluation showing a significant effect.

Intravenous iron versus oral iron

The Level I study by Reveiz et al (2011)[11] compared IV iron with oral iron in pregnant women with iron deficiency anaemia and found no significant differences in fetal outcomes (**Table 3.25**). There were no cases of low birth weight in either study group and no difference in neonatal birth weight (g) (3 trials; MD 54.29; 95% CI –170.11, 278.68).

One RCT published after the review by Reveiz et al (2011)[11] was identified that used the same treatment comparison in pregnant women with anaemia. Gupta et al (2013)[18] examined the effect of iron on birth weight (g) (2607 ±253.28 vs 2568 ±244.19) and period of gestation (weeks) (38.48 ±1.36 vs 38.31 ±1.47), noting no significant differences between treatment groups.

Intravenous iron plus folic acid versus oral iron plus folic acid

Two Level II studies that compared IV iron and folic acid with oral iron were identified in the literature (**Table 3.26**). Bencaiova et al (2009)[12] examined the effect of two different doses of IV

iron on mean birth weight (g) (3325 ±482 or 3178 ±705 vs 3361 ±567) and gestational age <37 weeks at birth (1/61 or 4/49 vs 4/119) in non-anaemic pregnant women. No significant differences between treatment groups were observed.

Kochhar et al (2013) assessed IV iron plus folic acid in pregnant women with moderate iron deficiency anaemia. The study reported mean birth weights (g) (2870 ±680 vs 2695 ±765) and gestational age (38 ±1 vs 37 ±2) but the results were not significantly different between treatment groups.

Intramuscular iron versus oral iron with folic acid

The Level I study by Reveiz et al (2011)[11] included one trial that compared IM iron to oral iron with folic acid in pregnant women with iron deficiency anaemia (**Table 3.27**). The study reported mean birth weight (g) but the result was not significant (1 trial; 2610 ±420 vs 2630 ±480; MD –20.00; 95% CI –164.35, 124.35).

Table 3.23 Oral iron versus placebo – measures of fetal outcome

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population *Subgroup analysis*	Setting Location	Intervention vs comparator	Outcome	Results			
						Iron N/N (%) Mean ±SD	Placebo N/N (%) Mean ±SD	Risk estimate (95% CI) Mean difference	*Statistical significance* P-value
LEVEL I EVIDENCE									
DURING PREGNANCY									
Pena-Rosas et al (2012)[10] Level I *Good*	Systematic review of 60 RCTs and quasi-RCTs 6 trials[a] N = 1136	Pregnant women of any gestational age and parity	Norway, USA, Gambia, Iran, Australia	Iron vs no treatment/placebo	Low birth weight (<2500 g)	25/582 (4.3%)	38/554 (6.9%)	0.63 [0.30, 1.32]	No significant difference P=0.22 Moderate heterogeneity I^2=45%
		Anaemic at start of supplementation *0 trials* *N = 0*	NA			0	0	0.0 [0.0, 0.0]	NA
		Non-anaemic at start of supplementation *5 trials[a]* *N = 955*	Norway, USA, Iran, Australia			22/489 (4.5%)	33/466 (7.1%)	0.65 [0.25, 1.66]	No significant difference P=0.36 Substantial heterogeneity I^2=58%
		Unspecified or mixed anaemia status *1 trial* *N = 181*	Gambia			3/93 (3.2%)	5/88 (5.7%)	0.57 [0.14, 2.31]	No significant difference P=0.43
	Systematic review of 60 RCTs and quasi-RCTs 3 trials (Cogswell 2003, Eskeland 1997),[37,51] each with unclear risk of bias and (Makrides 2003),[38] with low/unclear risk of bias N = 697	Pregnant women of any gestational age and parity	USA, Norway, Australia	Iron vs no treatment/placebo	Very low birth weight (<1500 g)	2/361 (0.6%)	4/336 (1.2%)	0.55 [0.03, 9.07]	No significant difference P=0.68 Substantial heterogeneity I^2=54%

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population *Subgroup analysis*	Setting Location	Intervention vs comparator	Outcome	Results			
						Iron N/N (%) Mean ±SD	Placebo N/N (%) Mean ±SD	Risk estimate (95% CI) Mean difference	*Statistical significance* P-value
	Systematic review of 60 RCTs and quasi-RCTs 6 trials[a] N = 1713	Pregnant women of any gestational age and parity	England, Norway, Iran, USA, Australia, Hong Kong	Iron vs no treatment/placebo	Premature birth (<37 weeks gestation)	57/852 (6.7%)	70/861 (8.1%)	0.82 [0.58, 1.14]	No significant difference P=0.24 No significant heterogeneity I^2=0%
		Anaemic at start of supplementation *0 trials* *N = 0*	NA			0	0	0.0 [0.0, 0.0]	NA
		Non-anaemic at start of supplementation *5 trials*[a] *N = 851*	England, Norway, Iran, USA, Australia			30/433 (6.9%)	40/418 (9.6%)	0.72 [0.45, 1.13]	No significant difference P=0.15 No significant heterogeneity I^2=0%
		Unspecified or mixed anaemia status *1 trial* *N = 862*	Hong Kong			27/419 (6.4%)	30/443 (6.8%)	0.95 [0.58, 1.57]	No significant difference P=0.85
	Systematic review of 60 RCTs and quasi-RCTs 3 trials (Cogswell 2003, Eskeland 1997),[37,51] each with unclear risk of bias and (Makrides 2003),[38] with low/unclear risk of bias N = 690	Pregnant women of any gestational age and parity	Norway, USA, Australia	Iron vs no treatment/placebo	Very premature birth (<34 weeks gestation)	3/357 (0.8%)	10/333 (3.0%)	0.32 [0.10, 1.09]	No significant difference P=0.069 No significant heterogeneity I^2=0%
	Systematic review of 60 RCTs and quasi-RCTs 8 trials[a] N = 1259	Pregnant women of any gestational age and parity	England, Finland, Norway, USA, Iran, Scotland, Niger, Australia	Iron vs no treatment/placebo	Birthweight (g)	NR	NR	15.81 [–61.14, 92.76]	No significant difference P=0.69 Moderate heterogeneity I^2=40%

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population *Subgroup analysis*	Setting Location	Intervention vs comparator	Outcome	Results			
						Iron N/N (%) Mean ±SD	Placebo N/N (%) Mean ±SD	Risk estimate (95% CI) Mean difference	*Statistical significance* P-value
		Anaemic at start of supplementation *0 trials* *N = 0*	NA			0	0	0.0 [0.0, 0.0]	NA
		Non-anaemic at start of supplementation *6 trials*[a] *N = 889*	England, Finland, Norway, USA, Iran, Australia			NR	NR	19.19 [–101.86, 140.25]	No significant difference P=0.76 Substantial heterogeneity I^2=54%
		Unspecified or mixed anaemia status *2 trials* *N = 370*	Scotland, Niger			NR	NR	0.90 [–86.32, 88.12]	No significant difference P=0.98 No significant heterogeneity I^2=0%

Abbreviations: CI, confidence interval; Hb, haemoglobin; NR, not reported; RCT, randomised controlled trial; SD, standard deviation

[a] Pena-Rosas (2012)[10] included one additional trial (Hemminki et al, 1991)[31] that compared routine oral iron with selective oral iron, which was removed for this review

Table 3.24 Oral iron + folic acid versus placebo – measures of fetal outcome

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Iron + folic acid N/N (%) Mean ±SD	Placebo N/N (%) Mean ±SD	Risk estimate (95% CI) Mean difference	*Statistical significance* P-value
LEVEL I EVIDENCE									
DURING PREGNANCY									
Pena-Rosas et al (2012)[10] Level I *Good*	Systematic review of 60 RCTs and quasi-RCTs 2 trials (Christian 2003, Taylor 1982),[45,52] each with unclear risk of bias N = 1311	Pregnant women of any gestational age and parity	Nepal, England	Iron + folic acid vs no treatment/placebo	Low birth weight (<2500 g)	220/659 (33.4%)	262/652 (40.2%)	1.07 [0.31, 3.74]	No significant difference P=0.91 Moderate heterogeneity I^2=29%
	Systematic review of 60 RCTs and quasi-RCTs 1 trial (Taylor 1982),[45] with unclear risk of bias N = 48	Pregnant women of any gestational age and parity	England	Iron + folic acid vs no treatment/placebo	Very low birth weight (<1500 g)	2/24 (8.3%)	0/24 (0.0%)	5.00 [0.25, 98.96]	No significant difference P=0.29
	Systematic review of 60 RCTs and quasi-RCTs 3 trials (Christian 2003, Lee 2005, Taylor 1982),[43-45] each with unclear risk of bias N = 1497	Pregnant women of any gestational age and parity	Nepal, South Korea, England	Iron + folic acid vs no treatment/placebo	Premature birth (<37 weeks gestation)	149/768 (19.4%)	140/729 (19.2%)	1.55 [0.40, 6.00]	No significant difference P=0.53 Moderate heterogeneity I^2=34%
		Anaemic at start of supplementation *0 trials* *N = 0*	NA			0	0	0.0 [0.0, 0.0]	NA

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Iron + folic acid N/N (%) Mean ±SD	Placebo N/N (%) Mean ±SD	Risk estimate (95% CI) Mean difference	*Statistical significance* P-value
		Non-anaemic at start of supplementation *0 trials* *N = 0*	NA			0	0	0.0 [0.0, 0.0]	NA
		Unspecified or mixed anaemia status *3 trials* *N = 1497*	Nepal, South Korea, England			149/768 (19.4%)	140/729 (19.2%)	1.55 [0.40, 6.00]	No significant difference P=0.53 Moderate heterogeneity I^2=34%
	Systematic review of 60 RCTs and quasi-RCTs 2 trials (Lee 2005, Taylor 1982),[43,45] each with unclear risk of bias N = 92	Pregnant women of any gestational age and parity	South Korea, England	Iron + folic acid vs no treatment/placebo	Very premature birth (<34 weeks gestation)	2/48 (4.2%)	0/44 (0.0%)	5.00 [0.25, 98.96]	No significant difference P=0.29 No significant heterogeneity I^2=0%
	Systematic review of 60 RCTs and quasi-RCTs 2 trials (Christian 2003, Taylor 1982),[44,45] each with unclear risk of bias N = 1365	Pregnant women of any gestational age and parity	Nepal, England	Iron + folic acid vs no treatment/placebo	Birth weight (g)	NR	NR	MD 57.73 [7.66, 107.79]	*Favours iron + folic acid* P=0.024 No significant heterogeneity I^2=2%

Abbreviations: CI, confidence interval; Hb, haemoglobin; MD, mean difference; NR, not reported; RCT, randomised controlled trial; SD, standard deviation

Table 3.25 Intravenous iron versus oral iron – measures of fetal outcomes

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						IV iron N/N (%) Mean ±SD	Oral iron N/N (%) Mean ±SD	Risk estimate (95% CI) Mean difference	*Statistical significance* P-value
LEVEL I EVIDENCE									
DURING PREGNANCY									
Reveiz et al (2011)[11] Level I *Good*	Systematic review of 23 RCTs 1 trial (Singh 1998),[53] with low/unclear risk of bias N = 100	Pregnant women with a diagnosis of anaemia (Hb levels under 11 g/dL, or other tests for anaemia as defined by trialists) attributed to iron deficiency	Singapore	IV iron vs oral iron	Preterm labour	0/50 (0.0%)	0/50 (0.0%)	0.0 [0.0, 0.0]	NA
					Low birth weight (under 2500 g)	0/50 (0.0%)	0/50 (0.0%)	0.0 [0.0, 0.0]	NA
					Small-for-gestational age	8/50 (16.0%)	5/50 (10.0%)	1.60 [0.56, 4.56]	No significant difference P=0.38
	Systematic review of 23 RCTs 3 trials (Al 2005, Bayoumeu 2002),[33,34] each with unclear risk of bias and (Singh 1998)[53] with low/unclear risk of bias N = 237	Pregnant women with a diagnosis of anaemia (Hb levels under 11 g/dL, or other tests for anaemia as defined by trialists) attributed to iron deficiency	Turkey, France, Singapore	IV iron vs oral iron	Neonatal birth weight (g)	NR	NR	MD: 54.29 [–170.11, 278.68]	No significant difference P=0.64 Substantial heterogeneity I^2=62%
LEVEL II EVIDENCE									
DURING PREGNANCY									
Gupta et al (2013)[18] Level II *Fair*	1 RCT N = 100	Pregnant women between 24 and 34 weeks gestation with anaemia (Hb 7.0–9.0 g/dL and serum ferritin <15n g/mL)	Single centre, India	IV iron sucrose (as per calculated dose) + mebendazole (100 mg twice daily for 3 days) vs oral ferrous sulphate (200 mg thrice daily for 4 weeks) + mebendazole (100 mg twice daily for 3 days)	Babies carried to term	45/50 (90%)	44/50 (88%)	NR	P=NR
					Period of gestation (weeks)	38.48 ± 1.36	38.31 ± 1.47	NR	No significant difference (reported in text) P=NR
					Birth weight (g)	2607 ± 253.28	2568 ± 244.19	NR	No significant difference (reported in text) P=NR

Abbreviations: CI, confidence interval; Hb, haemoglobin; IV, intravenous; MD, mean difference; NR, not reported; RCT, randomised controlled trial; SD, standard deviation

Table 3.26 Intravenous iron + folic acid versus oral iron + folic acid – measures of fetal outcome

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results				
						IV iron + folic acid		Oral iron + folic acid	Risk estimate (95% CI)	*Statistical significance* P-value
						N/N (%) Mean ±SD		N/N (%) Mean ±SD		
LEVEL II EVIDENCE										
DURING PREGNANCY										
Bencaiova et al (2009)[12] Level II *Fair*	1 RCT N = 260	Non-anaemic (Hb ≥10.5 g/dL) pregnant women between the 15th and 20th week of gestation	Single centre, Switzerland	IV iron sucrose (either two doses of 200 mg or three doses of 200 mg) + folic acid vs oral ferrous sulphate (80 mg daily) + folic acid	Gestational age at birth (<37 weeks)	1/61 (1.6%) *two doses	4/49 (8.2%) *three doses	4/119 (3.4%)	NR	No significant difference P=0.741
					Birth weight (g)	3325 ±482 *two doses	3178 ±705 *three doses	3361 ±567	NR	No significant difference P=0.131
					Gestational age at birth (weeks)	40 ±2 *two doses	39 ±3 *three doses	40 ±2	NR	*Favours IV iron* P=0.035
Kochhar et al (2013)[21] Level II *Fair*	1 RCT N = 100	Women between 24–34 weeks of gestation, with moderate iron deficiency anaemia (Hb 7.0–9.0 g/dL, ferritin <15n g/mL)	Two hospitals in India	IV iron sucrose (divided doses of 200 mg each) + mebendazole (100 mg twice daily for 3 days) and folic acid (5 mg daily) vs oral ferrous sulphate (200 mg, three times a day for 4 weeks) + mebendazole (100 mg twice daily for 3 days) and folic acid (5 mg daily)	Gestational age (weeks)	38 ±1		37 ±2	NR	No significant difference P=NR
					Birth weight (g)	2870 ±680		2695 ±765	NR	No significant difference P=NR

Abbreviations: CI, confidence interval; Hb, haemoglobin; IV, intravenous; NR, not reported; RCT, randomised controlled trial; SD, standard deviation

Table 3.27 Intramuscular iron versus oral iron + folic acid – measures of fetal outcomes

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						IM iron N/N (%) Mean ±SD	Oral iron + folic acid N/N (%) Mean ±SD	Risk estimate (95% CI) Mean difference	*Statistical significance* P-value
LEVEL I EVIDENCE									
DURING PREGNANCY									
Reveiz et al (2011)[11] Level I *Good*	Systematic review of 23 RCTs 1 trial (Kumar 2005),[50] with high/unclear risk of bias N = 150	Pregnant women with a diagnosis of anaemia (Hb levels under 11 g/dL, or other tests for anaemia as defined by trialists) attributed to iron deficiency	India	IM iron sorbitol citric acid vs oral iron + folic acid	Mean birth weight (g)	2610 ±420	2630 ±480	MD –20.00 [–164.35, 124.35]	No significant difference P=0.79

Abbreviations: CI, confidence interval; Hb, haemoglobin; IM, intramuscular; MD, mean difference; NR, not reported; RCT, randomised controlled trial; SD, standard deviation

Mortality

Maternal, perinatal and neonatal mortality were assessed in multiple treatment comparisons with evidence available for oral iron versus no treatment or placebo, oral iron with folic acid versus no treatment or placebo and IV iron versus oral iron. None of the included studies were sufficiently powered to detect differences in maternal deaths.

The systematic review did not identify any evidence relating to mortality for the comparisons of IV iron with oral iron versus oral iron, IV iron versus oral iron with folic acid, IV iron with folic acid versus oral iron with folic acid, IV iron versus IM iron, IV iron versus IM iron with oral iron, IM iron versus oral iron or IM iron versus oral iron with folic acid.

Oral iron versus no treatment or placebo

The Level I study by Pena-Rosas et al (2012)[10] identified one trial in pregnant women comparing oral iron to placebo that reported on maternal mortality (**Table 3.28**). No maternal deaths were reported in either treatment arms (1 trial; 0/24 (0%) vs 0/23 (0%)). The study was not sufficiently powered to detect differences in maternal death.

The Level III study by McCaw-Binns et al (1994)[29,30] examined the use of iron supplementation in pregnant women and reported an effect favouring iron for antepartum fetal deaths (OR 1.42; 95% CI 1.09, 1.84) after adjustment for a number of potential confounders including: medical conditions, social, environmental and behavioural variables, and gestational age at birth. An effect favouring iron for all perinatal deaths (OR 1.26; 95% CI 1.07, 1.50) was also reported, but the relationship between perinatal death and quality of care was stronger. Although an effect favouring iron was observed in the unadjusted analyses for deaths from immaturity and intrapartum asphyxia, the statistical significance of these effects were not maintained after adjustments for potential confounders.

Oral iron plus folic acid versus no treatment or placebo

The Level I study by Pena-Rosas et al (2012)[10] identified one trial that examined the effect of oral iron and folic acid on maternal and neonatal mortality (**Table 3.29**). No significant difference was observed in maternal deaths (1 trial; 0/111 (0%) vs 0/20 (0%)) or neonatal deaths (3 trials; 29/849 (3.4%) vs 40/944 (4.2%); RR 0.81; 95% CI 0.51, 1.30). The three trials which examined neonatal deaths were analysed further in subgroup analyses, with data evaluated based on the anaemia status of the participating mothers in each trial. This additional evaluation did not find any statistically significant difference between treatment groups.

The Level III study by Titaley et al (2012)[28] examined the effect of oral iron and folic acid on early neonatal mortality (HR 0.48; 95% CI 0.30, 0.79) and all neonatal mortality (HR 0.51; 95% CI 0.33, 0.79); with an effect favouring iron and folic acid supplement use during pregnancy reported. These results remained statistically significant following adjustment for two different models of care (days 1-7 postnatal care and day 1 postnatal care).

Intravenous iron versus oral iron

The Level I study by Reveiz et al (2011)[11] identified two trials that examined the effect of IV iron on maternal and neonatal mortality in pregnant women with anaemia (**Table 3.30**). There was no difference in either outcome, with none of the included studies recording any events in either study group for maternal mortality (1 trial; 0/50 (0%) vs 0/50 (%)) or neonatal mortality (2 trials; 0/74 (0%) vs 0/73 (0%)).

None of the Level II studies published after the review by Reveiz et al (2011)[11] reported mortality as an outcome.

Table 3.28 Iron versus placebo – maternal and perinatal mortality

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Iron N/N (%) Mean ±SD	No iron N/N (%) Mean ±SD	Risk estimate (95% CI) Mean difference Odds ratio	*Statistical significance* P-value
LEVEL I EVIDENCE									
DURING PREGNANCY									
Pena-Rosas et al (2012)[10] Level I *Good*	Systematic review of 60 RCTs and quasi-RCTs 1 trial (Eskeland 1997),[37] with unclear risk of bias N = 47	Pregnant women of any gestational age and parity	Norway	Iron vs no treatment/placebo	Maternal death (death while pregnant or within 42 days of termination of pregnancy)	0/24 (0.0%)	0/23 (0.0%)	0.0 [0.0, 0.0]	No significant difference P = not applicable
LEVEL III EVIDENCE									
McCaw-Binns et al (1994)[29,30] Level III *Fair*	1 case-control study N=11 766	Pregnant women delivering over a defined time period	Jamaica	Iron vs no iron	Perinatal deaths – all cause (unadjusted)	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 birth (N=1009 PND, N=7645 SURV)	NR	NR	1.26 [1.07, 1.50]	*Favours iron* P < 0.01
					Logistic regression analysis was undertaken in three steps comprising all medical factors previously shown to be independently related to each type of perinatal death. First, the medical factors (medical conditions) 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.				
					Antepartum fetal deaths (unadjusted)	265/6846 (3.9%)	237/3434 (6.9%)	1.84 [1.54, 2.20]	*Favours iron*[a] P < 0.00001

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Iron	No iron	Risk estimate (95% CI) Mean difference Odds ratio	*Statistical significance* P-value
						N/N (%) Mean ±SD	N/N (%) Mean ±SD		
					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 age at birth (N=386 APFD, N=8263 SURV)	NR	NR	1.42 [1.09, 1.84]	*Favours iron* P < 0.01
					Logistic regression analysis was undertaken in three steps comprising all medical factors previously shown to be independently related to each type of perinatal death. First, the medical factors (medical conditions) 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.				
					Intrapartum asphyxia	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 birth *(N=467 IPA, N=7813 SURV)*	NR	NR	NR	No significant difference
					Logistic regression analysis was undertaken in three steps comprising all medical factors previously shown to be independently related to each type of perinatal death. First, the medical factors (medical conditions) 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.				

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Iron N/N (%) Mean ±SD	No iron N/N (%) Mean ±SD	Risk estimate (95% CI) Mean difference Odds ratio	*Statistical significance* P-value
					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	No significant difference
					Logistic regression analysis was undertaken in three steps comprising all medical factors previously shown to be independently related to each type of perinatal death. First, the medical factors (medical conditions) 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.				

Abbreviations: APFD, antepartum fetal deaths; CI, confidence interval; Hb, haemoglobin; IPA, deaths from intrapartum asphyxia; PND, all perinatal deaths combined; RCT, randomised controlled trial; SD, standard deviation; SURV, babies who survived the first week of life

[a] OR, 95% CIs and p-values calculated post-hoc

Table 3.29 Oral iron + folic acid versus placebo – maternal and perinatal mortality

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population Subgroup analysis	Setting Location	Intervention vs comparator	Outcome	Results			
						Iron+ folic acid N/N (%) Mean ±SD	Placebo N/N (%) Mean ±SD	Risk estimate (95% CI) Mean difference Hazard ratio	*Statistical significance* P-value
LEVEL I EVIDENCE									
DURING PREGNANCY									
Pena-Rosas et al (2012)[10] Level I Good	Systematic review of 60 RCTs and quasi-RCTs 1 trial (Lee 2005),[43] with unclear risk of bias N = 131	Pregnant women of any gestational age and parity	South Korea	Iron + folic acid vs no treatment/ placebo	Maternal death (death while pregnant or within 42 days of termination of pregnancy)	0/111 (0.0%)	0/20 (0.0%)	0.0 [0.0, 0.0]	No significant difference P=not applicable
	Systematic review of 60 RCTs and quasi-RCTs 3 trials (Barton 1994),[41] with low/unclear risk of bias and (Christian 2003, Taylor 1982),[44,45] each with unclear risk of bias N = 1793	Pregnant women of any gestational age and parity	Ireland, Nepal, England	Iron + folic acid vs no treatment/ placebo	Neonatal death (within 28 days after birth)	29/849 (3.4%)	40/944 (4.2%)	0.81 [0.51, 1.30]	No significant difference P=0.39 No significant heterogeneity I^2=0%
		Anaemic at start of supplementation *0 trials* *N = 0*	NA			0	0	0.0 [0.0, 0.0]	NA
		Non-anaemic at start of supplementation *1 trial* *N = 97*	Ireland			1/53 (1.9%)	0/44 (0.0%)	2.50 [0.10, 59.88]	No significant difference P=0.57
		Unspecified or mixed anaemia status *2 trials* *N = 1696*	Nepal, England			28/796 (3.5%)	40/900 (4.4%)	0.79 [0.49, 1.27]	No significant difference P=0.34 No significant heterogeneity I^2=0%

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population Subgroup analysis	Setting Location	Intervention vs comparator	Outcome	Results Iron+ folic acid N/N (%) Mean ±SD	Placebo N/N (%) Mean ±SD	Risk estimate (95% CI) Mean difference Hazard ratio	*Statistical significance* P-value
LEVEL III EVIDENCE									
Titaley et al (2012)[28] Fair	1 retrospective cohort study N=26 591	Women of reproductive age (15-49 years)	Indonesia	Iron + folic acid vs no treatment	Early neonatal mortality [a] (days 1-7 after birth) Unadjusted	107/17 958 (0.6%)	108/7482 (1.45%)	0.48 [0.30, 0.79]	*Favours iron plus folic acid* P < 0.01
					Adjusted model 1 (days 1-7 postnatal care)	NR	NR	0.51 [0.31, 0.82]	*Favours iron plus folic acid* P=0.01
					Adjusted model 2 (day 1 postnatal care)	NR	NR	0.49 [0.30, 0.79]	*Favours iron plus folic acid* P < 0.01
					Cox regression analysis was used to examine the association between neonatal mortality and study factors after controlling for covariates. 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 birth, sex of the child, and child size at birth based on mother's subjective assessment. All values were weighted for the sampling probability.				
					Early neonatal mortality [a] (occurring on the day of birth, day 1) *Adjusted model 2 (day 1 postnatal care)*	52/17 958 (0.29%)	53/7482 (0.70%)	0.40 [0.21, 0.79]	*Favours iron plus folic acid* P=0.01
					Early neonatal mortality [b] (occurring after the day of birth, days 2-7) *Adjusted model 2 (day 1 postnatal care)*	56/17 906 (0.31%)	55/7428 (0.73%)	0.54 [0.28, 1.05]	No significant difference P=0.07
					All neonatal mortality (days 1-31 after birth) [a] Unadjusted	NR	NR	0.51 [0.33, 0.79]	*Favours iron plus folic acid* P < 0.01
					Adjusted model 1 (days 1-7 postnatal care)	NR	NR	0.52 [0.33, 0.82]	*Favours iron plus folic acid* P=0.01

Study **Level of evidence** ***Quality***	**No. of trials** **Sample size included in analysis**	**Patient population** **Subgroup analysis**	**Setting** **Location**	**Intervention vs comparator**	**Outcome**	**Results**			
						Iron+ folic acid **N/N (%)** **Mean ±SD**	**Placebo** **N/N (%)** **Mean ±SD**	**Risk estimate (95% CI)** **Mean difference** **Hazard ratio**	***Statistical significance*** **P-value**
					Adjusted model 2 *(day 1 postnatal care)*	NR	NR	0.51 [0.32, 0.81]	*Favours iron plus folic acid* P=0.01

Abbreviations: CI, confidence interval; Hb, haemoglobin; NA, not applicable; RCT, randomised controlled trial; SD, standard deviation

[a] Data on 3307 cases were missing and were excluded from the analyses.

[b] Data on 3290 cases were missing and were excluded from the analyses.

Table 3.30 Intravenous iron versus oral iron – maternal and perinatal mortality

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						IV iron N/N (%) Mean ±SD	Oral iron N/N (%) Mean ±SD	Risk estimate (95% CI)	*Statistical significance* P-value
LEVEL I EVIDENCE									
DURING PREGNANCY									
Reveiz et al (2011) Level I *Good*	Systematic review of 23 RCTs 1 trial (Singh 1998), with low/unclear risk of bias N = 100	Pregnant women with a diagnosis of anaemia (Hb levels under 11 g/dL, or other tests for anaemia as defined by trialists) attributed to iron deficiency	Singapore	IV iron vs oral iron	Maternal mortality	0/50 (0.0%)	0/50 (0.0%)	0.0 [0.0, 0.0]	NA
	Systematic review of 23 RCTs 2 trials (Bayoumeu 2002), with unclear risk of bias and (Singh 1998), with low/unclear risk of bias N = 147	Pregnant women with a diagnosis of anaemia (Hb levels under 11 g/dL, or other tests for anaemia as defined by trialists) attributed to iron deficiency	France, Singapore	IV iron vs oral iron	Neonatal mortality	0/74 (0.0%)	0/73 (0.0%)	0.0 [0.0, 0.0]	NA

Abbreviations: CI, confidence interval; Hb, haemoglobin; IV, intravenous; NR, not reported; RCT, randomised controlled trial; SD, standard deviation

Secondary outcomes

Functional and performance status

No studies were identified that reported the effect of iron on functional and performance status in maternity patients; however, as this evidence has not strictly undergone the systematic review process (secondary outcomes were only extracted from studies that reported one or more primary outcomes), this outcome should be interpreted with caution.

3.2.2 Erythropoiesis stimulating agents versus no erythropoiesis stimulating agents for maternity patients

Background

Erythropoiesis stimulating agents (ESAs) promote bone marrow production of RBCs; however the ESAs can be associated with complications of therapy, particularly where the baseline Hb is near normal. Accordingly, the effectiveness of ESAs in treating anaemia in pregnancy must be balanced against these risks.

In Australia, ESAs are registered with the TGA for anaemia therapy in patients with chronic renal disease, non-myeloid malignancies and those scheduled for elective surgery with an expected moderate blood loss.

Methods

The systematic review examined the evidence for the use of ESAs versus no ESAs in maternity patients.

Because this is an intervention question, the levels of evidence are as detailed in **Section 3.1.1**. For the purposes of this review, a systematic review of Level III–2 or Level III–3 evidence was classified as Level III evidence.

For this question, the only evidence considered was Level III–2 or higher, published after 1985. In addition, for Level III evidence, the only studies considered were those that included at least 100 subjects.

Summary of evidence

The literature search identified no systematics reviews, RCTs or Level III studies that compared ESAs with no ESAs or specifically addressed the PICO criteria specified in the research protocol .

The literature search identified no literature pertaining to Australia's Aboriginal and Torres Strait Islander peoples relevant to this research question.

3.2.3 Erythropoiesis stimulating agents plus iron versus iron alone for maternity patients

Evidence statements – erythropoiesis stimulating agents		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES2.43	In women with iron deficiency anaemia in pregnancy, the effect on transfusion incidence of adding ESAs to iron is uncertain (See evidence matrix D2.A in Volume 2 of the technical report)	√√	NA	NA	√	√√
ES2.44	In women with postpartum iron deficiency anaemia, the effect on transfusion incidence of adding ESAs to iron is uncertain (See evidence matrix D2.A in Volume 2 of the technical report)	√√	√√	NA	√	√√

Evidence statements – erythropoiesis stimulating agents		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES2.45	In women with iron deficiency anaemia in pregnancy, the effect on laboratory values of adding ESAs to iron is uncertain (See evidence matrix D2.B in Volume 2 of the technical report)	√√	NA	NA	√	√√
ES2.46	In women with postpartum iron deficiency anaemia, the effect on laboratory values of adding ESAs to iron is uncertain (See evidence matrix D2.B in Volume 2 of the technical report)	√√	√	X	√√	√√
ES2.47	In women with iron deficiency anaemia in pregnancy, the effect on thromboembolic events of adding ESAs to iron is unknown (no evidence)	NA	NA	NA	NA	NA
ES2.48	In women with postpartum iron deficiency anaemia, the effect on thromboembolic events of adding ESAs to iron is uncertain (See evidence matrix D2.C in Volume 2 of the technical report)	√√	√√√	NA	√√	√√
ES2.49	In women with iron deficiency anaemia in pregnancy, the effect on fetal outcomes of adding ESAs to iron is uncertain (See evidence matrix D2.D in Volume 2 of the technical report)	√√	NA	NA	√	√√
ES2.50	In women with postpartum iron deficiency anaemia, the effect on fetal outcomes of adding ESAs to iron is unknown (no evidence)	NA	NA	NA	NA	NA
ES2.51	In pregnant women, the effect on maternal and perinatal mortality of adding ESAs to iron is unknown (no evidence)	NA	NA	NA	NA	NA
ES, evidence statement; ESA, erythropoiesis stimulating agent √√√=A; √√=B; √=C; X=D; NA, not applicable						

Recommendation – erythropoiesis stimulating agents	
R4	ESAs should not be routinely used in maternity patients (Grade C)
ESA, erythropoiesis stimulating agent; R, recommendation	

Practice point – erythropoiesis stimulating agents	
PP14	In maternity patients with anaemia, where an ESA is used, it should be combined with iron therapy[a]. [a] ESAs are currently registered with the TGA for anaemia therapy in patients with chronic renal disease, non-myeloid malignancies and those scheduled for elective surgery with an expected moderate blood loss.
ESA, erythropoiesis stimulating agent; PP, practice point	

Evidence gaps and areas of future research – erythropoiesis stimulating agents
• There is a need for further research that includes sufficient iron to make a difference to the ESA response.
Hb, Haemoglobin; IV, intravenous

Methods

The systematic review examined the evidence for the use of ESAs plus iron versus iron alone in maternity patients.

Because this is an intervention question, the levels of evidence are as detailed in **Section 3.1.1**. For the purposes of this review, a systematic review of Level III–2 or Level III–3 evidence was classified as Level III evidence.

For this question, the only evidence considered was Level III–2 or higher, published after 1985. In addition, for Level III evidence, only studies considered were those that included at least 100 subjects. A search of lower level evidence was only conducted for primary outcomes not addressed in higher level evidence only (see **Section 2.2**).

Summary of evidence

Two Level I studies[11,54] and two subsequently published Level II studies[55,56] were identified from the systematic review and hand searching process that evaluated the use of ESAs as an adjunct to iron therapy (see **Appendix C**, Volume 2) and reported primary outcomes relevant to our research question (see **Section 4.1**).

The literature search identified no literature pertaining to Australia's Aboriginal or Torres Strait Islander peoples relevant to this research question.

Level I evidence

There were two systematic reviews of RCTs that evaluated the use of ESAs with iron in maternity patients.[11,54] The main characteristics of these reviews are summarised in **Table 3.31**.

Both systematic reviews compare the use of erythropoietin (EPO) and iron with iron alone. Dodd et al (2004)[54] included six RCTs with data from 411 subjects. Data from this review were used in the assessment of transfusion incidence, laboratory measures and thromboembolic events. Reveiz et al (2011)[11] included 23 RCTs with data from 3198 subjects. Data from this review were used in the assessment of transfusion incidence, laboratory measures and fetal outcomes. There were no studies identified that reported mortality as an outcome.

Both of these systematic reviews focused on a specific subset of the maternity population and include trials conducted in a variety of countries. Dodd et al (2004)[54] included postpartum women with a haemoglobin (Hb) value less than 12 g/dL up to 6 weeks after birth, whereas Reveiz et al (2011)[11] included pregnant women with a diagnosis of anaemia and Hb levels less than 11 g/dL (or other tests for anaemia as defined by the trialists).

Table 3.31 Erythropoiesis stimulating agents in maternity patients – characteristics and quality of Level I evidence

Study	Study type ***Study quality***	Population **N**	Comparison	Outcomes
Dodd et al (2004)[54]	Systematic review *Good*	Women with a Hb value of <12 g/dL up to 6 weeks after birth N = 411	EPO + iron vs iron	Transfusion incidence Laboratory measures Thromboembolic events
Reveiz et al (2011)[11]	Systematic review *Good*	Pregnant women with a diagnosis of anaemia (Hb levels under 11 g/dL, or other tests for anaemia as defined by trialists) attributed to iron deficiency N = 3198	EPO + iron vs iron	Transfusion incidence Laboratory measures Measures of fetal outcome

Abbreviations: EPO, erythropoietin; Hb, haemoglobin

Level II evidence

The systematic reviews by Dodd et al (2004)[54] and Reveiz et al (2011)[11] were updated to identify more recent Level II evidence that examined the use of ESAs in maternity patients. Level II studies published after the literature search date conducted in the Dodd et al (2004)[54] systematic review were identified. Two relevant RCTs were retrieved during this process,[55,56] and are discussed further in the following section.

Both RCTs compared EPO plus iron with iron alone in postpartum women. The RCT described by Krafft et al (2011)[55] included postpartum women with an Hb value less than 8.5 g/dL and was conducted in a single centre in Switzerland. Wagstrom et al (2007)[56] was a pilot study that included postpartum women with Hb less than or equal to 8 g/dL, and was conducted across two hospitals in Sweden. This study randomised participants to three groups: two received differing doses of EPO as well as iron, and the third received iron alone. The main characteristics of these RCTs are summarised in **Table 3.32**.

Table 3.32 Erythropoiesis stimulating agents in maternity patients – characteristics and quality of Level II evidence

Study	Study type Study quality	Population N	Comparison	Outcomes
Krafft et al (2011)[55]	RCT Poor	Postpartum women with severe anaemia (Hb <8.5 g/dL) N = 40	EPO + iron vs iron	Transfusion incidence Laboratory measures Thromboembolic events
Wagstrom et al (2007)[56]	RCT Fair	Postpartum women with Hb ≤80 g/L within 72 hours after birth N = 60	EPO + iron vs iron	Laboratory measures

Abbreviations: EPO, erythropoietin; Hb, haemoglobin; RCT, randomised controlled trial

Level III evidence

The literature search did not identify any Level III–1 or Level III–2 studies that examined the effect of ESAs plus iron in maternity patients.

Results

Transfusion incidence

Both of the Level I studies reported transfusion incidence (**Table 3.33**), but neither reported any significant results.

Iron deficiency anaemia in pregnancy

Reveiz et al (2011)[11] included data from one RCT (40 participants) that did not report any participants requiring transfusions in either study group.

Postpartum iron deficiency anaemia

Dodd et al (2004)[54] included data from two RCTs (100 participants) and found no significant difference in the use of blood transfusions between the two groups (0/60 (0%) vs 2/40 (5%); RR 0.20; 95% CI 0.01, 3.92). The Level II study by Krafft et al (2011)[55] did not report any events in either study group.

Table 3.33 Erythropoiesis stimulating agents + iron versus iron – transfusion incidence

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						ESAs + iron N/N (%) Mean ±SD	Iron N/N (%) Mean ±SD	Risk estimate (95% CI) Mean difference	*Statistical significance* P-value
LEVEL I EVIDENCE									
DURING PREGNANCY									
Reveiz et al (2011)[11] Level I *Good*	Systematic review of 23 RCTs 1 trial (Breymann 2001)[57], with low/unclear risk of bias N = 40	Pregnant women with a diagnosis of anaemia (Hb levels under 11 g/dL, or other tests for anaemia as defined by trialists) attributed to iron deficiency	France	IV rhEPO with IV iron sucrose vs IV iron sucrose	Need for transfusion	0/20 (0%)	0/20 (0%)	0.0 [0.0, 0.0]	NA
Postpartum									
Dodd et al (2004)[54] Level I *Good*	Systematic review of 6 RCTs 2 trials (Breymann 2000,[58] Makrydimas 1998),[59] each with unclear risk of bias N = 100	Women with a Hb value of <12 g/dL up to 6 weeks after birth	Various (single centre study)	IV rhEPO with IV iron vs IV iron (1 RCT) or rhEPO sc + oral iron vs oral iron (1 RCT)	Use of blood transfusions	0/60 (0%)	2/40 (5%)	0.20 [0.01, 3.92]	No significant difference P=0.29 No significant heterogeneity I^2=0%
LEVEL II EVIDENCE									
POSTPARTUM									
Krafft et al (2011)[55] Level II *Fair*	RCT N = 40	Postpartum women with severe anaemia (Hb <8.5 g/dL)	Single centre, Switzerland	IV rhEPO with IV iron sucrose vs IV iron sucrose	Transfusion incidence	0	0	0.0 [0.0, 0.0]	NA

Abbreviations: CI, confidence interval; ESA, erythropoiesis stimulating agents; Hb, haemoglobin; IV, intravenous; RCT, randomised controlled trial; rhEPO, Recombinant human erythropoietin; sc, subcutaneous; SD, standard deviation

Laboratory measures

Laboratory measures were reported in all four of the included studies (**Table 3.34**).

Iron deficiency anaemia in pregnancy

The Level I study by Reveiz et al (2011)[11] included data from one RCT and did not find any significant differences in Hb levels below 11 g/dL between the two groups (1 trial; 1/20 (5%) vs 5/20 (25%); RR 0.20; 95% CI 0.03, 1.56).

Postpartum iron deficiency anaemia

The Level I study by Dodd et al (2004)[54] included data from three RCTs that found postpartum women treated with iron alone had a significantly higher Hb within 2 weeks of treatment than those treated with EPO and iron (g/dL) (1 trial; 10.7 ±1.1 vs 11.25 ±0.55; MD –0.55; 95% CI –0.99, –0.11) but this difference was not maintained as the trial progressed. There was no significant difference in Hb between the groups at 2–6 weeks after treatment (g/dL) (1 trial; 12.6 ±1.6 vs 12.3 ±0.8; MD 0.30; 95% CI –0.34, 0.94).

The Level II study by Krafft et al (2011)[55] found that postpartum women treated with EPO and iron had significantly higher Hb increases (g/dL) after 4 days (1 trial; 1.0 ±0.2 vs 0.5 ±0.1), 8 days (1 trial; 2.4 ±0.2 vs 1.9 ±0.1) and 15 days (1 trial; 3.9 ±0.1 vs 3.0 ±0.1). No significant differences were observed in Hb, haematocrit or ferritin levels between baseline and the end of treatment in this study. Wagstrom et al (2007)[56] found no significant differences in Hb or ferritin levels between treatment groups.

Table 3.34 Erythropoiesis stimulating agents + iron versus iron – laboratory measures

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						ESAs + iron N/N (%) Mean ±SD Median (range)	Iron N/N (%) Mean ±SD Median (range)	Risk estimate (95% CI) Mean difference	*Statistical significance* P-value
LEVEL I EVIDENCE									
DURING PREGNANCY									
Reveiz et al (2011)[11] Level I *Good*	Systematic review of 23 RCTs 1 trial (Breymann 2001),[57] with low/unclear risk of bias N = 40	Pregnant women with a diagnosis of anaemia (Hb levels under 11 g/dL, or other tests for anaemia as defined by trialists) attributed to iron deficiency	France	IV rhEPO + IV iron sucrose vs IV iron sucrose	Hb <11 g/dL at 4 weeks	1/20 (5%)	5/20 (25%)	0.20 [0.03, 1.56]	No significant difference P=0.12
POSTPARTUM									
Dodd et al (2004)[54] Level I *Good*	Systematic review of 6 RCTs 1 trial (Breymann 2000),[58] with unclear risk of bias N = 60	Women with a Hb value of <12 g/dL up to 6 weeks after birth	Various (single centre study)	IV rhEPO + IV iron vs IV iron	Hct >35% 2 weeks after treatment	32/40 (80%)	11/20 (55%)	1.45 [0.95, 2.23]	No significant difference P=0.084
	Systematic review of 6 RCTs 1 trial (Breymann 1996),[60] with unclear risk of bias N = 60	Women with a Hb value of <12 g/dL up to 6 weeks after birth	Various (single centre study)	rhEPO sc + iron vs iron *oral or IV iron	Hb (g/dL) within 2 weeks after treatment	10.7 ±1.1	11.25 ±0.55	–0.55 [–0.99, –0.11]	*Favours iron* P=0.014
					Hb (g/dL) >2 weeks to 6 weeks after treatment	12.6 ±1.6	12.3 ±0.8	0.30 [–0.34, 0.94]	No significant difference P=0.11
	Systematic review of 6 RCTs 1 trial (Makrydimas 1998),[59] with	Women with a Hb value of <12 g/dL up to 6 weeks after birth	Various (single centre study)	rhEPO sc + oral iron vs oral iron *folate also given to both groups	median Hb (g/dL) after 2 days after 4 days after 14 days after 39 days	 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

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results ESAs + iron N/N (%) Mean ±SD Median (range)	Iron N/N (%) Mean ±SD Median (range)	Risk estimate (95% CI) Mean difference	*Statistical significance* P-value
	unclear risk of bias N = NR				Hct (median %) after 2 days after 4 days after 14 days after 39 days	 25 (NR) 27 (NR) 32 (NR) 37 (NR)	 22 (NR) 24 (NR) 27 (NR) 35 (NR)	NR	NR
LEVEL II EVIDENCE									
POSTPARTUM									
Krafft et al (2011)[55] Level II *Fair*	RCT N = 40	Postpartum women with severe anaemia (Hb <8.5 g/dL)	Single centre, Switzerland	IV rhEPO + IV iron sucrose vs IV iron sucrose	Hb increase (g/dL) after 4 days after 8 days after 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	*Favours EPO + iron* P <0.05 (for all time periods)
					Hb (g/dL) Baseline End of treatment	 7.1 ±1.1 10.7 ±1.2	 7.5 ±0.7 10.5 ±0.7	NR	No significant difference P=NR
					Hct (%) Baseline End of treatment	 21.4 ±3.3 33.4 ±3.5	 22.8 ±2.2 32.9 ±1.9	NR	No significant difference P=NR
					Ferritin (µg/L) Baseline End of treatment	 46 ±73 187 ±89	 32 ±37 221 ±102	NR	No significant difference P=NR
Wagstrom et al (2007)[56] Level II *Fair*	RCT N = 60	Postpartum women with Hb ≤80 g/L within 72 hours after birth	Two hospitals in Sweden	10 000U rhEPO sc + IV iron sucrose vs 20 000 U rhEPO sc + IV iron sucrose vs iron sucrose	Hb (g/L) Day 0 Day 3 Day 7 Day 14	 75 ±5.1 ~ 81 ±NR ~ 94 ±NR ~ 102 ±NR (from graph)	75 ±4.6 ~ 79 ±NR ~ 92 ±NR ~ 102 ±NR (from graph)	73 ±4.7 ~ 77 ±NR ~ 90 ±NR ~ 102 ±NR (from graph)	NR	No significant between group differences P=0.589 Favours all three treatment groups P <0.001

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results				
						ESAs + iron	Iron		Risk estimate (95% CI) Mean difference	*Statistical significance* P-value
						N/N (%) Mean ±SD Median (range)	N/N (%) Mean ±SD Median (range)			
					Ferritin (µg/L) Day 0 Day 3 Day 7 Day 14	45 ±32.7 ~ 270 ±NR ~ 240 ±NR ~ 110 ±NR (from graph)	51 ±50.0 ~ 260 ±NR ~ 230 ±NR ~ 110 ±NR (from graph)	26 ±19.9 ~ 240 ±NR ~ 210 ±NR ~ 110 ±NR (from graph)	NR	No significant between group differences P=0.646 Significant increase from day 0 to day 3 P<0.001 Significantly higher at day 14 than at randomisation P<0.001

Abbreviations: CI, confidence interval; ESA, erythropoiesis stimulating agents; Hb, haemoglobin; Hct, haematocrit; IV, intravenous; NR, not reported; RCT, randomised controlled trial; rhEPO, Recombinant human erythropoietin; sc, subcutaneous; SD, standard deviation; U, Units

Thromboembolic events

Thromboembolic events were reported by one Level I study and one Level II study (**Table 3.35**).

Postpartum iron deficiency anaemia

The Level I study by Dodd et al (2004)[54] included data from two RCTs that reported on thromboembolic complications in postpartum women. No events in either study group were reported – two trials; 0/64 (0%) versus 0/32 (0%). Similarly, Krafft et al (2011)[55] did not report any events in either study group.

Table 3.35 Erythropoiesis stimulating agents + iron versus iron – thromboembolic events

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						ESAs + iron N/N (%) Mean ±SD	Iron N/N (%) Mean ±SD	Risk estimate (95% CI) Mean difference	*Statistical significance* P-value
LEVEL I EVIDENCE									
POSTPARTUM									
Dodd et al (2004)[54] Level I *Good*	Systematic review of 6 RCTs 2 trials (Breymann 2000, Lebrecht 1995),[58,61] each with unclear risk of bias N = 96	Women with a Hb value of <12 g/dL up to 6 weeks after birth	Various (single centre study)	IV rhEPO + IV iron vs IV iron	Thromboembolic complications	0/64 (0%)	0/32 (0%)	0.0 [0.0, 0.0]	NA
LEVEL II EVIDENCE									
POSTPARTUM									
Krafft et al (2011)[55] Level II *Fair*	RCT N = 40	Postpartum women with severe anaemia (Hb <8.5 g/dL)	Single centre, Switzerland	IV rhEPO + IV iron sucrose vs IV iron sucrose	Thromboembolic complications	0/40 (0%)	0/40 (0%)	0.0 [0.0, 0.0]	NA

Abbreviations: CI, confidence interval; ESA, erythropoiesis stimulating agents; Hb, haemoglobin; IV, intravenous ; NR, not reported; RCT, randomised controlled trial; rhEPO, recombinant human erythropoietin; SD, standard deviation

Measures of fetal outcome

Iron deficiency anaemia in pregnancy

Reveiz et al (2011)[11] identified the only study that reported data for measures of fetal outcome (**Table 3.36**). The study reported on birth before 37 weeks (1 trial; 0/20 (0%) vs 1/20 (5%); RR 0.33; 95% CI 0.01, 7.72) and birth weight (g) (1 trial; 3332 ±282 vs 3462 ±497; MD: –130.00; 95% CI –380.44, 120.44) but no significant differences between treatment groups were found. No other fetal outcomes were reported in the identified studies.

Mortality

None of the included studies reported mortality as an outcome.

Table 3.36 Erythropoiesis stimulating agents + iron versus iron – measures of fetal outcome

Study Level of evidence *Quality*	No. of trials Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						ESAs + iron N/N (%) Mean ±SD	Iron N/N (%) Mean ±SD	Risk estimate (95% CI) Mean difference	*Statistical significance* P-value
LEVEL I EVIDENCE									
DURING PREGNANCY									
Reveiz et al (2011)[11] Level I *Good*	Systematic review of 23 RCTs 1 trial (Breymann 2001),[57] with low/unclear risk of bias N = 40	Pregnant women with a diagnosis of anaemia (Hb levels under 11 g/dL, or other tests for anaemia as defined by trialists) attributed to iron deficiency	France	IV rhEPO with IV iron sucrose vs IV iron sucrose	Birth <37 weeks	0/20 (0%)	1/20 (5%)	0.33 [0.01, 7.72]	No significant difference P=0.49
					Birth weight (g)	3332 ±282	3462 ±497	MD: –130.00 [–380.44, 120.44]	No significant difference P=0.31

Abbreviations: CI, confidence interval; ESA, erythropoiesis stimulating agents; Hb, haemoglobin; IV, intravenous; MD, mean difference; NR, not reported; RCT, randomised controlled trial; rhEPO, recombinant human erythropoietin SD, standard deviation

Secondary outcomes

Functional and performance status

No studies were identified that reported the effect of ESAs on functional and performance status in maternity patients; however, as this evidence has not strictly undergone the systematic review process (secondary outcomes were only extracted from studies that reported one or more primary outcomes), this result should be interpreted with caution.

3.3 Question 3

Question 3 (Interventional)

In maternity patients, what is the effect of FFP, cryoprecipitate, fibrinogen concentrate, and/or platelet transfusion on patient outcomes?

FFP, fresh frozen plasma

3.3.1 Fresh frozen plasma

Evidence statements – fresh frozen plasma (bleeding patients)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES3.1	In patients with postpartum haemorrhage, the effect of FFP on maternal mortality is uncertain. (See evidence matrix D3.A in Volume 2 of the technical report)	X	√√√	NA	√√	√√
ES3.2	In patients with postpartum haemorrhage, the effect of FFP on transfusion requirements is uncertain (See evidence matrix D3.B in Volume 2 of the technical report)	X	NA	X	√√	√√
ES3.3	In patients with postpartum haemorrhage, the effect of FFP on transfusion-related SAEs (TACO, TRALI, other[a]) is unknown (no evidence).	NA	NA	NA	NA	NA
ES3.4	In patients with postpartum haemorrhage, the effect of FFP on the need for additional interventions to control bleeding is uncertain (See evidence matrix D3.C in Volume 2 of the technical report)	X	NA	NA	√√	√√

ES, evidence statement; FFP, fresh frozen plasma; TACO, transfusion-related circulatory volume overload; TRALI, transfusion-related acute lung injury
√√√=A; √√=B; √=C; X=D; NA, not applicable

Evidence statements – fresh frozen plasma (coagulopathic patients at risk of bleeding)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES3.5	In maternity patients with an abnormal coagulation profile who are at risk of bleeding, the effect of FFP on maternal mortality is uncertain. (See evidence matrix D3.A in Volume 2 of the technical report)	X	√√√	NA	√√	√√
ES3.6	In maternity patients with an abnormal coagulation profile who are at risk of bleeding, the effect of FFP on transfusion requirements is unknown (no evidence).	NA	NA	NA	NA	NA

Evidence statements – fresh frozen plasma (coagulopathic patients at risk of bleeding)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES3.7	In maternity patients with an abnormal coagulation profile who are at risk of bleeding, the effect of FFP on transfusion-related SAEs (TACO, TRALI, other[a]) is unknown (no evidence). [a] Other includes haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease, anaphylactic reactions	NA	NA	NA	NA	NA
ES3.8	In maternity patients with an abnormal coagulation profile who are at risk of bleeding, the effect of FFP on additional interventions to control bleeding is unknown (no evidence).	NA	NA	NA	NA	NA
ES, evidence statement; FFP, fresh frozen plasma; TACO, transfusion-related circulatory volume overload; TRALI, transfusion-related acute lung injury √√√=A; √√=B; √=C; X=D; NA, not applicable						

Practice points – bleeding maternity patients	
PP15	All providers of birthing services should develop a plan to manage obstetric haemorrhage. The plan should give consideration to local resources, transport and access to relevant specialist advice, blood products and equipment.
PP16	In women with major obstetric haemorrhage, in addition to clinical observations, the following parameters should be measured early and frequently: • temperature • acid–base status • ionised calcium • haemoglobin • platelet count • PT/INR • APTT • fibrinogen level With successful treatment, values should trend towards normal.

Practice points – bleeding maternity patients	
PP17	Values indicative of critical physiologic derangement include: • temperature <35°C • pH <7.2, base excess worse than –6, lactate >4 mmol/L • ionised calcium <1.1 mmol/L • platelet count <50 × 10^9/L • PT >1.5 × normal • INR >1.5 • APTT >1.5 × normal • fibrinogen level <2.0 g/L.
PP18	In women with major obstetric haemorrhage requiring massive transfusion, suggested doses of blood components are:[a] • FFP: 15 mL/kg • platelets: 1 adult therapeutic dose • cryoprecipitate: 3–4 g. [a] Or as directed by the haematologist/transfusion specialist. See Appendix E for dose equivalents
APTT, activated partial thromboplastin time; FFP, fresh frozen plasma; INR, international normalisation ratio; PP, practice point; PT, prothrombin time	

Practice points – coagulopathic patients at risk of bleeding	
PP19	In general, a platelet count ≥50 × 10^9/L is considered acceptable for vaginal or caesarean birth; however, lower platelet counts may be tolerated.
PP20	In maternity patients with abnormal coagulation tests who are not bleeding (note: concealed bleeding should be excluded), the *routine* use of cryoprecipitate or FFP is not supported. There was no evidence to define a threshold fibrinogen level or prothrombin ratio/INR that is associated with significant adverse events.
PP21	In maternity patients, underlying causes of coagulopathy should be assessed and treated. Where transfusion of platelets, cryoprecipitate or FFP is considered necessary, the risks and benefits should be considered for each patient, and expert guidance sought.
PP22	Maternity patients with pre-existing haematological conditions (such as thrombocytopenia, inherited or acquired disorders of coagulation) should have their condition optimised before giving birth and have a multidiscipline plan in place for birth and the postnatal period.
FFP, fresh frozen plasma; INR, international normalisation ratio; L, litre; PP, practice point; PT, prothrombin time	

Evidence gaps and areas of future research – FFP, cryoprecipitate, fibrinogen concentrate, and/or platelet transfusion

- There is a lack of evidence on optimal strategies for using blood components and plasma products including cryoprecipitate, fibrinogen concentrate and platelet transfusion in the management of obstetric haemorrhage.
- There is a need for further research on the effect of early administration of fibrinogen on progression to severe PPH and whether there is an advantage to having access to fibrinogen concentrate.
- There is a need for further guidance on platelet counts and coagulation test results for surgical and normal births.

Background

Fresh frozen plasma (FFP) contains all the coagulation factors present in normal plasma and is primarily transfused in the maternity setting to correct coagulation during PPH. Other situations may include the maternity patient requiring medical care for liver disease, coagulation factor deficiencies or thrombotic thrombocytopenic purpura (TTP); for these indications, refer to *Patient Blood Management Guidelines: Module 3 – Medical*.

In maternity patients, FFP is often used in patients with abnormal coagulation test results, under the assumptions that these tests accurately predict bleeding, and that transfusion will reduce that risk. The use of plasma is associated with a range of side effects including infection, allergic reactions, hemolysis, transfusion-related circulatory volume overload (TACO) and transfusion-related acute lung injury (TRALI). Therefore, the risks and benefits of FFP transfusion in maternity patients need to be carefully considered before use.

Methods

The systematic review examined the efficacy and safety results of studies comparing FFP with either (i) no FFP or (ii) FFP using a different transfusion protocol (e.g. restrictive vs liberal transfusion) in maternity patients.

As this is an intervention question, the levels of evidence are as detailed in **Section 3.1.1**.

For the purposes of this review, a systematic review of Level III–2 to Level III–3 evidence was classified as Level III evidence.

For this question, the only evidence considered was Level III–2 or higher, published after 1985.

The literature search identified no systematics reviews or RCTs that specifically addressed the PICO criteria specified in the research protocol. The search identified two Level III–2 cohort studies.

Summary of the evidence

Two studies[62,63] were identified from the systematic review and hand searching process (see **Appendix C**, Volume 2) that examined the use of FFP in maternity patients and reported primary outcomes relevant to our research question (see **Section 4.1**).

The literature search identified no literature pertaining to Australia's Aboriginal and Torres Strait Islander peoples relevant to this research question.

Level I evidence

The literature search identified no systematic reviews comparing FFP transfusion strategies in maternity patients.

Level II evidence

The literature search identified no RCTs comparing FFP transfusion strategies in maternity patients.

Level III evidence

Two retrospective cohort studies of fair quality were identified from the systematic review and hand searching process (see **Appendix C**, Volume 2). The main characteristics of these studies are summarised in **Table 3.37**.

Pasquier et al (2013)[62] conducted a retrospective cohort study that examined data from all women diagnosed with severe postpartum haemorrhage at a tertiary university maternity unit in France. The study was conducted over a 4-year period from 2006 to 2009, and included 142 women with severe postpartum haemorrhage (PPH). Patients were included in the study if they were treated with sulprostone and required transfusion with RBCs within 6 hours of giving birth. Patients were then stratified according to the need for additional interventions to control bleeding.

For the purposes of this review, only a subset of the data presented in the study was relevant. That is, the data that was abstracted from the study related to the subset of patients that received FFP and RBC transfusion, compared with those who received RBC transfusion alone. Pasquier et al (2013)[62] also presented a subanalysis that used propensity scoring to assess the effect of a high FFP:RBC ratio compared to a low ratio on bleeding control. Those results are discussed in **Section 3.3.3**.

The study by Reyal et al (2004)[63] was a retrospective cohort study that examined 19,182 women who gave birth between January 1992 and December 1998 in a single teaching hospital in France. The objective of the study was to examine the accuracy of PPH risk factors in determining women at risk of severe PPH and transfusion. Of the 19,182 women included in the study, 44 received a transfusion of RBC or FFP (or both) in the 21 days following birth in the presence of a haemorrhagic complication. Outcomes assessment included PPH and transfusion risk factors, complications (e.g. hysterectomy) and transfusion volume.

Table 3.37 Fresh frozen plasma – characteristics and quality of Level III evidence

Study	Study type *Study quality*	Population N	Intervention N	Comparator N	Outcomes
Pasquier (2013)[62]	Retrospective cohort study *Fair*	Women with severe PPH (>500 mL) who delivered after 24 weeks gestation, were treated with sulprostone and required transfusion with RBC within 6 hours of birth N = 142	FFP N = 41	No FFP N = 101	Maternal mortality Transfusion volume FFP:RBC ratio over time Additional intervention to control bleeding
Reyal (2004)[63]	Retrospective cohort study *Fair*	Maternity patients (>24 weeks of amenorrhea) in one high-risk obstetric unit N = 19182	Transfusion immediately postpartum N = 44[a]	No transfusion N = 19138	Transfusion volume Additional intervention to control bleeding

Abbreviations: FFP, fresh frozen plasma; NR, not reported; PPH, postpartum haemorrhage; RBC, red blood cell

[a] Out of 44 patients who received transfusion, 20 patients received RBC only and 24 received FFP (19 patients received RBC and FFP, 5 patients received FFP only).

Results

Maternal mortality

Two retrospective cohort studies examined the effect to of FFP on maternal mortality. A summary of the results is presented in **Table 3.38**.

Pasquier et al (2013)[62] included patients with severe postpartum haemorrhage and the study by Reyal et al (2004)[63] included patients with and without haemorrhagic complications. No maternal deaths were reported in the FFP arm of either study.

Table 3.38 Fresh frozen plasma versus no fresh frozen plasma/different protocol – maternal mortality

Study Level of evidence *Quality*	Study type Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						FFP N/N (%)	No FFP / different protocol N/N (%)	Risk estimate [95% CI]	*Statistical significance* P-value
LEVEL III EVIDENCE									
POSTPARTUM HAEMORRHAGE									
Pasquier et al (2013)[62] Level III–2 *Fair*	Retrospective cohort study N = 142	Women with severe PPH (>500 mL) who delivered after 24 weeks gestation, were treated with sulprostone and required transfusion with RBC within 6 hours of birth	Tertiary university maternity unit France	FFP + RBC vs RBC	Maternal mortality	0/41	0/101	NR	P=NR
MIXED POPULATION (HAEMORRHAGIC AND NO HAEMORRHAGIC COMPLICATIONS)									
Reyal et al (2004)[63] Level III–2 *Fair*	Retrospective cohort study N = 19138	Women who had singleton or multiple pregnancy, birth >24 weeks of amenorrhea	Single teaching hospital France	FFP + RBC vs no transfusion	Maternal mortality	0/19	NR	NR	P=NR
				FFP vs no transfusion	Maternal mortality	0/5	NR	NR	P=NR

Abbreviations: CI, confidence interval; FFP, fresh frozen plasma; NR, not reported; PPH, postpartum haemorrhage; RBC, red blood cell

Transfusion volume

Transfusion volume was assessed in one study. **Table 3.39** provides a summary of these results.

Pasquier et al (2013)[62] found that a significantly greater mean volume of RBCs and platelets were transfused in patients who received FFP compared with those who did not receive FFP (both P<0.001). It is possible that the association was caused by selection bias, as patients who received FFP were likely to be more critically ill and have poorer clinical outcomes than those who did not receive FFP.

Table 3.39 Fresh frozen plasma versus no fresh frozen plasma/different protocol – transfusion volume

Study Level of evidence *Quality*	Study type Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						FFP Mean ±SD	No FFP Mean ±SD	Risk estimate [95% CI]	*Statistical significance* P-value
LEVEL III EVIDENCE									
Postpartum haemorrhage									
Pasquier et al (2013)[62] Level III–2 *Fair*	Retrospective cohort study N = 142	Women with severe PPH (>500 mL) who delivered after 24 weeks gestation, were treated with sulprostone and required transfusion with RBC within 6 hours of birth	Tertiary university maternity unit France	FFP vs no FFP	Volume of RBC (units)	6.8 ±5.3	2.7 ±1.2	NR	Favours no FFP P<0.001
					Volume of platelets (units)	0.49 ±0.98	0.01 ±0.1	NR	Favours no FFP P<0.001
					Volume of FFP	4.3 ±2.5	NA	NR	NR
						Median [IQR]	**Median [IQR]**		
					Volume of RBC (units)	2 [4.5]	2 [1]	NR	NR
					Volume of platelets (units)	0 [1]	0 [0]	NR	NR
					Volume of FFP	3 [4]	NA	NR	NR

Abbreviations: CI, confidence interval; FFP, fresh frozen plasma; IQR, interquartile range; NA, not applicable; NR, not reported; PPH, postpartum haemorrhage; RBC, red blood cell

Transfusion-related SAEs

There were no studies identified that reported on transfusion-related serious adverse events (TACO, TRALI, haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease, anaphylactic reactions) in maternity patients receiving FFP transfusion strategies.

Additional interventions to control bleeding

One study reported on the need for additional interventions to control bleeding. **Table 3.40** provides a summary of these results.

Pasquier et al (2013)[62] examined the number of patients who underwent embolisation, arterial ligation and hysterectomy. A total of 23 (56%) patients in the FFP arm required at least one additional intervention (embolisation and/or arterial ligation and/or hysterectomy) compared with 29 patients (29%) who did not received FFP; however, the significance of intergroup differences was not reported. Subjects who received FFP were prone to severity bias with the decision to transfuse FFP at the discretion of the anaesthetist.

Table 3.40 Fresh frozen plasma versus no fresh frozen plasma/different protocol – additional interventions to control bleeding

Study Level of evidence *Quality*	Study type Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						FFP N/N (%)	No FFP N/N (%)	Risk estimate [95% CI]	*Statistical significance* P-value
LEVEL III EVIDENCE									
POSTPARTUM HAEMORRHAGE									
Pasquier et al (2013) Level III–2 *Fair*	Retrospective cohort study N = 142	Women with severe PPH (>500 mL) who delivered after 24 weeks gestation, were treated with sulprostone and required transfusion with RBC within 6 hours of birth	Tertiary university maternity unit France	FFP vs no FFP	Embolisation	10/41 (24%)	24/101 (24%)	NR	P=NR
					Arterial ligation	8/41 (20%)	4/101 (4%)	NR	P=NR
					Hysterectomy	13/41 (32%)	3/101 (3%)	NR	P=NR

Abbreviations: CI, confidence interval; FFP, fresh frozen plasma; NR, not reported; PPH, postpartum haemorrhage; RBC, red blood cell

Secondary outcomes

Laboratory measures

One study was identified that reported on laboratory measures (**Table 3.41**). Pasquier et al (2013) compared FFP to no FFP and reported statistically significant differences favouring no FFP for nadir platelets (giga/L) (88 ± 52 vs 158 ± 79), longest prothrombin time (s) (21.7 ± 7.2 vs 14.9 ± 2.2) and nadir fibrinogen (g/L) (1.1 ± 0.8 vs 2.7 ± 1.1).

Functional and performance status

No studies were identified that reported the effect of FFP on functional and performance status in maternity patients; however, as this evidence has not strictly undergone the systematic review process (secondary outcomes were only extracted from studies that reported one or more primary outcomes), this result should be interpreted with caution.

Table 3.41 Fresh frozen plasma versus no fresh frozen plasma/different protocol – secondary outcomes

Study Level of evidence *Quality*	Study type Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						FFP Mean ± SD	No FFP Mean ± SD	Risk estimate [95% CI]	*Statistical significance* P-value
LEVEL III EVIDENCE									
POSTPARTUM HAEMORRHAGE									
Pasquier et al (2013) Level III–2 *Fair*	Retrospective cohort study N = 142	Women with severe PPH (>500 mL) who delivered after 24 weeks gestation, were treated with sulprostone and required transfusion with RBC within 6 hours of birth	Tertiary university maternity unit France	FFP (N=41) vs no FFP (N=101)	Nadir platelets (giga/L)	88 ± 52	158 ± 79	NR	Favours no FFP P=0.001
					Longest prothrombin time (s)	21.7 ± 7.2	14.9 ± 2.2	NR	Favours no FFP P<0.001
					Nadir fibrinogen (g/L)	1.1 ± 0.8	2.7 ± 1.1	NR	Favours no FFP P<0.001

Abbreviations: CI, confidence interval; FFP, fresh frozen plasma; NR, not reported; PPH, postpartum haemorrhage; RBC, red blood cell

3.3.2 Cryoprecipitate, fibrinogen concentrate or platelet transfusion

Evidence statements – cryoprecipitate, fibrinogen concentrate, or platelet transfusion (bleeding patients)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES3.9	In patients with PPH, the effect of cryoprecipitate, fibrinogen concentrate, or platelet transfusion on maternal mortality is unknown (no evidence).	NA	NA	NA	NA	NA
ES3.10	In patients with PPH, the effect of cryoprecipitate, fibrinogen concentrate, or platelet transfusion on transfusion requirements is unknown (no evidence).	NA	NA	NA	NA	NA
ES3.11	In patients with PPH, the effect of cryoprecipitate, fibrinogen concentrate, or platelet transfusion on transfusion-related SAEs (TACO, TRALI, other[a]) is unknown (no evidence). [a] 'Other' includes haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease and anaphylactic reactions	NA	NA	NA	NA	NA
ES3.12	In patients with PPH, the effect of cryoprecipitate, fibrinogen concentrate, or platelet transfusion on the need for additional interventions to control bleeding is unknown (no evidence).	NA	NA	NA	NA	NA
ES, evidence statement; PPH, postpartum haemorrhage; TACO, transfusion-related circulatory volume overload; TRALI, transfusion-related acute lung injury √√√=A; √√=B; √=C; X=D; NA, not applicable						

Evidence statements – cryoprecipitate, fibrinogen concentrate, or platelet transfusion (coagulapathic patients at risk of bleeding)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES3.13	In maternity patients with an abnormal coagulation profile who are at risk of bleeding, the effect of cryoprecipitate, fibrinogen concentrate, or platelet transfusion on maternal mortality is unknown (no evidence).	NA	NA	NA	NA	NA
ES3.14	In maternity patients with an abnormal coagulation profile who are at risk of bleeding, the effect of cryoprecipitate, fibrinogen concentrate, or platelet transfusion on transfusion requirements is unknown (no evidence).	NA	NA	NA	NA	NA

Evidence statements – cryoprecipitate, fibrinogen concentrate, or platelet transfusion (coagulapathic patients at risk of bleeding)		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES3.15	In maternity patients with an abnormal coagulation profile who are at risk of bleeding, the effect of cryoprecipitate, fibrinogen concentrate, or platelet transfusion on transfusion-related SAEs (TACO, TRALI, other[a]) is unknown (no evidence). [a] 'Other' includes haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease and anaphylactic reactions	NA	NA	NA	NA	NA
ES3.16	In maternity patients with an abnormal coagulation profile who are at risk of bleeding, the effect of cryoprecipitate, fibrinogen concentrate, or platelet transfusion on the need for additional interventions to control bleeding is unknown (no evidence).	NA	NA	NA	NA	NA
ES, evidence statement; PPH, postpartum haemorrhage; TACO, transfusion-related circulatory volume overload; TRALI, transfusion-related acute lung injury √√√=A; √√=B; √=C; X=D; NA, not applicable						

Practice points – FFP, cryoprecipitate, fibrinogen concentrate, and/or platelet transfusion
See PP15 to PP22 listed in **Section 3.3.1**

Background

Fibrinogen and cryoprecipitate are therapeutic interventions used in for the correction of low fibrinogen levels. In maternity patients, fibrinogen and cryoprecipitate transfusions are used in patients with hypofibrinogenaemia under the assumptions that low fibrinogen levels accurately predict bleeding, and that transfusion will reduce that risk.

In Australia, fibrinogen concentrate is listed on the Australian Register of Therapeutic Goods for the treatment of acute bleeding in people with an absence or low level of human fibrinogen (congenital lack of fibrinogen). Its use in a maternity patient who has an abnormal coagulation profile without a congenital fibrinogen, would be considered 'off-label'.

Platelet transfusions are frequently used to correct thrombocytopenia in maternity patients. The use of platelet transfusion is associated with a range of side effects including bacterial contamination, allergic reactions, febrile reactions, venous thromboembolism, TRALI and TACO. Therefore, the risks and benefits of platelet transfusion in maternity patients need to be carefully considered prior to use.

Methods

The systematic review examined the efficacy and safety results of studies comparing fibrinogen, cryoprecipitate, and/or platelet transfusion with either (i) fibrinogen, cryoprecipitate or platelet

transfusion or (ii) fibrinogen, cryoprecipitate, or platelet transfusion using a different transfusion protocol in maternity patients.

As this is an intervention question, the levels of evidence are as detailed in **Section 3.1.1.** For the purposes of this review, a systematic review of Level III–2 to Level III–3 evidence was classified as Level III evidence.

For this question, only evidence published after 1985 that had been assessed as Level III–2 or higher was considered.

The literature search identified no systematics reviews, RCTs, or Level III-2 studies that specifically addressed the PICO criteria specified in the research protocol (see **Section 4.1**).

The literature search identified no literature pertaining to Australia's Aboriginal and Torres Strait Islander peoples relevant to this research question.

3.3.3 Combination or fixed ratio therapy

Evidence statements – combination or fixed ratio therapy (bleeding patients)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES3.17	In patients with postpartum haemorrhage, the effect of combination or fixed ratio therapy (FFP, cryoprecipitate, fibrinogen concentrate and/or platelet transfusion), on transfusion requirements is uncertain. (See evidence matrix D3.D in Volume 2 of the technical report)	X	NA	NA	√√	√√
ES3.18	In patients with postpartum haemorrhage, the effect of combination or fixed ratio therapy (FFP, plasma, cryoprecipitate, fibrinogen concentrate and/or platelet transfusion), on the need for additional interventions to control bleeding is uncertain. (See evidence matrix D3.E in Volume 2 of the technical report)	X	NA	X	√√	√√
ES, evidence statement; FFP, fresh frozen plasma √√√=A; √√=B; √=C; X=D; NA, not applicable						

Methods

The systematic review examined the efficacy and safety results of studies comparing combination or fixed ratios of FFP, fibrinogen, cryoprecipitate or platelet transfusion therapy with different combination or fixed ratios of FFP, fibrinogen, cryoprecipitate or platelet transfusion in maternity patients.

Because this is an intervention question, the levels of evidence were as shown above in **Section 3.1.1.** For the purposes of this review, a systematic review of Level III–1 to Level III–3 evidence was classified as Level III evidence.

For this question, only evidence published after 1985 that had been assessed as Level III–2 or higher was considered.

Summary of the evidence

One study[62] was identified from the systematic review and hand searching process (see **Appendix C,** Volume 2) that examined combination or fixed ratios of FFP, fibrinogen, cryoprecipitate or platelet transfusion therapy in maternity patients and reported primary outcomes relevant to our research question (see **Section 4.1**).

The literature search identified no literature pertaining to Australia's Aboriginal and Torres Strait Islander peoples relevant to this research question.

Level I evidence

The literature search identified no systematic reviews that examined combination or fixed ratio therapy in maternity patients.

Level II evidence

The literature search identified no RCTs that examined combination or fixed ratio therapy in maternity patients.

Level III evidence

One study[62] was identified from the systematic review and hand searching process (see **Appendix C**, Volume 2). The main characteristics of the study are summarised in **Table 3.42**.

Pasquier et al (2013) conducted a retrospective cohort study in which they examined data from all women diagnosed with severe postpartum haemorrhage at a tertiary university maternity unit in France. The study was conducted over a four-year period from 2006 to 2009 and included 142 women with severe PPH. Patients were included in the study if they were treated with sulprostone and required transfusion with RBCs within six hours of giving birth. Patients were then stratified according to the need for additional interventions to control bleeding.

Only a subset of the data presented in the study was relevant for this review. That is, the data that was abstracted from the study related to the subset of patients that received FFP and RBC transfusion, compared with those who received only RBC. Pasquier et al (2013) also presented a subanalysis, which used propensity scoring to assess the effect of a high FFP:RBC ratio compared to a low ratio on bleeding control.

Table 3.42 Combination therapy – characteristics and quality of Level III evidence

Study	Study type *Study quality*	Population N	Intervention N	Comparator N	Outcomes
Pasquier (2013)	Retrospective cohort study *Fair*	Women with severe PPH (>500 mL) who delivered after 24 weeks gestation, were treated with sulprostone and required transfusion with RBC within 6 hours of birth N = 142	High FFP:RBC ratio[a] N = NR	Low FFP:RBC ratio[b] N = NR	Additional interventions to control bleeding Transfusion volume

[a] Defined as >1 U of FFP for every 2 U of packed RBCs.
[b] Defined as ≤1 U of FFP for every 2 U of packed RBCs.

Results

Transfusion volume

Pasquier et al (2013) conducted weighted and unweighted analyses of RBC transfusion volume in women with severe PPH who received a high vs low ratio of FFP:RBC. Both analyses showed no significant difference between the treatment groups in terms of transfusion volume. A summary of the results is presented in **Table 3.43**.

Table 3.43 Combination/fixed ratio[a] versus different combination/fixed ratio – transfusion volume[b]

Study Level of evidence *Quality*	Study type Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						High FFP:RBC ratio Mean ±SD	Low FFP:RBC ratio Mean ±SD	Risk estimate [95% CI]	*Statistical Statistical significance* P-value
LEVEL III EVIDENCE									
Pasquier et al (2013) Level III–2 *Fair*	Retrospective cohort study N = 41 (subanalysis conducted for patients who received FFP)	Women with severe PPH (>500 mL) who delivered after 24 weeks gestation, were treated with sulprostone and required transfusion with RBC within 6 hours of giving birth followed by FFP	Tertiary university maternity unit France	High FFP:RBC ratio (N = NR) (>1 U of FFP for every 2 U of packed RBC) vs Low FFP:RBC ratio (N = NR) (≤1 U of FFP for every 2 U of packed RBCs)	Volume of RBC (units), unweighted analysis	5.5 ±3.1	12.7 ±9.0	NR	No significant difference P=0.08
					Volume of RBC (units), weighted analysis	5.9 ±3.3	8.5 ±6.5	NR	No significant difference P=0.19
					Propensity scoring was used to assess the effect of a high FFP:RBC ratio on bleeding control. The inverse probability of treatment weighting technique was used, where exposed and unexposed individuals are weighted to represent the population.				

Abbreviations: CI, confidence interval; FFP, fresh frozen plasma; NR, not reported; PPH, postpartum haemorrhage; RBC, red blood cell; U, unit

[a] Combination or fixed ratio of FFP, cryoprecipitate, fibrinogen concentrate or platelet transfusion

[b] In patients who received FFP

Additional interventions to control bleeding

Pasquier et al (2013) conducted an analysis of the need for additional interventions to control bleeding in maternity patients with severe PPH who received a 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). The analysis found that a high FFP:RBC ratio was associated with fewer requirements for additional intervention to control bleeding (embolisation and/or arterial ligation and/or hysterectomy), with an OR of 1.58 (95% CI 1.19, 2.10; P=0.003) reported. 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 summary of the results is presented in **Table 3.44**.

Table 3.44 Combination/fixed ratio[a] versus different combination/fixed ratio – additional interventions to control bleeding[b]

Study Level of evidence *Quality*	Study type Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						High FFP:RBC ratio	Low FFP:RBC ratio	Risk estimate [95% CI]	*Statistical Statistical significance* P-value
LEVEL III EVIDENCE									
POSTPARTUM HAEMORRHAGE									
Pasquier et al (2013) Level III–2 *Fair*	Retrospective cohort study N = 41 (subanalysis conducted for patients who received FFP)	Women with severe PPH (>500 mL) who delivered after 24 weeks gestation, were treated with sulprostone and required transfusion with RBC within 6 hours of birth	Tertiary university maternity unit France	High FFP:RBC ratio (>1 U of FFP for every 2 U of packed RBC) vs Low FFP:RBC ratio (≤1 U of FFP for every 2 U of packed RBCs)	Requirement for additional interventions, overall[c] (N/N)	NR	NR	OR: 1.58 [1.19–2.10]	Favours high FFP:RBC ratio P=0.003

Abbreviations: CI, confidence interval; FFP, fresh frozen plasma; NR, not reported; PPH, postpartum haemorrhage; RBC, red blood cell; U, unit

[a] Combination or fixed ratio of FFP, cryoprecipitate, fibrinogen concentrate or platelet transfusion

[b] In patients who received FFP

[c] Number of patients who required at least one additional intervention (embolisation and/or arterial ligation and/or hysterectomy)

Secondary outcomes

Laboratory measures

One study was identified that reported on laboratory measures (**Table 3.45**). Pasquier et al (2013) compared high and low FFP:RBC ratios, reporting no significant differences in nadir platelets (giga/L) (unweighted 91 ± 49 vs 57 ± 33, weighted 87 ± 49 vs 73 ± 28), nadir fibrinogen (g/L) (unweighted 1.2 ± 0.9 vs 1.1 ± 0.4, weighted 1.2 ± 0.4 vs 1.2 ± 0.9) or longest prothrombin time (s) (unweighted 18.0 ± 2.6 vs 18.4 ± 2.9, weighted 18.0 ± 2.6 vs 17.4 ± 2.5).

Functional and performance status

No studies were identified that reported the effect of combination or fixed ratio therapy on functional and performance status in maternity patients; however, as this evidence has not strictly undergone the systematic review process (secondary outcomes were only extracted from studies that reported one or more primary outcomes), this result should be interpreted with caution.

Table 3.45 Combination/fixed ratio[a] versus different combination/fixed ratio – secondary outcomes

Study Level of evidence *Quality*	Study type Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						High FFP:RBC ratio Mean ± SD	Low FFP:RBC ratio Mean ± SD	Risk estimate [95% CI]	*Statistical significance* P-value
LEVEL III EVIDENCE									
POSTPARTUM HAEMORRHAGE									
Pasquier et al (2013) Level III–2 *Fair*	Retrospective cohort study N = 41	Women with severe PPH (>500 mL) who delivered after 24 weeks gestation, were treated with sulprostone and required transfusion with RBC within 6 hours of birth	Tertiary university maternity unit France	High FFP:RBC ratio (>1 U of FFP for every 2 U of packed RBC) vs Low FFP:RBC ratio (≤1 U of FFP for every 2 U of packed RBCs)	Nadir platelets (giga/L), unweighted	91 ± 49	57 ± 33	NR	No significant difference P=0.04
					Nadir platelets (giga/L), weighted	87 ± 49	73 ± 28	NR	No significant difference P=0.29
					Nadir fibrinogen (g/L), unweighted	1.2 ± 0.9	1.1 ± 0.4	NR	No significant difference P=0.57
					Nadir fibrinogen (g/L), weighted	1.2 ± 0.4	1.2 ± 0.9	NR	No significant difference P=0.75
					Longest prothrombin time (s), unweighted	18.0 ± 2.6	18.4 ± 2.9	NR	No significant difference P=0.72
					Longest prothrombin time (s), weighted	18.0 ± 2.6	17.4 ± 2.5	NR	No significant difference P=0.52
					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.				

Abbreviations: CI, confidence interval; FFP, fresh frozen plasma; NR, not reported; PPH, postpartum haemorrhage; RBC, red blood cell; U, unit

[a] Combination or fixed ratio of FFP, cryoprecipitate, fibrinogen concentrate or platelet transfusion

3.4 Question 4

Question 4 (Interventional)

In maternity patients, what is the effect of non-obstetric strategies that aim to minimise blood loss in the peripartum period on transfusion and clinical outcomes?

3.4.1 Point of care testing

Evidence statements – point of care testing		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES4.1	In maternity patients, the effect of POC testing (thromboelastography and rotational thromboelastometry) on transfusion requirements is unknown (no evidence)	NA	NA	NA	NA	NA
ES4.2	In maternity patients, the effect of POC testing (thromboelastography and rotational thromboelastometry) on the need for additional interventions to control bleeding is unknown (no evidence)	NA	NA	NA	NA	NA
ES4.3	In maternity patients, the effect of POC testing (thromboelastography and rotational thromboelastometry) on maternal mortality is unknown (no evidence)	NA	NA	NA	NA	NA
ES4.4	In maternity patients, the effect of POC testing (thromboelastography and rotational thromboelastometry) on thromboembolic events is unknown (no evidence)	NA	NA	NA	NA	NA
ES, evidence statement; POC, point of care; √√√=A; √√=B; √=C; X=D; NA, not applicable						

Evidence gaps and areas of future research – point of care testing
• There is a lack of evidence on the role of POC testing (thromboelastography and rotational thromboelastometry) as a strategy to understand normal haemostatic changes that occur during normal birth and in the context of PPH, and the role of POC testing in the management of PPH.
POC, point of care; PPH, postpartum haemorrhage

Background

Thromboelastography and rotational thromboelastometry are whole-blood coagulation analysers that monitor dynamic changes in haemostasis and may help guide patient care. In maternity patients, monitoring changes of haemostasis may help clinicians in making the correct diagnosis, assess the cause of bleeding and improve the care of patients with unexplained blood loss.

Methods

The systematic review examined the evidence for the use of thromboelastography and rotational thromboelastometry compared with no thromboelastography or rotational thromboelastometry in maternity patients. Studies in a perioperative setting or critical bleeding/massive transfusion setting were excluded, because these have been covered in other modules of the PBM guidelines.

Because this is an intervention question, the levels of evidence were as shown above in **Section 3.1.1**.

For the purposes of this review, a systematic review of Level III–1 to Level III–3 evidence was classified as Level III evidence.

For this question, only evidence down to Level III–2 that had been published after 1985 was considered.

Summary of the evidence

There were no studies identified from the systematic review and hand searching process (See **Appendix C**, Volume 2) that examined the use of point of care testing in maternity patients and reported primary outcomes relevant to our research question (see **Section 4.1**).

The literature search identified no literature pertaining to Australia's Aboriginal and Torres Strait Islander peoples relevant to this research question.

3.4.2 Intraoperative cell salvage

Evidence statements – intraoperative cell salvage		Evidence	Consistency	Clinical impact	Generalisability	Applicability
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 (See evidence matrix D4.A in Volume 2 of the technical report)	X	NA	NA	X	√
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 (See evidence matrix D4.B in Volume 2 of the technical report)	X	NA	NA	X	√
ES4.7	In maternity patients the effect of intraoperative cell salvage on maternal mortality is unknown (no evidence)	NA	NA	NA	NA	NA
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 (See evidence matrix D4.C in Volume 2 of the technical report)	X	NA	NA	X	√
ES, evidence statement √√√=A; √√=B; √=C; X=D; NA, not applicable						

Practice points – intraoperative cell salvage	
PP23	In maternity patients, cell salvage should be considered if anticipated blood volume loss is likely to result in transfusion.[a] [a] In accordance with *Guidance for the provision of intraoperative cell salvage*[64]
PP24	In maternity patients who are at increased risk of bleeding and in whom transfusion is not an option, cell salvage should be considered.
PP25	Cell salvage requires a local procedural guideline that should include patient selection, use of equipment and reinfusion. All staff operating cell salvage devices should receive appropriate training, to ensure that they are familiar with and proficient in the technique.
PP26	In Rh D negative maternity patients receiving salvaged blood where the cord blood group is Rh D positive, a dose of Rh D immunoglobulin is required, with additional doses based on the result of assessment of fetomaternal haemorrhage test.

Evidence gaps and areas of future research – intraoperative cell salvage
• There is a lack of evidence on the role (if any) of cell salvage in maternity patients

Background

Intraoperative cell salvage involves the collection of blood lost during surgery, followed by reinfusion of the washed RBC. One of the key aims of cell salvage is the reduction of allogeneic transfusion, and the consequent reduction in transfusion-related adverse events. Blood loss during elective caesarean section is generally well-tolerated and does not normally require intervention (e.g. allogeneic transfusion). Therefore, intraoperative cell salvage is generally only considered in women with, or at risk of, major blood loss likely to result in transfusion.

Theoretical concerns over intraoperative cell salvage for obstetric surgery have not been borne out in clinical practice.

Methods

The systematic review examined the evidence for the use of intraoperative cell salvage compared with no intraoperative cell salvage in maternity patients.

Because this is an intervention question, the levels of evidence were as shown above in **Section 3.1.1.**

For the purposes of this review, a systematic review of Level III–1 to Level III–3 evidence was classified as Level III evidence.

For this question, only evidence down to Level III–2 that had been published after 1985 was considered.

Summary of the evidence

One Level II[65] and one Level III study[66] was identified from the systematic review and hand searching process (see **Appendix C**, Volume 2) that examined intraoperative cell salvage in maternity patients and reported primary outcomes relevant to our research question (see **Section 4.1**).

The literature search identified no literature pertaining to Australia's Aboriginal and Torres Strait Islander peoples relevant to this research question.

Level I evidence

The literature search identified no systematic reviews that examined the use of intraoperative cell salvage in maternity patients.

Level II evidence

The literature search identified one RCT that examined the use of intraoperative cell salvage in maternity patients (see **Appendix C,** Volume 2).[65] The main characteristics of the study are summarised in **Table 3.46**.

The RCT by Rainaldi et al (1998)[65] aimed to assess blood salvage during caesarean section and the effect of this procedure on perioperative haemoglobin concentration and postoperative hospital stay. The study also reported the amount of blood salvaged, the number of patients receiving homologous blood, and adverse events. Participants were randomly allocated to one of two groups, but the methods of randomisation or allocation concealment are not stated. The two groups were similar in age, height, and body weight. Of the 34 women earmarked for blood salvage, 15 did not require reinfusion, and the blood was subjected to a series of quality tests. The quality tests detected fetal haemoglobin in the blood from 3 patients, in which it was 1.8-

20%. In these three patients, fetal haemoglobin was also present in the maternal blood (1.5-1.8%). The authors reported no complications as a result of reinfusion of salvaged blood, but reported two patients with hyperpyrexia after transfusion of homologous blood and one patient with pulmonary oedema and ascites requiring intensive care.

Table 3.46 Intraoperative cell salvage – characteristics and quality of Level II evidence

Study	Study type *Study quality*	Population N	Intervention N	Comparator N	Outcomes
Rainaldi (1998)[65]	RCT *Poor*	Women undergoing caesarean section N = 68	Intraoperative cell salvage (if required) N = 34	No intraoperative cell salvage N = 34	Requirement for homologous RBC transfusion

Level III evidence

The literature search identified one study that examined the use of intraoperative cell salvage in maternity patients (see **Appendix C,** Volume 2). The main characteristics of the study are summarised in **Table 3.47**.

The study by Malik et al (2010)[66] was a retrospective cohort study that evaluated clinical outcomes in patients who were identified as being at high risk of massive obstetric haemorrhage. The aim of the study was to examine whether the use of intraoperative cell salvage decreased the need for homologous blood transfusion. A total of 147 patients were included in the study, all of whom were identified from an electronic database at a maternity unit in Leicester, UK. All participants had placenta previa or were Jehovah's Witnesses and underwent elective or emergency caesarean section between July 2005 and August 2008. Intraoperative cell salvage was used in 77 (52%) cases.

The study had a high risk of selection bias, because cell salvage was more likely to be used if massive blood loss was anticipated. There were also important differences between the intervention and comparator groups. For example, 60.0% of patients who did not undergo cell salvage had an emergency caesarean section compared to only 27.3% in the cell salvage group. The difference was primarily due to a lack of trained staff out-of-hours for emergency cases, but may represent important systematic differences between the two study groups.

Also, the intervention did not appear to be conducted with a large amount of success. The mean about of blood salvaged in the intervention group was 95.5 mL (range 0–1800 mL). Importantly, the median volume of blood salvaged from patients in the intervention group was 0 mL, indicating that no blood was salvaged from at least half of the patients in the cell salvage group. In addition, across the cell salvage group, only 13 units of blood were processed and re-transfused.

Table 3.47 Intraoperative cell salvage – characteristics and quality of Level III evidence

Study	Study type *Study quality*	Population N	Intervention N	Comparator N	Outcomes
Malik (2010)[66]	Retrospective cohort study *Poor*	Patients identified as being at high risk of massive obstetric haemorrhage who underwent emergency or elective caesarean section N = 147	Intraoperative cell salvage N = 77	No intraoperative cell salvage N = 70	Blood loss Salvaged blood Homologous blood transfusion Adverse events

Results

Transfusion incidence and volume

Transfusion incidence or volume was reported in two studies. Rainaldi et al (1998)[65] reported a significant difference in the incidence of homologous RBC transfusion (1/34 (2.9%) vs 8/34 (23.5%); P=0.01) comparing women who had blood salvaged during caesarean birth with women who did not have blood salvaged. A total of two units of homologous blood was transfused in the one patient who underwent cell salvage (5 days after surgery), however the total volume of blood transfused in the eight women who did not undergo cell salvage was not reported (number transfused between the first and fifth day).

Malik et al (2010)[66] reported that a total of 31 units of homologous blood were transfused in the patients who underwent cell salvage, compared to 29 units in the patients who did not. The significance of the result was not reported; however, the results suggest that the use of intraoperative cell salvage did not correspond to a decrease in the use of blood transfusion.

A summary of these results is presented in **Table 3.48**.

Table 3.48 Intraoperative cell salvage in maternity patients – transfusion incidence and volume

Study Level of evidence *Quality*	Study type Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Intraoperative cell salvage Total units n/N (%)	No Intraoperative cell salvage Total units n/N (%)	Risk estimate [95% CI]	*Statistical significance* P-value
LEVEL II EVIDENCE									
CAESAREAN BIRTH									
Rainaldi et al (1998)[65] Level II *Poor*	RCT N=68	Women undergoing caesarean section	Hospital Italy	Intraoperative cell salvage (n=34) vs no intraoperative cell salvage (n=34)	Homologous blood transfusion (total units per treatment arm)	2	NR	NR	NR
					Homologous RBC transfusion	1/34 (2.9%)	8/34 (23.5%)	NR	*Favours intraoperative cell salvage* P=0.01
LEVEL III EVIDENCE									
WOMEN WITH PLACENTA PROBLEMS OR IN WHOM TRANSFUSION IN NOT AN OPTION									
Malik et al (2010)[66] Level III–2 *Poor*	Retrospective cohort study N=147	Patients with placenta previa or Jehovah's Witnesses undergoing caesarean section	Hospital maternity unit UK	Intraoperative cell salvage (n=77) vs no intraoperative cell salvage (n=70)	Homologous blood transfusion (total units per treatment arm)	31	29	NR	NR

Abbreviations: CI, confidence interval; NR, not reported; RBC, red blood cell.

Additional interventions to control bleeding

The study by Malik et al (2010)[66] did not explicitly report the use of additional interventions to control bleeding. However, the authors did report that no patients in the cell salvage group needed to return to theatre (**Table 3.49**). No information was provided about the comparator group.

Table 3.49 Intraoperative cell salvage in maternity patients – additional interventions to control bleeding

Study Level of evidence *Quality*	Study type Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Intraoperative cell salvage N/N (%)	No intraoperative cell salvage N/N (%)	Risk estimate [95% CI]	*Statistical significance* P-value
LEVEL III EVIDENCE									
PATIENTS WITH PLACENTA PROBLEMS OR IN WHOM TRANSFUSION IN NOT AN OPTION									
Malik et al (2010)[66] Level III–2 *Poor*	Retrospective cohort study N = 147	Patients with placenta previa or Jehovah's Witnesses undergoing caesarean section	Hospital maternity unit UK	IOCS (N = 77) vs no IOCS (N = 70)	Return to theatre	0/77 (0%)	NR	NA	NA

Abbreviations: CI, confidence interval; IOCS, intraoperative cell salvage; NR, not reported

Thromboembolic events

Malik et al (2010)[66] found that no adverse outcomes, including thromboembolism, were reported in any patients in the cell salvage group (**Table 3.50**). No information was provided about thromboembolic events in the comparator group.

Table 3.50 Intraoperative cell salvage in maternity patients – thromboembolic events

Study Level of evidence *Quality*	Study type Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Intraoperative cell salvage N/N (%)	No Intraoperative cell salvage N/N (%)	Risk estimate [95% CI]	*Statistical significance* P-value
LEVEL III EVIDENCE									
PATIENTS WITH PLACENTA PROBLEMS OR IN WHOM TRANSFUSION IN NOT AN OPTION									
Malik et al (2010)[66] Level III–2 *Poor*	Retrospective cohort study N = 147	Patients with placenta previa or Jehovah's Witnesses undergoing caesarean section	Hospital maternity unit UK	IOCS (N = 77) vs no IOCS (N = 70)	Thromboembolism	0/77 (0%)	NR	NA	NA

Abbreviations: CI, confidence interval; IOCS, intraoperative cell salvage; NR, not reported

Secondary outcomes

Transfusion-related serious adverse events

There were no studies identified that reported on transfusion-related serious adverse events (TACO, TRALI, haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease, anaphylactic reactions) in maternity patients receiving intraoperative cell salvage. However, as this evidence has not strictly undergone the systematic review process (secondary outcomes were only extracted from studies that reported one or more primary outcomes), this result should be interpreted with caution.

Perinatal mortality

There were no studies identified that reported on perinatal mortality in maternity patients receiving intraoperative cell salvage. However, as this evidence has not strictly undergone the systematic review process (secondary outcomes were only extracted from studies that reported one or more primary outcomes), this result should be interpreted with caution.

3.4.3 Interventional radiology

Evidence statements – interventional radiology		Evidence	Consistency	Clinical impact	Generalisability	Applicability
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 (See evidence matrix D4.D in Volume 2 of the technical report)	X	√	X	√√	√√
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 (See evidence matrix D4.E in Volume 2 of the technical report)	X	√	X	√√	√√
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 (See evidence matrix D4.F in Volume 2 of the technical report)	√	NA	NA	√√	√√
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 (See evidence matrix D4.G in Volume 2 of the technical report)	√	X	NA	√√	√√
ES4.13	In women with major obstetric haemorrhage, the effect of interventional radiology (iliac balloon catheters or embolisation only) on transfusion requirements is unknown (no evidence)	NA	NA	NA	NA	NA
ES4.14	In women with major obstetric haemorrhage, the effect of interventional radiology (iliac balloon catheters or embolisation only) on the need for additional interventions to control bleeding is unknown (no evidence)	NA	NA	NA	NA	NA
ES4.15	In women with major obstetric haemorrhage, the effect of interventional radiology (iliac balloon catheters or embolisation only) on maternal mortality is unknown (no evidence)	NA	NA	NA	NA	NA
ES4.16	In women with major obstetric haemorrhage, the effect of interventional radiology (iliac balloon catheters or embolisation only) on thromboembolic events is unknown (no evidence)	NA	NA	NA	NA	NA
ES, evidence statement √√√=A; √√=B; √=C; X=D; NA, not applicable						

Practice points – interventional radiology	
PP27	Preventative IR may be appropriate in selected maternity patients; however, the risk of complications from this procedure should be balanced against the potential benefits.
PP28	Although the role of therapeutic IR in the treatment of major obstetric haemorrhage is unknown, it may be considered in the overall approach to management.

Evidence gaps and areas of future research – interventional radiology
• The safety of interventional radiological techniques has not been established in maternity patients. Direct procedural complications of arterial thrombosis and dissection have been reported, but rates and outcomes following complications are unknown.

Background

Iliac balloon catheters and transcatheter arterial embolisation are typically used in maternity patients in two scenarios: to treat major bleeding or (prophylactically) as part of the management of morbidly adherent placenta. These interventions aim to block the principal vessels supplying the uterus as a means to control bleeding and preserve fertility. These require access to imaging technology and an experienced interventional radiologist. Interventional radiology may be less efficacious in maternity patients than in other patients because of the extensive collateral pelvic circulation. Potential safety concerns include fetal exposure to radiation if catheterisation occurs before birth and direct complications include arterial thrombosis and dissection.

Methods

The systematic review examined the evidence for the use of interventional radiology (iliac balloon catheters or embolisation) in maternity patients.

Because this is an intervention question, the levels of evidence were as shown above in **Section 3.1.1.** For the purposes of this review, a systematic review of Level III–1 to Level III–3 evidence was classified as Level III evidence.

For this question, only evidence down to Level III–2 that had been published after 1985 was considered.

Summary of the evidence

Six studies were identified from the systematic review and hand searching process (see **Appendix C**, Volume 2) that examined the use of interventional radiology in maternity patients and reported primary outcomes relevant to our research question (see **Section 4.1**).

The literature search identified no literature pertaining to Australia's Aboriginal and Torres Strait Islander peoples relevant to this research question.

Level I evidence

The literature search identified two systematic reviews that examined the use of interventional radiology in maternity patients. However, the reviews contained only Level III and Level IV evidence and are therefore discussed below under 'Level III evidence'.

Level II evidence

The literature search identified no RCTs that examined the use of interventional radiology in maternity patients.

Level III evidence

The literature search identified four studies (see **Appendix C**, Volume 2). The main characteristics of the studies are summarised in **Table 3.51**.

The literature search also identified two systematic reviews of Level III and Level IV evidence that examined the use of interventional radiology in maternity patients. The systematic reviews presented the findings of the Level III studies by Bodner et al (2006),[67] Levine et al (1999)[68] and Shrivastava et al (2007),[69] identified through our search, but did not include any post-hoc or pooled analyses. As such, the primary studies have been assessed and form the basis of the following evidence review.

The objective of the retrospective cohort study by Ballas et al (2012)[70] was to compare outcomes between maternity patients with pathology-proven placenta accreta who did and did not receive preoperative uterine artery balloon catheters (UAB). All patients with placenta accrete or percreta who had undergone caesarean hysterectomy between 1990 and 2011 were identified from a database at the University of California, USA. Of the 117 patients included in the study, 59 had UABs placed preoperatively and 58 did not have UABs placed and formed the control group. Ballas et al (2012)[70] also presented a subgroup analysis of patients within the intervention arm, based on whether or not the UAB catheter was inflated. Outcome assessment included estimated blood loss, the need for transfusion and volume of blood products transfused, operative time and complications related to the catheters.

The proportion of patients with a pre-birth diagnosis of invasive placentation was significantly higher in the UAB group than in the comparator group (95.3% vs 45.9%, respectively; P<0.01). In addition, there were significantly more cases of placenta percreta, as opposed to accreta, diagnosed pathologically in the UAB group compared to the no UAB group (59.3% vs 13.8%, respectively; P<0.01). These differences imply that there may have been systematic differences between patients in the intervention and comparator groups (i.e. selection bias).

The study by Shrivastava et al (2007)[69] was a retrospective cohort study based on hospital databases and billing records from two medical facilities in the USA. Of the 69 women included in the study, 19 underwent occlusive balloon catheterisation of the anterior division of the internal iliac artery prior to caesarean hysterectomy and 50 underwent caesarean hysterectomy without prophylactic placement of an intravascular balloon catheter. The primary outcomes of the study were estimated blood loss, transfused blood product, operative time and postoperative hospital days.

Bodner et al (2006)[67] also evaluated clinical outcomes of patients with placenta accreta/percreta who did and did not undergo endovascular intervention. The study included 28 patients and examined several outcomes including volume of transfused blood products, estimated blood loss, postoperative morbidity and mortality and total hospital days. The six patients in the intervention arm underwent prophylactic balloon occlusion of the anterior division of the internal iliac arteries. Five of those patients underwent caesarean hysterectomy, and uterine curettage was conducted in the other. Twenty-two patients who underwent caesarean hysterectomy without endovascular intervention formed the comparator group.

Importantly, the authors of the study acknowledged the fact that the treatment pathway of patients in the study was affected by referral bias. Specifically, patients with a prenatal diagnosis of placenta accreta and 'especially those with a more complicated prenatal course' fell into the embolisation group.

The study by Levine et al (1999)[68] was a prospective cohort study that examined the clinical outcomes of pelvic artery balloon catheterisation in patients with placenta accreta. All patients with an antenatal sonographic diagnosis of placenta accreta who attended a single hospital in the USA between 1994 and 1997 were offered prophylactic preoperative pelvic artery balloon catheterisation. A total of five women were included in the intervention group. The comparator group was made up of four women who were delivered by caesarean hysterectomy for unsuspected placenta accreta during the same time period.

The sample size was unlikely to be powered to detect a treatment difference. In addition, 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.

Table 3.51 Interventional radiology – characteristics and quality of Level III evidence

Study	Study type *Study quality*	Population N	Intervention N	Comparator N	Outcomes
Ballas (2012)	Retrospective cohort study *Fair*	Patients with pathology-proven placenta accreta/percreta who underwent caesarean hysterectomy between 1990–2011 N = 117	UAB catheters placed in the proximal internal iliac artery N = 59	No UAB catheters N = 58	Need for transfusion of blood products Units of blood transfused
Shrivastava (2007)	Retrospective cohort study *Fair*	Patients with presumed placenta accreta or one of its variants who underwent caesarean hysterectomy between 1995–2006 N = 69	Preoperative iliac balloon catheterisation N = 19	No iliac balloon catheterisation N = 50	Transfused blood products Development of DIC Febrile morbidity
Bodner (2006)[67]	Retrospective cohort study *Fair*	Women with a diagnosis of placenta accreta/percreta between 2000 and 2002 N = 28	Balloon occlusion and transcatheter embolisation N = 6	No balloon occlusion or transcatheter embolisation N = 22	Volume of transfused blood products Postoperative morbidity and mortality
Levine (1999)[68]	Prospective cohort study *Poor*	Women with placenta accreta at a single hospital between 1994 and 1997 N = 9	Pelvic artery balloon catheterisation N = 5	No pelvic artery balloon catheterisation N = 4	Transfusion requirements Complications

Abbreviations: DIC, disseminated intravascular coagulation; PPH, postpartum haemorrhage; UAB, uterine artery balloon

Results

Transfusion incidence and volume

Transfusion incidence was reported in two studies, as summarised in **Table 3.52**. In the study by Ballas et al (2012)[70], 46 patients in both the intervention and comparator arm received a transfusion of PRBC, FFP and platelets, which represented 78% and 79% of patients, respectively. Levine et al (1999)[68] did not report any statistically significant differences in transfusion incidence between patients who underwent pelvic artery balloon catheterisation and those who did not.

Transfusion volume was reported in two systematic reviews and four Level III studies, as summarised in **Table 3.53**. As mentioned above, the systematic reviews did not present any additional analyses and are not discussed further.

Bodner et al (2006)[67] found no significant difference in the mean units of PRBC transfused between the women who underwent balloon occlusion or embolisation and those who did not (P=0.47). Similarly, Shrivastava et al (2007)[69] and Levine et al (1999)[68] found no significant differences between the intervention and control arms based on transfusion volume.

Ballas et al (2012)[70] found no significant difference between the mean units of PRBC or FFP transfused in patients who underwent UAB catheterisation compared to those who did not (P=0.14 and P=0.17, respectively). However, a categorical analysis of the number of patients who received a massive transfusion (≥6 units PRBC) found a significantly greater proportion of patients who did not undergo UAB catheterisation required a massive transfusion (52% vs 31%; P=0.03).

Table 3.52 Interventional radiology in maternity patients – transfusion incidence

Study Level of evidence *Quality*	Study type Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Interventional radiology N/N (%)	No interventional radiology N/N (%)	Risk estimate (95% CI)	*Statistical Statistical significance* P-value
LEVEL III EVIDENCE									
PLACENTA PROBLEMS									
Dilauro et al (2012)[71]	SR of Level III and Level IV studies[a]	Women with placenta accreta	Various settings USA	Balloon catheterisation (±embolisation) vs no balloon catheterisation or embolisation	Results for the SR were presented individually for the included Level III studies with no post-hoc or pooled analyses reported. As no additional information was provided in the SR 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 was obtained from the primary studies and is presented in this table separately.[67-69]				
Omar et al (2012)[72]	SR of Level III and Level IV studies[a]	Women with placenta accreta	Various settings USA	Balloon catheterisation (±embolisation) vs no balloon catheterisation or embolisation	Results for the SR were presented individually for the included Level III studies with no post-hoc or pooled analyses reported. As no additional information was provided in the SR 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 was obtained from the primary studies and is presented in this table separately.[67-69]				
Ballas et al (2012)[70] Level III–2 *Fair*	Retrospective cohort study N = 117	Women with pathology-proven placenta accreta/percreta that underwent caesarean hysterectomy	Hospital and university database USA	UAB catheters (placed in the proximal internal iliac artery) (N = 59) vs no UAB catheters (N = 58)	Transfusion incidence (includes PRBC, FFP and platelets)	46/59 (78%)	46/58 (79%)	NR	No significant difference P=0.37
	Subgroup analysis N = 59	*All women included in the primary study who received UAB catheter*		*UAB catheters inflated (N = 30) vs UAB catheters uninflated (N = 29)*	Transfusion incidence	28/30 (93.3%)	18/29 (62.1%)	NR	Favours uninflated UAB P=0.005
Levine et al (1999)[68] Level III–2 *Poor*	Prospective cohort study N = 9	Women with placenta accreta	Single hospital USA	Pelvic artery balloon catheterisation[b] (N = 5) vs no catheterisation (N = 4)	Transfusion incidence (packed RBCs)	4/5 (80%)	4/4 (100%)	NR	P=NR
					Transfusion incidence (FFP)	1/5 (20%)	0/4 (0%)	NR	P=NR
					Transfusion incidence (platelets)	1/5 (20%)	0/4 (0%)	NR	P=NR

Abbreviations: CI, confidence interval; NR, not reported; RBC, red blood cell; SR, systematic review; UAB, uterine artery balloon

[a] Sample size included in the analysis for Level III studies was equivalent to the sample size in each of the individual studies as no pooled analysis was conducted. Data for each of the individual Level III studies deemed to be eligible for inclusion in the current guideline are presented in this table separately.

[b] For the five patients undergoing balloon catheterisation, catheters were placed in the internal iliac arteries (N = 7), its anterior division (N = 1), or the uterine arteries (N = 2)

Table 3.53 Interventional radiology in maternity patients – transfusion volume

Study Level of evidence *Quality*	Study type Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Interventional radiology Mean ±SD N/N (%) median (range)	No interventional radiology Mean ±SD N/N (%) median (range)	Risk estimate (95% CI)	*Statistical Statistical significance* P-value
LEVEL III EVIDENCE									
PATIENTS WITH PLACENTA PROBLEMS									
Dilauro et al (2012)[71]	SR of Level III and Level IV studies[a]	Women with placenta accreta	Various settings USA	Balloon catheterisation (±embolisation) vs no balloon catheterisation or embolisation	Results for the SR were presented individually for the included Level III studies with no post-hoc or pooled analyses reported. As no additional information was provided in the SR 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 was obtained from the primary studies and is presented in this table separately.[67-69]				
Omar et al (2012)[72]	SR of Level III and Level IV studies[a]	Women with placenta accreta	Various settings USA	Balloon catheterisation (±embolisation) vs no balloon catheterisation or embolisation	Results for the SR were presented individually for the included Level III studies with no post-hoc or pooled analyses reported. As no additional information was provided in the SR 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 was obtained from the primary studies and is presented in this table separately.[67-69]				
Ballas et al (2012)[70] Level III–2 *Fair*	Retrospective cohort study N = 117	Women with pathology-proven placenta accreta/percreta that underwent caesarean hysterectomy	Hospital and university database USA	UAB catheters (placed in the proximal internal iliac artery) (N = 59) vs no UAB catheters (N = 58)	Volume PRBC transfused (units)	4.7 ±2.1	5.9 ±1.7	NR	No significant difference P=0.14
					Volume FFP transfused (units)	3.9 ±2.1	5.2 ±2.3	NR	No significant difference P=0.17
					Volume platelets transfused (units)	2.1 ±2.1	2.1 ±1.9	NR	No significant difference P=0.89
					Massive transfusion (≥ 6 units PRBCs)	18/59 (31%)	30/58 (52%)	NR	*Favours UAB* P=0.03
	Subgroup analysis N = 59	*All women included in the primary study who received UAB catheter*		UAB catheters inflated (N = 30) vs UAB catheters uninflated (N = 29)	Volume PRBC transfused (units)	5.7	3.4	NR	*Favours uninflated* UAB P=0.02
Shrivastava et al (2007)[69] Level III–2	Retrospective cohort study N = 69	Women who underwent caesarean	Hospital databases and billing records	Iliac balloon catheterisation (N = 19) vs no iliac balloon catheterisation (N = 50)	Volume of transfusion (units, blood products)	10 (0–43)	6.5 (0–50)	NR	No significant difference P=0.60

Study Level of evidence *Quality*	Study type Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Interventional radiology Mean ±SD N/N (%) median (range)	No interventional radiology Mean ±SD N/N (%) median (range)	Risk estimate (95% CI)	*Statistical Statistical significance* P-value
Fair		hysterectomy for presumed placenta accreta or one of its variants	from two medical facilities USA		Volume of transfusion excluding intraoperatively diagnosed cases (units, blood products)	10 (0–43)	8 (0–54)	NR	No significant difference P=0.81
					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).				
					Transfusion dose in transfused patients (units, packed RBCs)	5.5	4.0	NR	No significant difference P=NS
					Transfusion dose in transfused patients (units, FFP)	10	0	NR	P=NR
					Transfusion dose in transfused patients (units, platelets)	2	0	NR	P=NR
Bodner et al (2006)[67] Level III–2 *Fair*	Retrospective cohort study N = 28	Women with a diagnosis of placenta accreta/percreta	Single centre, teaching hospital USA	Iliac balloon occlusion and transcatheter embolisation with Gelfoam pledgets (N = 6) vs no balloon occlusion or embolisation (N = 22)	Volume of blood transfused (units, packed RBCs)	6.5	6.3	NR	No significant difference P=0.47
					A two-sample, one-tailed Student's t-test was performed				

Abbreviations: CI, confidence interval; NR, not reported; RBC, red blood cell; SR, systematic review; UAB, uterine artery balloon

[a] Sample size included in the analysis for Level III studies was equivalent to the sample size in each of the individual studies as no pooled analysis was conducted. Data for each of the individual Level III studies deemed to be eligible for inclusion in the current guideline are presented in this table separately.

Additional intervention to control bleeding

One systematic review and three Level III studies examined the need for additional interventions to control bleeding in maternity patients who were exposed to interventional radiology (**Table 3.54**). As mentioned above, the systematic review did not present any additional analyses and is not discussed further.

The three cohort studies examined additional interventions such as hysterectomy, uterine artery ligation and pelvic artery embolisation. None of the studies reported the statistical significance of intergroup differences.

Table 3.54 Interventional radiology in maternity patients – additional interventions to control bleeding

Study Level of evidence *Quality*	Study type Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Interventional radiology N/N (%)	No interventional radiology N/N (%)	Risk estimate (95% CI)	*Statistical significance* P-value
LEVEL III EVIDENCE									
PLACENTA PROBLEMS									
Dilauro et al (2012)[71]	SR of Level III and Level IV studies[a]	Women with placenta accreta	Various settings USA	Balloon catheterisation (±embolisation) vs no balloon catheterisation or embolisation	Results for the SR were presented individually for the included Level III studies with no post-hoc or pooled analyses reported. As no additional information was provided in the SR 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 was obtained from the primary studies and is presented in this table separately.[67-69]				
Shrivastava et al (2007)[69] Level III–2 *Fair*	Retrospective cohort study N = 69	Women who underwent caesarean hysterectomy for presumed placenta accreta or one of its variants	Hospital databases and billing records from two medical facilities USA	Iliac balloon catheterisation (N = 19) vs no iliac balloon catheterisation (N = 50)	Need for reoperation [b]	4/19 (21%)	6/50 (12%)	NR	P=NR
Bodner et al (2006)[67] Level III–2 *Fair*	Retrospective cohort study N = 28	Women with a diagnosis of placenta accreta/percreta	Single centre, teaching hospital USA	Iliac balloon occlusion and transcatheter embolisation with Gelfoam pledgets (N = 6) vs no balloon occlusion or embolisation (N = 22)	Overall	6/6 (100%)	22/22 (100%)	NR	P=NR
					Hysterectomy	5/6 (83%)[c]	22/22 (100%)	NR	P=NR
					Uterine artery ligation	0/6 (0%)	5/22 (23%)	NR	P=NR
Levine et al (1999)[68] Level III–2 *Poor*	Prospective cohort study N = 9	Women with placenta accreta	Single hospital USA	Pelvic artery balloon catheterisation [d] (N = 5) vs no catheterisation (N = 4)	Hysterectomy [e]	4/5 (80%)[f]	4/4 (100%)	NR	P=NR
					Pelvic artery embolisation	0/5 (0%)	1/4 (25%)	NR	P=NR

Abbreviations: CI, confidence intervals; NR, not reported, USA, United States

[a] Sample size included in the analysis for Level III studies was equivalent to the sample size in each of the individual studies as no pooled analysis was conducted. Data for each of the individual Level III studies deemed to be eligible for inclusion in the current guideline are presented in the table separately

[b] The authors did not specify what this entailed or for what purpose (i.e. may not have been specifically to control bleeding)

[c] 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

[d] For the five patients undergoing balloon catheterisation, catheters were placed in the internal iliac arteries (N = 7), its anterior division (N = 1), or the uterine arteries (N = 2)

[e] Birth by caesarean hysterectomy was listed as a requirement for being included in the comparator group

[f] One patient had partial accreta and required only a caesarean section

Maternal mortality

One of the included studies examined the effect of iliac balloon occlusion or embolisation on maternal mortality, as summarised in **Table 3.55**. Bodner et al (2006)[67] reported no maternal deaths in either the intervention or comparator arm.

Table 3.55 Interventional radiology in maternity patients – maternal mortality

Study Level of evidence *Quality*	Study type Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Interventional radiology N/N (%)	No interventional radiology N/N (%)	Risk estimate (95% CI)	*Statistical significance* P-value
LEVEL III EVIDENCE									
PLACENTA PROBLEMS									
Bodner et al (2006)[67] Level III–2 *Fair*	Retrospective cohort study N = 28	Women with a diagnosis of placenta accreta/percreta	Single centre, teaching hospital USA	Iliac balloon occlusion and transcatheter embolisation with Gelfoam pledgets (N = 6) vs no balloon occlusion or embolisation (N = 22)	Maternal mortality	0/6 (0%)	0/22 (0%)	NR	P=NR

Abbreviations: CI, confidence intervals; NR, not reported

Thromboembolic events

Thromboembolic events were evaluated in two retrospective cohort studies, as summarised in **Table 3.56**.

Neither of the two studies[67,69] reported complete outcome data thromboembolic events, therefore it was not possible to compare the occurrence of those events between those patients who received an endovascular intervention and those that did not.

Table 3.56 Interventional radiology in maternity patients – Thromboembolic events

Study Level of evidence *Quality*	Study type Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Interventional radiology N/N (%)	No interventional radiology N/N (%)	Risk estimate (95% CI)	*Statistical significance* P-value
LEVEL III EVIDENCE									
PLACENTA PROBLEMS									
Shrivastava et al (2007)[69] Level III–2 *Fair*	Retrospective cohort study N = 69	Women who underwent caesarean hysterectomy for presumed placenta accreta or one of its variants	Hospital databases and billing records from two medical facilities USA	Iliac balloon catheterisation (N = 19) vs no iliac balloon catheterisation (N = 50)	Thrombosis	2/19 (10.5%)[a]	NR	NR	P=NR
Bodner et al (2006)[67] Level III–2 *Fair*	Retrospective cohort study N = 28	Women with a diagnosis of placenta accreta/percreta	Single centre, teaching hospital USA	Iliac balloon occlusion and transcatheter embolisation with Gelfoam pledgets (N = 6) vs no balloon occlusion or embolisation (N = 22)	Myocardial infarction	NR	1/22 (5%)	NR	P=NR

Abbreviations: CI, confidence interval; NR, not reported

[a] One patient had an internal iliac artery thrombosis; one had a femoral artery thrombosis.

Secondary outcomes

Transfusion-related serious adverse events

There were no studies identified that reported on transfusion-related serious adverse events (TACO, TRALI, haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease, anaphylactic reactions) in maternity patients receiving interventional radiology. However, as this evidence has not strictly undergone the systematic review process (secondary outcomes were only extracted from studies that reported one or more primary outcomes), this result should be interpreted with caution.

Perinatal mortality

Two studies were identified that reported on perinatal mortality in maternity patients receiving interventional radiology (**Table 3.57**). Bodner et al (2006)[67] compared iliac balloon occlusion and transcatheter embolisation with Gelfoam pledgets with no balloon occlusion or embolisation in women with a diagnosis of placenta accreta/percreta and reported no perinatal deaths in either study group. Similarly, Levine et al (1999)[68] reported no perinatal deaths in either group following a comparison of pelvic artery balloon catheterisation with no catheterisation in women with placenta accreta.

However, as this evidence has not strictly undergone the systematic review process (secondary outcomes were only extracted from studies that reported one or more primary outcomes), this result should be interpreted with caution.

Table 3.57 Interventional radiology in maternity patients – Secondary outcomes

Study Level of evidence *Quality*	Study type Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Interventional radiology N/N (%)	No interventional radiology N/N (%)	Risk estimate (95% CI)	*Statistical significance* P-value
LEVEL III EVIDENCE									
PLACENTA PROBLEMS									
Bodner et al (2006)[67] Level III–2 Fair	Retrospective cohort study N = 28	Women with a diagnosis of placenta accreta/percreta	Single centre, teaching hospital USA	Iliac balloon occlusion and transcatheter embolisation with Gelfoam pledgets (N = 6) vs no balloon occlusion or embolisation (N = 22)	Fetal mortality	0/6 (0%)	0/22 (0%)	NR	P=NR
Levine et al (1999)[68] Level III–2 Poor	Prospective cohort study N = 9	Women with placenta accreta	Single hospital USA	Pelvic artery balloon catheterisation [a] (N = 5) vs no catheterisation (N = 4)	Neonatal mortality	0/5 (0%)	0/4 (0%)	NR	P=NR

Abbreviations: CI, confidence interval; NR, not reported;

[a] For the five patients undergoing balloon catheterisation, catheters were placed in the internal iliac arteries (n=7), its anterior division (n=1), or the uterine arteries (n=2)

3.4.4 Recombinant activated factor VII

Evidence statements –recombinant activated factor VII		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES4.17	In women with massive PPH, the effect of rFVIIa compared with no recombinant activated factor VII on transfusion requirements is uncertain (See evidence matrix D4.H in Volume 2 of the technical report)	X	√	NA	√√	√
ES4.18	In women with massive PPH, the effect of rFVIIa compared with no rFVIIa on the need for additional interventions to control bleeding (hysterectomy and uterine artery embolisation) is uncertain (See evidence matrix D4.I in Volume 2 of the technical report)	X	√√	NA	√√	√
ES4.19	In women with massive PPH, the effect of rFVIIa compared with no rFVIIa on maternal mortality is uncertain (See evidence matrix D4.J in Volume 2 of the technical report)	X	√	NA	√√	√
ES4.20	In women with massive PPH, the effect of rFVIIa compared with no rFVIIa on thromboembolic events is uncertain (See evidence matrix D4.K in Volume 2 of the technical report)	X	√	NA	√√	√
ES, evidence statement; PPH, postpartum haemorrhage; rFVIIa, recombinant activated factor VII √√√=A; √√=B; √=C; X=D; NA, not applicable						

Practice points – recombinant activated factor VII	
PP29	The administration of rFVIIa may be considered in maternity patients with life-threatening haemorrhage, but only after conventional measures (including surgical haemostasis and appropriate blood component therapy) have failed.[a] [a] Refer to PP8, PP9 in Patient Blood Management Guidelines: Module 1 – Critical Bleeding/Massive Transfusion and PP20 in Patient Blood Management Guidelines: Module 2 – Perioperative. NB: rFVIIa is not licensed for this use. Its use should only be considered in exceptional circumstances.
PP30	Ideally, rFVIIa should only be administered to maternity patients as part of a locally adapted MTP. The MTP should include strict attention to the control of bleeding, physiological and metabolic parameters, coagulation status and temperature maintenance.
PP31	When rFVIIa is administered to maternity patients with life-threatening haemorrhage, an initial dose of 90 µg/kg is suggested.

Evidence gaps and areas of future research – recombinant activated factor VII
• There is a lack of evidence on whether the administration of rFVIIa, in addition to standard obstetric, surgical, and transfusion approaches, reduces morbidity and mortality in women with severe haemorrhage. • There is a need for further research on whether early administration of rFVIIa can prevent hysterectomy in women with severe haemorrhage.

Background

Recombinant activated factor VII (rFVIIa) is used for the control of bleeding and prophylaxis for surgery in patients with inhibitors to coagulation factors FVIII or FIX, congenital factor VII deficiency and Glanzmann's thrombasthenia (with glycoprotein IIb-IIIa, and/or antibodies to human leukocyte antigen plus refractoriness to platelet infusion). However, the role of rFVIIa as an additional haemostatic agent in managing severe haemorrhage in maternity patients has not been established, and has the potential to increase the risk of thromboembolism.

In Australia, rFVIIa is not licensed for use in major bleeding and its role should be limited to major ongoing bleeding where standard obstetric, surgical and transfusion approaches have been unsuccessful.

Methods

The systematic review examined the evidence for the use of rFVIIa compared with no rFVIIa in maternity patients.

Because this is an intervention question, the levels of evidence were as shown above in **Section 3.1.1.** For the purposes of this review, a systematic review of Level III–1 to Level III–3 evidence was classified as Level III evidence.

For this question, only evidence down to Level III–2 that had been published after 1985 was considered.

Summary of the evidence

Three studies were identified from the systematic review and hand searching process (see **Appendix C**, Volume 2) that examined rFVIIa in maternity patients and reported primary outcomes relevant to our research question (see **Section 4.1**).

The literature search identified no literature pertaining to Australia's Aboriginal and Torres Strait Islander peoples relevant to this research question.

Level I evidence

The literature search identified no systematic reviews that examined the use of rFVIIa in maternity patients.

Level II evidence

The literature search identified no RCTs that examined the use of rFVIIa in maternity patients.

Level III evidence

The literature search identified three Level III studies[73-75] that examined the use of rFVIIa in women with massive PPH (see **Appendix C**, Volume 2). The main characteristics of the studies are summarised in **Table 3.58.**

The study by Kalina et al (2011)[75] was a retrospective cohort study that examined the safety and efficacy of rFVIIa in maternity patients with massive PPH. The study was based on records of maternity patients who attended a Level One trauma centre in the USA between December 2003 and October 2006. Twenty-seven patients had massive PPH and received a massive transfusion, eight (29.6%) of whom received rFVIIa with doses ranging from 50 µg/kg to 100 µg/kg. The remaining 19 patients formed the control group. Outcome assessment included blood product administration, rates of thromboembolic events, hysterectomy, maternal and fetal mortality and surgical site infection.

It is likely that selection bias affected the results of the study by Kalina et al (2011). The two groups differed significantly on baseline severity of illness, with significantly higher APACHE II scores in the study group compared with controls (P=0.009). Patients also only received rFVIIa in circumstances where persistent coagulopathic bleeding existed after the first massive transfusion pack (including six units of PRBC) was transfused. In addition, the findings were based on a very small number of patients and it was unlikely that the study was adequately powered to detect any treatment difference on some outcomes.

Ahonen et al (2007)[73] conducted a retrospective cohort study of 48 maternity patients with massive PPH. The study was conducted at a tertiary referral hospital for high risk pregnancies in Finland and aimed to examine the efficacy of rFVIIa. The sample included 26 women who received rFVIIa, with a mean dose of 100 ±14 µg/kg, and 22 women who were treated for massive PPH during the same period, without the use of rFVIIa. The authors acknowledged that the decision to use rFVIIa was associated with a 'more profound haemorrhage'. It is therefore very likely that the result were affected by selection bias.

The authors concluded that rFVIIa should not be used to compensate for usual replacement therapies and that 'early and effective administration of RBC, fibrinogen concentrate, FFP and platelets as well as the control of uterine atony' remains the cornerstone of treatment in massive PPH.

The study by Hossain et al (2007)[74] was undertaken to examine whether patients with massive PPH benefit from the use of rFVIIa. The study was a retrospective cohort study, based on the records of 34 women who attended a single hospital in Karachi, Pakistan between March 2005 and October 2006. All women were treated according to a standard protocol for the management of PPH, which included surgical and medical measures such as internal iliac ligation, hysterectomy, uterotonic agents and prostaglandins. In addition, 18 women received rFVIIa, when all conventional medical and surgical methods failed to stop bleeding and rFVIIa was available at the hospital. Sixteen women did not receive rFVIIa and formed the control group.

There were no significant differences in most population characteristics (maternal age, parity, cause of bleeding, type of birth and surgical interventions); however, women in the rFVIIa group had worse haematological parameters than those in the control group at baseline and rFVIIa was only administered after other conventional methods failed.

Table 3.58 Recombinant activated factor VII – characteristics and quality of Level III evidence

Study	Study type *Study quality*	Population N	Intervention N	Comparator N	Outcomes
Kalina (2011)[75]	Retrospective cohort study *Poor*	Women with massive PPH (defined as any patient who received six or more units of PRBCs within the first 24 hours) N = 27	rFVIIa, NovoSeven® N = 8	No rFVIIa N = 19	Blood product administration Rates of pulmonary embolism, deep vein thrombosis, myocardial infarction Rates of hysterectomy Maternal and fetal mortality Surgical site infection Uterine artery embolisation
Ahonen (2007)[73]	Retrospective cohort study *Fair*	Women with major PPH at a tertiary referral hospital for high risk pregnancies N = 48	rFVIIa, NovoSeven® N = 26	No rFVIIa N = 22	Hg, platelet count TT, PT, aPTT, thrombin time Fibrinogen AT3, FV, FVIII, D-dimer Bleeding before rFVIIa Total bleeding RBC, platelets, FFP, fibrinogen concentrate
Hossain (2007)[74]	Retrospective cohort study *Fair*	Women with massive PPH (defined as blood loss >1,500 ml) N = 34	rFVIIa N = 18	No rFVIIa N = 16	Maternal mortality Correction of coagulation profile (PT, aPTT time) Transfusion of blood products Preservation of fertility (hysterectomy) Adverse drug events

Abbreviations: aPTT, activated partial thromboplastin; AT3, antithrombin–3; D-dimer, fibrin degradation products; FFP, fresh frozen plasma; FV, factor V; FVIII, factor VIII; Hg, haemoglobin; PPH, postpartum haemorrhage; PT, prothrombin time; RBC, red blood cell; rFVIIa, recombinant activated factor VII

Results

Transfusion incidence and volume

Transfusion incidence was reported by Ahonen et al (2007),[73] as summarised in **Table 3.59**. The study found that the number of patients needing fibrinogen concentrate was significantly greater in the group that received rFVIIa compared to those treated without it (P=0.014).

Transfusion volume was reported in all three studies, as summarised in **Table 3.60**.

Women with massive PPH

Ahonen et al (2007)[73] reported the mean volume of RBC, platelets and FFP that each of the study groups received. The results showed that the group who received rFVIIa also required a significantly greater volume of RBC (20 units) compared to subjects who did not receive rFVIIa (13 units; P=0.003). Similarly, the intervention group received a greater volume of platelets (23 units) compared to the control group (14 units; P=0.014). The volume of FFP transfused did not differ significantly between the two groups (12 vs 10 units; P=0.074).

The study by Kalina et al (2011)[75] produced similar results. The mean volume of PRBC transfused was 19.1 units in the rFVIIa group compared to 10.58 units in the group that did not receive rFVIIa (P=0.004). The control group also received significantly less units of cryoprecipitate on average (1.0 units) compared to the intervention group (2.6 units; p<0.001). The publication did not report the exact mean volume of FFP or platelets that each group received; however, neither was statistically significant.

In contrast, Hossain et al (2007)[74] found that those patients treated with rFVIIa required a significantly lower mean volume of PRBC (4.0 units) compared to subjects who did not receive rFVIIa (9.61 units; P=0.007).

Table 3.59 Recombinant activated factor VII in maternity patients – transfusion incidence

Study Level of evidence *Quality*	Study type Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						rFVIIa N/N (%)	No rFVIIa N/N (%)	Risk estimate [95% CI]	*Statistical significance* P-value
LEVEL III EVIDENCE									
MASSIVE POSTPARTUM HAEMORRHAGE									
Ahonen et al (2007)[73] Level III–2 *Fair*	Retrospective cohort study N = 48	Women with major PPH	Tertiary referral hospital for high risk pregnancies Finland	rFVIIa vs no rFVIIa	Fibrinogen concentrate	15/26 (57.7%)	5/22 (22.7%)	NR	*Favours no rFVIIa* P=0.014
					Compared using a chi-square test.				

Abbreviations: CI, confidence interval; FFP, fresh frozen plasma; NR, not reported; PPH, postpartum haemorrhage; PRBC, packed red blood cells; RBC, red blood cells; rFVIIa, recombinant activated factor VII

Table 3.60 Recombinant activated factor VII in maternity patients – transfusion volume

Study Level of evidence *Quality*	Study type Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results rFVIIa Mean ±SD (range)	No rFVIIa Mean ±SD (range)	Risk estimate [95% CI]	*Statistical significance* P-value
LEVEL III EVIDENCE									
MASSIVE POSTPARTUM HAEMORRHAGE									
Kalina et al (2011)[75] Level III–2 *Poor*	Retrospective cohort study N = 27	Women with massive PPH (defined as any patient who received six or more units of PRBCs within the first 24 hours)	Level One trauma centre USA	rFVIIa (N = 8) vs no rFVIIa (N = 19) All patients also received a massive transfusion via a MTP[a]	Units of PRBC transfused	19.1 ±7.8	10.58 ±5.2	NR	*Favours no rFVIIa* P=0.004
					Units of cryoprecipitate transfused	2.6 ±0.8	1.0 ±1.0	NR	*Favours no rFVIIa* P<0.001
					Units of FFP transfused	~7.7 ±NR (from graph)	~4.9 ±NR (from graph)	NR	No significant difference P=NR
					Units of platelets transfused	~5.0 ±NR (from graph)	~2.0 ±NR (from graph)	NR	No significant difference P=NR
					Continuous variables within groups were analysed with paired t-test, and independent t-test between groups				
Ahonen et al (2007)[73] Level III–2 *Fair*	Retrospective cohort study N = 48	Women with major PPH	Tertiary referral hospital for high risk pregnancies Finland	rFVIIa (N = 26) vs no rFVIIa (N = 22)	Units of RBC transfused	20 ±8 (7–39)	13 ±6 (6–26)	NR	*Favours no rFVIIa* P=0.003
					Units of platelets transfused	23 ±12 (8–54)	14 ±10 (8–48)	NR	*Favours no rFVIIa* P=0.014
					Units of FFP transfused	12 ±6 (4–22)	10 ±5 (4–18)	NR	No significant difference P=0.074
					A two-sample, two-tailed Student's t-test assuming unequal variances				
Hossain et al (2007)[74] Level III–2 *Fair*	Retrospective cohort study N = 34	Women with massive PPH (defined as blood loss >1,500 ml)	Single centre (Department of Obstetrics and Gynaecology/Surgical Intensive Care Unit) Pakistan	rFVIIa (N = 18) vs no rFVIIa (N = 16) All patients were also treated according to standard protocol for the management of PPH[b]	Units of PRBC transfused	4.0 ±4.46	9.61 ±6.7	NR	*Favours rFVIIa* P=0.007
					Unadjusted associations between treatment group were assessed using χ^2 tests for categorical variables				

Abbreviations: CI, confidence interval; FFP, fresh frozen plasma; MTP, massive transfusion protocol; NR, not reported; PPH, postpartum haemorrhage; PRBC, packed red blood cells; RBC, red blood cells; rFVIIa, recombinant activated factor VII

[a] According to the MTP 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.

[b] Including medical and surgical measures, such as use of uterotonic agents, prostaglandins, internal iliac ligation and hysterectomy.

Additional interventions to control bleeding

Women with massive PPH

The need for hysterectomy was reported in two of the included studies,[74,75] as summarised in **Table 3.61**. Total hysterectomies were performed in 61.1% of patients in the intervention arm in the study by Hossain et al (2007)[74] compared with 37.5% in the patients not treated with rFVIIa. The authors did not report the p-value; however, they stated that there was 'no significant difference' between the groups. Kalina et al (2011)[75] found that 85.7% of those treated with rFVIIa required a hysterectomy compared to 57.9% in the comparator group, which represented a non-significant difference (P=0.357).

Kalina et al (2011)[75] also reported that two patients in both the intervention and control arms required uterine artery embolisation, representing 28.6% and 10.5% of patients, respectively. The difference was not significant (P=0.29).

Finally, Ahonen et al (2007)[73] reported that six patients (23.1%) had a 'poor response to rFVIIa' which was defined as patients in which cessation of the bleeding necessitated a subsequent selective arterial embolisation or surgical intervention (laparotomy for haemostasis and/or arterial ligation). The need for additional interventions to control bleeding was not reported for the group of patients who did not receive rFVIIa.

Table 3.61 Recombinant activated factor VII in maternity patients – additional interventions to control bleeding

Study Level of evidence *Quality*	Study type Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						rFVIIa N/N (%)	No rFVIIa N/N (%)	Risk estimate [95% CI]	*Statistical significance* P-value
LEVEL III EVIDENCE									
MASSIVE POSTPARTUM HAEMORRHAGE									
Kalina et al (2011)[75] Level III–2 *Poor*	Retrospective cohort study N = 27	Women with massive PPH (defined as any patient who received six or more units of PRBCs within the first 24 hours)	Level One trauma centre USA	rFVIIa (N = 8) vs no rFVIIa (N = 19) All patients also received a massive transfusion via an MTP[a]	Hysterectomy	6/7 (85.7%)	11/19 (57.9%)	NR	No significant difference P=0.357
					Uterine artery embolisation	2/7 (28.6%)	2/19 (10.5%)	NR	No significant difference P=0.29
					Categorical variables were compared via a χ^2 or Fishers Exact test and statistical significance was denoted by a P≤0.05				
Ahonen et al (2007)[73] Level III–2 *Fair*	Retrospective cohort study N = 48	Women with major PPH	Tertiary referral hospital for high risk pregnancies Finland	rFVIIa (N = 26) vs no rFVIIa (N = 22)	'Poor'[b] response to rFVIIa	6/26 (23.1%)	NA	NA	NA
Hossain et al (2007)[74] Level III–2 *Fair*	Retrospective cohort study N = 34	Women with massive PPH (defined as blood loss >1,500 ml)	Single centre Department of Obstetrics and Gynaecology/Surgical Intensive Care Unit Pakistan	rFVIIa (N = 18) vs no rFVIIa (N = 16) All patients were also treated according to standard protocol for the management of PPH[c]	Total hysterectomy	11/18 (61.1%)	6/16 (37.5%)	NR	No significant difference P=NR
					Unadjusted associations between treatment groups were assessed using $\chi 2$ tests for categorical variables.				

Abbreviations: CI, confidence interval; MTP, massive transfusion protocol; NR, not reported; PPH, postpartum haemorrhage; rFVIIa, recombinant activated factor VII

[a] According to the MTP 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.

[b] When cessation of the bleeding necessitated a subsequent selective arterial embolisation or surgical interventions (laparotomy for haemostasis and/or arterial ligation).

[c] Including medical and surgical measures, such as use of uterotonic agents, prostaglandins, internal iliac ligation and hysterectomy.

Maternal mortality

Women with massive PPH

Hossain et al (2007)[74] conducted two separate analyses to assess the effect of rFVIIa on maternal mortality (**Table 3.62**). First, unadjusted associations between treatment groups were assessed using a χ^2 test. The analysis showed that there was no significant association between treatment with rFVIIa and maternal mortality, with an OR of 0.29 (95% CI 0.06, 1.26; P=0.09). Second, an adjusted odds ratio was calculated from the logistic regression model using a backward elimination strategy. Maternal mortality was adjusted for Hb and aPTT and shown to significantly favour treatment with rFVIIa, with an OR of 0.04 (95% CI 0.002, 0.83).

The retrospective cohort study by Kalina et al (2011)[75] reported no maternal deaths in either treatment arm.

Table 3.62 Recombinant activated factor VII in maternity patients – maternal mortality

Study Level of evidence *Quality*	Study type Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results rFVIIa N/N (%)	No rFVIIa N/N (%)	Risk estimate [95% CI]	*Statistical significance* P-value
LEVEL III EVIDENCE									
MASSIVE POSTPARTUM HAEMORRHAGE									
Kalina et al (2011)[75] Level III–2 *Poor*	Retrospective cohort study N = 27	Women with massive PPH (defined as any patient who received six or more units of PRBCs within the first 24 hours)	Level One trauma centre USA	rFVIIa (N = 8) vs no rFVIIa (N = 19) All patients also received a massive transfusion via an MTP[a]	Maternal mortality	0/8 (0%)	0/19 (0%)	NR	No significant difference P=NR
					Categorical variables were compared via a χ^2 or Fishers Exact test and statistical significance was denoted by a P≤0.05				
Hossain et al (2007)[74] Level III–2 *Fair*	Retrospective cohort study N = 34	Women with massive PPH (defined as blood loss >1,500 ml)	Single centre (Department of Obstetrics and Gynaecology/Surgical Intensive Care Unit) Pakistan	rFVIIa (N = 18) vs no rFVIIa (N = 16) All patients were also treated according to standard protocol for the management of PPH[b]	Maternal mortality (unadjusted analysis)	5/18 (28%)	8/16 (50%)	OR 0.29 [0.06, 1.26]	No significant difference P=0.09
					Maternal mortality (adjusted for Hb and aPTT)	5/18 (28%)	8/16 (570%)	OR 0.04 [0.002, 0.83]	*Favours rFVIIa* P=NR
					Unadjusted associations between treatment groups were assessed using χ^2 tests for categorical variables. Unadjusted and adjusted OR and 95% CIs 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.				

Abbreviations: aPTT, activated partial thromboplastin; CI, confidence interval; Hb, haemoglobin; MTP, massive transfusion protocol; NR, not reported; OR, odds ratios; PPH, postpartum haemorrhage; rFVIIa, recombinant activated factor VII

[a] According to the MTP 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.

[b] Including medical and surgical measures, such as use of uterotonic agents, prostaglandins, internal iliac ligation and hysterectomy.

Thromboembolic events

Women with massive PPH

Thromboembolic events were examined in all three of the included studies, as summarised in **Table 3.63**. Across the three studies only one thromboembolic event was reported. In the study by Ahonen et al (2007),[73] one patient who received rFVIIa developed a pulmonary embolism. None of the trials reported a significant association between treatment with rFVIIa and thromboembolic events.

Table 3.63 Recombinant activated factor VII in maternity patients – thromboembolic events

Study Level of evidence *Quality*	Study type Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						rFVIIa N/N (%)	No rFVIIa N/N (%)	Risk estimate [95% CI]	*Statistical significance* P-value
LEVEL III EVIDENCE									
MASSIVE POSTPARTUM HAEMORRHAGE									
Kalina et al (2011)[75] Level III–2 *Poor*	Retrospective cohort study N = 27	Women with massive PPH (defined as any patient who received six or more units of PRBCs within the first 24 hours)	Level One trauma centre USA	rFVIIa (N=8) vs no rFVIIa (N=19) All patients also received a massive transfusion via an MTP[a]	Deep vein thrombosis	0/8 (0%)	0/19 (0%)	NR	No significant difference P=NR
					Pulmonary embolism	0/8 (0%)	0/19 (0%)	NR	No significant difference P=NR
					Myocardial infarction	0/8 (0%)	0/19 (0%)	NR	No significant difference P=NR
					Categorical variables were compared via a χ^2 or Fishers Exact test and statistical significance was denoted by a $p \leq 0.05$				
Ahonen et al (2007)[73] Level III–2 *Fair*	Retrospective cohort study N = 48	Women with major PPH	Tertiary referral hospital for high risk pregnancies Finland	rFVIIa (N=26) vs no rFVIIa (N=22)	Pulmonary embolism	1	NR	NA	NA
Hossain et al (2007)[74] Level III–2 *Fair*	Retrospective cohort study N = 34	Women with massive PPH (defined as blood loss >1,500 ml)	Single centre Department of Obstetrics and Gynaecology/Surgical Intensive Care Unit Pakistan	rFVIIa (N=18) vs no rFVIIa (N=16) All patients were also treated according to standard protocol for the management of PPH[b]	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
					Unadjusted associations between treatment group were assessed using χ^2 tests for categorical variables				

Abbreviations: CI, confidence interval; MTP, massive transfusion protocol; NR, not reported; PPH, postpartum haemorrhage; rFVIIa, recombinant activated factor VII

[a] 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.

[b] Including medical and surgical measures, such as use of uterotonic agents, prostaglandins, internal iliac ligation and hysterectomy.

Secondary outcomes

Transfusion-related serious adverse events

There were no studies identified that reported on transfusion-related serious adverse events (TACO, TRALI, haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease, anaphylactic reactions) in maternity patients receiving recombinant activated factor VII. However, as this evidence has not strictly undergone the systematic review process (secondary outcomes were only extracted from studies that reported one or more primary outcomes), this result should be interpreted with caution.

Perinatal mortality

One study was identified that reported on perinatal mortality in women with massive postpartum haemorrhage receiving recombinant activated factor VII. Kallina et al (2011)[75] compared rFVIIa with no rFVIIa and reported no significant difference in fetal mortality (0/8 vs 2/19, P=0.39). However, as this evidence has not strictly undergone the systematic review process (secondary outcomes were only extracted from studies that reported one or more primary outcomes), this result should be interpreted with caution.

Table 3.64 Recombinant activated factor VII in maternity patients – secondary outcomes

Study Level of evidence *Quality*	Study type Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						rFVIIa N/N (%)	No rFVIIa N/N (%)	Risk estimate [95% CI]	*Statistical significance* P-value
LEVEL III EVIDENCE									
MASSIVE POSTPARTUM HAEMORRHAGE									
Kalina et al (2011)[75] Level III–2 *Poor*	Retrospective cohort study N = 27	Women with massive PPH (defined as any patient who received six or more units of PRBCs within the first 24 hours)	Level One trauma centre USA	rFVIIa (N=8) vs no rFVIIa (N=19) All patients also received a massive transfusion via an MTP[a]	Fetal mortality	0/8 (0%)	2/19 (10.5%)	NR	No significant difference P=0.39
					Categorical variables were compared via a χ^2 or Fishers Exact test and statistical significance was denoted by a $p \leq 0.05$				

Abbreviations: CI, confidence interval; FFP, fresh frozen plasma; MTP, massive transfusion protocol; NR, not reported; PPH, postpartum haemorrhage; PRBC, packed red blood cells; rFVIIa, recombinant activated factor VII

[a] According to the MTP 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.

3.4.5 Tranexamic acid

Evidence statements – tranexamic acid		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES4.21	In women giving birth by caesarean delivery, the effect of the routine use of antifibrinolytic therapy (TXA only), on transfusion requirements is uncertain (See evidence matrix D4.L in Volume 2 of the technical report)	√√	√	NA	√√	√
ES4.22	In women giving birth by vaginal delivery, the effect of the routine use of antifibrinolytic therapy (TXA only) on transfusion requirements is uncertain (See evidence matrix D4.M in Volume 2 of the technical report)	√√	NA	NA	√√	√
ES4.23	In women with postpartum haemorrhage after vaginal delivery, the effect of antifibrinolytic therapy (TXA only) on transfusion requirements is uncertain (See evidence matrix D4.N in Volume 2 of the technical report)	√√	NA	X	√√	√√
ES4.24	In women giving birth by caesarean delivery, the effect of the routine use of antifibrinolytic therapy (TXA only), on the need for additional interventions to prevent bleeding is uncertain (See evidence matrix D4.O in Volume 2 of the technical report)	√√	√√√	NA	√√	√
ES4.25	In women giving birth by vaginal delivery, the effect of the routine use of antifibrinolytic therapy (TXA only) on the need for additional interventions to control bleeding is uncertain (See evidence matrix D4.P in Volume 2 of the technical report)	√√	NA	NA	√√	√
ES4.26	In women with postpartum haemorrhage after vaginal delivery, the effect of antifibrinolytic therapy (TXA only) on the need for additional interventions to control bleeding is uncertain (See evidence matrix D4.Q in Volume 2 of the technical report)	√√	NA	NA	√√	√√
ES4.27	In women giving birth by caesarean delivery, the effect of the routine use of antifibrinolytics (TXA only) on maternal mortality is uncertain (See evidence matrix D4.R in Volume 2 of the technical report)	√	NA	NA	√√	√
ES4.28	In women giving birth by vaginal delivery, the effect of the routine use of antifibrinolytic therapy (TXA only) on maternal mortality is uncertain (See evidence matrix D4.S in Volume 2 of the technical report)	√√	NA	NA	√√	√

Evidence statements – tranexamic acid		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES4.29	In women with postpartum haemorrhage after vaginal delivery, the effect of antifibrinolytic therapy (TXA only) on maternal mortality is uncertain (See evidence matrix D4.T in Volume 2 of the technical report)	√√	NA	NA	√√	√√
ES4.30	In women giving birth by caesarean delivery, the effect of the routine use of antifibrinolytic therapy (TXA only) on thromboembolic events is uncertain (See evidence matrix D4.U in Volume 2 of the technical report)	√√	√√√	NA	√√	√
ES4.31	In women giving birth by vaginal delivery, the effect of the routine use of antifibrinolytic therapy (TXA only) on thromboembolic events is uncertain (See evidence matrix D4.V in Volume 2 of the technical report)	√√	NA	NA	√√	√
ES4.32	In women with postpartum haemorrhage after vaginal delivery, the effect of antifibrinolytic therapy (TXA only) on thromboembolic events is uncertain (See evidence matrix D4.W in Volume 2 of the technical report)	√√	NA	NA	√√	√√
ES4.33	In women with placenta problems or unspecified antepartum haemorrhage, the effect of antifibrinolytic therapy (TXA only), on thromboembolic events is uncertain (See evidence matrix D4.X in Volume 2 of the technical report)	X	NA	NA	√√	√√
ES, evidence statement; TXA, tranexamic acid √√√=A; √√=B; √=C; X=D; NA, not applicable						

Practice points – tranexamic acid	
PP32	In maternity patients with significant blood loss, the early use (within 3 hours of the onset of haemorrhage) of TXA may be considered. NB: The use of TXA in this context is considered 'off-label'
PP33	TXA should only be administered in the context of overall patient management; the protocol should include strict attention to the control of bleeding, physiological and metabolic parameters, coagulation status and temperature maintenance.
PP, practice point; TXA, tranexamic acid	

Evidence gaps and areas of future research – tranexamic acid
• Is there a benefit in prophylactic administration of TXA in women at high risk of major haemorrhage.[a] • What is the role (if any) for TXA in the management of PPH or APH?
[a] The World Maternal Antifibrinolytic Trial (The WOMAN Trial) is a large, multicentre, randomised, double-blinded, placebo controlled trial currently underway to investigate the effect of TXA administration early in the course of PPH

Background

Tranexamic acid is a synthetic derivative of the amino acid lysine that acts as an antifibrinolytic by competitively inhibiting the activation of plasminogen to plasmin, a molecule responsible for the degradation of fibrin. Tranexamic acid tablets and solution for injection are approved in Australia for a number of indications including cardiac surgery, total knee or hip arthroplasty, traumatic hyphaema and for patients with coagulopathies undergoing minor surgery.

There is strong evidence to support the use of TXA to reduce blood loss in the surgical and trauma populations (refer to *Patient Blood Management Guidelines: Module 2 – Perioperative*), and may be of benefit in maternity patients for the control of postpartum haemorrhage. In Australia, the use of TXA in this context is considered 'off-label'.

Methods

The systematic review examined the evidence for the use of tranexamic acid (TXA) compared with no TXA in maternity patients.

Because this is an intervention question, the levels of evidence were as shown above in **Section 3.1.1**. For the purposes of this review, a systematic review of Level III–1 to Level III–3 evidence has been classified as Level III evidence.

For this question, only evidence down to Level III–2 that had been published after 1985 was considered.

Summary of the evidence

Eight studies were identified from the systematic review and hand searching process (see **Appendix C,** Volume 2) that examined the use of tranexamic acid in maternity patients and reported primary outcomes relevant to our research question (see **Section 4.1**).

The literature search identified no literature pertaining to Australia's Aboriginal and Torres Strait Islander peoples relevant to this research question.

Level I evidence

The literature search identified no systematic reviews that examined the effect of tranexamic acid (TXA) in maternity patients that met our inclusion criteria.

Level II evidence

The literature search identified seven RCTs that examined the effect of TXA in maternity patients (see **Appendix C**, Volume 2). There were five studies that examined the routine use of TXA in women giving birth via caesarean section.[76-80] One study examined the routine use of TXA in women expected to give birth vaginally and one study investigated the effect of TXA on blood loss in women with postpartum haemorrhage after vaginal birth.[81] The main characteristics of the studies are summarised in **Table 3.65**.

Abdel-Aleem (2013)[76] was a single centre RCT conducted in Egypt that examined the effectiveness of TXA in 740 pregnant women who elected to give birth via caesarean section. The primary outcome was estimated mean blood loss. The study also reported other outcomes such as the incidence of PPH, the use of additional uterotonics or surgical interventions to control bleeding, mean changes in haematocrit and haemoglobin, number of hospital admission days, thromboembolic events and admission to ICU. 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.

Gai et al (2004)[77] was a multicentre RCT conducted in the People's Republic of China. A total of 180 primipara women who gave birth by caesarean section were randomised to receive TXA or no TXA. The primary outcomes were volume of blood loss and incidence of PPH (bleeding >400 mL within two hours after birth). The study also reported incidence of thromboembolic events.

Gungorduk et al (2011)[78] examined the effect of TXA in reducing blood loss during elective caesarean section. The study was conducted at a single teaching hospital in Turkey and included 330 women who received TXA and 330 who received placebo. The primary outcome was estimated blood loss, calculated via difference in haematocrit values. In addition, vital signs, laboratory measures, need for blood transfusion, thromboembolic events and several other outcomes were reported.

Senturk et al (2013)[79] assessed the efficacy and safety of TXA to reduce intrapartum and postpartum bleeding in patients who underwent an elective or emergency caesarean section. A total of 223 healthy women with normal pregnancies were randomised to receive TXA or placebo in a hospital in Turkey. The primary outcomes measured were volume of blood loss and laboratory values. The study also reported outcomes such as the need for transfusion and TXA side effects (nausea, vomiting and venous thrombosis).

Xu et al (2013)[80] conducted an RCT in the People's Republic of China which examined the effect of TXA on clinical outcomes in maternity patients who underwent a caesarean section. The results were based on a total of 176 primipara women, 88 of which received TXA. The remaining 88 patients were randomised to receive placebo and formed the control group. The primary outcome of the trial was volume of blood loss; however maternal mortality, transfusion incidence and thromboembolic events were also reported.

The RCT by Gungorduk et al (2013)[82] was conducted in a single centre in Turkey and examined the effect of TXA on blood loss during the third and fourth stages of labour. Women who were expected to give birth vaginally were randomised to receive either TXA or placebo intravenously at birth to the anterior shoulder. In addition to volume of blood loss, the study also examined outcomes such as incidence of PPH and severe PPH, need for blood transfusion and the need for additional uterotonic agents.

Ducloy-Bouthors et al (2011)[81] was a multicentre RCT conducted in five tertiary care centres or secondary obstetric units in France. A total of 152 women with PPH >800 mL within two hours of vaginal birth were randomised to receive TXA or no TXA. The primary outcome was volume of blood loss in PPH; however the study also examined the duration of blood loss, the need for invasive procedures, the need for transfusion, and side effects of TXA.

Table 3.65 Tranexamic acid – characteristics and quality of Level II evidence

Study	Study type *Study quality*	Population N	Intervention N	Comparator N	Outcomes
Caesarean birth					
Abdel-Aleem (2013)[76]	RCT *Fair*	Pregnant women with singleton fetus at ≥ 37 weeks gestation who underwent an elective caesarean section	1g TXA administered intravenously over 10 minutes before operation commenced	No TXA	Additional interventions to control bleeding (surgical procedures) Maternal mortality Thromboembolic events
Gai (2004)[77]	RCT *Fair*	Primipara women with singleton pregnancy, giving birth by caesarean section N = 180	1 g/10 mL TXA diluted with 20 mL 5% glucose administered intravenously over 5 minutes and 10 minutes before incision N = 91	No TXA N = 89	Thromboembolic events
Gungorduk (2011)[78]	RCT *Good*	Women undergoing elective caesarean section after 38 weeks of gestation N = 660	1 g/10 mL TXA diluted with 20 mL of 5% glucose administered intravenously over a 5-minute period and 10 minutes prior to incision N = 330	Placebo N = 330	Transfusion volume and incidence Additional interventions to control bleeding (surgical procedures) Thromboembolic events (DVT, myocardial infarction, stroke, renal failure, pulmonary embolism)
Senturk (2013)[79]	RCT *Good*	Healthy women with a normal pregnancy undergoing elective and urgent caesarean section N = 223	Four ampules equal to 20 cc and 1 g of TXA administered intravenously over 5 minutes before anaesthesia and 10 minutes before incision N = 101	Placebo N = 122	Transfusion incidence Additional interventions to control bleeding Thromboembolic events
Xu (2013)[80]	RCT *Fair*	Primipara women aged 22 to 34 years with a singleton pregnancy, scheduled to undergo caesarean section N = 176	10m g/kg TXA 200 ml normal saline infused intravenously over 10 – 20 minutes before anaesthesia N = 88	Placebo N = 88	Transfusion incidence Maternal mortality Thromboembolic events (DVT)

Vaginal birth					
Gungorduk (2013)[82]	RCT Good	Women with gestational age between 34 and 42 weeks, a live fetus, cephalic presentation and expected vaginal birth N = 454	1 g/10 mL TXA diluted in 20 mL 5% glucose administered intravenously at birth over 5-minutes N = 228	Placebo N = 226	Transfusion incidence Maternal mortality Additional interventions to control bleeding (surgical) Thromboembolic events
Postpartum haemorrhage after vaginal birth					
Ducloy-Bouthors (2011)[81]	RCT *Good*	Women with PPH (>800 mL) within 2 hours of vaginal birth N = 152	Loading dose of 4 g TXA in 50 mL normal saline infused over 1 h, then 1 g/h over 6 h N = 78	No TXA N = 74	Transfusion volume and incidence Maternal mortality Additional interventions to control bleeding (arterial embolisation, surgical arterial ligation, or hysterectomy) Thromboembolic events (DVT)

DVT, deep vein thrombosis; PPH, postpartum haemorrhage; RCT, randomised controlled trial; TXA, tranexamic acid

Level III evidence

The literature search identified one Level III study that examined the effect of TXA in maternity patients (see **Appendix C,** Volume 2). The main characteristics of the study are summarised in **Table 3.66**.

Lindoff et al (1993)[83] conducted a retrospective cohort study that examined the risk of thromboembolic events in maternity patients treated with TXA. A total of 2102 patients with various bleeding disorders during pregnancy (placental abruption, placenta previa or unspecified antepartum haemorrhage) were identified from a large cohort of patients at two teaching hospitals in Sweden between 1979 and 1988. The TXA group consisted of 256 patients, compared with 1,846 in the control (no TXA) group. Outcome assessment included complications during pregnancy and labour and arterial and venous thromboembolic complications.

Table 3.66 Tranexamic acid – characteristics and quality of Level III evidence

Study	Study type *Study quality*	Population N	Intervention N	Comparator N	Outcomes
Lindoff (1993)[83]	Retrospective cohort study Poor	Maternity patients with placental abruption, placenta previa or unspecified antepartum haemorrhage N = 2102	TXA N = 256	No TXA N = 1846	Thromboembolic events (thromboembolism, PE, DVT)

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; TXA, tranexamic acid

Results

Transfusion incidence or volume

Transfusion incidence was reported in five studies and transfusion volume was reported in two studies, as summarised in **Table 3.67**.

Women giving birth via caesarean section

Three studies[78-80] examined the effect of TXA (at varying doses ranging from ranging from 10m g/kg to 1g) on transfusion volume or incidence in maternity patients who underwent elective and/or urgent caesarean section. Senturk et al (2013)[79] reported no transfusions in either the TXA or placebo groups. Gungorduk et al (2011)[78] reported that, on average, 1.5 units of PRBC were transfused in patients in whom blood transfusions were given and who received TXA. The average volume was 1.6 units among transfused patients in the placebo group. Gungorduk et al (2011)[78] also reported no significant difference in transfusion incidence between TXA and placebo treatments, with a relative risk of 3.5 (95% CI 0.7, 16.7; P=0.17). In contrast, Xu et al (2013)[80] reported a significantly higher incidence of packed RBC infusion in patients who received placebo (22%) compared with those who were treated with TXA (9%). Based on the primary data, the relative risk was calculated to be 0.41 (95% CI 0.19, 0.89; P=0.02). The transfusion rate in both the TXA and placebo arms of the study by Xu et al (2013)[80] seemed very high when Hb levels and other clinical indicators were taken into account. Also, the Hg threshold for transfusion and the number of patients that met the threshold does not match the number of patients transfused. The authors did not provide any insights that would explain the very high transfusion incidence.

Women giving birth via vaginal birth

There was one study that examined the effect of TXA on transfusions incidence in women giving birth by vaginal birth who were at risk of PPH. Gungorduk et al (2013)[82] found no significant difference in the incidence of transfusion between patients who received TXA and those who did not, with a relative risk of 3.01 (95% CI 0.31, 28.74; P=0.37) reported.

Women with PPH after vaginal birth

The RCT by Ducloy-Bouthors et al (2011)[81] examined the effect of TXA on transfusion volume and incidence in women with active, severe PPH after vaginal birth. The authors found no significant difference between women treated with TXA compared with those that did not receive TXA, based on the incidence of PRBC transfusion before six hours or through day 42 or on the volume of PRBC transfused before six hours. However, the study found that the total transfusion volume was significantly lower in the TXA group compared with the no TXA group through day 42 ($p<0.001$). The results also showed that a significantly smaller proportion of patients treated with TXA received additional procoagulant treatment (fibrinogen, FFP) than those who did not receive TXA (1.4% vs 9.7%; P=0.001).

Table 3.67 Tranexamic acid in maternity patients – transfusion incidence or volume

Study Level of evidence *Quality*	Study type Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						TXA N/N (%) Mean	No TXA N/N (%) Mean	Risk estimate [95% CI]	*Statistical significance* P-value
LEVEL II EVIDENCE									
CAESAREAN BIRTH									
Senturk et al (2013)[79] Level II *Good*	RCT N = 223	Healthy women with normal pregnancy who underwent elective or emergency caesarean section	Hospital Turkey	TXA vs placebo administered prior to incision *All patients received oxytocin after removal of placenta	Transfusion incidence	0[a]	0[a]	NR	NR
Xu et al (2013)[80] Level II *Fair*	RCT N = 174	Primipara women with a singleton pregnancy who underwent a caesarean section	Hospital People's Republic of China	TXA vs placebo administered prior to incision *After birth, all patients were given oxytocin in normal saline by IV drip over 30 minutes and IV methylergometrine	Infusion of PRBC	8/88 (9%)	19/86 (22%)	RR 0.41 [0.19, 0.89][b]	*Favours TXA* P=0.02[b]
Gungorduk et al (2011)[78] Level II *Good*	RCT N = 660	Healthy women undergoing elective caesarean section at more than 38 weeks estimated gestation	Single teaching hospital Turkey	TXA vs placebo administered prior to incision *After birth, all patients received IV bolus of oxytocin, then oxytocin in lactated Ringer's solution and cefazolin diluted in normal saline administered over a 5-minute period	PRBC transfusion	2/330 (0.6%)	7/330 (2.1%)	RR 3.5 [0.7–16.7]	No significant difference P=0.17
					Mean volume of PRBC transfusion in transfused patients (units)	1.5[c]	1.6[d]	NR	NR
VAGINAL BIRTH									
Gungorduk et al (2013)[82] Level II *Good*	RCT N = 439	Women in labour with gestational age between 34 and 42 weeks and expected vaginal birth	Single teaching hospital Turkey	TXA vs placebo administered prior to birth *All patients underwent 'active management' of the third stage of labour[e]	Requirement for blood transfusion	1/220 (0.5%)	3/219 (1.4%)	RR 3.01 [0.31–28.74]	No significant difference P=0.37

Study Level of evidence *Quality*	Study type Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						TXA N/N (%) Mean	No TXA N/N (%) Mean	Risk estimate [95% CI]	*Statistical significance* P-value
POSTPARTUM HAEMORRHAGE AFTER VAGINAL BIRTH									
Ducloy-Bouthors et al (2011)[81] Level II *Good*	RCT N = 151[f]	Women with PPH after vaginal birth (PPH defined as blood loss >800 ml within 2 hours of birth)	5 tertiary care centres and 3 secondary obstetric units France	TXA (N=78) vs no TXA (N=74) *All patients were allowed PRBCs and colloids according to French guidelines The use of additional procoagulant treatment was permitted only in cases involving intractable bleeding FFP, platelets and fibrinogen concentrate was not permitted before 2hrs after inclusion	PRBC transfusion before 6 hours (ITT)	10/77 (13%)	13/74 (18%)	NR	No significant difference P=0.17
					PRBC transfusion before 6 hours (PP)	7/72 (10%)	12/72 (17%)	NR	No significant difference P=0.65
					PRBC transfusion total through day 42 (ITT)	12/77 (16%)[g]	20/74 (27%)	NR	No significant difference P=0.16[b]
					PRBC transfusion total through day 42 (PP)	9/72 (13%)	19/72 (28%)[g]	NR	No significant difference P=0.08b
					Additional procoagulant treatment (fibrinogen, FFP)	1/72 (1.4%)	7/72 (9.7%)	NR	*Favours TXA* P=0.001
						Total units	Total units		
					Total units PRBC administered before 6 hours (ITT)	22[g]	38[g]	NR	No significant difference P=0.27[f]
					Total units PRBC administered before 6 hours (PP)	18	32[g]	NR	No significant difference P=0.44[f]
					Total units PRBC administered through day 42 (ITT)	28	62	NR	*Favours TXA* P<0.001
					Total units PRBC administered through day 42 (PP)	24	56[g]	NR	*Favours TXA* P<0.001

Abbreviations: CI, confidence interval; FFP, fresh frozen plasma; ITT, intention-to-treat; IV, intravenous; NR, not reported; OR, odds ratio; PP, per-protocol; PPH, postpartum haemorrhage; PRBC, packed red blood cells; RCT, randomised controlled trial; RR, relative risk; TXA, tranexamic acid.

[a] Denominator was not reported.

[b] Calculated post-hoc using outcome results for each treatment arm.

[c] Calculated post-hoc: 1 patient received 1 unit and 1 patient received 2 units.

[d] Calculated post-hoc: 4 patients received 1 units, 2 patients received 2 units, 1 patient received 3 units.

[e] 'Active' management included prophylactic injection of oxytocin within 2 minutes of birth, early clamping of the umbilical cord, and controlled cord traction following birth.

[f] Refers to the number of women in the ITT analyses. 144 women were included in the PP analyses out of 152 randomised patients.

[g] The value specified in the table differs from the published data. The author was contacted to clarify data and has acknowledged and corrected the error.

Additional interventions to control bleeding

The use of additional interventions to control bleeding was reported in five studies, as summarised in **Table 3.68**.

Women giving birth via caesarean

In women giving birth by caesarean , Senturk et al (2013)[79] reported that hysterectomy and artery ligation were not deemed to be necessary for any patients in the study, regardless of whether or not they received TXA or placebo. Similarly, Abdel-Aleem et al (2013)[76] and Gungorduk et al (2011)[78] found that no patient in the study required additional surgical interventions (such as a B-lynch suture, uterine artery ligation or caesarean hysterectomy).

Women giving birth via vaginal birth

The same research group assessed the effect of TXA on blood loss during the third and fourth stages of labour in women giving birth via vaginal birth.[82] No surgical interventions for PPH were needed in either the TXA or placebo group.

Women with active PPH after vaginal birth

The study by Ducloy-Bouthors et al (2011)[81] reported on the use of additional interventions to control bleeding, including arterial embolisation, surgical arterial ligature or hysterectomy and late postpartum curettage in women with active PPH after vaginal birth. The authors reported no significant differences in the use of additional interventions to control bleeding comparing patients who received TXA with those who did not.

Table 3.68 Tranexamic acid in maternity patients – additional interventions to control bleeding

Study Level of evidence *Quality*	Study type Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						TXA N/N (%)	No TXA N/N (%)	Risk estimate [95% CI]	*Statistical significance* P-value
LEVEL II EVIDENCE									
CAESAREAN BIRTH									
Abdel-Aleem et al (2013)[76] Level II *Fair*	RCT N=740	Pregnant women with a singleton fetus at ≥ 37 weeks gestation who underwent an elective caesarean section	University hospital Egypt	TXA (N = 373) vs no TXA (N = 367) *All patients received oxytocin (5IU IV bolus and 20IU IV infusion)	Additional surgical interventions to control PPH	0[a]	0[a]	NR	NR
Senturk et al (2013)[79] Level II *Good*	RCT N = 223	Healthy women with normal pregnancy who underwent elective or emergency caesarean section	Hospital Turkey	TXA (N = 101) vs placebo (N = 122) administered prior to incision *All patients received oxytocin after removal of placenta	Additional interventions to control bleeding (hysterectomy, artery ligation)	0[a]	0[a]	NR	NR
Gungorduk et al (2011)[78] Level II *Good*	RCT N = 660	Healthy women undergoing elective caesarean section at more than 38 weeks estimated gestation	Single teaching hospital Turkey	TXA (N = 330) vs placebo (N = 330) administered prior to incision *After birth, all patients received IV bolus of oxytocin, then oxytocin in lactated Ringer's solution and cefazolin diluted in normal saline administered over a 5-minute period	Additional interventions to control bleeding: surgical procedures (B-lynch suture, uterine artery ligation, hysterectomy)	0[a]	0[a]	NR	NR
VAGINAL BIRTH									
Gungorduk et al (2013)[82] Level II *Good*	RCT N = 439	Women in labour with gestational age between 34 and 42 weeks and expected vaginal birth[c]	Single teaching hospital Turkey	TXA (N = 220) vs placebo (N = 219) administered prior to birth *All patients underwent 'active management' of the third stage of labour[b]	Additional interventions to control bleeding: surgical interventions	0[a]	0[a]	NR	NR
POSTPARTUM HAEMORRHAGE AFTER VAGINAL BIRTH									
Ducloy-Bouthors et al	RCT N = 151[c]	Women with PPH after vaginal birth (PPH	5 tertiary care centres and 3	TXA (N = 78) vs no TXA (N = 74)	Arterial embolisation (ITT)	5/77 (6.5%)	5/74 (6.8%)	NR	No significant difference P=0.94

Study Level of evidence *Quality*	Study type Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						TXA N/N (%)	No TXA N/N (%)	Risk estimate [95% CI]	*Statistical significance* P-value
(2011)[81] Level II *Good*		defined as blood loss >800 ml within 2 hours of birth)	secondary obstetric units France	*All patients were allowed PRBCs and colloids according to French guidelines[d]	Arterial embolisation (PP)	4/72 (5.5%)	5/72 (6.9%)	NR	No significant difference P=0.73
					Surgical arterial ligature or hysterectomy (ITT)	0[a]	2/74 (2.7%)	NR	No significant difference P=0.24
					Surgical arterial ligature or hysterectomy (PP)	0[a]	2/72 (2.8%)	NR	No significant difference P=0.5
					Late postpartum curettage – after day 7 (ITT)	1/77 (1.3%)	2/74 (2.7%)	NR	No significant difference P=1.0
					Late postpartum curettage – after day 7 (PP)	1/72 (1.4%)	2/72 (2.8%)	NR	No significant difference P=1.0

Abbreviations: CI, confidence interval; FFP, fresh frozen plasma; ITT, intention-to-treat; IU, International Unit; IV, intravenous; NR, not reported; PP, per-protocol; PPH, postpartum haemorrhage; RCT, randomised controlled trial; TXA, tranexamic acid

[a] Denominator was not reported.

[b] 'Active' management included prophylactic injection of oxytocin within 2 minutes of birth, early clamping of the umbilical cord, and controlled cord traction following birth.

[c] Refers to the number of women in the ITT analyses. 144 women were included in the PP analyses out of 152 randomised patients.

[d] The use of additional procoagulant treatment was permitted only in cases involving intractable bleeding. FFP, platelets and fibrinogen concentrate was not permitted before 2hrs after inclusion.

Maternal mortality

Maternal mortality was reported in four RCTs that assessed the effect of TXA administered before caesarean section,[80] prior to vaginal birth,[82] or in women with postpartum haemorrhage after vaginal birth.[81] All four studies reported no maternal deaths in either the TXA or no TXA/placebo treatment arms; however, it was noted that the studies were not powered to detect differences in maternal death (**Table 3.69**).

Table 3.69 Tranexamic acid in maternity patients – maternal mortality

Study Level of evidence *Quality*	Study type Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						TXA	No TXA	Risk estimate [95% CI]	*Statistical significance* P-value
LEVEL II EVIDENCE									
CAESAREAN BIRTH									
Abdel-Aleem et al (2013)[76] Level II *Fair*	RCT N=740	Pregnant women with a singleton fetus at ≥ 37 weeks gestation who underwent an elective caesarean section	University hospital Egypt	TXA (N = 373) vs no TXA (N = 367) All patients received oxytocin (5IU IV bolus and 20IU IV infusion)	Maternal mortality	0[a]	0[a]	NR	NR
Xu et al (2013)[80] Level II *Fair*	RCT N = 174	Primipara women with a singleton pregnancy who underwent a caesarean section	Hospital People's Republic of China	TXA (N = 88) vs placebo (N = 86) After birth, all patients were given oxytocin in normal saline by IV drip over 30 minutes and IV methylergometrine	Maternal mortality	0[a]	0[a]	NR	NR
VAGINAL BIRTH									
Gungorduk et al (2013)[82] Level II *Good*	RCT N = 439	Women in labour with gestational age between 34 and 42 weeks and expected vaginal birth[b]	Single teaching hospital Turkey	TXA (N = 220) vs placebo (N = 219) All patients underwent 'active management' of the third stage of labour[c]	Maternal mortality	0[a]	0[a]	NR	NR
POSTPARTUM HAEMORRHAGE AFTER VAGINAL BIRTH									
Ducloy-Bouthors et al (2011)[81] Level II *Good*	RCT N = 151[c]	Women with PPH after vaginal birth (PPH defined as blood loss >800 ml within 2 hours of birth)	5 tertiary care centres and 3 secondary obstetric units France	TXA (N = 78) vs no TXA (N = 74) All patients were allowed PRBCs and colloids according to French guidelines[d]	Maternal mortality	0[a]	0[a]	NR	NR

Abbreviations: CI, confidence interval; FFP, fresh frozen plasma; ITT, intention-to-treat; IV, intravenous; NR, not reported; PP, per-protocol; PPH, postpartum haemorrhage; RCT, randomised controlled trial; TXA, tranexamic acid.

[a] Denominator was not reported.

[b] Women were excluded following birth if they underwent caesarean section.

[c] 'Active' management included prophylactic injection of oxytocin within 2 minutes of birth, early clamping of the umbilical cord, and controlled cord traction following birth.

[c] Refers to the number of women in the ITT analyses. 144 women were included in the PP analyses out of 152 randomised patients.

[d]The use of additional procoagulant treatment was permitted only in cases involving intractable bleeding. FFP, platelets and fibrinogen concentrate was not permitted before 2hrs after inclusion.

Thromboembolic events

Thromboembolic events were reported in seven RCTs and one retrospective cohort study, as summarised in **Table 3.70**. None of the studies reported a significant difference between women who received TXA and those who did not, based on thromboembolic events such as deep vein thrombosis and pulmonary embolisms. Since the event rate is low, it is likely that the studies were not sufficiently powered to detect differences between treatment arms for this outcome.

Women giving birth via caesarean birth

In women giving birth by caesarean section, Abdel-Aleem (2013),[76] Senturk (2013)[79] or Gungorduk (2011)[78] reported no thromboembolic events in either treatment groups. Gai (2004)[77] reported nil thromboembolic events in the intervention group but results were not reported for the comparator group. In the study by Xu (2013),[80] there was no statistically significant difference between treatment groups for deep vein thrombosis (P=0.38).

Women giving birth via vaginal birth

Gungorduk (2013)[82] reported no thromboembolic events in either treatment group.

Women with active PPH after vaginal birth

In women with severe postpartum haemorrhage after vaginal birth, Ducloy-Bouthors (2011)[81] reported that 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).

In the retrospective cohort study described by Lindhoff (1993),[83] there was no difference between treatment groups 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. Women who received TXA in this study had more severe bleeding complications, and were presumed to be more prone to thrombosis.

Table 3.70 Tranexamic acid in maternity patients – thromboembolic events

Study Level of evidence *Quality*	Study type Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						TXA N/N (%)	No TXA N/N (%)	Risk estimate [95% CI]	*Statistical significance* P-value
LEVEL II EVIDENCE									
CAESAREAN BIRTH									
Abdel-Aleem et al (2013)[76] Level II *Fair*	RCT N=740	Pregnant women with a singleton fetus at ≥ 37 weeks gestation who underwent an elective caesarean section	University hospital Egypt	TXA (N=373) vs no TXA (N=367) *All patients received oxytocin (5IU IV bolus and 20IU IV infusion)	Serious adverse effects (e.g. thromboembolism)	0[a]	0[a]	NR	NR
Senturk et al (2013)[79] Level II *Good*	RCT N=223	Healthy women with normal pregnancy who underwent elective or emergency caesarean section	Hospital Turkey	TXA (N=101) vs placebo (N=122) administered prior to incision *All patients received oxytocin after removal of placenta	Thromboembolic events	0[a]	0 [a]	NR	NR
Xu et al (2013)[80] Level II *Fair*	RCT N=174	Primipara women with a singleton pregnancy who underwent a caesarean section	Hospital People's Republic of China	TXA (N=88) vs placebo (N=86) administered prior to incision *After birth, all patients were given oxytocin in normal saline by IV drip over 30 minutes and IV methylergometrine	Deep vein thrombosis	2[a]	2[a]	NR	No significant difference P=0.38
Gungorduk et al (2011)[78] Level II *Good*	RCT N=660	Healthy women undergoing elective caesarean section at more than 38 weeks estimated gestation	Single teaching hospital Turkey	TXA (N = 330) vs placebo (N = 330) administered prior to incision *After birth, all patients received IV bolus of oxytocin, then oxytocin in lactated Ringer's solution and cefazolin diluted in normal saline administered over a 5-minute period	Thromboembolic events (DVT, myocardial infarction, stroke, renal failure, pulmonary embolism)	0[a]	0[a]	NR	NR
Gai et al (2004)[77] Level II *Fair*	RCT N=180	Primipara women with a singleton pregnancy who underwent a caesarean section	Multicentre hospital setting People's Republic of China	TXA (N = 91) vs no TXA (N = 89) administered prior to incision *After birth, all patients received oxytocin (IV drip and into intra-uterine wall)	Thromboembolic events	0[b]	NR	NR	NR
VAGINAL BIRTH									
Gungorduk et	RCT	Women in labour with	Single teaching	TXA (N=220) vs placebo	Thromboembolic events	0[a]	0[a]	NR	NR

Study Level of evidence *Quality*	Study type Sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						TXA N/N (%)	No TXA N/N (%)	Risk estimate [95% CI]	*Statistical significance* P-value
al (2013)[82] Level II *Good*	N=439	gestational age between 34 and 42 weeks and expected vaginal birth[c]	hospital Turkey	(N=219) administered prior to birth *All patients underwent 'active management' of the third stage of labour[b]					
POSTPARTUM HAEMORRHAGE AFTER VAGINAL BIRTH									
Ducloy-Bouthors et al (2011)[81] Level II *Good*	RCT N=151[c]	Women with PPH after vaginal birth (PPH defined as blood loss >800 ml within 2 hours of birth)	5 tertiary care centres and 3 secondary obstetric units France	TXA (N=78) vs no TXA (N=74) *All patients were allowed PRBCs and colloids according to French guidelines[d]	Deep vein thrombosis (ITT)	2/77 (3%)	1/74 (1%)	NR	No significant difference P=0.4
					Deep vein thrombosis (PP)	2/72 (3%)	1/72 (1%)	NR	No significant difference P=0.37
LEVEL III EVIDENCE									
PLACENTA PROBLEMS OR UNSPECIFIED ANTEPARTUM HAEMORRHAGE									
Lindoff et al (1993)[83] Level III–2 *Poor*	Retrospective cohort study N=2102	Women with placental abruption, placenta previa or unspecified antepartum haemorrhage	Two hospitals Sweden	TXA (N=256) vs no TXA (N=1846)	Thromboembolism	2/256 (0.78%)	4/1846 (0.22%)	3.6 [0.7–17.8]	No significant difference P>0.16
				TXA + caesarean section (N=169) vs no TXA + caesarean section (N=443)	Thromboembolism	1/169 (0.59%)	4/443 (0.90%)	0.65 [0.1–5.8]	No significant difference P>0.16
					Pulmonary embolism	1/169 (0.59%)	1/443 (0.23%)	NR	NR
					Deep vein thrombosis	NR	3/443 (0.68%)	NR	NR
					Subgroup analysis of women who gave birth by caesarean section				

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; FFP, fresh frozen plasma; ITT, intention-to-treat; IV, intravenous; NR, not reported; OR, odds ratio; PP, per-protocol; PPH, postpartum haemorrhage; RCT, randomised controlled trial; TXA, tranexamic acid

[a] Denominator was not reported.

[b] 'Active' management included prophylactic injection of oxytocin within 2 minutes of birth, early clamping of the umbilical cord, and controlled cord traction following birth.

[c] Refers to the number of women in the ITT analyses. 144 women were included in the PP analyses out of 152 randomised patients.

[d] The use of additional procoagulant treatment was permitted only in cases involving intractable bleeding. FFP, platelets and fibrinogen concentrate was not permitted before 2hrs after inclusion.

Secondary outcomes

Transfusion-related serious adverse events

There were no studies identified that reported on transfusion-related serious adverse events (TACO, TRALI, haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease, anaphylactic reactions) in maternity patients receiving tranexamic acid. However, as this evidence has not strictly undergone the systematic review process (secondary outcomes were only extracted from studies that reported one or more primary outcomes), this result should be interpreted with caution.

Perinatal mortality

There were no studies identified that reported on perinatal mortality in maternity patients receiving tranexamic acid. However, as this evidence has not strictly undergone the systematic review process (secondary outcomes were only extracted from studies that reported one or more primary outcomes), this result should be interpreted with caution.

4 Appendixes

4.1 Appendix 1 Research question structure

The structures of the foreground research questions developed for this module are presented in **Table 4.1** (generic questions relevant to all modules of the patient blood management guidelines) and **Table 4.2** (questions specific to the obstetric and maternity patient blood management guidelines).

The research questions were all intervention-based and structured according to the PICO criteria. Use of the PICO framework facilitates the systematic review process as it improves conceptual clarity of the clinical problem, allows more complex search strategies, results in more precise search results, and allows evidence to be selected appropriately.

The population element of the framework (subgroups and stratification) is intended to provide the systematic reviewers with logical datasets for presentation and analysis of the available data. The systematic reviewers searched down to the lowest level of evidence to find studies relating to each of the specified subgroups shown in bold (for example, bleeding and non-bleeding patients), but not the minor subgroups (not shown in bold) within those. The systematic review process stopped at the highest level of evidence available to address the primary outcomes and subgroups shown in bold, irrespective of what minor subgroups were covered.

The term ‘maternity’ was chosen to represent the patient population of interest throughout the module and technical reports (instead of ‘obstetric’). This is because ‘maternity’ refers to pregnant women, and women at the time of childbirth and in the recuperative period following birth, whereas ‘obstetrics’ refers to a branch of medicine that deals with the care of women during pregnancy and childbirth. The systematic reviewers referred to the term ‘obstetric’ when developing the research protocol however no distinction was made between the two terms when reviewing the evidence.

Table 4.1 Structure of generic research questions

1. What is the effect of RBC (allogeneic) transfusion on patient outcomes? Intervention vs. Comparator = (1) vs. (1), (2) vs. (2) [Intervention foreground question]				
Population[a]	**Intervention**	**Comparison**	**Outcomes**	**Other SR considerations**
All obstetric and maternity patients (includes pregnant/postpartum up to 6 weeks) Subgroups: Bleeding patients • Postpartum haemorrhage (primary [24 hours] and secondary [up to 6 weeks]) • Antepartum haemorrhage • Placenta problems (previa/abruption/morbidly adherent placenta/ abnormal placentation/ placenta accreta) • Ectopic pregnancy • Miscarriage Non-bleeding patients • Pregnant vs postpartum • Cardiac disease • Anaemia due to ineffective erythropoiesis (haemoglobinopathy, sickle) Stratify by: Anaemia status according to Hb level or anaemic vs non-anaemic Haemorrhage severity (massive/severe/major) or volume of blood loss	1. RBC (allogeneic) transfusion (including dose) 2. Restrictive transfusion (by study definition)	3. No transfusion (or alternative doses) 4. Liberal transfusion (by study definition)	Primary • Maternal [any stage of pregnancy to 6 weeks post] and perinatal [20 weeks gestation to 28 days postpartum] mortality • Functional and performance status [post natal depression, breast feeding rates]b • Measures of fetal outcome (birthweight, gestation, preterm delivery) – *antepartum haemorrhage and anaemia subgroups only* Secondary • Transfusion-related SAEs (TACO, TRALI, other[c]) including infection • Thromboembolic events (stroke, MI, DVT, PE)	• Identify any evidence in Indigenous populations • Limit: studies published after 1985[d] • Restrict to Level III-2 studies (N>100) and higher

2. What is the effect of non-transfusion interventions to increase haemoglobin concentration on morbidity, mortality and need for RBC blood transfusion? [Intervention Foreground Question]				
Population[a]	**Intervention**	**Comparison**	**Outcomes**	**Other SR considerations**
All obstetric and maternity patients (includes pregnant/postpartum [up to 6 weeks]) Subgroups: • Pregnant or postpartum (up to 6 weeks) • Post APH • Post PPH • Placenta problems (previa/abruption/morbidly adherent placenta/ abnormal placentation/ placenta accreta) • Cardiac disease • Anaemia due to ineffective erythropoiesis [haemoglobinopathy, sickle] • Ectopic pregnancy • Miscarriage/termination of pregnancy Stratify by: Anaemia status according to Hb level or anaemic vs non-anaemic	1. ESAs 2. Oral and/or parenteral iron therapy (IV or IM) 3. Combination of these [Nb. Look at all ESA and iron dose regimens]	1. No intervention or any active head-to-head (e.g. 1 vs. 2, 1 vs. 3) 2. No intervention or any active head-to-head (e.g. 1 vs. 2, 2 vs. 3) 3. Different combination of above	Primary • Transfusion dose/volume (in transfused patients only) or transfusion incidence • Laboratory measures: Hb, Hct, ferritin • Thromboembolic events (stroke, MI, DVT, PE) – *ESA intervention only* • Measures of fetal outcome (birthweight, gestation, preterm delivery) • Maternal [any stage of pregnancy to 6 weeks post] and perinatal [20 weeks gestation to 28 days postpartum] mortality (including fetal mortality) Secondary • Functional and performance status [post natal depression, breast feeding rates][b]	• Identify any evidence in Indigenous populations • Include studies that compare modes of administration of iron therapy (i.e. oral vs parenteral) • SR will exclude studies that only compare different doses of ESAs (without placebo or iron arms) • Include studies with non-anaemic patients at baseline (prophylaxis and treatment) • Restrict Level III-2 studies to studies (N>100) and higher • Limit: Iron studies published after 1970[e] • Limit: ESA studies after 1985[f] Notes: • Include all doses of iron (and combinations with ascorbic acid/ folate). EWG to advise how these will be categorised (eg therapeutic/ preventative)

3. What is the effect of FFP, cryoprecipitate, fibrinogen concentrate, and/or platelet transfusion on patient outcomes? *Intervention vs. Comparator = (1) vs. (1), (2) vs. (2), etc* [Intervention foreground question]				
Population[a]	**Intervention**	**Comparison**	**Outcomes**	**Other SR considerations**
All obstetric and maternity patients (includes pregnant/postpartum [up to 6 weeks]) Subgroups: Bleeding patients • Postpartum haemorrhage (primary [24 hours] and secondary [up to 6 weeks]) • Antepartum haemorrhage • Placenta problems (previa/abruption/morbidly adherent placenta/ abnormal placentation/ placenta accreta) • Ectopic pregnancy • Miscarriage • Coagulopathy (DIC, AFE) Non-bleeding patients who are at risk of bleeding • Coagulopathy (liver disease, amniotic fluid embolism) and thrombocytopenia • TTP <u>Stratify by</u>: Volume of blood loss major/severe	1. FFP 2. Cryoprecipitate 3. Platelet transfusion 4. Fibrinogen concentrate 5. Combination or fixed ratio	1. No FFP or FFP using a different FFP transfusion protocol 2. No cryoprecipitate or cryoprecipitate using a different cryoprecipitate transfusion protocol 3. No platelet transfusion or platelet transfusion using a different platelet transfusion protocol 4. No fibrinogen concentrate or fibrinogen using a different fibrinogen transfusion protocol 5. Different combination/ratio	<u>Primary</u> • Maternal mortality [any stage of pregnancy to 6 weeks post] • Transfusion volume (in transfused patients only) or transfusion incidence [by product type] • Transfusion-related SAEs (TACO, TRALI, other[c]) • Additional interventions to control bleeding (only: hysterectomy, compression sutures, uterine packing [forms of], uterine artery ligation, radiological embolisation) -*bleeding patients only* <u>Secondary</u> • Laboratory measures: INR (PT/APTT), platelet count and fibrinogen level • Functional and performance status [post natal depression, breast feeding rates][b]	• Identify any evidence in Indigenous populations • <u>Limit:</u> studies published after 1985[d] • Restrict to Level III-2 studies and higher • May apply study size limits after examining the body of evidence • Details for population stratification will be further defined after studies have been reviewed. Notes: TTP population could refer to other module

Abbreviations: 15D, 15 dimension; ADL, Activities of Daily Living; AFE, amniotic fluid embolism; APH, antepartum haemorrhage; APTT, activated partial thromboplastin time; AQoL, Assessment of Quality of Life; DASI, Duke Activity Status Index; DIC, disseminated intravascular coagulation; DVT, deep vein thrombosis; EPDS, Edinburgh Postnatal Depression Scale; EQ-5D, EuroQol 5 dimension; ESA, erythropoiesis- stimulating agent; FFP, fresh frozen plasma; Hb, haemoglobin; HIV, human immunodeficiency virus; HUI, Health Utilities Index; IADL, Instrumental Activities of Daily Living; IM, intramuscular; INR, international normalised ratio; IV, intravenous; MI, myocardial infarction; MQoL, McGill Quality of Life Questionnaire; NHP, Nottingham Health Profile; PE, pulmonary embolism; PPH, postpartum haemorrhage; PT, prothrombin time; QWB, Quality of Well-Being; RBC, red blood cell; SAE, serious adverse event; SF-12, 12-item Short Form Health Survey; SF-36, 36-item Short Form Health Survey; TACO, transfusion associated circulatory overload; TRALI, transfusion-related acute lung injury; TTP, thrombotic thrombocytopaenic purpura; vs, versus

a The systematic reviewers will search down to the lowest level of evidence to find studies relating to each of the specified subgroups shown in **bold**, but not the minor subgroups (not shown in bold) within those.
b Only common, validated functional and performance status instruments will be included (e.g. EPDS, AQoL, Barthel ADL, 15D, DASI, EQ-5D, HUI2, HUI3, IADL, MQoL, NHP, QWB, RAND-36, SF-12, SF-36).
c Other includes haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease, anaphylactic reactions.
d Studies published prior to 1985 will be excluded (except primary studies if they are included as part of a systematic review published after this date). Around this date, the approach to transfusion therapy changed because of recognition of the risks of HIV and hepatitis. Papers published prior to that time are more likely to be of historical interest rather than to be useful as a basis for current practice.
e Studies related to iron published prior to 1970 will be excluded (except primary studies if they are included as part of a systematic review published after this date). The rationale provided by the CRG was that parenteral iron therapy was used more extensively in the 1970s and there may be some useful evidence in early literature.
f Studies related to the use of ESA will be excluded if they were published prior to 1985 (except primary studies if they are included as part of a systematic review published after this date), the time after which they became available.

Table 4.2 Structure of the research question specific to obstetric and maternity patient blood management

4. What is the effect of non-obstetric strategies that aim to minimise maternal blood loss in the peripartum period on transfusion and clinical outcomes? [Intervention Foreground Question]				
Population[a]	**Intervention**	**Comparison**	**Outcomes**	**Other SR considerations**
All obstetric and maternity patients (includes pregnant/postpartum [up to 6 weeks]) Subgroups: Bleeding patients • Postpartum haemorrhage (primary [24 hours] and secondary [up to 6 weeks]) • Antepartum haemorrhage • Placenta problems (previa/abruption/ morbidly adherent placenta/ abnormal placentation/ placenta accreta) • Ectopic pregnancy • Miscarriage Stratify by: • Anaemia status according to Hb level or anaemic vs non-anaemic • Haemorrhage severity (massive/severe/major) or volume of blood loss	1. POC testing (TEG and ROTEM) 2. Antifibrinolytic therapy (TXA only) 3. Intraoperative cell salvage 4. Recombinant activated factor VII 5. Interventional radiology (iliac balloon catheters or embolisation only)	1. No POC testing 2. No TXA 3. No intraoperative cell salvage 4. No recombinant activated factor VII 5. No iliac balloon catheters or embolisation	Primary • Transfusion dose/volume (in transfused patient only) or transfusion incidence (include all product types) • Maternal mortality [any stage of pregnancy to 6 weeks post] • Additional interventions to control bleeding (only: hysterectomy, compression sutures, uterine packing [forms of], uterine artery ligation, radiological embolisation) if not already used • Thromboembolic events (stroke, MI, DVT, PE) Secondary • Transfusion-related SAEs (TACO, TRALI, other[b]) • Perinatal mortality (including fetal mortality)	• Identify any evidence in Indigenous populations • Limit: studies published after 1985[c] • Restrict to Level III-2 studies and higher • May apply study size limits after examining the body of evidence

DVT, deep vein thrombosis; Hb, haemoglobin; MI, myocardial infarction; PE, pulmonary embolism; POC, point of care; SAE, serious adverse event; TACO, transfusion associated circulatory overload; TRALI, transfusion-related acute lung injury; TXA, tranexamic acid; vs, versus

a The systematic reviewers will search down to the lowest level of evidence to find studies relating to the specified subgroup shown in bold, but not the minor subgroups (not shown in bold) within this
b Other includes haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease, anaphylactic reactions
c Studies published prior to 1985 will be excluded (except primary studies if they are included as part of a systematic review published after this date). The choice of this date relates to the context of care

4.2 Appendix 2 Quality assessment

Each included study was assessed using the quality criteria for the relevant study type, as shown below. Studies were considered:

- good quality, with a low risk of bias, if they met all, or all but one, of the criteria
- fair quality, with a moderate risk of bias, if they did not meet two or three criteria
- poor quality, with a high risk of bias, if they did not meet four or more criteria

4.2.1 Systematic reviews

Study type:				Systematic review	
Citation:					
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[b]:					
Quality rating: [Good/Fair/Poor]				Systematic review:	
				Included studies:	

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. For quality assessment of systematic reviews, this should include a statement regarding the methodological quality of the studies included in the systematic review.

4.2.2 Randomised controlled trials

Study type:				Randomised controlled trial	
Citation:					
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[b]:					
Quality rating: [Good/Fair/Poor]					

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.

4.2.3 Cohort studies/ Concurrent control

Study type:				Cohort study	
Citation:					
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[b]:					
Quality rating: [Good/Fair/Poor]					

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.

4.2.4 Case-control studies

Study type:				Case-control study	
Citation:					
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]:					
Quality rating: [Good/Fair/Poor]					

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.

4.3 Appendix 3 Modified NHMRC evidence statement form

4.3.1 Evidence statement form

Key question(s):		Evidence table ref:
1. Evidence base (*number of studies, level of evidence and risk of bias in the included studies)*		
	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')*		
	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	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?)*		
	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 health-care context in terms of health services/delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care 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		
2. Consistency		
3. Clinical impact		
4. Generalisability		
5. Applicability		

EVIDENCE STATEMENT

Indicate any dissenting opinions

4.3.2 Recommendation form

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	RELEVANT ESF(S)
Indicate any dissenting opinions		
UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*		
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

4.4 Appendix 4 Consensus process for development of practice points

4.4.1 Background

Often, there are insufficient high-quality data in the contemporary clinical literature to produce clinical guidelines with an evidence-based recommendation. Thus, there remains a role for expert opinion and consensus in guidelines development. The use of expert opinion as a form of 'evidence' requires a formal consensus development process among the guidelines developers, with rigorous rules that will lead to the same attributes of validity, reliability and applicability demanded for more rigorous evidence-based practice methodology.

4.4.2 Role of the clinical/consumer reference group

The CRG provided expert opinion for the development of practice points relevant to the recommendation being considered under the consensus process.

The consensus process was followed only for recommendations where:

- the systematic review has found no Level I to III-2 evidence to address the relevant clinical question, or where recommendations developed by the systematic review process were ranked with a Grade D (poor) quality evidence base
- the CRG determines that additional clinical practice guidance is required for recommendations developed by the systematic review process that are graded above D
- the development of 'expert opinion' is required (e.g. for the background research questions)

Applying the consensus process to recommendations with Grade D (poor) evidence could result in:

- the rejection of the recommendation
- the confirmation of the recommendation
- the development of a 'practice point' to supplement the recommendation, or
- rejection of the recommendation and the development of a practice point on its own.

4.4.3 Chair of CRG meetings

The Chair of CRG meetings facilitated and guided the process of reaching a consensus decision on practice points. Specifically, the Chair's role was to:

- assist the CRG to define decisions that need to be made
- help the CRG through the stages of reaching an agreement
- keep the meeting moving
- focus discussion to the point at hand
- ensure that everyone has the opportunity to participate
- test whether consensus has been reached

The Chair helped to direct the consensus process, not its content, and did not make decisions for the CRG.

4.4.4 Development of practice points: overview of consensus decision-making process

The following process was used to develop practice points through consensus.

Stage 1 – Introduction

- **Describe the process.** The Chair described the consensus process, participants' roles and responsibilities, ground rules and guiding principles.
- **State where there is a need for practice point development.** The Chair described where evidence was not found or was considered inadequate to develop recommendations above Grade D, or where a practice point may be required to supplement recommendations.

Stage 2 – Open discussion

- **Clarify the practice point.** The Chair opened the floor to a general discussion and suggestions for practice point content. This time will not be used for raising objections or concerns, but to suggest content for the practice point. Suggestions were recorded in the relevant section of the draft results report.
- **State concerns.** When the CRG was satisfied that the practice point is complete, the Chair provided an opportunity for concerns or issues to be raised.

Stage 3 – Resolve concerns

- **Review concerns.** The group reviewed any concerns raised. If the concerns were many and the time was short, the discussion on practice point development was carried over to a later meeting.
- **Resolve concerns.** The Chair had the first option to resolve the listed concerns by:
    - clarifying the wording of the practice point
    - changing the wording of the practice point or adding a practice point to supplement the recommendation
    - explaining why the recommendation as stated is not in conflict with the CRG's values
    - seeing whether those with concerns will stand aside (i.e. "had concerns, but could live with them").

Stage 4 – First call for consensus

- When all concerns had been resolved, the Chair called for consensus.

Stage 5 – Consideration of CRG principles and values and second call for consensus

- When concerns had been adequately discussed but remained unresolved, the CRG assessed how the unresolved concerns related to CRG principles and values.
- After considering these principles, the Chair made one of the following conclusions:
    - the member withdrew the concern, consensus was reached and a practice point could be made (or a Grade D evidence-based recommendation confirmed)
    - the member stood aside so that a practice point could be made (or Grade D evidence-based recommendation confirmed), and the differing schools of thought were documented
    - the member was not willing to withdraw the concern or stand aside and the CRG declared itself blocked – the recommendation or practice point was not accepted.

4.4.5 Guiding principles and values

These principles and values were used throughout the development of consensus-based practice points:

- Consensus is reached where all members of the CRG strongly agree, or agree with the practice point. Consensus is not achieved on the basis of a 'majority'.
- The opinions of all members of the CRG are equally valid/important, notwithstanding that some members may have discipline-specific expert opinion.
- Where consensus is not reached (one or more members disagree or strongly disagree with the practice point), the dissenting members are allowed to present their case. This may be done immediately in the current meeting, or be carried over to the subsequent meeting to allow the members to succinctly formulate their concerns or provide other documentation/research.
- Issues of semantics, language or content, while recognised as important, should preferably not absorb discussion time within the CRG meetings.
- CRG members are respectfully asked to reflect upon their own values and conflicts of interests, and be mindful of the extent to which these may influence their opinions.

4.4.6 Ground rules

- Members agree to take turns speaking and not interrupt each other.
- Members agree to call each other by their first names, not 'he' or 'she'.
- Members agree to not blame, attack, or engage in put-downs and will ask questions of each other for the purposes of gaining clarity and understanding.
- Members agree to stay away from establishing hard positions and express themselves in terms of personal needs and interests and the outcomes that they wish to realise.
- Members agree to listen respectfully and sincerely try to understand the other person's needs and interests.
- Members recognise that, even when they do not agree, each of them is entitled to their own perspective.
- Members will not dwell on things that did not work in the past, but instead will focus on the future they would like to create.
- Members agree to make a conscious, sincere effort to refrain from unproductive arguing, venting, or narration, and agree to use their time during the meeting to work towards what they perceive to be their fairest and most constructive agreement possible.
- Members will speak up when something is not working for them during the consensus process.
- Members will request a break when they need to.
- Members will point out when they feel the Chair is not being impartial as to person and neutral as to result.
- CRG members not present at the meeting have the opportunity to provide feedback via an agreed electronic format (e.g. GovDex or email) when developed practice points are circulated to the entire CRG after the meeting.

5 References

1 National Health and Medical Research Council (NHMRC) and Australasian Society of Blood Transfusion (ASBT) (2001). *Clinical practice guidelines on the use of blood components*, NHMRC, Canberra, Australia. http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/cp78.pdf

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