UK National Screening Committee

Screening for Iron Deficiency Anaemia in Pregnancy

External review against programme appraisal criteria for the UK National Screening Committee

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Plain English summary

Iron deficiency anaemia (IDA) is the most common cause of anaemia in pregnancy and is caused by a lack of iron, which results in a reduced number of red blood cells. Anaemia is common among women during pregnancy; 20% of pregnant women have anaemia in the UK. Prior to this review, limited evidence suggested that pregnant women with anaemia are more likely to have a baby with low birth weight, give birth too early or need a blood transfusion. Anaemia can be treated with iron supplements.

Anaemia can be diagnosed by a blood test, where haemoglobin levels are checked. Anaemia can be mild, moderate or severe, depending on the haemoglobin level. Screening for mild and moderate anaemia is thought to be beneficial because many women do not notice any signs of anaemia.

In the UK, all pregnant women are tested for anaemia at their first booking visit and at 28 weeks of pregnancy. Pregnant women who are at an increased risk of anaemia may be tested more frequently.

At present, because of the current clinical practice, there is no national screening programme for anaemia in pregnancy in the UK. However, anaemia may be a suitable condition for a screening programme. Therefore, the purpose of this review is to determine whether there is enough evidence to support the introduction of a national screening programme.

This review aimed to find evidence on:

- how untreated iron deficiency with or without mild or moderate anaemia affects maternal and infant health;
- what benefits and harms are associated with treating IDA in pregnancy, compared with no treatment;
- what benefits and harms are associated with screening for IDA in pregnancy, compared with no screening.

There was not enough evidence to make a recommendation on a national screening programme for IDA in pregnancy. This is because:

- there was some evidence to suggest that women with anaemia during pregnancy may experience some problems, but this evidence is not of a very high quality;
- there was very little evidence on the protective effects of treatment for the mother and her baby;
- it is not clear what the benefits and harms associated with screening for IDA are, because no relevant evidence was identified.

Executive summary

Purpose of the review

This review was conducted to assess whether there is sufficient evidence to consider introducing a national screening programme for iron deficiency anaemia (IDA) in pregnancy.

Background

Anaemia is a condition that occurs when the number of red blood cells, or the concentration of haemoglobin within red blood cells, is reduced. Iron deficiency (ID) is defined as the decrease of the total content of iron in the body, and if this is sufficiently severe to reduce the production of red blood cells, it can cause IDA. IDA is the most common cause of anaemia in pregnancy; it is thought that iron deficiency (ID) underlies 90% of anaemia in the UK, and 24.4% of pregnant women are estimated to be anaemic at some stage during the antenatal period.[1] In the UK, anaemia in pregnancy is defined as haemoglobin <110 g/L in the first trimester, and haemoglobin <105 g/L in the second and third trimesters.[2] However, these thresholds are not based on substantial evidence and there is variation in what is considered to be normal during pregnancy.

Mild or moderate IDA in pregnancy can be asymptomatic; in order to offer iron supplementation, haemoglobin levels are therefore tested during pregnancy in the UK. The National Institute for Health and Care Excellence (NICE) guidance states that pregnant women should be offered testing for anaemia early in pregnancy (for example, during a booking appointment) and at 28 weeks' gestation, when other phlebotomy assessments are performed.[3] In 2006, the UK National Screening Committee (NSC) noted that clinical guidance had been published by NICE, but recommended that a nationally organised screening programme should not be implemented.

Testing for anaemia is long established in clinical practice and is widely recommended. In line with the NICE guidance, the British Society for Haematology (BSH) recommends that haemoglobin concentration should be routinely measured at booking and 28 weeks' gestation;[2] similarly, the Canadian Agency for Drugs and Technologies in Health (CADTH) recommends routine haemoglobin measurements during each trimester of pregnancy.[4] However, there is a notable lack of evidence for the benefits and harms of screening; in 2015 the United States Preventative Services Taskforce (USPSTF) deemed that the evidence base was insufficient to make a recommendation about screening for IDA.[5]

The aim of this review is to provide an evaluation of the volume and direction of the literature on this topic, with the intention of assessing whether the UK NSC's position regarding a national screening programme for IDA in pregnancy should be reconsidered.

Focus of the review

This review aimed to identify studies to provide evidence on screening and interventions for mild and moderate IDA in pregnancy. The review focuses on mild and moderate IDA because this population reflects the majority of the population that is likely to be detected in a national screening programme. Specifically, new evidence was collected to answer the following 3 questions:

1. what are the maternal and infant outcomes associated with untreated ID, with or without mild or moderate anaemia in pregnancy?
2. what are the benefits and harms of treating pregnant women for IDA, to pregnant women and their infants, compared with no treatment?
3. what are the benefits and harms of screening for IDA during pregnancy, compared with no screening?

Recommendation under review

In 2006, the UK NSC did not recommend a national screening programme, but noted that NICE had issued guidance in this area.

Findings and gaps in the evidence of this review

Within the scope of this review, 22 studies were included. Summaries of the question level results are presented below.

Question 1 – What are the maternal and infant outcomes associated with untreated ID, with or without mild or moderate anaemia in pregnancy?

IDA in pregnancy is normally treated with iron treatment and/or supplementation. This review did not identify any studies that explicitly included a cohort of women untreated with iron supplements or a prescription iron treatment. Therefore, the eligibility criteria were broadened to include studies in which iron treatment and/or supplementation in the study populations was unclear. A total of 18 studies (1 systematic literature review [SLR]; 2 prospective observational studies; 15 retrospective observational studies) of relevance to Question 1 were identified. Eight studies were judged to be at moderate risk of bias and were the primary source of data for this question; 3 were judged to be at serious risk of bias, primarily because they did not include key covariates in their analyses, and 7 were judged to be at critical risk of bias, primarily because they relied on univariate analyses.

Studies reported on 11 outcomes: depression, maternal transfusion, postpartum haemorrhage (PPH), caesarean section, infection during pregnancy, low birth weight, small for gestational age (SGA) birth, preterm birth, very preterm birth, neonatal intensive care unit (NICU) admission and perinatal mortality. A summary of the studies per outcome, and the direction and magnitude of any associations is presented in Table 1.

Table 1. Summary of the association between ID, with and without anaemia, during pregnancy and maternal and infant outcomes

	Exposure[a]	Number of studies[b]	Direction of association[c]	Strength of association (if relevant)[d]	Number of higher quality studies reporting an association[e]	Overall strength of evidence[f]
Maternal outcomes						
Depression	Anaemia	Retrospective: 1	Positive	Weak: 1	0	Poor
Transfusion	Anaemia	Retrospective: 5	Positive	Moderate: 1 Strong: 4	3	Moderate
PPH	Anaemia	Retrospective: 4	Inconsistent	NA	NA	Poor
	IDA	Retrospective: 1	No association	NA	0	Poor
	ID	Retrospective: 1 Prospective: 1	Inconsistent	NA	NA	Poor
Caesarean section	Anaemia	Retrospective: 2 Prospective: 1	Positive	Weak: 2 Moderate: 1	1	Poor
Infection during pregnancy	Anaemia	Prospective: 1	Positive	Weak: 1	0	Poor
Infant outcomes						
Low birth weight	Anaemia	Retrospective: 1 Prospective: 1 SLR: 1	Inconsistent	NA	NA	Poor
	IDA	Retrospective: 1	No association	NA	0	Poor
	ID	Prospective: 1	No association	NA	0	Poor
SGA at birth	Anaemia	Retrospective: 3 Prospective: 3	Inconsistent	NA	NA	Poor
	ID	Prospective: 1	No association	NA	0	Poor
Preterm birth	Anaemia	Retrospective: 3 Prospective: 2 SLR: 1	Inconsistent	NA	NA	Poor
	IDA	Retrospective: 1	Inconsistent	NA	NA	Poor
	ID	Retrospective: 2 Prospective: 1	No association	NA	0	Poor
Very preterm birth	Anaemia	Retrospective: 4	Positive	Weak: 2 Strong: 1 Exposure dependent: 1	3	Moderate
NICU admission	Anaemia	Retrospective: 1	Positive	Weak: 1	1	Poor
	ID	Prospective: 2	No association	NA	0	Poor
Perinatal mortality	Anaemia	Retrospective: 3	Varied by exposure (mild: negative association; moderate-to-severe: positive association)	NA	NA	Poor
	ID	Prospective:1	No association	NA	0	Poor

[a]Anaemia is a condition that occurs when the number of red blood cells, or the concentration of haemoglobin within red blood cells, is reduced. Iron deficiency (ID) is defined as the decrease of the total content of iron in the body, and if this is sufficiently severe to reduce the production of red blood cells, it can cause IDA. [b]Includes Haider 2013 SLR and meta-analysis, which provided evidence on preterm birth and low birth weight in studies of anaemia with unknown aetiology. [c]A positive association indicates that anaemia with/without ID is associated with an increase in a particular outcome; a negative association indicates that anaemia with/without ID is associated with a decrease in a particular outcome. [d]Strength of association took into consideration statistical significance and the size of OR/RR (weak: significant OR/RR = 1.0–<1.5 or non-significant OR/RR or descriptive statistics; moderate: significant OR/RR = ≥1.5–2.0; strong: significant OR/RR = ≥2.0. [e]Studies judged to be at moderate or low risk of bias and reporting statistically significant results from multivariate analyses. Outcomes with an inconsistent direction of association were marked 'NA' for this field. [f]The judgement on the overall strength of evidence takes into account the quality and quantity

of studies contributing to the evidence base for each outcome, including the quantity of studies providing evidence on the same exposure, and study characteristics (for example, study population size). This judgement is distinct to the strength of association, which takes into account the size of effect and statistical significance.
Abbreviations: NA: not applicable; NICU: neonatal intensive care unit; PPH: postpartum haemorrhage; SGA: small for gestational age.

This review identified moderate evidence to support an association between maternal anaemia of unspecified aetiology and increases in maternal transfusion and very preterm birth. Maternal anaemia and/or ID were also associated with an increase in depression, caesarean section, NICU admission and perinatal mortality; however, there were only a limited number of higher quality studies reporting an association for these outcomes, introducing uncertainty. Furthermore, for depression, there was additional uncertainty regarding the causality of the observed relationship. Inconsistent and typically poor-quality evidence was identified for PPH, low birth weight, SGA at birth and preterm birth. The strength of evidence for outcomes other than maternal transfusion and very preterm birth was therefore judged to be 'poor' overall.

Studies also commonly omitted important methodological information for establishing an association between untreated ID, with or without mild/moderate anaemia, and maternal and infant outcomes. Critically, no study reported on iron usage in women, therefore it was not possible to determine whether some women had been screened and subsequently prescribed iron, which may have impacted the observed results by modifying the ID (and anaemia), or whether any routine supplementation or dietary changes that occurred in the study were balanced between study cohorts or aligned to that of the UK. Moreover, there were concerns relating to the applicability of data to the population of women with mild and moderate anaemia, as it was not possible to confirm the severity of anaemia in the majority of study cohorts because studies did not reliably report haemoglobin levels of the study population.

Overall, this evidence summary therefore finds it difficult to draw robust conclusions about the relationship between ID, with or without anaemia, and adverse maternal and infant outcomes.

Question 2 – What are the benefits and harms of treating pregnant women for IDA to pregnant women and their infants?

Two low-quality, observational studies were identified to be of relevance to Question 2, investigating ferric carboxymaltose (FCM)[6] and undefined iron use,[7] compared with no treatment, in pregnant women. A SLR performed by the USPSTF and a structured review were also included within the evidence base for this review question, but neither included studies of relevance to the scope of this rapid review.

Overall, the amount and quality of evidence informing the evidence base for Question 2 precludes the formation of strong conclusions. Whilst there is some weak evidence to suggest a role of FCM treatment for IDA in preventing RBC transfusion, primary and secondary caesarean section and very preterm birth, this was observed in a single study judged to be at a critical risk of bias. Further poor-quality data implies that there is no difference in NICU admission between pregnant women treated with and without FCM, and that iron use is a risk factor for preterm birth. It is not possible to make

conclusions regarding the relationship between anaemia and very preterm birth due to the low quality of evidence.

In addition to the limitations related to study quality (both studies were judged to be at serious risk of bias), results from these observational studies were not validated by additional, independent studies of the same treatments. There were also concerns about differences in exposure (severity of anaemia at baseline and dose of iron received) between treated and untreated groups in both studies, and it is therefore unclear whether the observed differences in outcomes between treated and untreated women is attributable to treatment. Higher quality evidence would therefore be required to draw any robust conclusions on the benefits and harms of treating pregnant women for IDA.

Table 2. Summary of the association between treatment for IDA during pregnancy and maternal and infant outcomes

	Number of studies	Association (if any)	Number of higher quality studies[a]	Overall strength of evidence[b]
Maternal outcomes				
Transfusion	Retrospective: 1	Frequency of transfusion was greater in women who did not receive FCM during pregnancy (non-significant)	0	Poor
Caesarean section	Retrospective: 1	Frequency of primary and secondary caesarean section was greater in women who did not receive FCM during pregnancy	0	Poor
Infant outcomes				
Preterm birth	Retrospective: 1	Iron use was greater in individuals with term birth than preterm birth	0	Poor
Very preterm birth	Retrospective: 1	Frequency of very preterm birth was marginally greater in women who did not receive FCM during pregnancy	0	Poor
NICU admission	Retrospective: 1	Frequency of NICU admission was similar between women who did and did not receive FCM during pregnancy	0	Poor

[a]Studies judged to be at moderate or low risk of bias.
[b]The judgement on the overall strength of evidence takes into account the quality and quantity of studies contributing to the evidence base for each outcome, including the quantity of studies providing evidence on the same exposure, and study characteristics (for example, study population size). This judgement is distinct to the strength of association, which takes into account the size of effect and statistical significance.
Abbreviations: FCM: ferric carboxymaltose NICU: neonatal intensive care unit.

Question 3 – What are the benefits and harms of screening for IDA during pregnancy?

This rapid review identified 2 literature reviews (1 structured review and gap analysis and 1 SLR) that were relevant to Question 3. Neither review identified any studies that reported on the benefits and/or harms of screening versus no screening for IDA. As such, it is not possible to assess the benefits and harms of screening (Criterion 11 and 13 of the UK NSC criteria) for IDA in pregnancy.

Recommendations on screening

The UK NSC recognise that testing for IDA is a long established clinical practice in antenatal care in the UK, and that it is recommended in national guidance produced by NICE and the BSH.[2, 3]

Based on the overall synthesis of evidence against the UK NSC criteria, this rapid review did not identify new evidence to change the UK NSC's position that a national screening programme should not be recommended in the UK:

- no evidence was identified which reported on the potential harms of IDA in women who had not received treatment (either prescribed treatment or iron supplementation), however weak evidence from studies where it was unclear if women received iron treatment and/or supplementation suggested that there may be a clinical need to identify women with mild or moderate IDA, although the severity of this problem is unclear;
- the absence of studies that explored the benefits and harms of screening prevents an understanding of the number of women with asymptomatic IDA who would not otherwise be identified and the clinical implications of this; whether a national screening programme would provide greater benefits or result in further harms than the screening already undertaken in clinical practice is also unclear;
- the poor quality of the available evidence on the benefits and harms of treatment prevents robust conclusions being made.

Limitations

Methodological limitations included limiting the searches to only including peer-reviewed, English-language journal articles published since 2012 (Question 1) or 2014 (Questions 2 and 3). The titles, abstracts and full texts were screened by 1 reviewer, with a second reviewer verifying all included, 10% of excluded decisions and any articles where there was uncertainty about their inclusion.

Evidence uncertainties

The uncertainties of the evidence identified in this review primarily relate to the following factors:

- **iron supplementation and treatment**: for Question 1, no identified studies explicitly stated that they enrolled a cohort of women untreated with iron supplements or a prescription iron treatment, and the included studies did not report on treatment following testing as part of clinical practice, dietary changes, or the use of iron supplements by women. From the included evidence base, it is therefore not possible to determine the potential harms of IDA in untreated women, undermining the conclusions that can be drawn from the included studies; this is due to the potential impact of treatment, dietary changes and/or supplementation on observed maternal and neonatal outcomes through modification of the underlying ID and anaemia. Based on clinical

guidelines, it is likely that there is widespread testing and subsequent treatment in high income countries, meaning that the potential proportion of women treated and the associated impact of this on the evidence is high. Furthermore, it was also not possible to determine whether iron supplementation or treatment practices in the included studies were applicable to the UK or were balanced between study cohorts.

- **the aetiology of maternal anaemia**: although ID is thought to cause the majority of cases of anaemia during pregnancy,[8] the cause of the condition was not reported in the majority of studies, introducing uncertainties around the applicability of results to ID and IDA. The underlying aetiology of anaemia may impact upon the observed maternal and infant outcomes, and response following iron supplementation is dependent on whether other factors contribute to anaemia.[2]
- **the role of existing screening programmes**: screening for anaemia during pregnancy as part of clinical practice is commonplace in many of the countries this review sourced evidence from, adding further uncertainty.
- **the severity of maternal anaemia**: this was not reported by the majority of studies, although where reported, populations did consist primarily of women with mild and moderate anaemia. Furthermore, in studies identified for Question 2, it was unclear whether women who did and did not receive treatment had experienced similar exposures to anaemia. Severity of anaemia may influence the resulting severity or frequency of maternal and infant outcomes observed following iron treatment; as such, should testing for and subsequent treatment of IDA using UK thresholds be continued, the benefits and harms of treatment may differ to those observed in the studies providing evidence for Question 2.
- **the effect of gravidity on anaemia-related outcomes**: this review did not consider the effect of gravidity (the number of times a woman has been pregnant) on anaemia-related outcomes.
- **benefits and harms of treating for IDA during pregnancy**: only very poor evidence was identified to determine the association between treating for IDA during pregnancy and maternal and neonatal outcomes. It is therefore not possible to form any conclusions regarding the benefits and harms of treating IDA during pregnancy.
- **benefits and harms of screening for IDA during pregnancy**: no evidence was identified to determine the benefits and harms of screening for IDA during pregnancy, compared with no screening. As such, the benefits and harms of screening for IDA in pregnancy remain unclear.

To address the evidence uncertainties of this review, and in order to make a recommendation for a national screening programme for IDA in pregnancy, additional high-quality prospective studies and randomised trials of screening (for Question 3) are required. For Question 1, given the widespread screening for anaemia and subsequent treatment in pregnant women in high income countries, it would be unethical to conduct a study in which anaemic women are identified but not treated as per their local or national clinical guidelines; therefore, approaches for future studies could include investigating the impact of systematic screening versus current clinical practice on outcomes in pregnant women, such as one currently being conducted by Hull & East Yorkshire Hospitals NHS Trust.[9] Alternatively, the review inclusion criteria could be expanded to include studies in countries

where treatment and/or supplementation is less prevalent; however, this approach would be associated with a limited applicability to the UK setting and a high potential for confounding from a variety of factors (such as nutritional status of women, other underlying health conditions or infections, and ethnicity). Finally, data from a detailed analysis of oral iron supplementation may provide additional information with which to answer the review question; in the UK, the Primary prevention of maternal ANaemia to avoid preterm Delivery and other Adverse outcomes (PANDA) research programme is ongoing (due to complete in 2025) and may provide some evidence to answer some of the uncertainties.

Expert advice

This review was conducted with expert advice from:

Professor Marian Knight; Professor of Maternal and Child Population Health, National Perinatal Epidemiology Unit (NPEU), Nuffield Department of Population Health, University of Oxford.

Introduction and approach

Introduction

Iron deficiency (ID) is defined as the decrease of the total content of iron in the body. Iron deficiency anaemia (IDA) occurs when ID is sufficiently severe to reduce erythropoiesis. IDA is the most common cause of anaemia in pregnancy, accounting for 90% of cases of anaemia in the UK; in 2011, a multicentre UK-based study estimated that 24.4% of women were anaemic at some stage during the antenatal period.[1] Whilst IDA is the most frequent cause of anaemia in pregnancy, anaemia may also be caused by folate or vitamin B12 deficiency, autoimmune conditions, inherited disorders (thalassemia, sickle cell disease), and chronic infection; the underlying physiological mechanisms contributing to these different causes of anaemia may modify the women's presentation, as well as the potential response to treatment, and it is therefore important to understand the aetiology of disease when considering the outcomes associated with the disease and treatment.

IDA in pregnancy occurs due to the increased requirement for blood production to support the growing fetus, which is associated with a modest decrease in haemoglobin levels, a 2 to 3-fold increase in iron requirement and a 10 to 20-fold increase in folate requirement.[1] In pregnancy, iron depletion is primarily influenced by 2 factors:

- maternal iron levels at conception;
- iron absorption during gestation.

As such, risk factors for IDA in pregnancy include an iron-deficient diet, which may be associated with loss of appetite and vomiting caused by morning sickness or malnutrition, gastrointestinal issues affecting absorption, a short inter-pregnancy interval and pre-existing anaemia at conception.

Anaemia is most commonly diagnosed through evaluation of haemoglobin levels, and ID is determined based on assessment of serum ferritin.[2] In the UK, anaemia in pregnancy is defined in accordance with the definition provided by the British Society for Haematology (BSH) as haemoglobin <110 g/L in the first trimester, and <105 g/L in the second and third trimesters;[2] this is aligned with the thresholds used by the World Health Organization (WHO)[10] and Centers for Disease Control and Prevention (CDC).[11] ID is defined by the BSH as serum ferritin <30 µg/L.[2]

Although IDA in pregnancy can be symptomatic, symptoms are typically non-specific unless the anaemia is severe, and IDA can be asymptomatic when mild or moderate; symptoms include fatigue, shortness of breath, heart palpitations and pallor.[2] The thresholds to define the severity of anaemia according to the World Health Organization (WHO) are presented in Table 3; however, different classification thresholds can be used, some of which vary by trimester of pregnancy, introducing heterogeneity in the classification of anaemia between studies, or may not be relevant to the UK

population. Furthermore, haemoglobin level is a continuous variable, and as such, the classification of anaemia into different categories on this basis is often considered arbitrary.

Table 3. WHO thresholds used to define the severity of anaemia in pregnancy

Severity of anaemia	Haemoglobin (g/L)
Mild	100–109
Moderate	70–99
Severe	<70

Abbreviations: WHO: World Health Organization.

Guidelines on screening for anaemia in pregnancy

In the UK, haemoglobin levels are routinely tested during pregnancy, to identify asymptomatic anaemia so that iron supplementation can be offered. National Institute for Health and Care Excellence (NICE) guidance states that pregnant women should be offered testing for anaemia early in pregnancy (for example, during a booking appointment) and at 28 weeks' gestation, when other phlebotomy assessments are performed.[3] A summary of this guidance and other national and international guidelines on screening for anaemia in pregnancy are provided in

Table 4.

All guidelines note limited and weak evidence to support the benefits and harms of screening for IDA in pregnancy. However, the response of different organisations to this evidence varies. The Canadian Agency for Drugs and Technologies in Health (CADTH) recommended routine haemoglobin measurements at each trimester of pregnancy, whereas the United States Preventative Services Task Force (USPFTF) concluded that there was insufficient evidence to make a recommendation.[4, 5] In the UK, the BSH recommendation for screening was based on long-established clinical practice and the NICE guidance, rather than new evidence acquired following the NICE 2008 recommendation.[2, 3]

In 2006, the UK NSC noted that clinical guidance had been published by NICE covering screening for anaemia in pregnancy but recommended that a formal national screening programme should not be implemented.

Table 4. National and international guidelines on screening for anaemia in pregnancy

Organisation and publication date	Guidance
NICE 2008[3]	Pregnant women should be offered screening for anaemia. Screening should take place early in pregnancy (at the booking appointment) and at 28 weeks when other blood screening tests are being performed. This allows enough time for treatment if anaemia is detected. Haemoglobin levels outside the normal UK range for pregnancy (that is, 11 g/100 ml at first contact and 10.5 g/100 ml at 28 weeks) should be investigated and iron supplementation considered if indicated. This recommendation was based on 3 reviews which provided either no or inconclusive evidence of any beneficial or harmful effects on maternal or fetal outcomes. It was also noted that there was an absence of evidence to indicate the appropriate timing and recipients of iron supplementation during pregnancy.
USPSTF 2015[5]	In 2015, the USPSTF concluded that the current evidence is insufficient to assess the balance of benefits and harms of screening and treatment for IDA in pregnant women to prevent adverse maternal health and birth outcomes; this was consistent with the 2006 review by the USPSTF.
BSH 2019[2]	Routine iron supplementation for all women in pregnancy is not recommended in the UK. Haemoglobin concentration should be routinely measured at booking and at around 28 weeks' gestation. Unselected screening with routine use of serum ferritin is generally not recommended although individual centres with a particularly high prevalence of 'at risk' women may find this useful. For anaemic women, a trial of oral iron should be considered as the first line diagnostic test, whereby an increment demonstrated at 2 weeks is a positive result.
CADTH 2019[4]	Routine haemoglobin measurement at each trimester of pregnancy is generally recommended to assess IDA. Oral iron is the first line treatment with repeated measure of haemoglobin to assess compliance, correct administration and response to treatment. IV iron should be used in persons who are intolerant of, or do not respond to oral iron treatment, or those with moderately severe to severe anaemia. These conclusions were based on a review of 10 guidelines; it was noted that 1 guideline could not assess the benefits and harms of screening and iron supplementation in pregnant persons due to insufficient evidence. The quality of the evidence was unclear, and the review concluded that the recommendations should be interpreted with caution.

Abbreviations: BSH: British Society for Haematology; CADTH: Canadian Agency for Drugs and Technologies in Health; IDA: iron deficiency anaemia; IV: intravenous; NICE: National Institute for Health and Care Excellence; USPSTF: United States Preventive Services Taskforce.

NICE are undertaking an update of the 'Antenatal care for uncomplicated pregnancies' guidelines,[3] although NICE is not planning to undertake a formal evaluation of the evidence for screening for anaemia during pregnancy. Currently, there is the following placeholder question in the guideline's final scope: *'What is the effectiveness of performing routine blood tests to assess haemoglobin and iron status during pregnancy?'* with the caveat that '*The UK NSC is currently undertaking evaluation for screening related to this key area. We will liaise with the UK NSC to determine whether an evidence review will be required to complement their evaluation'.* Therefore, this evidence review

summary aimed to provide an evaluation of the volume and direction of the literature on this topic, with the intention of assessing if a national screening programme for IDA in pregnancy should be introduced in the UK. Specifically, new evidence was collected to answer the following 3 questions:

1. What are the maternal and infant outcomes associated with untreated ID, with or without mild or moderate anaemia in pregnancy?
2. What are the benefits and harms of treating pregnant women for IDA, to pregnant women and their infants?
3. What are the benefits and harms of screening for IDA during pregnancy?

A key focus of the review was to consider the strength and direction of evidence included in and since the search performed by the 2013 Nutrition Impact Model Study Group, reviewed by Haider in May 2012 (Question 1),[12] or since the search performed by the 2015 review and gap analysis by Rukuni in August 2014 (Questions 2 and 3).[13]

Objectives

This review aims to assess whether there is sufficient evidence to consider introducing a screening programme for IDA in pregnant women. The review will appraise evidence on the questions in

Table 5, which each relate to the criteria set out by the UK NSC for assessing the suitability of a screening programme.

Table 5. Key questions for the evidence summary, and relationship to UK NSC screening criteria

	Criterion	Key questions	Studies Included
	THE CONDITION		
1	The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.	What are the maternal and infant outcomes associated with untreated ID, with or without mild or moderate anaemia in pregnancy?	18 publications on 18 unique studies.
	THE INTERVENTION		
9	There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered.	What are the benefits and harms of treating pregnant women for IDA to pregnant women and their infants?	5 publications on 4 unique studies.
	THE SCREENING PROGRAMME		
11	There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (for example, Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.	What are the benefits and harms of screening for IDA during pregnancy?	3 publications on 2 unique studies.
13	The benefit gained by individuals from the screening programme should outweigh any harms for example from overdiagnosis, overtreatment, false positives, false reassurance, uncertain findings and complications.		

Abbreviations: ID: iron deficiency; IDA: iron deficiency anaemia; UK NSC: United Kingdom National Screening Committee.

Methods

The current review was conducted by Costello Medical, in keeping with the UK NSC evidence review process. Database searches were conducted on 2nd March 2020 to identify studies relevant to the questions detailed in

Table 5; searches were limited to studies published since 1st January 2012 for Question 1, and to studies published since 1st January 2014 for Questions 2 and 3.

Eligibility for inclusion in the review

The following review process was followed:

1. Each title was reviewed to efficiently exclude evidence from non-relevant geographic regions by 1 reviewer. A second independent reviewer validated all included and 10% of excluded articles. Any disagreements were resolved by discussion until a consensus was met.
2. Each abstract was reviewed against the inclusion/exclusion criteria by 1 reviewer. Where the applicability of the inclusion criteria was unclear, the article was included at this stage in order to ensure that all potentially relevant studies were captured. A second independent reviewer provided input in cases of uncertainty and validated all included and 10% of excluded articles. Any disagreements were resolved by discussion until a consensus was met.
3. Each full-text article was then reviewed against the inclusion/exclusion criteria by 1 reviewer, who determined whether the article was relevant to 1 or more of the review questions. A second independent reviewer provided input in cases of uncertainty and validated all included and 10% of excluded articles. Any disagreements were resolved by discussion until a consensus was met.

Eligibility criteria for each question are presented in Table 6, Table 7 and Table 8 below. For all questions, systematic literature reviews (SLRs) and meta-analyses were considered for inclusion. If the scope of an SLR or meta-analysis was very closely aligned to 1 of the questions of this review, it was included in its own right. However, where the scope was not closely aligned to 1 of the questions of this review but some of the included articles may have been of interest, the reference list of the SLR or meta-analysis was hand-searched. Any relevant primary research articles identified were included, but the SLR itself was excluded.

Table 6. Inclusion and exclusion criteria for Question 1

Domain	Population	Exposure	Comparator	Outcome	Study type	Setting	Other considerations
Inclusion criteria	Pregnant women who are asymptomatic for IDA and their infants	Untreated ID, with or without mild or moderate anaemia[a]	Pregnancies without ID or IDA	Risks of adverse maternal outcomes, including but not limited to: • Caesarean section • Infection during pregnancy • Transfusion • Postpartum haemorrhage • Postpartum mental health problems • Breastfeeding problems and duration Risks of adverse neonatal (defined as <2 years) outcomes, including but not limited to: • Low birth weight • Small for gestational age birth • Preterm birth (<37 weeks' gestation) • Very preterm birth (<34 weeks' gestation) • Perinatal mortality • Admission to neonatal care unit • Neurodevelopmental delay	Systematic reviews and meta-analyses, RCTs (non-interventional arms only), cohort studies, cross-sectional studies and case-control studies	Tier 1: Studies conducted in the UK Tier 2: Studies conducted in high income countries where the population, screening methods and technology are expected to be similar to that of the UK (OECD and EEA countries excluding Bulgaria, Chile, Israel, Japan, Romania, Turkey, South Korea and Mexico)	Articles published in the English language and since 2012
Exclusion criteria	Women who are not pregnant Cohorts selected for the presence of a specific	Any other prognostic factors if maternal ID or	Any other comparators	Any other outcomes	Any other study design, including case reports, case series, narrative reviews, editorials,	Studies in ineligible countries, or international studies where	Studies with full text not in the English language

Domain	Population	Exposure	Comparator	Outcome	Study type	Setting	Other considerations
	condition for example, women with a known haemoglobinopathy, women who are symptomatic and/or receiving treatment for IDA, women selected for other risk factors Multiple pregnancies	anaemia is not included			commentaries, letters, conference abstracts or other publication types that have not been peer-reviewed	outcomes for eligible countries are not presented separately to outcomes from ineligible countries	Studies published pre-2012

Footnotes: [a]This review did not identify any studies that explicitly included an untreated cohort of women. Therefore, the eligibility criteria were modified to include studies in which iron treatment and/or supplementation in the study populations was unclear.

Abbreviations: EEA, European Economic Area; ID: iron deficiency; IDA: iron deficiency anaemia; OECD, Organisation for Economic Co-ordination and Development; PICOS, Population Intervention, Comparator, Outcomes, Study Design; RCT, randomised controlled trial; UK, United Kingdom.

Table 7. Inclusion and exclusion criteria for Question 2

Domain	Population	Intervention	Comparator	Outcome	Study type	Setting	Other considerations
Inclusion criteria	Pregnant women with IDA	Oral iron supplementation, iron-fortified diet or combination of both Intravenous iron	No treatment	Risks of adverse maternal outcomes, including but not limited to: • Caesarean section • Infection during pregnancy • Transfusion • Postpartum haemorrhage • Postpartum mental health problems • Breastfeeding problems and duration • Adverse effects of treatment*	Tier 1: Systematic reviews and meta-analyses, RCTs and cohort studies Tier 2: Cross-sectional studies and case-control studies	Studies conducted in the UK or in high income countries where the population, screening methods and technology are expected to be similar to that of the UK (OECD and EEA countries excluding Bulgaria, Chile,	Articles published in the English language and since 2014

Domain	Population	Intervention	Comparator	Outcome	Study type	Setting	Other considerations
				Risks of adverse neonatal (defined as <2 years) outcomes, including but not limited to: • Low birth weight • Small for gestational age birth • Preterm birth (<37 weeks' gestation) • Very preterm birth (<34 weeks' gestation) • Perinatal mortality • Admission to neonatal care unit • Neurodevelopmental delay		Israel, Japan, Romania, Turkey, South Korea and Mexico)	
Exclusion criteria	Women who are not pregnant Multiple pregnancies	Any other interventions	Any other comparators	Any other outcomes	Any other study design, including case reports, case series, narrative reviews, editorials, commentaries, letters, conference abstracts or other publication types that have not been peer-reviewed	Studies in ineligible countries, or international studies where outcomes for eligible countries are not presented separately to outcomes from ineligible countries	Studies with full text not in the English language Studies published pre-2014

*****It was expected that adverse effects of treatment for ID in the population of interest would be passively captured through the rapid review; as such, relevant terms were not included in the search strategy. Where relevant adverse effects data was identified, they were extracted.
Abbreviations: EEA, European Economic Area; IDA: iron deficiency anaemia; OECD, Organisation for Economic Co-ordination and Development; PICOS, Population Intervention, Comparator, Outcomes, Study Design; RCT, randomised controlled trial; UK, United Kingdom.

Table 8. Inclusion and exclusion criteria for Question 3

Domain	Population	Intervention	Comparator	Outcome	Study type	Setting	Other considerations
Inclusion criteria	Pregnant women who are asymptomatic for IDA and their infants	Screening test to identify IDA	No screening for IDA	Risks of adverse maternal outcomes, including but not limited to: • Caesarean section • Infection during pregnancy • Transfusion • Postpartum haemorrhage • Postpartum mental health problems • Breastfeeding problems and duration Risks of adverse neonatal (defined as <2 years) outcomes, including but not limited to: • Low birth weight • Small for gestational age birth • Preterm birth (<37 weeks' gestation) • Very preterm birth (<34 weeks' gestation) • Perinatal mortality • Admission to neonatal care unit • Neurodevelopmental delay	Tier 1: Systematic reviews and meta-analyses, RCTs and cohort studies Tier 2: Cross-sectional studies and case-control studies	Studies conducted in the UK or in high income countries where the population, screening methods and technology are expected to be similar to that of the UK (OECD and EEA countries excluding Bulgaria, Chile, Israel, Japan, Romania, Turkey, South Korea and Mexico)	Articles published in the English language and since 2014
Exclusion criteria	Women who are not pregnant Cohorts selected for the presence of a specific condition for	Irrelevant index test or reference standard	Any other comparators	Any other outcomes	Any other study design, including case reports, case series, narrative reviews, editorials, commentaries, letters, conference	Studies in ineligible countries, or international studies where outcomes for eligible countries	Studies with full text not in the English language

Domain	Population	Intervention	Comparator	Outcome	Study type	Setting	Other considerations
	example, women with a known haemoglobinopathy, women who are symptomatic and/or receiving treatment for IDA, women selected for other risk factors Multiple pregnancies				abstracts or other publication types that have not been peer-reviewed	are not presented separately to outcomes from ineligible countries	Studies published pre-2014

Abbreviations: EEA, European Economic Area; IDA: iron deficiency anaemia; OECD, Organisation for Economic Co-ordination and Development; PICOS, Population Intervention, Comparator, Outcomes, Study Design; RCT, randomised controlled trial; UK, United Kingdom.

Appraisal for quality/risk of bias tool

The following tools were used to assess the quality and risk of bias of each study included in the review:

- non-randomised studies of interventions: ROBINS-I checklist
- SLRs: AMSTAR 2 checklist

Data synthesis

The available evidence was categorised and discussed according to the exposure: anaemia, iron deficiency anaemia (IDA) and iron deficiency (ID); this was to reflect the fact that different conditions and underlying aetiologies may result in different clinical outcomes.

Judgement on the overall strength of evidence (poor, moderate, strong) was based on the quality (low, moderate, high) and quantity (limited, sufficient) of included studies, including the quantity of studies providing evidence on the same exposure (ID, IDA, anaemia), and study characteristics (for example, study population size). Consistency in reported outcomes between studies was also considered.

Judgement on the strength of association between an exposure and outcome was developed based on reported effect sizes and statistical significance.

Databases/sources searched

The following databases were searched:

- MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print
- Embase
- The Cochrane Library, including the following
    - Cochrane Database of Systematic Reviews (CDSR)
    - Cochrane Central Register of Controlled Trials (CENTRAL)
- Database of Abstracts of Reviews of Effects (DARE)

Searches were run on 2nd March 2020. Full details of the searches, including the search strategy for each database, are presented in Appendix 1 — Search strategy.

Overall results

Database searches yielded 3,946 results, of which 22 records were judged to be relevant to 1 or more questions. One additional reference was identified through handsearching references, so 23 records, reporting on 22 studies, were ultimately included.

Appendix 2 — Included and excluded studies contains the full PRISMA flow diagram, along with a table of the included records and details of which questions these records were identified as being relevant to (Figure 1 and Table 33).

Question level synthesis

Criterion 1 — Association between iron deficiency anaemia (IDA) and adverse maternal and infant outcomes

1. The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.

The current rapid review searched for relevant data, published since 2012, relating to maternal and infant outcomes associated with untreated iron deficiency (ID), with and without anaemia, through the question:

Question 1 — What are the maternal and infant outcomes associated with untreated ID, with or without mild or moderate anaemia in pregnancy?

Eligibility for inclusion in the review

This rapid review searched for randomised controlled trials (RCTs; non-interventional arms only), systematic literature reviews (SLRs) and observational studies completed in the UK, or in similar high income countries. Studies were included if the population comprised pregnant women who were asymptomatic for IDA, and their infants (of the same pregnancy). In circumstances where this was not specified, it was assumed that women were asymptomatic for IDA. Gravidity was not specifically considered as part of the eligibility criteria and it was not used as a stratification factor when discussing results.

The exposure of interest for Question 1 was untreated ID, with or without mild or moderate anaemia, and the comparator was pregnancies without ID or IDA; this rapid review focussed on mild and moderate anaemia in order to determine the outcomes associated with a formal population screening programme for the condition. In studies where the exposure was only specified as anaemia, because 90% of anaemia in pregnancy is IDA,[8] it was assumed that the aetiology was IDA, resulting in inclusion. Furthermore, it was assumed that anaemia was mild or moderate, unless otherwise reported; this assumption was made because severe anaemia would be expected to present separately to hospital, and this would likely have been reported. Importantly, no studies identified explicitly stated that they included a cohort of women untreated with iron supplements or a prescription iron treatment; studies which did not report on iron usage, and in which it is unclear whether women received iron supplementation, were therefore included, to provide an evidence base for this review question.

Adverse maternal outcomes of interest included caesarean section, infection during pregnancy, transfusion, postpartum haemorrhage (PPH), postpartum mental health problems and breastfeeding problems. Infant outcomes included low birth weight, small for gestational age (SGA) at birth, preterm birth (<37 weeks' gestation), very preterm birth (<34 weeks' gestation), perinatal mortality, admission to neonatal intensive care unit (NICU) and neurodevelopmental delay. Full details of the eligibility criteria are presented in Table 6.

Studies published since 2012 were eligible for inclusion for Question 1. A SLR and meta-analysis (Haider 2013, searches conducted in 2012) was identified as being relevant to this review question and was used as a base from which to conduct this evidence review.

Description of the evidence

As no studies were identified that explicitly stated that they included an untreated cohort of women, the evidence base for Question 1 consists of studies which did not report on iron usage, and in which it was unclear whether women received iron supplementation.

A total of 17 observational studies (2 prospective, 15 retrospective) and 1 SLR and meta-analysis were identified that explored maternal and infant outcomes associated with untreated ID, with or without mild or moderate anaemia, compared to no anaemia, in pregnancy. Of the retrospective studies, 6 sought to identify risk factors for outcomes of interest, and 9 examined the impact of exposure (ID/IDA/anaemia) on outcomes of interest. Only 4 studies were identified that used IDA (n=1) or ID (n=3) as an exposure; reporting of serum ferritin measurements allows confirmation of whether ID was a contributing factor in the development of anaemia in these study populations. Most identified studies (72%) focused on the association between anaemia and adverse maternal and infant outcomes but did not specify the aetiology of the anaemia. Although ID remains the most common cause of anaemia, there is a clear requirement for authors to specify the aetiology of the cases of anaemia included within their studies, to provide an accurate assessment of iron-associated anaemia and associated adverse outcomes.

The review eligibility criteria specified that studies reporting on women with mild and moderate anaemia should be included (Table 6), and discussion of this review question considers the severity of anaemia as per the WHO thresholds (Table 3). However, the definitions of anaemia used varied between the included studies. The majority of studies defined the upper threshold for anaemia in line with the WHO, and would therefore have captured women with all severities of anaemia.[14-20] The definition of anaemia in 4 studies included only women with moderate to severe anaemia (as defined by the WHO),[21-24] and 1 study only included women with moderate anaemia.[25] The Haider 2013 SLR and meta-analysis included studies with definitions of anaemia ranging from haemoglobin <100 g/L to haemoglobin <115 g/L.[12]

Study information, such as haemoglobin values and study inclusion criteria, demonstrated that in 6 studies, the anaemic cohort either entirely or predominantly comprised women with mild and/or moderate anaemia.[14, 17, 18, 25-27] However, the majority of included studies did not report the baseline haemoglobin (or serum ferritin) levels so the severity of anaemia was unclear.[15, 16, 19, 21-24, 28-31] The applicability of the majority of studies to the review question is therefore unclear, as it is not possible to confirm whether the studies all considered the impact of mild and moderate anaemia.

There were 11 outcomes of relevance identified across the 18 included studies: depression, maternal transfusion, PPH, caesarean section, infection during pregnancy, low birth weight, SGA at birth, preterm birth, very preterm birth, NICU admission and perinatal mortality. Table 9 provides an overview of the characteristics of the included studies, with further details provided in Appendix 3 — Summary of individual studies.

Table 9. Summary of study characteristics for studies identified as relevant to Question 1

Study Country	Study design	Population	Exposure	Reported outcomes
SLR and meta-analyses				
Haider 2013[12]	SLR and meta-analysis	44 prospective cohort studies that allowed examination of the association of baseline anaemia with specified birth outcomes (compared with no anaemia)	Anaemia, defined differently in included studies, with definitions ranging from haemoglobin <100 g/L to haemoglobin <115 g/L	Preterm birth (<37 weeks' gestation) Low birth weight (<2,500 g)
Prospective studies				
Bencaiova 2014[14] Switzerland	Prospective longitudinal study	382 women with singleton pregnancies[a]	**Methodology definition:** Non-anaemic ID (n=123), defined as a serum ferritin <20 µg/L and haemoglobin ≥11.0 g/dL **Population characteristics**: Haemoglobin levels not reported	PPH Low birth weight Preterm birth (<37 weeks' gestation) Neonatal death Admission to NICU
Gaillard 2014[16] Netherlands	Prospective cohort study	7,317 women with singleton pregnancies that gave birth to live offspring	**Methodology definition:** Anaemia, defined as haemoglobin ≤11 g/dL or haematocrit ≤33% **Population characteristics**: Haemoglobin and haematocrit reported for the overall study cohort only (including both anaemic and non-anaemic women): • Mean (SD) haemoglobin was 12.0 (1.0) g//dL • Mean (SD) haematocrit was 36% (2.7)	Preterm birth Low birth weight SGA at birth
Retrospective studies examining the impact of exposure on outcomes of interest				
Beckert 2019[28] USA	Retrospective cohort study, with data obtained from hospital discharge database records	2,869,415 singleton births with gestations between 22- and 42-weeks' gestation, and birth weights within 3 SD of the mean for sex and gestational age	**Methodology definition:** Anaemia, defined as presence of an ICD-9[b] diagnostic code for anaemia, recorded during a hospital admission during pregnancy, or in the birth hospital discharge record **Population characteristics**: Haemoglobin levels not reported	Maternal blood transfusion SGA at birth Preterm birth (32–36 weeks' gestation) Very preterm birth (<32 weeks' gestation) Infant death within 1 year
Crispin 2019[19] Australia	Retrospective cohort study with comparison following a quality improvement intervention and a validation study	431 women with antenatal care at the study centre with blood tests performed during pregnancy (trimester 1: n=146; trimester 2: n=285)	**Methodology definition:** Anaemia, defined as <110 g/L during trimesters 1 and 3, and <105 g/L in the second trimester ID, defined as transferrin saturation of <20% or ferritin concentration of <30 µg/L **Population characteristics:** Haemoglobin levels not reported for women with pre-birth anaemia	Perinatal blood loss Gestational age at birth Birth weight
Khambalia 2015[31] Australia	Record-linkage cohort study	2,254 women attending Down's syndrome screening and who had serum samples available	**Methodology definition:** ID, defined as serum ferritin <12 µg/l or serum transferrin (≥21 nmol/l)	Preterm birth (<37 weeks' gestation)

Study Country	Study design	Population	Exposure	Reported outcomes
			Population characteristics: Haemoglobin levels not reported for study populations; serum ferritin not reported	
Khambalia 2016[31] Australia	Retrospective cohort study	3,795 women attending Down's syndrome screening and who had their results screened by Pathology North	**Methodology definition:** ID, defined as serum ferritin <12 µg/L, serum transferrin receptor ≥21.0 nmol/L, or total body iron <0 mg/kg **Population characteristics**: Serum ferritin (or haemoglobin) levels not reported	PPH Preterm birth SGA at birth NICU admission
Orlandini 2017[26] Italy	Retrospective cohort study	1,131 women who had spontaneous conception and who were admitted to hospital at ≥37 weeks' gestation	**Methodology definition:** Anaemia, defined as haemoglobin <11.0 g/dL in the third trimester (evaluated between 35- and 36-weeks' gestation) of pregnancy **Population characteristics**: Mean (SD) haemoglobin levels in the third trimester: • Anaemic: 10.45 (0.55) g/dL • Non-anaemic: 12.16 (0.76) g/dL All anaemic women had haemoglobin <11.0 g/dL and ≥9.0 g/dL, indicating that the population consisted entirely of women with mild to moderate anaemia; mean haemoglobin indicates majority of women likely had mild anaemia	Emergency caesarean section PPH
Petty 2018[17] USA	Retrospective cross-sectional chart review	8,039 women who gave birth in the maternity hospital between specified dates, and for whom antenatal haemoglobin concentration measurement was available	**Methodology definition:** Anaemia, defined as haemoglobin <11.0 g/dL **Population characteristics**: Mean (SD) haemoglobin levels indicate that the majority of women with anaemia likely had mild to moderate anaemia: • Women with antenatal anaemia: 9.2 (1.3) g/dL • Women without antenatal anaemia: 11.9 (0.74) g/dL	RBC transfusion
Rukuni 2016[23] Scotland	Retrospective cohort study	80,422 singleton pregnancies	**Methodology definition:** Moderate to severe anaemia, defined as haemoglobin ≤10 g/dL, identified at any time before birth **Population characteristics**: Haemoglobin levels not reported	PPH Maternal transfusion Preterm birth (<37 weeks' gestation) Low birth weight (<2,500 g) Very low birthweight (<1,500 g) NICU admission Early neonatal death

Study Country	Study design	Population	Exposure	Reported outcomes
Smith 2019[18] Canada	Retrospective cohort study	515,270 pregnant women who gave birth at or after 20 weeks' gestation	**Methodology definition:** Anaemia, defined as haemoglobin <11 g/dL during the third trimester or in the birth admission, based on ICD-10 codes D50 to 64 and O99.0 for anaemia assigned during the birth admission but prior to birth[a] **Population characteristics**: Haemoglobin levels not reported for study population (or sub-populations); however study populations were categorised based on the presence of no anaemia (haemoglobin >11 g/dL), mild anaemia (haemoglobin 9–10.9 g/dL) and moderate anaemia (haemoglobin 7–8.9 g/dL)	Caesarean section Antepartum and intrapartum-postpartum maternal transfusion Preterm birth (<37 weeks' gestation) Very preterm birth (<32 weeks' gestation) SGA live birth (less than 10th centile) NICU (special care nursery) admission Perinatal death
Wiegersma 2019[30] Sweden	Retrospective register-based cohort study	532,232 offspring born to 299,768 mothers	**Methodology definition:** Anaemia, defined as an ICD-coded[b] diagnosis of anaemia complicating pregnancy or IDA registered up to 1 calendar year before the birth of the index person **Population characteristics**: Haemoglobin levels not reported	Caesarean section Infection during pregnancy
Retrospective studies seeking to identify risk factors for outcomes of interest				
Beta 2013[15] Poland	Case-control study	1,865 singleton pregnancies delivering a phenotypically normal neonate at or after 23 weeks' gestation	**Methodology definition:** Anaemia, defined as haemoglobin <11 g/dL **Population characteristics**: Haemoglobin levels not reported	Preterm birth (spontaneous birth 34 weeks' gestation)
Biguzzi 2012[27] Italy	Retrospective cohort study	6,011 women aged ≥18 years, who had haemoglobin levels measured within 1 month of birth	**Methodology definition:** Anaemia (not defined) **Population characteristics:** Mean (range) haemoglobin levels reported by outcome indicate that no women had severe anaemia: • Women with blood loss ≥500 mL: 11.9 (7.8, 16.5) g/dL • Women with blood loss <500 mL: 12.0 (7.3, 15.8)	PPH (≥500 mL blood loss)
Ehrenthal 2012[25] USA	Retrospective cohort study	59,282 women giving birth (by caesarean or vaginal birth) at 20 or more completed gestational weeks and with a birth weight of ≥350 g	**Methodology definition:** Mild to moderate anaemia, defined as haemoglobin ≤10.5 and >9.5 g/dL **Population characteristics**: Haemoglobin levels not reported; however, the methodology definition indicates inclusion of only women with mild to moderate anaemia	Perinatal transfusion
Nyflot 2017[24] Norway	Case-control study	1,064 cases (severe PPH) and 2,059 controls (no severe PPH)	**Methodology definition:** Moderate to severe anaemia, defined as haemoglobin ≤9.0 g/dL at the start of pregnancy	PPH

Study Country	Study design	Population	Exposure	Reported outcomes
			Population characteristics: Haemoglobin levels not reported	
Räisänen 2013[22] Finland	Retrospective population-based case-control study	1,390,742 singleton births	**Methodology definition:** Moderate to severe anaemia, defined as haemoglobin <100 g/L **Population characteristics**: Haemoglobin levels not reported	Preterm birth (<37 weeks' gestation)
Räisänen 2014[21] Finland	Retrospective population-based cohort study	511,938 singleton births	**Methodology definition:** Moderate to severe anaemia, defined as haemoglobin <100 g/L **Population characteristics**: Haemoglobin levels not reported	Major depression (physician diagnosed)

[a]Only a subset of the study population in Bencaiova 2014 was considered relevant to this rapid review; Groups 1 and 3 in the study were not considered relevant because women either likely received treatment for their anaemia or their anaemia was not caused by ID, respectively. [b]The ICD is the international standard for defining and reporting diseases and health conditions. The ICD contains different codes for items such as diseases and symptoms.

Abbreviations: EPDS: Edinburgh Postnatal Depression Score; ICD: International Classification of Diseases; ID: iron deficiency; IDA: iron deficiency anaemia; NICU: neonatal intensive care unit; PPH: postpartum haemorrhage; RBC: red blood cell; SD: standard deviation; SGA: small for gestational age; SLR: systematic literature review; USA: United States of America; WHO: World Health Organization.

Quality assessment

The quality of the 17 included observational studies was appraised using the ROBINS-I checklist,[32] whilst the quality of 1 SLR was assessed using AMSTAR 2.[33] A summary of these quality assessments is presented in Table 10 and Table 11, whilst the full appraisals are available in Table 59 and Table 60 (Appendix 4 — Appraisal for quality and risk of bias). The overall risk of bias for the included observational studies was judged to be moderate for 7 studies,[16, 18, 22-24, 27, 28] serious for 3 studies,[21, 25, 31] and critical in 7 studies.[14, 15, 17, 19, 26, 29, 30] Each quality assessment domain for the observational studies is considered below, and the assessment of the SLR is presented separately at the end of this section.

Table 10. Summary of ROBINS-I assessments for non-RCTs evaluating the adverse effects of IDA in pregnancy

Study	Bias due to:							Overall risk of bias
	Confounding	Participant selection	Classification of interventions	Deviations from intended interventions[a]	Missing data	Measurement of outcomes	Selection of the reported result	
Beckert 2019[28]	Moderate	Low	Low	Not assessed	Low	Low	Low	Moderate
Bencaiova 2014[14]	Critical	Low	Low	Not assessed	Low	Low	Low	Critical
Beta 2013[15]	Critical	Moderate	Low	Not assessed	Low	Low	Low	Critical
Biguzzi 2012[27]	Moderate	Moderate	Moderate	Not assessed	Moderate	Low	Low	Moderate
Crispin 2019[19]	Critical	Low	Low	Not assessed	Serious	Low	Low	Critical
Ehrenthal 2012[25]	Serious	Low	Low	Not assessed	Serious	Low	Low	Serious
Gaillard 2014[16]	Moderate	Moderate	Low	Not assessed	Moderate	Low	Low	Moderate
Khambalia 2015[31]	Serious	Serious	Low	Not assessed	Moderate	Low	Low	Serious
Khambalia 2016[29]	Critical	Low	Low	Not assessed	Low	Low	Low	Critical
Nyflot 2017[24]	Moderate	Moderate	Low	Not assessed	Moderate	Moderate	Low	Moderate
Orlandini 2017[26]	Critical	Moderate	Low	Not assessed	Moderate	Low	Low	Critical
Petty 2018[17]	Critical	Low	Low	Not assessed	Moderate	Moderate	Low	Critical
Raisanen 2013[22]	Moderate	Low	Low	Not assessed	Low	Low	Low	Moderate
Raisanen 2014[21]	Serious	Low	Low	Not assessed	Low	Low	Low	Serious
Rukuni 2016[23]	Moderate	Low	Low	Not assessed	Low	Low	Low	Moderate
Smith 2019[18]	Moderate	Low	Low	Not assessed	Low	Low	Low	Moderate
Wiegersma 2019[30]	Critical	Low	Low	Not assessed	Low	Low	Low	Critical

[a]The domain 'deviations from intended interventions' was not assessed in the quality assessment for Question 1; bias due to iron supplementation and its potential role in influencing exposure (for example, increasing iron levels to the point where a women is no longer considered iron deficient/anaemic) was instead evaluated under the 'confounding' domain which considers the potential for exposure switching in 1 of the signalling questions.
Abbreviations: IDA: iron deficiency anaemia; RCT: randomised controlled trial.

Confounding

No observational study was judged to be at a low risk of bias due to confounding; 7 were considered to be at moderate risk of bias,[16, 18, 22-24, 27, 28] 3 at serious risk of bias,[21, 25, 31] and 7 at critical risk of bias.[14, 15, 17, 19, 26, 29, 30] Studies judged to be at a moderate risk of bias controlled for relevant confounding variables within appropriate multivariate statistical models. Studies judged to be at serious risk of bias adjusted for some sources of confounding during their analyses but did not include key variables (such as parity and socio-demographic characteristics known to affect iron status) within their multivariate models. Out of those judged to be at a critical risk of bias in this domain, 5 did not use multivariate statistical methods to control for confounding,[14, 15, 17, 19, 26] and 2 further studies only reported results of unadjusted naïve comparisons for the outcomes of interest to this review.[29, 30]

The possibility and consequences of women switching between exposures (for example, a woman initially diagnosed as anaemic becoming non-anaemic) was also considered in this domain; the change in haemoglobin and serum ferritin over time was not reported for the majority of studies, therefore it was not possible to assess the impact of any change in exposure caused by iron. No study reported on iron use in the relevant enrolled population.[14-19, 21-31] In the included studies, it was therefore not possible to determine whether iron supplementation could have impacted upon the women's exposure over time and thus influenced the observed results, or whether iron use was balanced between study groups.

Participant selection

The risk of bias was judged to be low in 11 studies.[14, 17-19, 21-23, 25, 28-30] Five studies were judged to be at a moderate risk of bias because women were selected based on characteristics observed after the identification of exposure and outcomes of interest.[15, 16, 24, 26, 27] One study was considered to be at serious risk of bias because it selected women based on characteristics observed after the identification of the exposure and provided little information on the eligibility criteria.[31]

Classification of interventions

Almost all the observational studies (16/17) provided a clear definition of the exposure and were consequently assessed to be at a low risk of bias for this domain. Anaemia was typically defined by threshold values (for example, anaemia defined as haemoglobin <11.0 g/dL), although 2 studies relied on International Classification of Diseases (ICD) codes.[28, 30] One study was judged to be at moderate risk of bias.[27]

Deviations from intended interventions

This domain was not independently assessed; bias due to iron supplementation and its potential role in influencing exposure (resulting in deviations from IDA/ID/anaemia) was considered under the confounding domain.

Missing data

Risk of bias due to missing data was judged to be low in 9 studies,[14, 15, 18, 21-23, 28-30] moderate in 6,[16, 17, 24, 26, 27, 31] and serious in 2.[19, 25] Studies where it was unclear how women were excluded from the analysis,[24, 26] where women were excluded due to missing data on exposure status,[16, 17, 31] or where there was a large amount of missing information,[27] were classified as being at moderate risk of bias. Of the 2 studies classified as being at serious risk of bias, the volume of missing data could not be assessed.[19, 25] In addition, the proportion of women missing exposure measures seemed to be unbalanced across exposure groups in 1 study,[19] whilst in the second study, women that were missing data on either outcomes or other variables used in the analysis were excluded, with no sensitivity analyses performed to explore the impact of this on results.[25]

Outcome measurements

Of the studies included in the evidence base for Question 1, 15 studies were judged to be at low risk of bias in this domain, due to the use of objective and consistently assessed outcomes.[7, 14-31, 34-38] Two studies were judged to be at a moderate risk of bias in their outcome measurements;[17, 24] blood loss was visually estimated by the attending physician or midwife in Nyflot 2017, and it was unclear how individual physician estimates varied across exposure groups, introducing some uncertainty around the comparability of outcomes.[24] In Petty 2018, there was concern that the number of red blood cell (RBC) transfusion units used may have been influenced by prior knowledge of the women's haemoglobin status.[17]

Selection of the reported result

All observational studies (n=17) were judged to be at a low risk of bias in this domain. The possibility of multiple outcome measures was judged to be low. Some studies reported multiple analyses with adjustments made for different variables; these were presented transparently and was reasonable within the context of the studies. Where effect estimates were calculated for subgroups (for example, differing severity of anaemia), outcomes were presented for each and the subgroup analyses were considered appropriate within the context of the specific study.

Systematic literature review

Haider 2013 was the only SLR included for Question 1. It was judged to meet all but 3 of the quality assessment criteria outlined by AMSTAR 2 (Table 11).[33] The report did not contain an explicit statement that the review methods were established prior to review conduct, nor was there mention of PROSPERO registration or a reference to a published trial protocol. The sources of funding for the studies included within the SLR were also not reported. Finally, the method used to assess risk of bias of included studies was systematic and covered key domains but was not a specifically designed and validated quality assessment tool. In addition, a more in-depth assessment of cohort study quality, which included assessing sample selection, exposure/outcome measurements and selective reporting, would have been desirable.

Table 11. Summary of AMSTAR-2 assessment for the SLR evaluating the adverse effects of IDA in pregnancy

Question	Haider 2013[12]
Did the research questions and inclusion criteria for the review include the components of PICO? (Yes/No)	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? (Yes/Partial Yes/No)	No
Did the review authors explain their selection of the study designs for inclusion in the review? (Yes/No)	Yes
Did the review authors use a comprehensive literature search strategy? (Yes/Partial Yes/No)	Yes
Did the review authors perform study selection in duplicate? (Yes/No)	Yes
Did the review authors perform data extraction in duplicate? (Yes/No)	Yes
Did the review authors provide a list of excluded studies and justify the exclusions? (Yes/Partial Yes/No)	Yes
Did the review authors describe the included studies in adequate detail? (Yes/Partial Yes/No)	Yes
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? (Yes/Partial Yes/No)	Partial yes
Did the review authors report on the sources of funding for the studies included in the review? (Yes/No)	No
If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results? (Yes/No/No meta-analysis conducted)	Yes
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? (Yes/No/No meta-analysis conducted)	Yes
Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review? (Yes/No)	Yes
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? (Yes/No)	Yes
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? (Yes/No/No meta-analysis conducted)	Yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for the review? (Yes/No)	Yes

Abbreviations: IDA: iron deficiency anaemia; PICO: population, intervention, comparator, outcome; RoB: risk of bias; SLR: systematic literature review.

Results

Systematic review and meta-analysis

A systematic review of 22 prospective cohort studies conducted in high income countries, performed by the Nutrition Impact Model Study Group in 2013,[12] assessed the association between anaemia and a range of birth outcomes relevant to Question 1; the definition of anaemia varied between studies, ranging from haemoglobin <100 g/L to haemoglobin <115 g/L. The review pooled results from 22 prospective cohort studies (data from 650,125 pregnant women) completed in high income countries.[12] The meta-analysis found a statistically significant but weak association between preterm birth (<37 weeks' gestation) and anaemia in women from high income countries (adjusted odds ratio [OR] 1.26; 95% confidence interval [CI] 1.02 to 1.57; p<0.001; 12 studies).[12] This association was present for anaemia during the first or second trimester, but not the third.[12] A trend was also observed between anaemia and low birth weight, although this was not significant.[12]

Whilst Haider 2013 reported on other neonatal outcomes, such as SGA at birth and stillbirth, the data included in these analyses were derived primarily from low income countries that were not considered to be sufficiently similar to the UK to be relevant to this review.

Haider 2013 concluded that prospective cohort studies showed a significantly increased risk of preterm birth with first or second trimester anaemia.[12] However, the definition of anaemia in the included studies varied, potentially limiting the applicability of these results to the current review question. The authors stated that further evidence is required to explore the association, magnitude and duration of adverse clinical outcomes and ID with and without anaemia in pregnancy.

Observational studies

The identified observational studies reported on the association between IDA (n=1), anaemia (aetiology unspecified; n=13) and ID (n=3) with the following outcomes:

- maternal outcomes
  - depression (n=1)
  - transfusion (n=5)
  - PPH (n=7)
  - caesarean section (n=3)
  - infection during pregnancy (n=1)
- infant outcomes
  - low birth weight (n=4)
  - SGA at birth (n=5)
  - preterm birth (n=9)
  - very preterm birth (n=4)
  - NICU admission (n=4)
  - perinatal mortality (n=4)

Maternal outcomes

Depression

There was limited evidence for an association between anaemia and depression during pregnancy (Table 12). One study was identified, which looked at risk factors for depression. Räisänen 2014 found that women with physician-diagnosed depression during pregnancy have higher odds of anaemia than women with no major depression (adjusted OR: 1.49; 95% CI: 1.22 to 1.81), although the cross-sectional design of this study meant that temporality could not be assessed.[21] Furthermore, there is uncertainty regarding the causality of this relationship, specifically whether anaemia results in an increased likelihood of depression or vice versa.

Table 12. Association between anaemia in pregnancy and maternal depression

Study	Exposure definition	Women included in analysis	Results	Study design [Risk of bias]
Studies reporting on anaemia				
Räisänen, 2014[21] Finland	Haemoglobin <100 g/L	511,938	Women with physician-diagnosed depression during pregnancy, treated in specialist centres, have higher odds of anaemia than women with no major depression during pregnancy (adjusted OR: 1.49; 95% CI 1.22 to 1.81)[a]	Cross-sectional [Serious]

[a]Adjusted by history of depression prior to pregnancy, maternal age, parity, smoking status, marital status, socioeconomic status, prior miscarriages, prior terminations, IVF, anaemia, gestational diabetes, pre-existing diabetes, fear of childbirth and fetal sex.
Abbreviations: CI: confidence interval; OR: odds ratio.

Maternal transfusion

Maternal transfusion was reported as an outcome in 5 studies reporting anaemia as the exposure (Table 13).[17, 18, 23, 25, 28] All 5 studies reported an increased rate of transfusion in women with anaemia compared to those without anaemia.[17, 18, 23, 25, 28] Beckert 2019, a large study of high quality, reported an adjusted risk ratio (RR) for maternal blood transfusion in anaemic women (compared to women with no anaemia) of 6.8 (95% CI: 6.7 to 6.9) using a sample of 2,869,415 singleton births in the US.[28] Additionally, Smith 2019 observed a dose-response relationship between increased odds of both antepartum transfusion and intrapartum-postpartum transfusion for mildly and moderately anaemic women in a large study (n=515,270) judged to be at moderate risk of bias.[18] This dose-response relationship is further supported by data from Ehrenthal 2012, which indicated a dose-dependent increase in odds of transfusion in moderately anaemic women across modes of birth (vaginal and caesarean).[25] However, whilst a large study cohort (n=59,282), this study was judged to be at serious risk of bias, limiting the reliability of these results.[25]

Overall, there is moderate evidence to suggest that anaemia during pregnancy is associated with an increase in the frequency of maternal transfusion.[17, 18, 23, 25, 28] Furthermore, this evidence is highly applicable to the population of women with mild or moderate anaemia in the UK, with several supporting studies confirmed to include predominantly mildly or moderately anaemic women.[17, 18, 25]

Table 13. Association between anaemia in pregnancy and maternal transfusion

Study	Exposure definition	Women included in analysis	Results	Study design [Risk of bias]
Studies reporting on anaemia				
Beckert 2019[28] United States	**Anaemia**, defined as presence or absence of ICD-9 diagnostic code for anaemia.	2,869,415	Women with anaemia (n=284,780), n (%) = 20,167 (7.1) required blood transfusion. Women with no anaemia (n=2,584,635), n (%) = 9,548 (0.4) required blood transfusion. Adjusted RR (95% CI)[a] = 6.8 (6.7 to 6.9).	Cohort (retrospective) [Moderate]
Ehrenthal 2012[25] United States	**Anaemia**, defined as haemoglobin ≤10.5 and >9.5 g/dL	59,282	Vaginal birth Women with moderate anaemia have significantly higher odds of perinatal transfusion than non-anaemic women (adjusted OR[b] 2.09; 95% CI 1.37 to 3.19). Caesarean section Women with moderate anaemia have significantly higher odds of perinatal transfusion than non-anaemic women (adjusted OR[b] 3.08; 95% CI 2.29 to 4.15).	Cohort (retrospective) [Serious]
Petty, 2018[17] United States	**Anaemia**, defined as haemoglobin <11.0 g/dL	8,039	Women with antenatal anaemia have higher odds of receiving an RBC transfusion (OR 4.97; 95% CI 3.38 to 7.31; p=0.0001); this is regardless of mode of birth.	Cross-sectional chart review (retrospective) [Critical]
Rukuni, 2016[23] Scotland	**Anaemia**, defined as haemoglobin <10.0 g/dL	80,422	Women with severe antenatal anaemia, having a singleton birth, have higher odds of transfusion compared to women without anaemia (adjusted OR[c] 1.87; 95% CI 1.65 to 2.13).	Cohort (retrospective) [Moderate]
Smith 2019[18] Canada	**Anaemia**, defined as third trimester haemoglobin <11.0 g/dL, or diagnosis of anaemia made during the birth admission but before birth (based on ICD10 codes)	515,270	Antepartum transfusion Adjusted OR of requiring antepartum transfusion versus non-anaemic women (n=449,364): • Mild anaemia (n=60,590): OR 2.17 (95% CI 1.28 to 3.66) • Moderate anaemia (n=2,195): OR 94.2 (95% CI 60.2 to 147.5) Intrapartum-postpartum transfusion Unadjusted OR of requiring antepartum versus non-anaemic women (n=449,364): • Mild anaemia (n=60,590): 2.45 (95% CI 1.74 to 3.45) • Moderate anaemia (n=2,195): OR 21.3 (95% CI 12.2 to 37.3)	Cohort (retrospective) [Moderate]

[a]Adjusted for race, age, timing of entry into prenatal care, number of prenatal care visits, healthcare insurance plan, participation in supplemental nutrition programme, BMI, drug use, smoking, parity and interpregnancy interval. [b]Multivariate regression, adjusted for gestational age at birth, marital status and year. [c]Adjusted for age, parity, smoking status, ethnicity, socio-economic status, BMI and chronic kidney disease.
Abbreviations: CI: confidence interval; ICD: International Classification of Diseases; OR: odds ratio; RR: risk ratio.

Postpartum haemorrhage (PPH)

Inconsistent evidence for an association between untreated ID, with or without mild or moderate anaemia, and PPH was identified. PPH was reported as an outcome in 1 IDA study,[19] 2 ID studies[14, 29] and 4 anaemia studies (Table 14).[23, 24, 26, 27] Of these studies, 2 definitively included predominantly mildly or moderately anaemic women in their study cohorts.[26, 27]

Outcomes from the 3 observational studies judged to be at moderate risk of bias, and exploring the association between anaemia and PPH, were inconsistent.[23, 24, 27] Rukuni 2016 reported a significantly lower odds of PPH in anaemic women, compared with women without anaemia.[23] By contrast, Nyflot 2017 reported that anaemia, diagnosed at the start of pregnancy, was a strong

independent risk factor for severe PPH,[24] whilst Biguzzi 2016 reported that the odds of PPH decreased by 16% per 1 g/dL incremental increase in antenatal haemoglobin.[27] All 3 studies were of reasonable size, although the study cohort in Rukuni 2016 was considerably larger than that of the other 2 studies.[23, 24, 27] However, the strength of the results from Rukuni 2016 is limited, as the authors acknowledged that the observed outcome may be due to treatment effects not controlled for in the analysis and active management of the third stage of labour in women known to have antenatal anaemia.[23] There was no evidence for an association between IDA or ID and PPH, although these results were derived from univariate analyses in studies judged to be at critical risk of bias.[14, 19, 29]

Table 14. Association between IDA, anaemia and ID in pregnancy and PPH

Study	Exposure definition	Women included in analysis	Results	Study design [Risk of bias]
Studies reporting on IDA				
Crispin 2019[19] Australia	**IDA**, defined as haemoglobin less than 110 g/L during trimesters 1 and 3, and less than 105 gL^{-1} in the second trimester	Trimester 1 = 42 Trimester 2 = 480	There was no difference in the amount of perinatal bleeding recorded between women who were anaemic and non-anaemic in early pregnancy.	Cohort (retrospective) [Critical]
Studies reporting on anaemia				
Biguzzi 2012[27] Italy	**Anaemia,** impact of 1 g/dL increases in antenatal haemoglobin (1 month pre-birth)	6,011	The odds of PPH decreased approximately 16% per 1 g/dL increment in antenatal haemoglobin in a multivariate analysis (OR 0.84; 95% CI 0.78 to 0.90; p<0.0001)[a]	Cohort (retrospective) [Moderate]
Nyflot 2017[24] Norway	**Anaemia**, defined as haemoglobin ≤9.0 g/dL, recorded at start of pregnancy	3,123	In a multivariate logistic model, anaemia diagnosed at the start of pregnancy was a strong independent risk factor for severe PPH (cases: 74/1,064 [7.0%]; controls: 38/2,059 [1.9%]; adjusted OR 4.27; 95% CI 2.79 to 6.54; p<0.001).	Case-control [Moderate]
Orlandini 2017[26] Italy	**Mild anaemia** in the third trimester (35- and 36-weeks' gestation), defined as haemoglobin ≥9 g/dl and ≤11 g/dl	11,31	There was no statistical difference between the rates of PPH in women with mild anaemia (1/156) compared to non-anaemic women (13/975).	Cohort (retrospective) [Critical]
Rukuni, 2016[23] Scotland	**Anaemia,** defined as haemoglobin <10.0 g/dL	80,422	Women with severe antenatal anaemia, having a singleton birth, have a significantly lower odds of PPH compared to women without anaemia (adjusted OR[b] 0.92; 95% CI 0.86 to 0.98; p=0.007).	Cohort (retrospective) [Moderate]
Studies reporting on ID				
Bencaiova 2014[14] Switzerland	**ID,** defined as a serum ferritin <20 µg/L and haemoglobin ≥11.0 g/dL	382	Frequency of PPH: • Women with non-anaemic ID (n=123), n (%) = 7 (5.7); p versus normal = 0.11. • Women without ID (n=189) = 21 (11.1).	Prospective longitudinal study [Critical]
Khambalia 2016[29] Australia	**ID**, defined as <12 µg/L serum ferritin	3,795	Iron deficient (n=742) = 20 (2.7%) women had PPH. Iron replete (n=3,053) = 120 (3.9%) women had PPH. p>0.05	Cohort (retrospective) [Critical]

[a]The odds ratio for each variable was adjusted for the presence of all other variables in a multiple logistic regression model. Information on all putative risk factors complete in 4,748 women (79%). [b]Adjusted for age, parity, smoking status, ethnicity, socio-economic status, BMI and chronic kidney disease.
Abbreviations: CI: confidence interval; ID: iron deficiency; IDA: iron deficiency anaemia; OR: odds ratio; PPH: postpartum haemorrhage.

Caesarean section

Caesarean section was reported as an outcome in 3 anaemia studies (Table 15).[18, 26, 30] Two studies reported descriptive statistics suggesting that a higher proportion of women with anaemia underwent caesarean section.[26, 30] Smith 2019 provided the strongest evidence, reporting a significantly higher odds of caesarean birth in anaemic versus non-anaemic women that suggested a dose-response relationship (mild anaemia adjusted OR: 1.17; 95% CI: 1.14 to 1.19; moderate anaemia adjusted OR: 1.86; 95% CI: 1.67 to 2.08).[18] Smith 2019 enrolled a large study cohort (n=515,270), lending strength to the observed results. Furthermore, the majority of studies reporting on caesarean section (3/5), including Smith 2019, were confirmed to include women with mild or moderate anaemia.[18, 26, 35] However, despite the consistency in the direction of effect and the moderate strength of association reported by Smith 2019, the evidence for a statistically significant increase in caesarean section was limited overall, and the quality of the evidence was poor.

Table 15. Association between anaemia in pregnancy and caesarean section

Study	Exposure definition	Women included in analysis	Results	Study design [Risk of bias]
Studies reporting on anaemia				
Orlandini 2017[26] Italy	**Mild anaemia** in the third trimester (35- and 36-weeks' gestation), defined as haemoglobin ≥9 g/dL and ≤11 g/dL.	1,131	Women with mild anaemia (25/156) showed a higher rate of emergency caesarean section (p=0.006) than non-anaemic women (69/975). The rate of emergency caesarean section was significantly higher (p=0.003) in those carrying male than those carrying female foetuses.	Cohort (retrospective) [Critical]
Smith 2019[18] Canada	**Anaemia**, defined as third trimester haemoglobin <11 g/dL, or diagnosis of anaemia made during the delivery admission but before delivery (based on ICD10 codes)	515,270	Adjusted OR of requiring caesarean section versus non-anaemic women (n=449,364): • Mild anaemia (n=60,590): OR 1.17 (95% CI 1.14 to 1.19) • Moderate anaemia (n=2,195): OR 1.86 (95% CI 1.67 to 2.08)	Cohort (retrospective) [Moderate]
Wiegersma 2019[30] Sweden	**Anaemia**, defined using ICD codes (anaemia complicating pregnancy or IDA)	532,232 births (from 299,768 women)	Women with anaemia: 10,433 / 31,018 (33.6%). Women without anaemia: 78,225 / 501,214 (15.6%).	Cohort (prospective) [Critical]

Abbreviations: CI: confidence interval; ICD: International Classification of Diseases; OR: odds ratio; WHO: World Health Organization.

Infection during pregnancy

Infection during pregnancy was reported as an outcome in 1 study (Table 16).[30] This study reported that a higher proportion of women with anaemia were hospitalised for infection during pregnancy, compared with women without anaemia (women with anaemia: 2,373 / 31,018 [7.7%]; women

without anaemia: 17,229 / 501,214 [3.4%]).[30] However, despite the large sample size (532,232 births from 299,768 women), only descriptive statistics were reported, the study was judged to be at critical risk of bias, and this outcome was not independently assessed in multiple studies.

Table 16. Association between anaemia and infection during pregnancy

Study	Exposure definition	Women included in analysis	Results	Study design [Risk of bias]
Studies reporting on anaemia				
Wiegersma 2019[30] Sweden	**Anaemia**, ICD code (anaemia complicating pregnancy or IDA)	532,232 births (from 299,768 women)	Women with anaemia: 2,373 / 31,018 (7.7%) hospitalised for infection during pregnancy. Women without anaemia: 17,229 / 501,214 (3.4%) hospitalised for infection during pregnancy.	Cohort (prospective) [Critical]

Abbreviations: ICD: International Classification of Diseases; IDA: iron deficiency anaemia.

Infant outcomes

Low birth weight

Low birth weight was reported as an outcome in 1 IDA study,[19] 1 ID study,[14] and in 2 studies where the cause of the anaemia was unclear (Table 17).[16, 23] Studies considering exposure to IDA and ID observed no significant difference in the occurrence of low birth weight between women with and without ID and IDA.[14, 19] Both studies were judged as being at critical risk of bias and included a small number of women in their analyses.[14, 19]

Evidence from higher quality studies was inconsistent. Two observational studies reported reduced numbers of low birth weight infants in women with anaemia compared to those without anaemia.[16, 23] However, only Rukuni 2016 reported that this association was statistically significant for low birth weight (<2,500 g; adjusted OR: 0.77; 95% CI: 0.69 to 0.86), whilst also reporting a non-significant association with very low birth weight (<1,500 g; adjusted OR: 0.81; 95% CI: 0.62 to 1.06).[23] This is inconsistent with the increased odds of low birth weight in prenatal anaemic women, compared with non-anaemic women, reported in the Haider 2013 meta-analysis.[12] Overall, inconsistencies in the direction of effect meant that the relationship between ID, with or without anaemia, and low birth weight was inconclusive.

Table 17. Association between IDA, anaemia and ID in pregnancy and low birth weight

Study	Exposure definition	Women included in analysis	Results	Study design [Risk of bias]
Studies reporting on IDA				
Crispin 2019[19] Australia	**IDA**, defined as haemoglobin less than 110 g/L during trimesters 1 and 3, and less than 105 gL^{-1} in the second trimester	Trimester 1 = 42 Trimester 2 = 480	There was no difference in birth weights recorded between women who were anaemic and non-anaemic in early pregnancy	Cohort (retrospective) [Critical]
Studies reporting on anaemia				
Gaillard, 2014[16] Netherlands	**Anaemia**, defined as haemoglobin ≤11 g/dL Haematocrit ≤33%	7,317	The risk of low birth weight was reduced in women with anaemia (47/983), compared to those without anaemia (241/5,251); this was not significant[a]	Cohort (prospective) [Moderate]

Haider, 2013[12] SLR	Haemoglobin <11.5 g/dL	NA	In high income countries, prenatal anaemia increased the risk of low birth weight compared with no anaemia; adjusted OR 1.21; 95% CI 0.95 to 1.53; p=0.12; 6 studies	SLR [NA]
Rukuni, 2016[23] Scotland	**Anaemia**, defined as haemoglobin <10.0 g/dL	80,422	Women with severe antenatal anaemia, having a singleton birth, have a lower odds of low birth weight (<2,500 g; adjusted OR[c] 0.77; 95% CI 0.69 to 0.86) and very low birth weight (<1,500 g; adjusted OR[b] 0.81; 95% CI 0.62 to 1.06) compared to women without anaemia	Cohort (retrospective) [Moderate]
Studies reporting on ID				
Bencaiova 2014[14] Switzerland	**ID,** defined as a serum ferritin <20 µg/L and haemoglobin ≥11.0 g/dL	382	Frequency of low birth weight: • Women with non-anaemic ID (n=123), n (%) = 7 (5.7); p versus normal = 0.211 • Women without anaemia or iron depletion (n=189) = 19 (10.1)	Prospective longitudinal study [Critical]

[a]RRs were adjusted for gestational age at enrolment and at blood sampling, maternal age, BMI, parity, ethnicity, education, alcohol consumption during pregnancy, smoking during pregnancy, folic acid supplement use and multivitamin use. Observed associations were attenuated after adjustment for confounding factors. Adjusted for age, parity, smoking status, ethnicity, socio-economic status, BMI and chronic kidney disease.
Abbreviations: CI: confidence interval; ID: iron deficiency; IDA: iron deficiency anaemia; NA: not applicable; OR: odds ratio; SLR: systematic literature review; WHO: World Health Organization.

Small for gestational age (SGA) at birth

SGA at birth was reported as an outcome in 1 study of ID,[29] and 4 studies of anaemia (

Table 18).[16, 18, 28, 30] The association between ID, with and without anaemia, and SGA was found to be inconsistent,[16, 28, 29] and varied based on the timing and severity of anaemia, and obstetric history.

Wiegersma 2019 reported that children born to mothers with anaemia diagnosed at ≤30 weeks' gestation were more likely to be born SGA compared with children whose mothers were not diagnosed with anaemia, whereas those born to mothers diagnosed with anaemia at >30 weeks' gestation were more likely to be born large for gestational age.[30] Results came from an unadjusted analysis and were consequently at critical risk of confounding.[30]

Smith 2019 reported a statistically significantly lower odds of SGA for women with mild anaemia and a higher, but non-significant odds of SGA for women with moderate anaemia.[18] Smith 2019 enrolled a large cohort of women and was judged to be at a moderate risk of bias.[18]

Overall, weaknesses in study design and inconsistent results prevent a robust assessment of the relationship of SGA with ID and anaemia.

Table 18. Association between anaemia and ID in pregnancy and SGA at birth

Study	Exposure definition	Women included in analysis	Results	Study design [Risk of bias]
Studies reporting on anaemia				
Beckert 2019[28] United States	**Anaemia**, defined as the presence or absence of ICD-9 diagnostic code for anaemia	2,869,415	Frequency of SGA at birth: • Women with anaemia (n=284,780), n (%) = 22,936 (8.1) • Women with no anaemia (n=2,584,635), n (%) = 215,610 (8.3) Adjusted RR (95% CI)[a] = 0.9 (0.9 to 0.9)	Cohort (retrospective) [Moderate]
Gaillard, 2014[16] Netherlands	**Anaemia**, defined as haemoglobin ≤11 g/dL or haematocrit ≤33%	7,317	The risk of SGA at birth was increased in women with anaemia (54/982), compared to those without anaemia (241/5,239); this was not significant[b]	Cohort (prospective) [Moderate]
Smith 2019[18] Canada	**Anaemia**, defined as third trimester haemoglobin <11 g/dL, or diagnosis of anaemia made during the birth admission but before birth (based on ICD10 codes)	515,270	Adjusted OR of SGA at birth versus non-anaemic women (n=449,364): • Mild anaemia (n=60,590): 0.83 (95% CI 0.80 to 0.86) • Moderate anaemia (n=2,195): 1.13 (95% CI 0.97 to 1.33)	Cohort (retrospective) [Moderate]
Wiegersma 2019[30] Sweden	**Anaemia**, defined using ICD codes (anaemia complicating pregnancy or IDA)	532,232 births (from 299,768 women)	Frequency of SGA at birth: • Women with anaemia: 684 / 31,018 (2.2%) • Women without anaemia: 11,761 / 501,214 (2.3%) Children born to mothers with anaemia diagnosed at 30 weeks' gestation or less were more likely to be born SGA (OR, 2.81; 95% CI, 2.26 to 3.50) compared with children whose mothers were not diagnosed with anaemia, whereas children whose mothers were diagnosed with anaemia at greater than 30 weeks' gestation were more likely to be born large for gestational age (OR, 1.76; 95% CI, 1.66 to 1.87)	Cohort (prospective) [Critical]
Studies reporting on ID				
Khambalia 2016[29] Australia	**ID**, defined as <12 µg/L serum ferritin	3,795	Frequency of SGA infants born: • Iron deficient (n=742) = 46 (6.6%) women • Iron replete (n=3,053) = 213 (7.6%) women p>0.05	Cohort (prospective) [Critical]

[a]Adjusted for maternal characteristics (race, age, timing of entry into prenatal care, number of prenatal care visits, healthcare insurance plan, participation in supplemental nutrition programme, BMI, drug use, smoking, parity and interpregnancy interval) and significant obstetric outcomes. SGA at birth and infant death within 1 year also adjusted for gestational age. [b]RRs were adjusted for gestational age at enrolment and at blood sampling, maternal age, BMI, parity, ethnicity, education, alcohol consumption during pregnancy, smoking during pregnancy, folic acid supplement use and multivitamin use. Observed associations were attenuated after adjustment for confounding factors.
Abbreviations: CI: confidence interval; ICD: International Classification of Diseases; IDA: iron deficiency anaemia; OR: odds ratio; RR: risk ratio; SGA: small for gestational age; WHO: World Health Organization.

Preterm birth

Preterm birth was reported as an outcome in 1 IDA study,[19] 6 anaemia studies,[12, 16, 18, 23, 28, 30] and 3 ID studies (Table 19).[14, 29, 31] One IDA study and 3 ID studies reported that there was no evidence for a significant association between ID and IDA and preterm birth.[14, 19, 29, 31]

Evidence for an association between anaemia and preterm birth was inconsistent and, given the large number of studies exploring this association, only results from those judged as being at moderate risk of bias are discussed. Two large studies reported no association between anaemia and preterm birth,[23, 28] and 1 further study reported non-significant increases in the frequency of

preterm birth with maternal anaemia.[16] However, 1 study reported significant increases in preterm birth with maternal anaemia;[18] this study reported a positive dose-response relationship and was conducted specifically in women with mild and moderate anaemia.[18] This observed increase in preterm birth is consistent with the Haider 2013 SLR and meta-analysis, which reported an increase in preterm birth in anaemic women from high income countries in their meta-analysis.[12, 18]

Overall, the review found a lack of evidence for an association between either IDA or ID and preterm birth, and inconsistent evidence to support an increase in preterm birth with maternal anaemia of unspecified aetiology.

Table 19. Association between IDA, anaemia and ID in pregnancy and preterm birth

Study	Exposure definition	Women included in analysis	Results	Study design [Risk of bias]
Studies reporting on IDA				
Crispin 2019[19] Australia	**IDA,** was defined as haemoglobin less than 110 g/L during trimesters 1 and 3, and less than 105 gL^{-1} in the second trimester	Trimester 1 = 42 Trimester 2 = 480	No difference in the gestational age at birth was recorded between women who were anaemic and non-anaemic in early pregnancy	Cohort (retrospective) [Critical]
Studies reporting on anaemia				
Beckert 2019[28] United States	**Anaemia**, defined as presence or absence of ICD-9 diagnostic code for anaemia	2,869,415	Frequency of preterm birth (32 to 23 weeks' gestation: • Women with anaemia (n=284,780), n (%) = 21,069 (7.4) • Women with no anaemia (n=2,584,635), n (%) = 148,662 (5.8) Adjusted RR (95% CI)[a] = 1.0 (1.0 to 1.1)	Cohort (retrospective) [Moderate]
Gaillard, 2014[16] Netherlands	**Anaemia**, defined haemoglobin ≤11 g/dL or haematocrit ≤33%	7,317	The risk of preterm birth was increased in women with anaemia (60/998), compared to those without anaemia (260/5,288); this was not significant[b]	Cohort (prospective) [Moderate]
Haider, 2013[12] SLR	Haemoglobin <11.5 g/dL	NA	In high income countries, anaemia was found to increase the odds of preterm birth: adjusted OR 1.26; 95% CI 1.02, 1.57; p<0.001; 12 studies. Significantly higher odds of preterm birth with first or second trimester anaemia (adjusted OR 1.21; 95% CI 1.13 to 1.30; I^2=0%; 7 studies) but not with third trimester anaemia (adjusted OR 1.20; 95% CI 0.80 to 1.79; I^2=90%; 6 studies)	SLR [NA]
Rukuni, 2016[23] Scotland	**Anaemia**, defined as haemoglobin <10.0 g/dL	80,422	Women with severe antenatal anaemia, having a singleton birth, have similar odds of preterm birth (<37 weeks' gestation) compared to women without anaemia (adjusted OR[c] 0.97; 95% CI 0.88 to 1.07; p=0.554)	Cohort (retrospective) [Moderate]
Smith 2019[18] Canada	**Anaemia**, defined as third trimester haemoglobin <11 g/dL, or diagnosis of anaemia made during the birth admission but before birth (based on ICD-10 codes)	515,270	Adjusted OR of preterm birth (<37 weeks' gestation) versus non-anaemic women (n=449,364): • Mild anaemia (n=60,590): 1.09 (95% CI 1.05 to 1.12) • Moderate anaemia (n=2,195): 2.26 (95% CI 2.02 to 2.54)	Cohort (retrospective) [Moderate]
Wiegersma 2019[30] Sweden	**Anaemia**, defined with ICD codes (anaemia	532,232 births (from	Frequency of preterm birth (induced and spontaneous): • Women with anaemia: 2,731[d] / 31,018 (8.8%)	Cohort (prospective) [Critical]

Study	Exposure definition	Women included in analysis	Results	Study design [Risk of bias]
	complicating pregnancy or IDA)	299,768 women)	• Women without anaemia: 26,846[d] / 501,214 (5.3%) Children born to mothers with anaemia diagnosed at 30 weeks' gestation or less were more likely to be born preterm (OR, 7.10; 95% CI, 6.28 to 8.03) compared with children whose mothers were not diagnosed with anaemia, whereas children whose mothers were diagnosed with anaemia at greater than 30 weeks' gestation were more likely to be born post term (OR, 1.56; 95% CI, 1.49 to 1.62)	
Studies reporting on ID				
Bencaiova 2014[14] Switzerland	**ID,** defined as a serum ferritin <20 µg/L and haemoglobin ≥11.0 g/dL	382	Frequency of preterm birth: • Women with non-anaemic ID (n=123), n (%) = 7 (5.7); p versus normal = 0.287 • Women without anaemia or iron depletion (n=189) = 18 (9.5)	Prospective longitudinal study [Critical]
Khambalia, 2015[31] Australia	**ID**, defined as serum ferritin <12 µ/L or Soluble transferrin receptor ≥21 nmol/l	2,254	There is no significant association between ID, measured using serum ferritin in early pregnancy, and preterm birth (OR 0.86; 95% CI 0.57 to 1.30)	Cohort (retrospective) [Serious]
Khambalia 2016[29] Australia	**ID**, defined as <12 µg/L serum ferritin	3,795	Frequency of preterm birth (<37 weeks' gestation): • Iron deficient (n=742) = 28 (4.0%) women • Iron replete (n=3,053) = 112 (4.0%) women p>0.05	Cohort (retrospective) [Critical]

[a]Adjusted for maternal characteristics (race, age, timing of entry into prenatal care, number of prenatal care visits, healthcare insurance plan, participation in supplemental nutrition programme, BMI, drug use, smoking, parity and interpregnancy interval) and significant obstetric outcomes. SGA at birth and infant death within 1 year also adjusted for gestational age. [b]RRs were adjusted for gestational age at enrolment and at blood sampling, maternal age, BMI, parity, ethnicity, education, alcohol consumption during pregnancy, smoking during pregnancy, folic acid supplement use and multivitamin use. Observed associations were attenuated after adjustment for confounding factors. Adjusted for age, parity, smoking status, ethnicity, socio-economic status, BMI and chronic kidney disease. [c]Adjusted for age, parity, smoking status, ethnicity, socio-economic status, BMI and chronic kidney disease. [d]Sum of reported preterm (induced) and preterm (spontaneous) births.
Abbreviations: CI: confidence interval; ICD: International Classification of Diseases; ID: iron deficiency; IDA: iron deficiency anaemia; NA: not applicable; OR: odds ratio; RR: risk ratio; SLR: systematic literature review.

Very preterm birth

Very preterm birth was reported as an outcome in 4 anaemia studies (Table 20).[15, 18, 22, 28] All 4 studies reported significant increases in the occurrence of very preterm birth with maternal anaemia, although the strength of these results varied between studies.[15, 18, 22, 28] Three of the studies were considered to be at moderate risk of bias and therefore results from these studies are prioritised.

Beckert 2019 reported an adjusted RR of 1.1 (95% CI: 1.1 to 1.1) for very preterm birth (<32 weeks' gestation) comparing anaemic with non-anaemic women in a large sample population (n=2,869,415).[28] Räisänen 2013 reported that anaemia was associated with significantly higher odds of extremely preterm (<28 weeks' gestation) singleton birth (adjusted OR 2.48; 95% CI: 1.82 to 3.38) and moderate odds of very preterm (28 to 31+6 weeks' gestation) singleton birth (adjusted OR 1.48; 95% CI: 1.08 to 2.04) in a sample of 1,390,742 women.[22] Smith 2019 also reported significant increases in very preterm birth (<32 weeks' gestation) by anaemia severity (mild anaemia adjusted OR: 1.30; 95% CI: 1.21 to 1.39; moderate anaemia adjusted OR: 3.23; 95% CI: 3.23 to 4.83).[18] Overall, there was moderate evidence to suggest that maternal anaemia, of unspecified aetiology, is associated with an increase in very preterm birth.[15, 18, 22, 28]

Table 20. Association between anaemia in pregnancy and very preterm birth

Study	Exposure definition	Women included in analysis	Results	Study design [Risk of bias]
Studies reporting on anaemia				
Beckert 2019[28] United States	**Anaemia**, defined based on the presence or absence of ICD-9 diagnostic code for anaemia	2,869,415	Frequency of very preterm birth (<32 weeks' gestation): • Women with anaemia (n=284,780), n (%) = 4,349 (1.5) • Women with no anaemia (n=2,584,635), n (%) = 18,978 (0.7) Adjusted RR (95% CI)[a] = 1.1 (1.1 to 1.1)	Cohort (retrospective) [Moderate]
Beta 2013[15] Poland	**Anaemia**, defined as haemoglobin <11 g/dL	1,865	11/31 (35.4%) women with spontaneous very preterm birth (<34 weeks' gestation) diagnosed with anaemia; 886/1,834 (16.1%) of those with term birth diagnosed with anaemia. Univariate logistic regression analysis showed that maternal anaemia, diagnosed during pregnancy, is associated with an increase in the risk of spontaneous preterm birth (11/31 with anaemia) compared to term birth (OR 2.754; 95% CI 1.805 to 4.488; p<0.001)	Case-control [Critical]
Räisänen, 2013[22] Finland	**Anaemia**, defined as haemoglobin <100 g/L	1,390,742	Anaemia is associated with a significantly higher risk of 'extremely preterm' (<28 weeks' gestation) singleton birth (adjusted OR 2.48; 95% CI 1.82 to 3.38) and a moderate risk of 'very preterm' (28 to 31+6 weeks' gestation) singleton birth (adjusted OR 1.48; 95% CI 1.08 to 2.04); anaemia is not significantly associated with a higher odds of 'moderately preterm' (32 to 36+6 weeks' gestation) birth (adjusted OR 0.99; 95% CI 0.88 to 1.12)	Case-control [Moderate]
Smith 2019[18] Canada	**Anaemia**, defined as third trimester haemoglobin <11 g/dL, or diagnosis of anaemia made during the birth admission but before birth (based on ICD-10 codes)	515,270	Adjusted OR of very preterm birth (<32 weeks' gestation) versus non-anaemic women (n=449,364): • Mild anaemia (n=60,590): 1.30 (95% CI 1.21 to 1.39) • Moderate anaemia (n=2,195): 3.95 (95% CI 3.23 to 4.83)	Cohort (retrospective) [Moderate]

[a]Adjusted for maternal characteristics (race, age, timing of entry into prenatal care, number of prenatal care visits, healthcare insurance plan, participation in supplemental nutrition programme, BMI, drug use, smoking, parity and interpregnancy interval) and significant obstetric outcomes. SGA at birth and infant death within 1 year also adjusted for gestational age.
Abbreviations: CI: confidence interval; ICD: International Classification of Diseases; OR: odds ratio; RR: risk ratio.

Neonatal intensive care unit (NICU) admission

NICU admission was reported as an outcome in 2 studies of women with anaemia,[18, 23] and 2 studies of women with ID (Table 21).[14, 29] Neither the 2 ID studies, nor 1 anaemia study, reported any evidence for an association between the exposures and NICU admission.[14, 23, 29] However, the studies of ID were both judged to be at critical risk of bias, with only univariate analyses performed.[14, 29] One anaemia study, judged to be of moderate risk of bias, reported an increased odds of NICU admission for both mild and moderate anaemia in a cohort of 515,270 women.[18]

Overall, the evidence identified on the association between maternal anaemia and increased odds of NICU admission was limited but of moderate strength, generally consistent and included evidence from a study that included predominantly mildly or moderately anaemic women.[18] However, there was a lack of high quality studies exploring the impact of ID on the rate of NICU admission.

Table 21. Association between anaemia and ID in pregnancy and NICU admission

Study	Exposure definition	Women included in analysis	Results	Study design [Risk of bias]
Studies reporting on anaemia				
Rukuni, 2016[23] Scotland	**Anaemia**, defined as haemoglobin <10.0 g/dL	80,422	Neonates born to women with severe antenatal anaemia, having a singleton birth, have similar odds of admission to NICU compared to those born to women without anaemia (adjusted OR[a] 1.01; 95% CI 0.94 to 1.09)	Cohort (retrospective) [Moderate]
Smith 2019[18] Canada	**Anaemia**, defined as third trimester haemoglobin <11 g/dL, or diagnosis of anaemia made during the birth admission but before birth (based on ICD-10 codes)	515,270	Adjusted OR of special care nursery (NICU) admission versus non-anaemic women (n=449,364): • Mild anaemia (n=60,590): 1.21 (95% CI 1.17 to 1.25) • Moderate anaemia (n=2,195): 2.52 (95% CI 2.22 to 2.85)	Cohort (retrospective) [Moderate]
Studies reporting on ID				
Bencaiova 2014[14] Switzerland	**ID**, defined as a serum ferritin <20 µg/L and haemoglobin ≥11.0 g/dL	382	Frequency of admission to NICU: • Women with non-anaemic ID (n=123), n (%) = 0 (0); p versus normal = 1 • Women without anaemia or iron depletion (n=189) = 1 (0.5)	Prospective longitudinal study [Critical]
Khambalia 2016[29] Australia	**ID**, defined as <12 µg/L serum ferritin	3,795	Frequency of infant requiring NICU admission: • Iron deficient (n=742) = 35 (15.6) • Iron replete (n=3,053) = 117 (14.7%) p>0.05	Cohort (prospective) [Critical]

[a]Adjusted for age, parity, smoking status, ethnicity, socio-economic status, BMI and chronic kidney disease.
Abbreviations: CI: confidence interval; ICD: International Classification of Diseases; ID: iron deficiency; IDA: iron deficiency anaemia; NICU: neonatal intensive care unit; OR: odds ratio.

Perinatal mortality

Perinatal mortality was reported as an outcome in 1 study of women with ID[14] and 3 studies of women with anaemia (Table 22).[18, 23, 28] There was no significant difference in the frequency of neonatal death identified between iron supplemented women with ID versus iron supplemented women without anaemia or iron depletion, although this was only explored in a univariate analysis.[14] One study reported no association between anaemia and perinatal mortality,[28] whilst 1 study reported non-significant increases in perinatal mortality with moderate-to-severe maternal anaemia, defined as haemoglobin <10.0 g/dL,[23] and 1 study reported differential odds of perinatal death in anaemic women compared with non-anaemic women, based on the severity of anaemia.[18]

Smith 2019 reported a reduced odds of perinatal death for mildly anaemic women and increased odds of perinatal death for women with moderate anaemia.[18] Smith 2019 was judged to be at a moderate risk of bias and was conducted using large study populations.[18]

Overall, there is limited evidence to suggest that moderate-to-severe anaemia may be associated with increased odds of perinatal mortality, whilst mild anaemia may be associated with lower odds of perinatal mortality.[18, 23]

Table 22. Association between anaemia and ID in pregnancy and perinatal mortality

Study	Exposure definition	Women included in analysis	Results	Study design [Risk of bias]
Studies reporting on anaemia				
Beckert 2019[28] United States	**Anaemia**, defined on the presence or absence of ICD-9 diagnostic code for anaemia	2,869,415	Frequency of infant death within 1 year: • Women with anaemia (n=284,780), n (%) = 1,049 (0.4) • Women with no anaemia (n=2,584,635), n (%) = 5,498 (0.2) Adjusted RR (95% CI)[a] = 1.0 (1.0 to 1.1)	Cohort (retrospective) [Moderate]
Rukuni, 2016[23] Scotland	**Anaemia**, defined as haemoglobin <10.0 g/dL	80,422	Neonates born to women with severe antenatal anaemia, having a singleton birth, have higher odds of early neonatal death compared to those born to women without anaemia (adjusted OR[b] 1.17; 95% CI 0.76 to 1.79)	Cohort (retrospective) [Moderate]
Smith 2019[18] Canada	**Anaemia**, defined as third trimester haemoglobin <11 g/dL, or diagnosis of anaemia made during the birth admission but before birth (based on ICD-10 codes)	515,270	Adjusted OR of perinatal death for mild anaemia versus non-anaemic women (n=449,364): 0.61 (95% CI 0.53 to 0.70). Unadjusted OR of perinatal death for moderate anaemia versus non-anaemic women (n=449,364): 1.99 (95% CI 1.37 to 2.88)	Cohort (retrospective) [Moderate]
Studies reporting on ID				
Bencaiova 2014[14] Switzerland	**ID,** defined as a serum ferritin <20 µg/L and haemoglobin ≥11.0 g/dL	382	Frequency of neonatal death: • Women with non-anaemic ID (n=123), n (%) = 0 (0); p versus normal = 1 • Women without anaemia or iron depletion (n=189) = 1 (0.5)	Prospective longitudinal study [Critical]

[a]Adjusted for maternal characteristics (race, age, timing of entry into prenatal care, number of prenatal care visits, healthcare insurance plan, participation in supplemental nutrition programme, BMI, drug use, smoking, parity and interpregnancy interval) and significant obstetric outcomes. SGA at birth and infant death within 1 year also adjusted for gestational age. [b]Adjusted for age, parity, smoking status, ethnicity, socio-economic status, BMI and chronic kidney disease.
Abbreviations: CI: confidence interval; ICD: International Classification of Diseases; ID: iron deficiency IDA: iron deficiency anaemia; RR: risk ratio; WHO: World Health Organization.

Conclusions

An overview of the evidence for an association between ID, with and without mild or moderate anaemia, during pregnancy and maternal and infant outcomes from studies in which it is unclear if the enrolled women received iron treatment and/or supplementation is presented in

Table 23. This review identified moderate evidence to support an association between maternal anaemia of unspecified aetiology and increases in very preterm birth and maternal transfusion. Positive associations between ID, with or without anaemia, during pregnancy and several other maternal and infant outcomes (maternal: depression, caesarean section; infant: NICU admission, perinatal mortality) were only found in a limited number of higher quality observational studies, introducing uncertainty. Furthermore, for depression, there was additional uncertainty regarding the causality of the observed relationship. Inconsistent and typically poor-quality evidence was identified for PPH, low birth weight, SGA at birth and preterm birth (<37 weeks' gestation), which precludes the formation of any conclusions regarding the direction and strength of any potential association.

Notably, the aetiology of maternal anaemia was not specified in a high proportion of included studies. Although the majority of anaemia during pregnancy is caused by ID,[8] the absence of information about the biological cause of anaemia in these studies introduces uncertainty around the applicability of results to ID and IDA;[8] indeed, for several outcomes, results were inconsistent between anaemic populations and those populations that were confirmed to be ID (including IDA). Furthermore, the severity of anaemia experienced by anaemic women included in the majority of studies remains unclear, although it is likely that the majority of women were not severely anaemic; as such, it is not possible to definitively confirm whether the observed outcomes are reflective of those observed in the population that would be identified in a screening programme (women with untreated ID, with or without mild or moderate anaemia).

The included studies did not clearly report the use of iron supplements or treatments in the enrolled population. Therefore, it was difficult to evaluate whether unreported use of iron supplements or treatments had an effect on the relationship between ID, with or without anaemia, and maternal and infant outcomes. The lack of studies reporting on an untreated population of women in a relevant setting is understandable; given the widespread use of testing in clinical practice and long-standing recommendations to treat anaemic women in local and national guidelines (for example, the British Society of Haematology [BSH] guidelines), it would be unethical to conduct a study in which women were not offered treatment following a diagnosis of anaemia. As an alternative, studies evaluating temporal changes in haemoglobin level may be useful to understand the influence of this confounding factor and permit robust adjustment in analyses. Evidence from studies that did not meet the review eligibility criteria but adjusted for iron use in the enrolled population suggest that there may be an association between maternal ID and an increased risk of antenatal depression[34] and SGA birth (first trimester ID);[20] however, this evidence comes from studies of limited quality and may not be reflective of outcomes after adjustment for iron use, as these studies were not systematically identified.

Overall, there remains considerable uncertainty about the relationship between ID, with or without mild or moderate anaemia, and adverse maternal and infant outcomes.

Table 23. Summary of the association between ID, with and without anaemia, during pregnancy and maternal and infant outcomes

	Exposure[a]	Number of studies[b]	Direction of association[c]	Strength of association (if relevant)[d]	Number of higher quality studies reporting an association[e]	Overall strength of evidence[f]
Maternal outcomes						
Depression	Anaemia	Retrospective: 1	Positive	Weak: 1	0	Poor
Transfusion	Anaemia	Retrospective: 5	Positive	Moderate: 1 Strong: 4	3	Moderate
PPH	Anaemia	Retrospective: 4	Inconsistent	NA	NA	Poor
	IDA	Retrospective: 1	No association	NA	0	Poor
	ID	Retrospective: 1 Prospective: 1	Inconsistent	NA	NA	Poor
Caesarean section	Anaemia	Retrospective: 2 Prospective: 1	Positive	Weak: 2 Moderate: 1	1	Poor
Infection during pregnancy	Anaemia	Prospective: 1	Positive	Weak: 1	0	Poor
Infant outcomes						
Low birth weight	Anaemia	Retrospective: 1 Prospective: 1 SLR: 1	Inconsistent	NA	NA	Poor
	IDA	Retrospective: 1	No association	NA	0	Poor
	ID	Prospective: 1	No association	NA	0	Poor
SGA at birth	Anaemia	Retrospective: 3 Prospective: 3	Inconsistent	NA	NA	Poor
	ID	Prospective: 1	No association	NA	0	Poor
Preterm birth	Anaemia	Retrospective: 3 Prospective: 2 SLR: 1	Inconsistent	NA	NA	Poor
	IDA	Retrospective: 1	Inconsistent	NA	NA	Poor
	ID	Retrospective: 2 Prospective: 1	No association	NA	0	Poor
Very preterm birth	Anaemia	Retrospective: 4	Positive	Weak: 2 Strong: 1 Exposure dependent: 1	3	Moderate
NICU admission	Anaemia	Retrospective: 1	Positive	Weak: 1	1	Poor
	ID	Prospective: 2	No association	NA	0	Poor
Perinatal mortality	Anaemia	Retrospective: 3	Varied by exposure (mild: negative association; moderate-to-severe: positive association)	NA	NA	Poor
	ID	Prospective:1	No association	NA	0	Poor

[a]Anaemia is a condition that occurs when the number of red blood cells, or the concentration of haemoglobin within red blood cells, is reduced. Iron deficiency (ID) is defined as the decrease of the total content of iron in the body, and if this is sufficiently severe to reduce the production of red blood cells, it can cause IDA. [b]Includes Haider 2013 SLR and meta-analysis, which provided evidence on preterm birth and low birth weight in studies of anaemia with unknown aetiology. [c]A positive association indicates that anaemia with/without ID is associated with an increase in a particular outcome; a negative association indicates that anaemia with/without ID is associated with a decrease in a particular outcome. [d]Strength of association took into consideration statistical significance and the size of OR/RR (weak: significant OR/RR = 1.0–<1.5 or non-significant OR/RR or descriptive statistics; moderate: significant OR/RR = ≥1.5–2.0; strong: significant OR/RR = ≥2.0. [e]Studies judged to be at moderate or low risk of bias and reporting statistically significant results from multivariate analyses. Outcomes with an inconsistent direction of association were marked 'NA' for this field. [f]The judgement on the overall strength of evidence takes into account the quality and quantity

of studies contributing to the evidence base for each outcome, including the quantity of studies providing evidence on the same exposure, and study characteristics (for example, study population size). This judgement is distinct to the strength of association, which takes into account the size of effect and statistical significance.
Abbreviations: NA: not applicable; NICU: neonatal intensive care unit; PPH: postpartum haemorrhage; SGA: small for gestational age.

Summary of Findings Relevant to Criterion 1: Criterion not met

Quantity: A total of 18 studies (17 observational and 1 meta-analysis) were identified exploring the association between untreated ID, with or without mild or moderate anaemia, and adverse maternal and infant outcomes in pregnancy. Most of the identified studies (13/18) explored the relationship between anaemia and maternal and/or infant outcomes. Only 3 studies reported on ID only.

Quality: The quality of included studies for Question 1 varied. Seven observational studies were assessed to be at a critical risk of bias, primarily because they relied on univariate analyses susceptible to confounding. Three studies were judged to be at serious risk of bias, primarily because they did not include key covariates in their analyses. The remaining 7 observational studies, as well as the meta-analysis, were judged to be at moderate risk of bias and were the primary source of data for this question. The number of women included in the studies varied considerably (range: 382 to 2,869,415), although most studies (n=16) included over 1,000 women. None of the observational studies were judged to be at a low risk of bias due to confounding. The possibility and consequences of women switching between exposures (for example, a woman initially diagnosed as anaemic becoming non-anaemic) was also considered in this domain; the change in haemoglobin and serum ferritin over time was not reported for the majority of studies, therefore it was not possible to assess the impact of any change in exposure caused by iron use.

None of the included studies reported on iron use in the relevant enrolled population; it was therefore not possible to determine whether unreported iron supplementation, dietary changes or treatment could have impacted upon the women's exposure over time and thus influenced the observed results, or whether iron use was balanced between study groups.

Applicability: All observational studies were conducted in high income countries considered to have sufficiently similar healthcare systems and maternity service provision to the UK setting; 1 study was completed in the UK. One study reported anaemia measurements that aligned with the UK context, 2 defined anaemia as haemoglobin <110 g/L without specifying the trimester it was measured. The applicability of the included studies to the population of women with mild and moderate anaemia is unclear, as most studies did not specify the severity of anaemia in their methodology and did not report sufficient haemoglobin data. Consequently, whilst most of the studies of anaemia used an upper threshold to define anaemia that was broadly aligned with the UK setting (haemoglobin <110 g/L), the proportion of women with severe anaemia in these studies is unclear. Most included studies defined ID as serum ferritin <12 µg/L, which is not aligned with the UK definition of ID.

Consistency: For maternal outcomes, the effect of IDA, with or without anaemia, was inconsistent for PPH. The direction of effect of anaemia on maternal depression, transfusion, caesarean section and infection during pregnancy was consistent. However, there were a limited number of studies for depression (n=1) and infection during pregnancy (n=1), whilst evidence for caesarean section mostly came from descriptive statistics (2/3). For infant outcomes, the effect of IDA with or without anaemia was inconsistent for low birth weight, SGA at birth and preterm birth. A consistent effect was reported for anaemia and very preterm birth. The effect was generally consistent for NICU, whilst evidence for an association between anaemia and perinatal mortality was mixed (moderate-to-severe anaemia: higher odds; mild anaemia: lower odds).

Conclusions: No studies that enrolled a population of women that were explicitly untreated with iron supplements or a prescription iron treatment and were directly relevant to Question 1 were identified, therefore the eligibility criteria were expanded to include studies where it was unclear if women received iron treatment and/or supplementation. Consequently, it was not possible to evaluate the implications of iron use on maternal and infant outcomes or to determine whether such practices were in line with that of untreated pregnant women in the UK; based on clinical guidelines, is likely that there is widespread testing in clinical practice and subsequent treatment in high income countries, meaning that the potential unobserved impact of this on the evidence is high. In addition to this, the quality and consistency of the 18 included studies was low, and it is therefore not possible to draw robust conclusions on an association between untreated ID, with or without mild or moderate anaemia, and maternal and infant outcomes. Additional uncertainties are introduced because the aetiology of maternal anaemia was not specified in a high proportion of included studies. Although the majority of anaemia during pregnancy is caused by ID, the absence of information about the biological cause of anaemia in these studies introduces uncertainty around the applicability of results to ID and IDA; for several outcomes, results were inconsistent between anaemic populations and those populations that were confirmed to have ID (including IDA).

Despite these uncertainties, the highest quality evidence suggested that women with anaemia during pregnancy may experience higher rates of maternal transfusion and very preterm birth. However, even for these outcomes, further high-quality studies (such as that currently being conducted at the Hull & East Yorkshire Hospitals NHS Trust)[9] that provide confirmatory findings would be desirable because the highest quality evidence was still poor and largely inconsistent. Overall, on the basis of the evidence identified in this rapid review, it is difficult to draw robust conclusions about the relationship between ID, with or without anaemia, and adverse maternal and infant outcomes; as such, Criterion 1 is not met due to a lack of evidence.

Criterion 9 – Benefits and harms of treating IDA

9. There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered.

This rapid review searched for contemporary evidence (published since 2014) outlining the benefits and harms of treating pregnant women for IDA and their infants through the question:

Question 2 — What are the benefits and harms of treating pregnant women for IDA to pregnant women and their infants?

Eligibility for inclusion in the review

This review searched for SLRs and meta-analyses, RCTs and cohort studies conducted in UK or similar high income countries, although relevant case-control studies were also considered. Studies were included if they considered a patient population of pregnant women with IDA and if the interventions of interest included oral iron supplementation, iron-fortified diet, a combination of iron supplementation/fortified diet and intravenous (IV) iron versus no iron treatment. Gravidity was not specifically considered as part of the eligibility criteria for this review.

For inclusion in the review, studies were required to report relevant adverse maternal and/or infant outcomes. Adverse maternal outcomes of interest included caesarean section, infection during pregnancy, transfusion, PPH, postpartum mental health problems and breastfeeding problems. Adverse effects of iron treatment were also considered; these were not predefined separately, and instead were passively captured throughout the conduct of the review. Infant outcomes included low birth weight, SGA at birth, preterm birth (<37 weeks' gestation), very preterm birth (<34 weeks' gestation), perinatal mortality, admission to NICU and neurodevelopmental delay. Full details of the eligibility criteria for Question 2 are presented in Table 7.

Studies published since 2014 were eligible for inclusion for Question 2. A previously conducted structured review and gap analysis (Rukuni 2015, searches conducted in 2014) was identified that evaluated the evidence regarding treatment of ID and IDA in pregnancy against the UK NSC criteria; Rukuni 2015 was therefore the basis from which to conduct this current review.

Description of the evidence

One structured review (Rukuni 2015),[13] a systematic review (SLR) conducted by the US Preventative Services Task Force (USPSTF) (Cantor 2015 [manuscript] and McDonagh 2015 [technical report]),[39,

[40] a retrospective cohort study (Arora 2015)[7] and a case-control study (Pels 2015)[6] were identified for Question 2.

For the observational studies identified (Arora 2015 and Pels 2015), it was unclear whether the intervention and control groups were similar in terms of baseline anaemia.[6, 7] In Arora 2015, whilst it was likely that the women with reported iron use were also anaemic, as the data was collected retrospectively and treatment was likely to follow treatment guidelines, this was not explicitly stated in the publication.[7] Pels 2015 specified strict treatment criteria for women to be offered FCM (haemoglobin <9.7 g/dL, despite oral iron), suggesting that the control group would have had a different level of baseline anaemia (haemoglobin ≥9.7 g/dL, implying mild anaemia, or non-anaemic) to the FCM-treated group.[6] In Pels 2015, women treated with FCM were moderately anaemic prior to treatment with median (IQR) haemoglobin levels of 8.4 g/dL (7.7 to 8.9) at first treatment, rising to 10.7 (9.8 to 11.5) g/dL at delivery, and the control group contained a mixture of non-anaemic and moderately-to-mildly anaemic women at delivery (median [IQR] haemoglobin at delivery: 10.8 g/dL [9.8 to 11.8]).[6]

Rukuni 2015 was a structured review and gap analysis, which aimed to appraise the evidence against the UK NSC criteria as to whether a national screening programme could reduce the prevalence of ID and/or IDA in pregnancy, and consequently improve maternal and fetal outcomes.[13] The USPSTF SLR searched for evidence of benefits from treating IDA during pregnancy; this SLR also searched for evidence of harms from treating IDA during pregnancy, although the specified outcomes of interest were adverse events that were not included in this rapid review.[39, 40]

Characteristics of the 2 observational studies and 2 literature reviews are summarised in

Table 24. Further details of the observational studies and literature reviews are provided in Appendix 3 — Summary of individual studies.

Table 24. Characteristics of observational studies included for Question 2

Study Country	Study design	Population	Exposure	Intervention	Reported outcomes
Literature reviews					
Rukuni 2015[13]	Structured review and gap analysis	NR	ID and IDA (not defined)	Prenatal iron (Haider 2013) and IV, oral and intramuscular iron (Reveiz 2011)	Maternal: infections Infant: low birth weight, neonatal death
USPSTF SLR[39, 40]	SLR and meta-analysis	0 studies were identified discussing benefits of treating IDA	IDA (serum ferritin <12 µg/L, haemoglobin <11 g/dL and haematocrit level <33%)	NA	Maternal: caesarean and postpartum depression Infant: low birth weight
Retrospective studies					
Arora 2015[7] High income: Slovakia, Czech Republic Middle income: Hungary, Romania, Ukraine	Retrospective review of birth records conducted in 6 centres across 5 countries	Total: 37,661 singleton births (both vaginal and caesarean; 10.27% of which were preterm births) Slovakia: n=7,256 (4.86% of which were preterm birth) Czech Republic: n=5,483 (10.67% of which were preterm births) The other countries included in this study were of middle income and so irrelevant to this review.	Anaemia (not defined) **Note**: Arora 2015 does not report whether anaemic individuals were the same as those who were reported as using iron	Iron use (not defined) Recommendations for treatment varied across countries	Risk factors for preterm birth (<37 weeks' gestation)
Pels 2015[6] Netherlands	Case-control study; retrospective review of digital birth records	64 cases, defined as pregnant women who had received at least 1 dose of FCM during their pregnancy due to anaemia [timing unspecified] 64 controls, defined as pregnant women who were either non-anaemic or had anaemia to a lesser degree not necessitating IV iron treatment	Anaemia during advanced gestation (haemoglobin <9.7 g/dL)	IV FCM (median dose 1,000 mg) Women with haemoglobin <9.7 g/dL despite oral iron treated with FCM Timing of intervention was not specified, but it can be inferred that at least 75% of the case cohort received treatment in the final weeks of pregnancy (median time of first treatment 244 days, IQR: 224 to 256 days)	Maternal transfusion, caesarean section, very preterm birth and admission to NICU

Abbreviations: FCM: ferric carboxy maltose; ID: iron deficiency; IDA: iron deficiency anaemia; IQR: interquartile range; IV: intravenous; NA: not applicable; NICU: neonatal intensive care unit; NR; not reported.

Quality assessment

Literature reviews

The quality of the Rukuni 2015 structured review and gap analysis and the USPSTF SLR was appraised using the AMSTAR-2 checklist (Table 25);[13, 39, 40] the full appraisals are presented in Table 62 (Appendix 4 — Appraisal for quality and risk of bias).

Rukuni 2015 was judged to meet only 1 of the quality assessment criteria outlined by AMSTAR-2 and is therefore of poor quality; however, it should be noted that Rukuni 2015 was a structured review, rather than a formal SLR, limiting the utility of the AMSTAR-2 checklist. In particular, Rukuni 2015 did not provide a sufficiently detailed description of the eligibility criteria for inclusion in the review, nor provide sufficient information on the methods used.[13] The combined information on methods, provided for the USPSTF SLR, indicated that the SLR met all but 2 of the AMSTAR-2 quality assessment criteria.[39, 40]

Table 25. Summary of AMSTAR-2 assessment for literature reviews evaluating the benefits and harms of treatment for IDA in pregnancy

Question	Rukuni 2015[13]	USPSTF SLR (Cantor 2015[39] and McDonagh 2015[40])
Did the research questions and inclusion criteria for the review include the components of PICO? (Yes/No)	No	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? (Yes/Partial Yes/No)	No	No
Did the review authors explain their selection of the study designs for inclusion in the review? (Yes/No)	No	No
Did the review authors use a comprehensive literature search strategy? (Yes/Partial Yes/No)	Yes	Yes
Did the review authors perform study selection in duplicate? (Yes/No)	Not reported	Yes
Did the review authors perform data extraction in duplicate? (Yes/No)	Not reported	Yes
Did the review authors provide a list of excluded studies and justify the exclusions? (Yes/Partial Yes/No)	No	Yes
Did the review authors describe the included studies in adequate detail? (Yes/Partial Yes/No)	No	Yes
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? (Yes/Partial Yes/No)	Not reported	Yes
Did the review authors report on the sources of funding for the studies included in the review? (Yes/No)	No	Yes
If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results? (Yes/No/No meta-analysis conducted)	No meta-analysis conducted	Yes
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence	No meta-analysis conducted	Yes

synthesis? (Yes/No/No meta-analysis conducted)		
Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review? (Yes/No)	No	Yes
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? (Yes/No)	No	Yes
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? (Yes/No/No meta-analysis conducted)	No meta-analysis conducted	Yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for the review? (Yes/No)	No	Yes

Abbreviations: IDA: iron deficiency anaemia; PICO: population, intervention, comparator, outcome; RoB: risk of bias; SLR: systematic literature review.

Observational studies

The quality of the 2 included observational studies was appraised using the ROBINS-I checklist;[32] a summary is presented in Table 26 and the full appraisals are presented in Table 61 (Appendix 4 — Appraisal for quality and risk of bias). The overall risk of bias was judged to be serious for Arora 2015 and critical for Pels 2015.[6, 7]

Table 26. Summary of ROBINS-I assessments for non-RCTs evaluating the adverse effects of treatment for IDA in pregnancy

Study	Bias due to:							
	Confounding	Participant selection	Classification of interventions	Deviations from intended interventions	Missing data	Measurement of outcomes	Selection of the reported result	Overall risk of bias
Arora 2015[7]	Serious	Moderate	Serious	Low	Moderate	Low	Low	Serious
Pels 2015[6]	Critical	Serious	Low	Low	Low	Low	Low	Critical

Abbreviations: IDA: iron deficiency anaemia; RCT: randomised controlled trial.

Confounding

The risk of bias was judged to be serious for Arora 2015, and critical for Pels 2015. Arora 2015 did not provide any information on potentially confounding variables, with women grouped by the use of iron and the extent to which women switched treatment unclear. Whilst multivariate analyses were performed in Arora 2015 to adjust for potential confounding, many key covariates that may have affected the association between anaemia and preterm birth were not controlled for. Pels 2015 was judged to be at a critical risk of confounding because the 2 groups included in the study were likely to have differed in terms of baseline anaemia, although women in the control group were selected to be a match for cases.

Participant selection

The risk of bias due to participant selection was judged to be moderate for Arora 2015, and serious for Pels 2015. In Arora 2015, the gestational age at intervention was not specified in the eligibility criteria and was not reported in the study publication, and the timing of exposure to ferric carboxymaltose (FCM) is therefore unclear; no adjustment techniques were used to mitigate for the risk of bias in this domain. In Pels 2015, participant selection was based on the presence or absence of the intervention of interest, and, as for Arora 2015, the gestational age at intervention was neither specified in the exclusion criteria nor reported in the study publication.

Classification of interventions

Arora 2015 was judged to be at a serious risk of bias as it failed to define iron usage or specify its timing in the study publication. Furthermore, it was unclear whether individuals with reported iron use were also those who were anaemic. The intervention was clearly defined in Pels 2015, and so the study was judged to be at a low risk of bias.

Deviations from intended interventions

Both Arora 2015 and Pels 2015 were judged to be at a low risk of bias in this domain. For both studies, it was unclear whether there were deviations from the intended intervention. In addition, neither study discussed compliance with treatment or the effect of this on study results. However, if deviations had occurred, given the observational nature of the studies, this was expected to be in line with clinical practice.

Missing data

Bias due to missing data was judged to be moderate in Arora 2015, and low in Pels 2015. In Arora 2015, it was unclear how the analysis dealt with missing data for iron use. For relevant outcomes, data was available for >95% of women in Pels 2015, with no exclusions based on missing baseline characteristics.

Outcome measurements
Both Arora 2015 and Pels 2015 were judged to be at a low risk of bias, as they both investigated objective outcomes which were likely assessed consistently without being influenced by knowledge of the received intervention.

Selection of the reported result
Both Arora 2015 and Pels 2015 were judged to be at a low risk of bias in this domain. The possibility of multiple outcome measurements was judged to be not relevant to the outcomes recorded, and it was deemed unlikely that multiple definitions of the intervention would have been explored.

Results

Literature reviews
Rukuni 2015 reported that relevant evidence supporting Criterion 9 of the UK NSC criteria was identified in their structured review. However, evidence was only available for comparisons between different interventions, and not for comparisons between a relevant intervention and a comparator of no treatment.[12, 41] Therefore, the Rukuni 2015 structured review did not identify any evidence of relevance to Question 2.

The USPSTF SLR similarly identified no randomised trials or observational studies comparing the benefits of IDA treatment that met the inclusion criteria.[39, 40] The USPSTF SLR noted an older poor-quality observational study (n=103) from 1969 that examined the effects of iron treatment (2 oral formulations and IV iron compared with placebo). Although there was a significant increase in haemoglobin levels during the first month of therapy for all groups receiving iron therapy compared with the placebo group, there was no significant difference between treatment groups in haemoglobin or serum iron values at 36 weeks.[40, 42]

Observational studies
The identified studies reported on maternal transfusion, caesarean section, preterm and very preterm birth, and NICU admission. Key results for each of the outcomes are presented in

Table 27. Full details of the included studies and their results can be found in Appendix 3 — Summary of individual studies.

Table 27. Outcomes associated with the treatment of anaemia in pregnancy

Study	Intervention and comparator	Women included in analysis	Results	Study design [Risk of bias]
Maternal Outcomes				
Maternal transfusion				
Pels 2015[6] Netherlands	IV FCM (median dose 1000 mg) vs no treatment	128	Frequency of transfusion • Anaemic women who received FCM during pregnancy (n=64), n (%) = 2 (3%) • Women who did not receive FCM during pregnancy (n=64), n (%) = 3 (5%) • P=0.20	Case-control [Critical]
Caesarean section				
Pels 2015[6] Netherlands	IV FCM (median dose 1000 mg) vs no treatment	128	Frequency of primary[a] caesarean: • Anaemic women who received FCM during pregnancy (n=64), n (%) = 9 (14%) • Women who did not receive FCM during pregnancy (n=64), n (%) = 12 (19%) Frequency of secondary[a] caesarean: • Anaemic women who received FCM during pregnancy (n=64), n (%) = 5 (8%) • Women who did not receive FCM during pregnancy (n=64), n (%) = 8 (13%)	Case-control [Critical]
Infant outcomes				
Preterm birth				
Arora 2015[7] Czech Republic and Slovakia	Iron supplement use vs no iron supplement use	Czech Republic: 5,483 Slovakia: 7,256	Czech Republic: Of women with preterm and term births, 7.9% and 11.1% used iron, respectively Slovakia: Of individuals with preterm and term births, 60.3% and 38.6% used iron, respectively. Iron use was a significant risk factor for preterm birth, with an adjusted RR of 0.4 (95% CI 0.2 to 0.9; p=0.02) **Note:** For both populations, it is unclear whether individuals who received iron were also those who had anaemia	Cohort (retrospective) [Serious]
Very preterm birth				
Pels 2015[6] Netherlands	IV FCM (median dose 1000 mg) vs no treatment	128	Frequency of very preterm birth (<34 weeks' gestation): • Anaemic women who received FCM during pregnancy (n=64), n=0 • Women who did not receive FCM during pregnancy (n=64), n=2	Case-control [Critical]
NICU admission				
Pels 2015[6] Netherlands	IV FCM (median dose 1000 mg) vs no treatment	128	Frequency of NICU admission: • Anaemic women who received FCM during pregnancy (n=64), n=5 • Women who did not receive FCM during pregnancy (n=64), n=5	Case-control [Critical]

[a]Primary caesarean section is where a woman undergoes the procedure for the first time. A secondary caesarean section occurs when the woman has already undergone a previous caesarean section.
Abbreviations: FCM: ferric carboxymaltose; ICU: intensive care unit; IV: intravenous; NICU: neonatal intensive care unit.

Maternal Outcomes

Maternal transfusion

Maternal transfusion was reported by Pels 2015.[6] Pels 2015 reported a non-significant reduction in requirement for RBC transfusion between the proportion of anaemic women who received FCM

during pregnancy and women who did not receive FCM during pregnancy (3% vs 5%; p=0.20). However, this study was judged to be at critical risk of bias and these results are unadjusted naïve comparisons from a cohort of only 128 women, limiting the reliability of the observed results.

Caesarean section

Caesarean section was reported by Pels 2015.[6] The frequency of primary caesarean section was observed to be lower in women who received FCM during pregnancy, occurring at 14% compared with 19% in women who did not receive FCM. Similarly, the frequency of secondary caesarean section was lower in women who received FCM during pregnancy (8%) compared with women who did not receive FCM during pregnancy (13%). The relationship between receipt of FCM during pregnancy and mode of birth (spontaneous vaginal, assisted vaginal, primary caesarean, secondary caesarean) was shown to be non-significant (p=0.29). Importantly, Pels 2015 was judged to be at a critical risk of bias, and the observed relationship is based on unadjusted naïve comparisons in a study cohort of only 128 women; as such, no conclusions can be drawn regarding the association between use of FCM and caesarean section in pregnant women.

Infant outcomes

Preterm birth

Preterm birth, defined as birth at <37 weeks' of gestation, was reported by Arora 2015.[7] In women from Slovakia, iron use was shown to be a significant risk factor for preterm birth (adjusted RR: 0.4; 95% CI: 0.2 to 0.9; p=0.02); of individuals with preterm and term births, 60.3% and 38.6% used iron, respectively. Contrastingly, in women from Czech Republic, 7.9% and 11.1% of individuals with preterm and term births used iron, respectively (RR not reported). As noted above, it is not clear whether women who took iron were also those recorded as being anaemic. Furthermore, this study was judged to be at serious risk of bias, and the timing and nature of iron use is unclear, limiting the conclusions that can be formed from this data.

Very preterm birth

Very preterm birth, defined as birth at <34 weeks' of gestation, was reported by Pels 2015.[6] Very preterm birth was observed in 0% women who received FCM during pregnancy, compared with 3% of women who did not receive FCM during pregnancy. No statistical tests were performed on this comparison. Pels 2015 was judged to be at critical risk of bias and relied on unadjusted naïve comparisons in a study cohort of only 128 women. It is not possible to make conclusions regarding the relationship between anaemia and very preterm birth due to the low quality of evidence.

NICU admission

NICU admission was reported by Pels 2015, who reported that the proportion of women whose neonates were admitted to NICU was the same in individuals who did and did not receive FCM during pregnancy (12.8%).[6] No statistical tests were performed. Alone, these results are not sufficient to confirm the absence of a difference in NICU admissions in women who did and did not receive FCM

during pregnancy; the results are from unadjusted naïve comparisons in a study cohort of only 128 women, and the study was judged to be at critical risk of bias.

Conclusions

A low volume of low-quality evidence was found evaluating the benefits and adverse maternal and infant outcomes associated with treatment for IDA in pregnancy. Rukuni 2015, the structured review that formed the basis of Question 2, did not identify any studies of relevance. An SLR performed by the USPSTF in 2015 similarly identified no randomised trials or observational studies that met the inclusion criteria and that explored the benefits of treating IDA during pregnancy, concluding that rigorous studies are needed to fully understand the short- and long-term effect of routine iron supplementation and screening for IDA in pregnancy on women and their infants.[39, 40] Two further observational studies were identified, 1 of which examined undefined iron use in pregnancy, whereas the other evaluated the use of FCM during pregnancy. Both studies considered anaemic women with an unspecified iron status. Data was available for the following outcomes: maternal transfusion, caesarean section, preterm and very preterm birth, and NICU admission.

Pels 2015, the case-control study evaluating treatment with and without IV FCM, reported an increased proportion of women not treated with FCM requiring RBC transfusion (not significant), undergoing both primary and secondary caesarean (not significant), and giving birth at <34 weeks' gestation (significance not reported), compared with women treated with FCM. No difference was observed in the proportion of women whose neonates were admitted to NICU between these populations. However, this study was judged to be at a critical risk of bias, and the analyses were unadjusted naïve comparisons from a cohort of 128 women, precluding the formation of any conclusions on the relationship between treatment with FCM during pregnancy and multiple maternal outcomes. Furthermore, interpretation of results is complicated by the inconsistencies in exposure to anaemia between the intervention and control groups, meaning that it is not possible to attribute the observed differences in outcomes to FCM use, and these results are not supported by data from any other studies.

Preterm birth was evaluated in Arora 2015, with data from Slovakia and Czech Republic presented as representative of data from high income countries. Prenatal iron use was shown to be a significant risk factor for preterm birth in Slovakia, although this relationship was not observed in Czech Republic. However, it is not possible to conclude the nature of the relationship between iron use and preterm birth; whilst conducted in a reasonably sized study cohort (Slovakia n=7,256; Czech Republic n=5,483), this study was judged to be of serious risk of bias, the study results are not validated in additional studies and the data from the 2 countries was inconsistent. Moreover, as it is unclear whether women who received iron were also anaemic, it is not possible to confirm that the observed outcomes are relevant to the population of interest to this review or whether the 2 groups (iron versus no iron) were balanced.

Given the volume and quality of the evidence identified for Question 2, and issues of attribution, it is not possible to draw robust conclusions from the data; further evidence is therefore required.

Summary of Findings Relevant to Criterion 9: Criterion not met

Quantity: Only 1 structured review, 1 SLR and 2 observational studies on the benefits and adverse maternal and infant outcomes associated with treatment for IDA versus no treatment were identified as relevant to Question 2. The structured review and USPSTF SLR did not identify any relevant studies. For each outcome reported, only 1 observational study provided relevant evidence.

Quality: Pels 2015, which provided evidence for all but 1 of the outcomes reported in this question, was deemed to be of critical risk of bias, and Arora 2015, which provided evidence related to preterm birth, was judged to be of serious risk of bias. This was primarily related to the high likelihood of bias due to confounding. The structured review was judged to only meet one criterion from the AMSTAR-2 checklist and was therefore considered low quality. The USPSTF review met 14/16 AMSTAR-2 criteria and was consequently considered high quality.

Applicability: The applicability of the treatment protocols from the observational studies to the UK setting is unclear. In the UK, first-line treatments for IDA include oral iron supplementation, an iron-fortified diet or a combination of both. In women with confirmed IDA who are intolerant of, or do not respond to oral iron, or where the severity of symptoms requires prompt management (<100 g/L in third trimester), IV iron can also be used, although this is only recommended in the second trimester for safety reasons.[2] However, in Pels 2015, women with haemoglobin <9.7 g/dL despite oral medication were eligible for FCM treatment, and in Arora 2015, it was only reported that treatment recommendations varied across the region. Pels 2015 evaluated anaemia during advanced gestation, and the timing of haematological testing was not reported in Arora 2015; as such, it is unclear whether these studies are applicable to the pregnancy haematological testing schedule used in the UK. Both studies were evaluated in high income countries that are deemed to be similar to the UK setting.

Consistency: The 2 observational studies identified as relevant to Question 2 did not evaluate the same interventions and did not evaluate the same outcomes. As such, the results observed in both studies have not been validated by a second, independent study.

Conclusions: The rapid review identified relevant evidence from 2 low quality observational studies. Both studies were deemed to be at a high risk of bias, precluding the formation of any robust conclusions. In addition, study results were not validated by other independent studies, and the applicability of results to the UK setting is unclear. The structured review and USPSTF SLR that were included did not identify any relevant studies on this topic and therefore contributed no evidence to this rapid review; the study authors drew similar conclusions to this rapid review.

Without further studies to determine the adverse maternal and infant outcomes associated with treatment for IDA in pregnancy, Criterion 9 is not met.

Criteria 11 and 13 – Benefits and harms of screening for IDA

11. There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (such as Down's syndrome or cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.

13. The benefit gained by individuals from the screening programme should outweigh any harms for example from overdiagnosis, overtreatment, false positives, false reassurance, uncertain findings and complications.

This rapid review searched for relevant data from high quality RCTs and non-RCTs (including SLRs, cohort studies, cross-sectional and case-control studies), published since 2014, that could indicate whether an IDA screening programme in pregnant women would be effective in reducing mortality and morbidity and answer the following review question:

Question 3 — What are the benefits and harms of screening for IDA during pregnancy?

Eligibility for inclusion in the review

This review sought to identify RCTs, SLRs and cohort studies conducted in the UK or in a high income country judged to be similar in terms of population, screening methods and technology. Relevant cross-sectional and case-control studies were also considered. Studies were eligible for inclusion if the population comprised pregnant women who were asymptomatic for IDA, and their infants (of the same pregnancy). In circumstances where this was not specified, it was assumed that women were asymptomatic. Gravidity was not specifically considered as part of the eligibility criteria for this review.

The intervention of interest was a screening test to identify IDA, and studies needed to include a comparator of no screening for IDA to be included. Eligible studies were required to report relevant adverse maternal and/or infant outcomes. Adverse maternal outcomes of interest included caesarean section, infection during pregnancy, transfusion, PPH, postpartum mental health problems and breastfeeding problems; infant outcomes included low birth weight, SGA at birth, preterm birth (<37 weeks' gestation), very preterm birth (<34 weeks' gestation), perinatal mortality, admission to NICU and neurodevelopmental delay. Full details of the eligibility criteria are presented in Table 8.

Studies published since 2014 were eligible for inclusion for Question 3. A structured review and gap analysis (Rukuni 2015, searches conducted in 2014) was identified that evaluated the evidence

regarding screening for ID and IDA in pregnancy against the UK NSC criteria; this review was utilised as the starting point from which to conduct this current review.

Description of the evidence

Two reviews were identified as relevant for Question 3.[13, 35, 39] As previously described, Rukuni 2015 was a structured review and gap analysis, which evaluated evidence for whether a population screening programme could reduce the prevalence of ID and/or IDA in pregnancy, and improve the resulting maternal and fetal outcomes, against the UK NSC criteria.[13] The USPSTF SLR searched for evidence on the benefits of screening for IDA during pregnancy. Although the USPSTF SLR also searched for evidence of harms from screening for IDA, the specified outcomes of interest (overdiagnosis, anxiety, labelling) were not included in this rapid review.[39, 40]

Quality assessment

Literature reviews

The quality of the Rukuni 2015 structured review and gap analysis and the USPSTF SLR was appraised using the AMSTAR-2 checklist (Table 28). The full appraisals are presented in Table 62 (Appendix 4 — Appraisal for quality and risk of bias). A brief discussion of these assessments can be found in the quality assessment section for literature reviews under Question 2.

Table 28. Summary of AMSTAR-2 assessment for the literature reviews evaluating the benefits and harms of screening for IDA in pregnancy

Question	Rukuni 2015[13]	USPSTF SLR (Cantor 2015[39] and McDonagh 2015[40])
Did the research questions and inclusion criteria for the review include the components of PICO? (Yes/No)	No	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? (Yes/Partial Yes/No)	No	No
Did the review authors explain their selection of the study designs for inclusion in the review? (Yes/No)	No	No
Did the review authors use a comprehensive literature search strategy? (Yes/Partial Yes/No)	Yes	Yes
Did the review authors perform study selection in duplicate? (Yes/No)	Not reported	Yes
Did the review authors perform data extraction in duplicate? (Yes/No)	Not reported	Yes
Did the review authors provide a list of excluded studies and justify the exclusions? (Yes/Partial Yes/No)	No	Yes
Did the review authors describe the included studies in adequate detail? (Yes/Partial Yes/No)	No	Yes
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? (Yes/Partial Yes/No)	Not reported	Yes

Did the review authors report on the sources of funding for the studies included in the review? (Yes/No)	No	Yes
If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results? (Yes/No/No meta-analysis conducted)	No meta-analysis conducted	Yes
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? (Yes/No/No meta-analysis conducted)	No meta-analysis conducted	Yes
Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review? (Yes/No)	No	Yes
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? (Yes/No)	No	Yes
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? (Yes/No/No meta-analysis conducted)	No meta-analysis conducted	Yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for the review? (Yes/No)	No	Yes

Abbreviations: IDA: iron deficiency anaemia; PICO: population, intervention, comparator, outcome; RoB: risk of bias; SLR: systematic literature review.

Results

The review and gap analysis performed by Rukuni 2015 attempted to identify data relevant to Criterion 11 and 13.[13] However, the review did not identify any screening programmes or randomised trials of screening programmes for ID or IDA in pregnancy.[13] Although the authors speculated that the benefits of screening would outweigh the risks, the lack of data from a formal evaluation was identified as a major gap in the evidence to support the introduction of a screening programme.

Similarly, the USPSTF SLR identified no randomised trials or observational studies comparing clinical outcomes between pregnant women who were screened or not screened for IDA. Therefore, the USPSTF SLR did not identify any evidence of relevance to Question 3.

Conclusions

This rapid review did not identify any evidence of relevance to Question 3.

Summary of Findings Relevant to Criterion 11 and 13: Criterion not met

This rapid review identified 2 studies of relevance to Question 3, a structured review and gap analysis (Rukuni 2015) and a SLR (performed by the USPSTF). The structured review was judged to be of limited quality and did not identify any evidence that considered the relationship between screening for IDA in pregnancy and adverse maternal and/or infant outcomes; the USPSTF SLR was conducted to a high quality, but similarly did not identify any evidence to inform Question 3.

The lack of evidence supporting Criteria 11 and 13 precludes drawing any conclusions on the appropriateness of screening for IDA in pregnancy. As such, Criteria 11 and 13 are not met.

Review summary

Conclusions and implications for policy

This rapid review did not identify new evidence to change the UK National Screening Committee (NSC)'s position that a national screening programme should not be recommended in the UK at this time. Three questions were considered in this rapid review: (1) What are the maternal and infant outcomes associated with untreated iron deficiency (ID), with or without mild or moderate anaemia in pregnancy?; (2) What are the benefits and harms of treating pregnant women for IDA to pregnant women and their infants?; (3) What are the benefits and harms of screening for IDA during pregnancy?

Overall, 22 relevant studies were identified in this rapid review, with the majority (n=18) deemed relevant for Question 1; notably, the evidence base for Question 1 consisted of studies in which it was not clear whether women received iron treatment and/or supplementation, rather than an untreated population of women. Importantly, for all review questions, most of the observational studies were judged to be at a serious risk of bias or worse (n=12).

Importantly, for Question 1, no studies stated whether included women received iron supplementation and/or active treatment for their anaemia; studies where this was unclear were therefore included. As such, it was not possible to determine whether some women had been screened and subsequently prescribed iron, which may have impacted the observed results by modifying the ID (and anaemia). This was a major limitation that meant an association between untreated ID, with or without mild/moderate anaemia, and maternal and infant outcomes was difficult to establish.

For Question 1, the identified studies reported on 11 outcomes of relevance: depression, maternal transfusion, postpartum haemorrhage (PPH), caesarean section, infection during pregnancy, low birth weight, small for gestational age (SGA) at birth, preterm birth, very preterm birth, neonatal intensive care unit (NICU) admission and perinatal mortality. Moderate evidence was identified that suggested that women with anaemia during pregnancy may experience higher rates of maternal transfusion[17, 18, 23, 25, 28] and very preterm birth,[15, 18, 22, 28] although the quality and consistency of included studies prevents generation of robust conclusions for the other reported outcomes of relevance. As such, further, high-quality studies would be required to validate the observed relationship between ID, with and without anaemia, in pregnancy and adverse maternal and infant outcomes; further evidence would also be desirable for the outcomes of maternal transfusion and very preterm birth. No studies reported on infant neurodevelopmental delay.

The relevance of the results from studies included for Question 1 to the UK setting was unclear. Only 1 of the included studies were completed in the UK.[23] In the UK, anaemia in pregnancy is defined as

haemoglobin <110 g/L in the first trimester, and <105 g/L in the second and third trimesters, whilst a serum ferritin level of <30 µg/l is considered indicative of ID.[2] Contrastingly, the included studies used a variety of thresholds to define anaemia, and the reporting of haematological testing was not consistent; some studies failed to report the definition of anaemia, and others determined the presence or absence of anaemia based on International Classification of Diseases codes. Furthermore, the severity of anaemia in most of the included studies was unclear. It was therefore not possible to determine whether the observed outcomes were reflective of those observed in the population that would be screened by a national screening programme (women with ID, with or without mild or moderate anaemia).

For Question 2, 2 retrospective studies evaluating the adverse maternal and infant outcomes associated with treatment for IDA (prenatal iron use and ferric carboxymaltose [FCM]) versus no treatment were identified,[6, 7] as well as a structured review and SLR.[13, 39, 40] The structured review and SLR did not identify any relevant evidence for Question 2. The 2 retrospective observational studies provided evidence for 2 maternal outcomes (transfusion and caesarean section) and 3 infant outcomes (preterm birth, very preterm birth and NICU admission), however only 1 study provided relevant evidence for each outcome and treatment reported; as such, the results observed in both studies have not been evaluated by additional, independent studies. For both observational studies, there were concerns over whether treatment and control groups had similar severities of anaemia, and therefore whether the observed results could be attributed to treatment or whether they are the result of differing baseline exposure to anaemia. Given concerns related to risk of bias, and validation of results, no conclusions can be drawn regarding the adverse maternal and infant outcomes associated with treatment for IDA in pregnancy and further studies are necessary. Furthermore, the generalisability of these studies to UK clinical practice is not clear; specifically, it is unclear whether the thresholds at which iron treatment is given are aligned.

For Question 3, 1 structured review and 1 SLR were identified for inclusion.[13, 35, 39] Neither review identified any evidence with which to determine the benefits and harms of screening for IDA during pregnancy, compared to no screening. As such, the benefits and harms of screening for IDA in pregnancy remain unclear.

Finally, most of the identified studies explored the relationship between anaemia and maternal and/or infant health outcomes, without specifying the underlying aetiology of anaemia. Whilst ID is known to be the most common cause of anaemia during pregnancy, accounting for anaemia in 90% of pregnant women,[8] other aetiologies can occur. As such, the generalisability of the data from women with anaemia to the IDA population is not clear. Furthermore, for multiple outcomes, inconsistent results were reported between the anaemic and ID/IDA populations. No robust conclusions can be drawn regarding these data due to the low quantity and quality of the available data for ID and IDA.

In summary, the adverse maternal and infant outcomes associated with untreated, asymptomatic IDA, and the benefits and harms associated with both screening for and treating IDA remain unclear,

and no robust conclusions can be drawn for any of the questions. This aligns with guidelines produced by the National Institute for Health and Care Excellence (NICE), the United States Preventative Services Task Force and the Canadian Agency for Drugs and Technologies in Health. Whilst the UK NSC recognise that testing for IDA is a long established clinical practice in UK antenatal care, which is recommended in guidance produced by NICE and the British Society for Haematology,[2, 3] this rapid review did not identify new evidence to change the UK NSC's position that a formal national screening programme should not be recommended.

Limitations

This review only included peer-reviewed journal publications and excluded publications that were not peer-reviewed. Grey literature was not searched. This may have led to the exclusion of relevant evidence. However, this is an accepted methodological adjustment for a rapid review and is unlikely to have resulted in the review missing any pivotal studies.

Only studies published in English were included, and the full text for one study was not available.

Appendix 1 — Search strategy

Electronic databases

The search strategy included searches of the databases shown in Table 29. MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print and Embase were searched simultaneously using Ovid SP. The Cochrane Library databases were searched simultaneously via the Wiley Online platform. Database of Abstracts of Reviews of Effects (DARE) was searched via the Centre for Reviews and Dissemination (CRD) website. Searches were performed simultaneously for all questions.

Table 29. Summary of electronic database searches and dates

Database	Platform	Searched on date	Date range of search
MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print	Ovid SP	2nd March 2020	1946 to 28th February 2020
Embase	Ovid SP	2nd March 2020	1974 to 28th February 2020
The Cochrane Library, including: - Cochrane Database of Systematic Reviews (CDSR) - Cochrane Central Register of Controlled Trials (CENTRAL)	Wiley Online	2nd March 2020	CDSR: Issue 2 of 12, February 2020 CENTRAL: Issue 2 of 12, February 2020
Database of Abstracts of Reviews of Effects (DARE)	Centre for Reviews and Dissemination, University of York	2nd March 2020	DARE: Issue 2 of 4, April 2015

Search Terms

Search terms included combinations of free text and subject headings (Medical Subject Headings [MeSH] for MEDLINE, and Emtree terms for Embase), grouped into the following categories:

- disease area: anaemia in pregnancy
- study design: RCTs, non-RCTs and observational studies
- other term group: maternal and infant outcomes

Search terms for MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print and Embase are shown in Table 30, search terms for the Cochrane Library databases are shown in Table 31, and search terms for DARE are shown in Table 32.

Table 30. Search strategy for MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print and Embase (Searched via Ovid SP)

Term group	#	Search terms	Results
Anaemia	1	exp Anemia, Iron-Deficiency/ or exp iron deficiency anemia/ or exp iron deficiency/	47309
	2	(iron adj3 (deficien$ or deplet$ or shortage or insufficien$ or low) or (low adj3 (h?emoglobin or Hb))).ti,ab,kw,kf.	75639
	3	Anemia/	225358
	4	(an?emi$).ti,ab,kw,kf.	357572
	5	or/1-4	487998
Pregnancy	6	exp Pregnancy/ or Prenatal Care/ or (pregnan$ or gestation$ or prenatal$ or antenatal$ or pre-natal$ or ante-natal$ or maternal$).ti,ab.	2300841
Maternal outcomes	7	exp Pregnancy Outcome/	129535
	8	(pregnancy outcome$).ti,ab,kw,kf.	59685
	9	exp Cesarean section/	137819
	10	((rate$ or incidence or prevalence) adj3 (C?esarean section or C?esarean delivery or C section)).ti,ab,kw,kf.	16051
	11	exp Pregnancy Complications, Infectious/ or pregnancy complication/	252082
	12	((infect$ or transfusion) adj3 pregn$).ti,ab,kw,kf.	29856
	13	exp Pregnancy Complications, Hematologic/ or blood transfusion/	295116
	14	exp Postpartum Hemorrhage/	20234
	15	((postpartum or post partum or puerperal or postnatal or post natal) adj3 h?emorrhage).ti,ab,kw,kf.	17415
	16	exp Depression, Postpartum/ or exp puerperal depression/ or exp postnatal depression/	8072
	17	((postpartum or post partum or puerperal or postnatal or post natal) adj3 (mental health or depress$ or mental disorder)).ti,ab,kw,kf.	16772
	18	exp Breast Feeding/ or exp lactation/	168081
	19	((breastfeeding or breast feeding or lactat$) adj3 (problem$ or duration or length or time)).ti,ab,kw,kf.	17359
	20	or/7-19	855914
	21	exp "parameters concerning the fetus, newborn and pregnancy"/	361367
Infant outcomes	22	((neonatal or infant or f?etal or newborn) adj outcome$).ti,ab,kw,kf.	42260
	23	exp Infant, Low Birth Weight/ or exp low birth weight/	94309
	24	(low birth weight or low birthweight).ti,ab,kw,kf.	76883
	25	Exp Infant, Small for Gestational Age/ or exp small for date infant/	22255
	26	(small for gestational age or SGA or small for date).ti,ab,kw,kf.	33613
	27	Premature Birth/ or prematurity/ or Obstetric Labor, Premature/ or premature labor/	164663
	28	((premature or pre-term or preterm or early) adj3 (birth or labo?r)).ti,ab,kw,kf.	89625
	29	exp Perinatal Mortality/ or exp Perinatal Death/	30709
	30	(intrauterine fetal demise or IUFD or stillbirth or still birth or stillborn or ((antenatal or postnatal or perinatal) adj3 (death or mortality))).ti,ab,kw,kf.	60944

Term group	#	Search terms	Results
	31	Intensive Care Units, Neonatal/ or Intensive Care, Neonatal/ or neonatal intensive care unit/ or newborn intensive care/	53960
	32	((NICU or hospital or special care or intensive care) adj3 admission$).ti,ab,kw,kf.	157916
	33	Neurodevelopmental Disorders/ or Developmental Disabilities/ or developmental delay/ or developmental disorder/	225576
	34	((neurodevelopmental or intellect$) adj3 (delay or disorder$)).ti,ab,kw,kf.	29689
	35	or/21-34	1001079
RCTs	36	exp Randomized Controlled Trials as Topic/	308322
	37	exp Randomized Controlled Trial/	1093719
	38	exp Random Allocation/	188337
	39	exp Randomization/	188337
	40	exp Double Blind Method/	326044
	41	exp Single Blind Method/	66177
	42	exp Single Blind Procedure/	38049
	43	exp Double Blind Procedure/	169817
	44	exp Crossover Procedure/	62255
	45	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).ti,ab,kf.	404192
	46	exp Clinical Trial/	2319040
	47	Clinical trial, phase i.pt.	19967
	48	Clinical trial, phase ii.pt.	32077
	49	Clinical trial, phase iii.pt.	16223
	50	Clinical trial, phase iv.pt.	1835
	51	exp Phase 1 Clinical Trial/ or exp Clinical trial, phase I/	76825
	52	exp Phase 2 Clinical Trial/ or exp Clinical trial, phase II/	111153
	53	exp Phase 3 Clinical Trial/ or exp Clinical trial, phase III/	61649
	54	exp Phase 4 Clinical Trial/ or exp Clinical trial, phase IV/	5626
	55	Controlled clinical trial.pt.	93545
	56	Randomized controlled trial.pt.	500433
	57	Multicenter study.pt.	266667
	58	Clinical trial.pt.	521309
	59	exp Clinical Trials as Topic/	653633
	60	trial$.ti.	670638
	61	(clinical adj trial$).ti,ab,kf.	869806
	62	exp Placebos/	381249
	63	exp Placebo/	346515
	64	placebo$.ti,ab,kf.	516135
	65	randomly allocated.ti,ab,kf.	62420
	66	(allocated adj2 random$).ti,ab,kf.	69532
	67	random allocation.ti,ab,kf.	3673
	68	random assignment.ti,ab,kf.	5157
	69	randomized.ti,ab.	1239063
	70	randomised.ti,ab.	250392
	71	randomisation.ti,ab,kf.	21471
	72	randomization.ti,ab,kf.	71509
	73	randomly.ti,ab.	762608

Term group	#	Search terms	Results
	74	RCT.ti,ab,kf.	57750
	75	Open-label trial$.ti,ab,kf.	9246
	76	Open-label stud$.ti,ab,kf.	21302
	77	Non-blinded stud$.ti,ab,kf.	300
	78	or/36-77	4674946
Non-RCTs and observational studies	79	exp Cohort Studies/	2513201
	80	exp Cohort Analysis/	2513201
	81	cohort analy$.ti,ab,kf.	20853
	82	(cohort adj (study or studies)).ti,ab,kf.	485223
	83	exp Cross-sectional studies/	655646
	84	(cross-sectional adj (study or studies)).ti,ab,kf.	366027
	85	exp Longitudinal Studies/ or exp Longitudinal study/	267679
	86	Longitudinal.ti,ab,kf.	559853
	87	exp Follow-Up Studies/	2140600
	88	exp Follow-Up/	1506133
	89	(follow up adj (study or studies)).ti,ab,kf.	112127
	90	exp Prospective Studies/ or exp Prospective study/	1113239
	91	(Prospective adj (study or studies)).ti,ab,kf.	424760
	92	(evaluation adj (study or studies)).ti,ab,kf.	12680
	93	exp Retrospective Studies/ or exp Retrospective study/	1685850
	94	retrospective$.ti,ab.	1900108
	95	(chart adj3 review).ti,ab,kf.	117772
	96	exp Observational studies/ or exp Observational study/	264942
	97	(observational adj (study or studies)).ti,ab,kf.	262966
	98	((single arm or single-arm) adj3 (study or studies or trial$)).ti,ab,kf.	15783
	99	or/79-98	6734711
Exclusion terms	100	("Conference Abstract" or "Conference Review" or comment or editorial or note or case reports or news or news release).pt.	8588068
	101	(case stud$ or case report$).ti,ab.	1041796
	102	historical article/ or case study/	2500666
	103	animals/ not humans/	5591520
	104	or/100-103	15046354
Combinations	105	20 or 35	1667169
	106	78 or 99	10261390
	107	5 and 6 and 105 and 106	9233
	108	107 not 104	7562
	109	limit 108 to yr=2012-current	3965
	110	remove duplicates from 109	2822

Table 31. Search strategy for the Cochrane Library Databases (Searched via the Wiley Online platform)

Term group	#	Search terms	Results
Anaemia	1	[mh "Anemia, Iron-Deficiency"] or [mh "iron deficiency anemia"] or [mh "iron deficiency"]	1269

Term group	#	Search terms	Results
	2	(iron NEAR/3 (deficien* or deplet* or shortage or insufficien* or low) or low NEAR/3 (h?emoglobin or Hb)):ti,ab,kw	4452
	3	[mh ^Anemia]	2347
	4	(an?emi*):ti,ab,kw	95318
	5	{OR #1-#4}	96718
Pregnancy	6	[mh Pregnancy] or [mh ^"Prenatal Care"] or (pregnan* or gestation* or prenatal* or antenatal* or pre-natal* or ante-natal* or maternal*):ti,ab	71135
Maternal outcomes	7	[mh "Pregnancy Outcome"]	3520
	8	(pregnancy NEXT outcome?):ti,ab,kw	6300
	9	[mh "Cesarean section"]	2989
	10	((rate* or incidence or prevalence) NEAR/3 ("C?esarean section" or "C?esarean delivery" or "C ?section")):ti,ab,kw	25
	11	[mh "Pregnancy Complications, Infectious"] or [mh ^"pregnancy complication"]	2733
	12	((infect* or transfusion) NEAR/3 pregn*):ti,ab,kw	1842
	13	[mh "Pregnancy Complications, Hematologic"] or [mh ^"blood transfusion"]	2106
	14	[mh "Postpartum Hemorrhage"]	621
	15	((postpartum or "post partum" or puerperal or postnatal or "post natal") NEAR/3 h?emorrhage):ti,ab,kw	1879
	16	[mh "Depression, Postpartum"]	545
	17	((postpartum or "post partum" or puerperal or postnatal or "post natal") NEAR/3 ("mental health" or depress* or "mental disorder")):ti,ab,kw	1741
	18	[mh "Breast Feeding"] or [mh ^lactation]	2174
	19	((breastfeeding or "breast feeding" or lactat*) NEAR/3 (problem* or duration or length or time)):ti,ab,kw	1189
	20	{OR #7-#19}	20113
	21	((neonatal or infant or f?etal or newborn) NEXT outcome*):ti,ab,kw	3906
Infant outcomes	22	[mh "Infant, Low Birth Weight"]	2136
	23	("low birth weight" or "low birthweight"):ti,ab,kw	5372
	24	[mh ^"Premature Birth"] or [mh ^"Obstetric Labor, Premature"]	2067
	25	[mh "Infant, Small for Gestational Age"]	272
	26	("small for gestational age" or SGA or "small for date").ti,ab,kw	1397
	27	((premature or pre-term or preterm or early) NEAR/3 (birth or labo?r)):ti,ab,kw	6548
	28	[mh "Perinatal Mortality"] or [mh "Perinatal Death"]	157
	29	("intrauterine fetal demise" or IUFD or stillbirth or "still birth" or stillborn or ((antenatal or postnatal or perinatal) NEAR/3 (death or mortality))):ti,ab,kw	2181
	30	[mh ^"Intensive Care Units, Neonatal"] or [mh ^"Intensive Care, Neonatal"]	969
	31	((NICU or hospital or "special care" or "intensive care") NEAR/3 admission*):ti,ab,kw	12969
	32	[mh "Neurodevelopmental Disorders"] or [mh ^"Developmental Disabilities"]	7477
	33	((neurodevelopmental or intellect*) NEAR/3 (delay or disorder*)):ti,ab,kw	580
	34	{OR #21-#33}	36577
Combinations	35	#20 OR #34	52585
	36	#5 and #6 and #35	2104

Term group	#	Search terms	Results
	37	#36 in CDSR February 2012–February 2020	210
	38	#36 in CENTRAL 2012–2020	914

Table 32. Search strategy for Database of Abstracts of Reviews of Effects (Searched via the Centre for Reviews and Dissemination website)

Term group	#	Search terms	Results
Anaemia	1	MeSH DESCRIPTOR Anemia, Iron-Deficiency EXPLODE ALL TREES	68
	2	((iron NEAR2 (deficien* or deplet* or shortage or insufficien* or low) or (deficien* or deplet* or shortage or insufficien* or low) NEAR2 iron or low NEAR2 (h?emoglobin or Hb) or (h?emoglobin or Hb) NEAR2 low))	145
	3	MeSH DESCRIPTOR Anemia	185
	4	((an?emi*))	734
	5	(#1 or #2 or #3 or #4)	751
Pregnancy	6	MeSH DESCRIPTOR Pregnancy EXPLODE ALL TREES	2574
	7	MeSH DESCRIPTOR Prenatal Care	192
	8	(#6 or #7)	2586
	9	((pregnan* or gestation* or prenatal* or antenatal* or pre-natal* or ante-natal* or maternal*))	5087
	10	(#8 or #9)	5114
Maternal outcomes	11	MeSH DESCRIPTOR Pregnancy Outcome EXPLODE ALL TREES	502
	12	(("pregnancy outcome*"))	574
	13	MeSH DESCRIPTOR Cesarean section EXPLODE ALL TREES	238
	14	(((rate* or incidence or prevalence) NEAR2 ("C?esarean section" or "C?esarean delivery" or C?section) or ("C?esarean section" or "C?esarean delivery" or C?section) NEAR2 (rate* or incidence or prevalence)))	128
	15	MeSH DESCRIPTOR Pregnancy Complications, Infectious EXPLODE ALL TREES	229
	16	(((infect* or transfusion) NEAR2 pregn* or pregn* NEAR2 (infect* or transfusion)))	285
	17	MeSH DESCRIPTOR Pregnancy Complications, Hematologic EXPLODE ALL TREES	29
	18	MeSH DESCRIPTOR blood transfusion	379
	19	(#17 or #18)	408
	20	MeSH DESCRIPTOR Postpartum Hemorrhage EXPLODE ALL TREES	51
	21	(((postpartum or "post partum" or puerperal or postnatal or "post natal") NEAR2 h?emorrhage or h?emorrhage NEAR2 (postpartum or "post partum" or puerperal or postnatal or "post natal")))	122
	22	MeSH DESCRIPTOR Depression, Postpartum EXPLODE ALL TREES	67
	23	(((postpartum or "post partum" or puerperal or postnatal or "post natal") NEAR2 ("mental health" or depress* or "mental disorder") or ("mental health" or	124

Term group	#	Search terms	Results
		depress* or "mental disorder") NEAR2 (postpartum or "post partum" or puerperal or postnatal or "post natal")))	
	24	MeSH DESCRIPTOR Breast Feeding EXPLODE ALL TREES	131
	25	MeSH DESCRIPTOR lactation	18
	26	(#24 or #25)	143
	27	(((breastfeeding or "breast feeding" or lactat*) NEAR2 (problem* or duration or length or time) or (problem* or duration or length or time) NEAR2 (breastfeeding or "breast feeding" or lactat*)))	45
	28	(#11 or #12 or #13 or #14 or #15 or #16 or #19 or #20 or #21 or #22 or #23 or #26 or #27)	1886
Infant outcomes	29	(((neonatal or infant or f?etal or newborn) NEAR1 outcome* or outcome* NEAR1 (neonatal or infant or f?etal or newborn)))	428
	30	MeSH DESCRIPTOR Infant, Low Birth Weight EXPLODE ALL TREES	166
	31	(("low birth weight" or "low birthweight"))	391
	32	MeSH DESCRIPTOR Infant, Small for Gestational Age EXPLODE ALL TREES	21
	33	(("small for gestational age" or SGA or "small for date"))	97
	34	MeSH DESCRIPTOR Premature Birth	143
	35	MeSH DESCRIPTOR Obstetric Labor, Premature	128
	36	(#34 or #35)	256
	37	(((premature or pre-term or preterm or early) NEAR2 (birth or labo?r) or (birth or labo?r) NEAR2 (premature or pre-term or preterm or early)))	555
	38	MeSH DESCRIPTOR Perinatal Mortality EXPLODE ALL TREES	22
	39	MeSH DESCRIPTOR Perinatal Death EXPLODE ALL TREES	1
	40	(#38 or #39)	22
	41	(("intrauterine fetal demise" or IUFD or stillbirth or "still birth" or stillborn or ((antenatal or postnatal or perinatal) NEAR2 (death or mortality)) or ((death or mortality) NEAR2 (antenatal or postnatal or perinatal))))	332
	42	MeSH DESCRIPTOR Intensive Care Units, Neonatal	64
	43	MeSH DESCRIPTOR Intensive Care, Neonatal	46
	44	(#42 or #43)	108
	45	(((NICU or hospital or "special care" or "intensive care") NEAR2 admission* or admission* NEAR2 (NICU or hospital or "special care" or "intensive care")))	1189
	46	MeSH DESCRIPTOR Neurodevelopmental Disorders EXPLODE ALL TREES	626
	47	MeSH DESCRIPTOR Developmental Disabilities	85
	48	(#46 or #47)	626
	49	(((neurodevelopmental or intellect*) NEAR2 (delay or disorder*) or (delay or disorder*) NEAR2 (neurodevelopmental or intellect*)))	33
	50	(#29 or #30 or #31 or #32 or #33 or #36 or #37 or #40 or #41 or #44 or #45 or #48 or #49)	3059
Combinations	51	(#28 or #50)	4472
	52	(#5 and #10 and #51)	59
	53	(#52) IN DARE FROM 2012 TO 2020	23

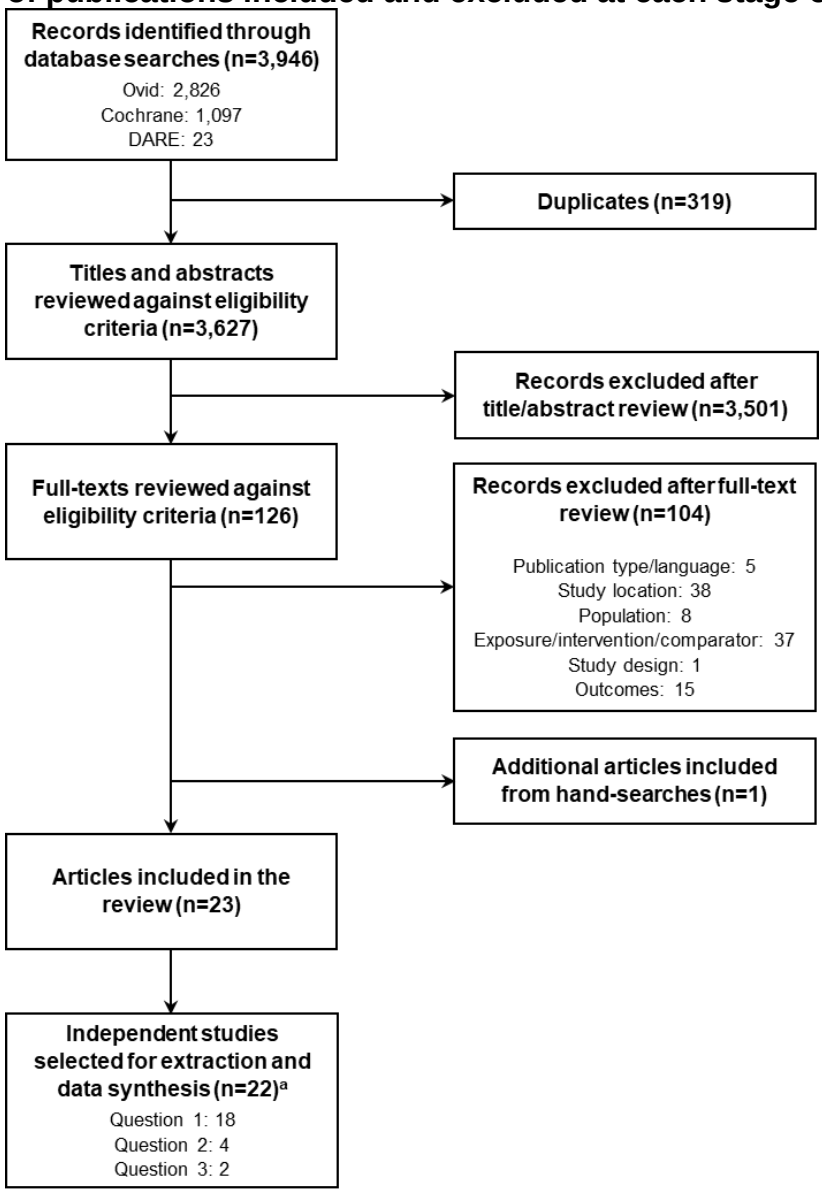
Results were imported into EndNote and de-duplicated.

Appendix 2 — Included and excluded studies

PRISMA flowchart

Figure 1 summarises the volume of publications included and excluded at each stage of the review. Twenty-two studies were ultimately judged to be relevant to 1 or more review questions and were considered for extraction. Publications that were included or excluded after the review of full-text articles are detailed below.

Figure 1. Summary of publications included and excluded at each stage of the review



[a]22 independent studies were selected for extraction as Cantor 2015 and McDonagh 2015 reported methods and results for the same systematic literature review.

Publications included after review of full-text articles

The 23 publications ultimately included are summarised in Table 33 below.

Table 33. Summary of publications included after review of full-text articles, and the question(s) each publication was identified as being relevant to

Study	Question	Exposure (Q1), intervention (Q2) or screening programme (Q3)
Beckert 2019[28]	Q1	Anaemia (ICD-9 diagnostic codes for anaemia)
Bencaiova 2014[14]	Q1	Non-anaemic ID (serum ferritin <20 µg/L and haemoglobin ≥11.0 g/dL)
Beta 2013[15]	Q1	Anaemia (haemoglobin <11 g/dL)
Biguzzi 2012[27]	Q1	Anaemia (impact of 1 g/dL increases in antenatal haemoglobin 1-month pre-delivery)
Cantor 2015[39]	Q2, Q3	NA
Crispin 2019[19]	Q1	Anaemia (haemoglobin <110 g/L in first and third trimesters, <105 g/L in second trimester)
Ehrenthal 2012[25]	Q1	Anaemia (haemoglobin ≤10.5 and >9.5 g/L, severe anaemia defined as haemoglobin ≤9.5 g/L)
Gaillard 2014[16]	Q1	Anaemia (haemoglobin ≤11 g/dL, haematocrit ≤33%)
Haider 2013[12]	Q1	Anaemia (haemoglobin <11.5 g/dL)
Khambalia 2015[31]	Q1	ID (serum ferritin <12 µg/L or soluble transferrin receptor ≥21 nmol/l)
Khambalia 2016[29]	Q1	ID (serum ferritin <12 µg/L)
McDonagh 2015[40]	Q2, Q3	NA
Nyflot 2017[24]	Q1	Anaemia (haemoglobin ≤9.0 g/dL, recorded at start of pregnancy)
Orlandini 2017[26]	Q1	Anaemia (mild, third trimester, haemoglobin ≥9 g/dl and ≤11 g/dl)
Petty 2018[17]	Q1	Anaemia (haemoglobin <11 g/dL)
Räisänen 2013[22]	Q1	Anaemia (haemoglobin <100 g/L)
Räisänen 2014[21]	Q1	Anaemia (haemoglobin <100 g/L)
Rukuni 2016[23]	Q1	Anaemia (haemoglobin <10.0 g/dL)
Smith 2019[18]	Q1	Anaemia (third trimester haemoglobin <11 g/dL, or diagnosis of anaemia made during the delivery admission but before delivery [based on ICD-10 codes])
Wiegersma 2019[30]	Q1	Anaemia (ICD-10 diagnostic codes for anaemia)
Arora 2015[7]	Q2	Anaemia (not defined)
Pels 2015[6]	Q2	Ferric carboxymaltose
Rukuni 2015[13]	Q2, Q3	NA

Abbreviations: ICD: International Classification of Diseases; ID: iron deficiency; IDA: iron deficiency anaemia.

Publications excluded after review of full-text articles

Of the 126 publications included after the review of titles and abstracts, 98 were ultimately judged not to be relevant to this review. These publications, along with reasons for exclusion, are listed in Table 34.

Table 34. Publications excluded after review of full-text articles

Reference	Reason for exclusion
Abalos, E., Chamillard, M., Diaz, V., Tuncalp, O. and Gulmezoglu, A. M. Antenatal care for healthy pregnant women: a mapping of interventions from existing guidelines to inform the development of new WHO guidance on antenatal care. BJOG: An International Journal of Obstetrics & Gynaecology. 2016; 123 (4): 519-28.	SLR scope not aligned; majority low income countries.
Abraha, I., Bonacini, M. I., Montedori, A., Di Renzo, G. C., Angelozzi, P., Micheli, M., Germani, A., Carloni, D., Scaccetti, A., Palmieri, G., Casali, M., Nenz, C. M. G., Gargano, E., Pazzaglia, M., Agea, E., Berchicci, L., Tesoro, S., Albi, N., Minelli, O., Pasqua, B. L., Onorato, M., Epicoco, G. and Marchesi, M. Oral iron-based interventions for prevention of critical outcomes in pregnancy and postnatal care: An overview and update of systematic reviews. Journal of Evidence-Based Medicine. 2019; 12 (2): 155-166.	SLR scope not aligned; majority low income countries.
Alwan, N. A., Cade, J. E., McArdle, H. J., Greenwood, D. C., Hayes, H. E. and Simpson, N. A. Maternal iron status in early pregnancy and birth outcomes: insights from the Baby's Vascular health and Iron in Pregnancy study. British Journal of Nutrition. 2015. 113 (12): 1985-92.	Irrelevant population; proportion of enrolled cohort received iron supplementation.
Australian New Zealand Clinical Trials Registry (ANZCTR). Should we treat iron deficiency anaemia of pregnancy with lactoferrin? A randomised controlled trial. Available from: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=367050. 2014.	Irrelevant comparator.
Ahmadzia, H. K., Phillips, J. M., James, A. H., Rice, M. M. and Amdur, R. L. Predicting peripartum blood transfusion in women undergoing cesarean delivery: A risk prediction model. PLoS ONE. 2018; 13 (12) (e0208417).	Pre-selected cohort.
Alwan, N. A., Cade, J. E., Greenwood, D. C., Deanfield, J. and Lawlor, D. A. Associations of maternal iron intake and hemoglobin in pregnancy with offspring vascular phenotypes and adiposity at age 10: Findings from the Avon Longitudinal Study of Parents and Children. PLoS ONE. 2014; 9 (1) (e84684).	Irrelevant outcomes.
Amstad Bencaiova, G., Krafft, A., Zimmermann, R. and Burkhardt, T. Treatment of Anemia of Chronic Disease with True Iron Deficiency in Pregnancy. Journal of pregnancy. 2017; 4265091.	Irrelevant comparator.
Amstad Bencaiova, G., Vogt, D. R. and Hoesli, I. Serum hepcidin and iron status parameters in pregnant women and the association with adverse maternal and fetal outcomes: A study protocol for a prospective cohort study. BMJ Open. 2019; 9 (11) (e032280).	Irrelevant comparator.
Aranda, N., Hernandez-Martinez, C., Arija, V., Ribot, B. and Canals, J. Haemoconcentration risk at the end of pregnancy: effects on neonatal behaviour. Public health nutrition. 2017; 20 (8): 1405-1413.	Irrelevant outcomes.

Aranda, N., Ribot, B., Viteri, F., Cavalle, P. and Arija, V. Predictors of haemoconcentration at delivery: Association with low birth weight. European Journal of Nutrition. 2013; 52 (6): 1631-1639.	Irrelevant exposure.
Ardic, C., Usta, O., Omar, E., Yildiz, C., Memis, E. and Zeren Ozturk, G. Relationship between anaemia during pregnancy and preterm delivery. Journal of Obstetrics and Gynaecology. 2019; 39 (7): 903-906.	Irrelevant study location.
Arija, V., Ribot, B. and Aranda, N. Prevalence of iron deficiency states and risk of haemoconcentration during pregnancy according to initial iron stores and iron supplementation. Public health nutrition. 2013; 16 (8): 1371-1378.	Irrelevant outcomes.
Auerbach, M., Bahrain, H. F., James, S. E., Nicoletti, M., Lenowitz, S., London, N., Smith, S. and Derman, R. Results of the first American prospective study of intravenous iron in oral iron-intolerant iron-deficient gravidas. American Journal of Medicine. 2017; 130 (12): 1402-1407.	Pre-selected cohort.
Badfar, G., Shohani, M., Soleymani, A. and Azami, M. Maternal anemia during pregnancy and small for gestational age: a systematic review and meta-analysis. Journal of Maternal-Fetal & Neonatal Medicine. 2019; 32 (10): 1728-1734.	SLR scope not aligned; majority low income countries.
Bakacak, M., Avci, F., Ercan, O., Kostu, B., Serin, S., Kiran, G., Bostanci, M. S. and Bakacak, Z. The effect of maternal hemoglobin concentration on fetal birth weight according to trimesters. Journal of Maternal-Fetal and Neonatal Medicine. 2015; 28 (17): 2106-2110.	Irrelevant study location.
Baraka, M. A., Steurbaut, S., Laubach, M., Coomans, D. and Dupont, A. G. Iron status, iron supplementation and anemia in pregnancy: Ethnic differences. Journal of Maternal-Fetal and Neonatal Medicine. 2012; 25 (8): 1305-1310.	Irrelevant study scope.
Berglund, S. K., Torres-Espinola, F. J., Garcia-Valdes, L., Segura, M. T., Martinez-Zaldivar, C., Padilla, C., Rueda, R., Perez Garcia, M., McArdle, H. J. and Campoy, C. The impacts of maternal iron deficiency and being overweight during pregnancy on neurodevelopment of the offspring. British Journal of Nutrition. 2017; 118 (7): 533-540.	Irrelevant exposure.
Bermudez, L., Garcia-Vicent, C., Lopez, J., Torro, M. I. and Lurbe, E. Assessment of ten trace elements in umbilical cord blood and maternal blood: Association with birth weight. Journal of Translational Medicine. 2015; 13 (1) (291).	Irrelevant exposure.
Brown, H. K., Speechley, K. N., MacNab, J., Natale, R. and Campbell, M. K. Maternal, fetal, and placental conditions associated with medically indicated late preterm and early term delivery: A retrospective study. BJOG: An International Journal of Obstetrics and Gynaecology. 2016; 123 (5): 763-770.	Irrelevant population.
Buzaglo, N., Harlev, A., Sergienko, R. and Sheiner, E. Risk factors for early postpartum hemorrhage (PPH) in the first vaginal delivery, and obstetrical outcomes in subsequent pregnancy. Journal of Maternal-Fetal and Neonatal Medicine. 2015; 28 (8): 932-937.	Irrelevant study location.
Cakmak, B. D., Turker, U. A., Oztas, S., Arik, M. and Ustunyurt, E. The effect of first trimester hemoglobin levels on pregnancy outcomes. Turk Jinekoloji ve Obstetrik Dernegi Dergisi. 2018; 15 (3): 165-170.	Irrelevant study location.
Calje, E. and Skinner, J. The challenge of defining and treating anemia and iron deficiency in pregnancy: A study of New Zealand midwives' management of iron status in pregnancy and the postpartum period. Birth (Berkeley, Calif.). 2017; 44 (2): 181-190.	Irrelevant outcomes.

Chatterjee, R., Shand, A., Nassar, N., Walls, M. and Khambalia, A. Z. Iron supplement use in pregnancy - Are the right women taking the right amount? Clinical Nutrition. 2016; 35 (3): 741-747.	Irrelevant outcomes.
Chinese Clinical Trials Registry (ChiCTR). Impact of iron-rich food on iron metabolism, gestation status and birth outcomes in pregnant women: a randomized controlled trial. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR1800017574. 2018.	Irrelevant study location.
Chiossi, G., Palomba, S., Costantine, M. M., Falbo, A. I., Harirah, H. M., Saade, G. R. and La Sala, G. B. Reference intervals for hemoglobin and hematocrit in a low-risk pregnancy cohort: implications of racial differences. Journal of Maternal-Fetal & Neonatal Medicine. 2019; 32 (17): 2897-2904.	Irrelevant study scope.
Col Madendag, I., Eraslan Sahin, M., Madendag, Y., Sahin, E., Demir, M. B., Acmaz, B., Acmaz, G. and Muderris, I. I. The effect of iron deficiency anemia early in the third trimester on small for gestational age and birth weight: a retrospective cohort study on iron deficiency anemia and fetal weight. BioMed Research International. 2019; (7613868).	Irrelevant study location.
Dama, M., Van Lieshout, R. J., Mattina, G. and Steiner, M. Iron Deficiency and Risk of Maternal Depression in Pregnancy: An Observational Study. Journal of Obstetrics and Gynaecology Canada. 2018. 40 (6): 698-703.	Irrelevant population; proportion of enrolled cohort received iron supplementation.
Daru, J., Allotey, J., Pena-Rosas, J. P. and Khan, K. S. Serum ferritin thresholds for the diagnosis of iron deficiency in pregnancy: a systematic review. Transfusion Medicine. 2017; 27 (3): 167-174.	Irrelevant outcomes.
Daru, J., Cooper, N. A. M. and Khan, K. S. Systematic review of randomized trials of the effect of iron supplementation on iron stores and oxygen carrying capacity in pregnancy. Acta Obstetricia et Gynecologica Scandinavica. 2016; 95 (3): 270-279.	SLR scope not aligned; majority low income countries.
Detlefs, S., McKinney, J., Salmanian, B., Sangi-Haghpeykar, H. and Aagaard, K. M. 389: normalization of hemoglobin is associated with a lower rate of preterm birth in anemic patients. American journal of obstetrics and gynecology. 2020; 222 (1): S257-S258	Irrelevant publication type.
Drukker, L., Hants, Y., Farkash, R., Ruchlemer, R., Samueloff, A. and Grisaru-Granovsky, S. Iron deficiency anemia at admission for labor and delivery is associated with an increased risk for Cesarean section and adverse maternal and neonatal outcomes. Transfusion. 2015; 55 (12): 2799-806.	Irrelevant study location.
Figueiredo, A., Gomes-Filho, I. S., Silva, R. B., Pereira, P. P. S., Mata, F., Lyrio, A. O., Souza, E. S., Cruz, S. S. and Pereira, M. G. Maternal Anemia and Low Birth Weight: A Systematic Review and Meta-Analysis. Nutrients. 2018; 10 (5): 12.	SLR scope not aligned; majority low income countries and irrelevant population.
Gaillard, A., Le Strat, Y., Mandelbrot, L., Keita, H. and Dubertret, C. Predictors of postpartum depression: Prospective study of 264 women followed during pregnancy and postpartum. Psychiatry Research. 2014; 215 (2): 341-346.	Irrelevant study population.
Gunes, T., Yildirim, S., Gokahmetoglu, S., Korkut, S., Ozturk, M. A. and Kurtoglu, S. Maternal and cord blood hepcidin levels based on gestational weeks in term and preterm infants. Pediatric Hematology Oncology Journal. 2016; 1 (Supplement 2): 23-27.	Irrelevant study location.

Hamm, R. F., Blauvelt, C., Wang, E. Y. and Srinivas, S. K. Effectiveness of antepartum intravenous iron sucrose: dose timing and impact on outcomes. Journal of Maternal Fetal and Neonatal Medicine. 2019.	Irrelevant scope.
Heidkamp, R., Clermont, A. and Phillips, E. Modeling the impact of nutrition interventions on birth outcomes in the Lives Saved Tool (LiST). Journal of Nutrition. 2017; 147 (11): 2188S-2193S.	Unclear population.
Janbek, J., Sarki, M., Specht, I. O. and Heitmann, B. L. A systematic literature review of the relation between iron status/anemia in pregnancy and offspring neurodevelopment. European Journal of Clinical Nutrition. 2019; 73 (12): 1561-1578.	SLR scope not aligned; irrelevant study outcomes.
Jayasinghe, C., Polson, R., van Woerden, H. C. and Wilson, P. The effect of universal maternal antenatal iron supplementation on neurodevelopment in offspring: a systematic review and meta-analysis. BMC Pediatrics. 2018; 18 (1): 150	SLR scope not aligned; included studies not relevant.
Jelliffe-Pawlowski, L. L., Baer, R. J., Blumenfeld, Y. J., Ryckman, K. K., O'Brodovich, H. M., Gould, J. B., Druzin, M. L., El-Sayed, Y. Y., Lyell, D. J., Stevenson, D. K., Shaw, G. M. and Currier, R. J. Maternal characteristics and mid-pregnancy serum biomarkers as risk factors for subtypes of preterm birth. BJOG: An International Journal of Obstetrics and Gynaecology. 2015; 122 (11): 1484-1493.	Irrelevant outcomes.
Jwa, S. C., Fujiwara, T., Yamanobe, Y., Kozuka, K. and Sago, H. Changes in maternal hemoglobin during pregnancy and birth outcomes. BMC Pregnancy & Childbirth. 2015; 15: 80.	Irrelevant study location.
Kalem, P., Benli, A. R., Koroglu, M., Benli, N. C., Koyuncu, M., Cesur, O. and Dane, P. B. K. The effect of ferritin, vitamin B12 and folic acid on pregnancy outcomes. International Journal of Clinical and Experimental Medicine. 2016; 9 (11): 22413-22417.	Irrelevant study location.
Kang, S. Y., Kim, H. B. and Sunwoo, S. Association between anemia and maternal depression: A systematic review and meta-analysis. Journal of Psychiatric Research. 2020; 122: 88-96.	SLR scope not aligned; majority irrelevant study locations.
Koyuncu, K., Turgay, B., Sukur, Y. E., Yildirim, B., Ates, C. and Soylemez, F. Third trimester anemia extends the length of hospital stay after delivery. Turk Jinekoloji ve Obstetrik Dernegi Dergisi. 2017; 14 (3): 166-169.	Irrelevant study location.
Leonard, D., Buttner, P., Thompson, F., Makrides, M. and McDermott, R. Anaemia in pregnancy among Aboriginal and Torres Strait Islander women of Far North Queensland: A retrospective cohort study. Nutrition & dietetics: the journal of the Dietitians Association of Australia. 2018; 75 (5): 457-467.	Unclear exposure.
Maeda, Y., Ogawa, K., Morisaki, N., Tachibana, Y., Horikawa, R. and Sago, H. Association between perinatal anemia and postpartum depression: A prospective cohort study of Japanese women. International Journal of Gynecology and Obstetrics. 2020; 148 (1): 48-52.	Irrelevant study location.
Malinowski, A. K., D'Souza, R., Khan, K. S., Shehata, N., Malinowski, M. and Daru, J. Reported Outcomes in Perinatal Iron Deficiency Anemia Trials: A Systematic Review. Gynecologic and Obstetric Investigation. 2019; 84 (5): 417-434	Irrelevant outcomes.

Masukume, G., Khashan, A. S., Kenny, L. C., Baker, P. N. and Nelson, G. Risk factors and birth outcomes of anaemia in early pregnancy in a nulliparous cohort. PLoS ONE. 2015. 10 (4) (e0122729).	Irrelevant population; proportion of enrolled cohort received iron supplementation.
Miller, E. M. Iron status and reproduction in US women: National health and nutrition examination survey, 1999-2006. PLoS ONE. 2014; 9 (11) (e112216).	Irrelevant exposure.
Mitra, A. K. and Khoury, A. J. Universal iron supplementation: a simple and effective strategy to reduce anaemia among low-income, postpartum women. Public health nutrition. 2012; 15 (3): 546-553.	Irrelevant population.
Morisaki, N., Togoobaatar, G., Vogel, J. P., Souza, J. P., Rowland Hogue, C. J., Jayaratne, K., Ota, E., Mori, R., Maternal, W. H. O. M. S. o. and Newborn Health Research, N. Risk factors for spontaneous and provider-initiated preterm delivery in high and low Human Development Index countries: a secondary analysis of the World Health Organization Multicountry Survey on Maternal and Newborn Health. BJOG: an international journal of obstetrics and gynaecology. 2014; 101-109.	Irrelevant study location.
Nair, M., Knight, M. and Kurinczuk, J. J. Risk factors and newborn outcomes associated with maternal deaths in the UK from 2009 to 2013: a national case-control study. BJOG: An International Journal of Obstetrics & Gynaecology. 2016; 123 (10): 1654-62.	Irrelevant outcomes.
Nair, M., Churchill, D., Robinson, S., Nelson-Piercy, C., Stanworth, S. J. and Knight, M. Association between maternal haemoglobin and stillbirth: a cohort study among a multi-ethnic population in England. British Journal of Haematology. 2017. 179 (5): 829-837.	Irrelevant population; methodology suggests women may have received iron supplementation or active treatment.
Nair, M., Knight, M., Robinson, S., Nelson-Piercy, C., Stanworth, S. J. and Churchill, D. Pathways of association between maternal haemoglobin and stillbirth: Path-analysis of maternity data from two hospitals in England. BMJ Open. 2018; 8 (4) (e020149).	Irrelevant study design.
ClinicalTrials.gov. Effect of Ascorbic Acid Supplementation in Pregnancy on Anemia (AAA). https://clinicaltrials.gov/show/NCT03564756. 2018.	Irrelevant intervention.
ClinicalTrials.gov. Vitamin B12 Pregnancy Supplementation. https://clinicaltrials.gov/show/NCT03522428. 2018.	Irrelevant population and intervention.
Nwaru, B. I., Hayes, H., Gambling, L., Craig, L. C., Allan, K., Prabhu, N., Turner, S. W., McNeill, G., Erkkola, M., Seaton, A., McArdle, H. J. and Devereux, G. An exploratory study of the associations between maternal iron status in pregnancy and childhood wheeze and atopy. British Journal of Nutrition. 2014; 112 (12): 2018-27.	Irrelevant outcomes.
Ota, E., Ganchimeg, T., Morisaki, N., Vogel, J. P., Pileggi, C., Ortiz-Panozo, E., Souza, J. P. and Mori, R. Risk factors and adverse perinatal outcomes among term and preterm infants born small-for-gestational-age: Secondary analyses of the WHO multi-country survey on maternal and newborn health. PLoS ONE. 2014; 9 (8) (e105155).	Irrelevant location.
Paesano, R., Pietropaoli, M., Berlutti, F. and Valenti, P. Bovine lactoferrin in preventing preterm delivery associated with sterile inflammation. Biochemistry & Cell Biology. 2012; 90 (3): 468-75.	Irrelevant intervention and comparator.

Park, C. Y. and Eicher-Miller, H. A. Iron deficiency is associated with food insecurity in pregnant females in the United States: National Health and Nutrition Examination Survey 1999-2010. Journal of the Academy of Nutrition and Dietetics. 2014; 114 (12): 1967-1973.	Irrelevant exposure.
Park, Y. S. and Hoh, J. K. Complex and irregular heart rate dynamics in fetuses compromised by maternal anemia as a high-risk pregnancy. Journal of Perinatal Medicine. 2015; 43 (6): 741-748.	Irrelevant study location.
Pena-Rosas, J. P., De-Regil, L. M., Dowswell, T. and Viteri, F. E. Intermittent oral iron supplementation during pregnancy. Cochrane database of systematic reviews (Online). 2012; 7: CD009997.	Date of publication.
Pena-Rosas, J. P., De-Regil, L. M., Dowswell, T. and Viteri, F. E. Daily oral iron supplementation during pregnancy. Cochrane database of systematic reviews (Online). 2012; 12: CD004736	Date of publication.
Qassim, A., Gergis, R. G., Jeffries, B., Grivell, R. M. and Grzeskowiak, L. E. Use of intravenous iron polymaltose in the management of iron deficiency in pregnancy: A retrospective cohort study. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2018; 58 (2): 163-169.	Lack of comparator.
Qassim, A., Grivell, R. M., Henry, A., Kidson-Gerber, G., Shand, A. and Grzeskowiak, L. E. Intravenous or oral iron for treating iron deficiency anaemia during pregnancy: systematic review and meta-analysis. Medical Journal of Australia. 2019; 211 (8): 367-373.	Irrelevant study location.
Qassim, A., Mol, B. W., Grivell, R. M. and Grzeskowiak, L. E. Safety and efficacy of intravenous iron polymaltose, iron sucrose and ferric carboxymaltose in pregnancy: A systematic review. Australian & New Zealand Journal of Obstetrics & Gynaecology. 2018; 58 (1): 22-39.	Irrelevant comparator.
Radhika, A. G., Sharma, A. K., Perumal, V., Sinha, A., Sriganesh, V., Kulshreshtha, V. and Kriplani, A. Parenteral Versus Oral Iron for Treatment of Iron Deficiency Anaemia During Pregnancy and post-partum: A Systematic Review. Journal of Obstetrics and Gynecology of India. 2019; 69 (1): 13-24.	Irrelevant comparator.
Radon-Pokracka, M., Huras, H., Spaczynska, J., Janas, P. and Ossowski, P. Influence of antenatal anemia on the route of delivery and neonatal outcomes. Ginekologia i Poloznictwo. 2016; 41 (3): 48-51, 9-12.	Irrelevant study location.
Radon-Pokracka, M., Huras, H., Spaczynska, J., Nowak, M., Ossowski, P. and Janas, P. Relationship between preterm birth, neonatal outcomes and low maternal hemoglobin level. Journal of Maternal-Fetal & Neonatal Medicine. 2016; 29: 66.	Irrelevant publication type.
Rahman, M. M., Abe, S. K., Rahman, M. S., Kanda, M., Narita, S., Bilano, V., Ota, E., Gilmour, S. and Shibuya, K. Maternal anemia and risk of adverse birth and health outcomes in low- and middle-income countries: Systematic review and meta-analysis. American Journal of Clinical Nutrition. 2016; 103 (2): 495-504.	Irrelevant study location.
Räisänen, S., Gissler, M., Nielsen, H. S., Kramer, M. R., Williams, M. A. and Heinonen, S. Social disparity affects the incidence of placental abruption among multiparous but not nulliparous women: A register-based analysis of 1,162,126 singleton births. European Journal of Obstetrics and Gynecology and Reproductive Biology. 2013; 171 (2): 246-251.	Irrelevant outcomes.

Räisänen, S., Kancherla, V., Gissler, M., Kramer, M. R. and Heinonen, S. Adverse perinatal outcomes associated with moderate or severe maternal anaemia based on parity in Finland during 2006-10. Paediatric and Perinatal Epidemiology. 2014. 28 (5): 372-380.	Irrelevant population; methodology suggests women may have received iron supplementation or active treatment.
Rassjo, E. B., Byrskog, U., Samir, R. and Klingberg-Allvin, M. Somali women's use of maternity health services and the outcome of their pregnancies: A descriptive study comparing Somali immigrants with native-born Swedish women. Sexual and Reproductive Healthcare. 2013; 4 (3): 99-106.	Unclear exposure.
Ribot, B., Aranda, N., Giralt, M., Romeu, M., Balaguer, A. and Arija, V. Effect of different doses of iron supplementation during pregnancy on maternal and infant health. Annals of Hematology. 2013; 92 (2): 221-229.	Outcomes not reported in relevant population.
Ribot, B., Aranda, N., Viteri, F., Hernandez-Martinez, C., Canals, J. and Arija, V. Depleted iron stores without anaemia early in pregnancy carries increased risk of lower birthweight even when supplemented daily with moderate iron. Human Reproduction. 2012; 27 (5): 1260-1266.	Irrelevant exposure.
Ribot, B., Ruiz-Diez, F., Abajo, S., March, G., Fargas, F. and Arija, V. Prevalence of anaemia, risk of haemoconcentration and risk factors during the three trimesters of pregnancy. Nutricion Hospitalaria. 2018; 35 (1): 123-130.	Irrelevant exposure.
Roy, A., Fuentes-Afflick, E., Fernald, L. C. H. and Young, S. L. Pica is prevalent and strongly associated with iron deficiency among Hispanic pregnant women living in the United States. Appetite. 2018; 120 (): 163-170.	Unclear exposure.
Senturk, M. B., Cakmak, Y., Soydan, S. D., Polat, M. and Karateke, A. Time and number of antenatal visits in low socio-economic population: Outcomes and related factors. Journal of Clinical and Analytical Medicine. 2016; 7 (3).	Irrelevant study location.
Sheldon, W. R., Blum, J., Vogel, J. P., Souza, J. P., Gulmezoglu, A. M., Winikoff, B., Maternal, W. H. O. M. S. o. and Newborn Health Research, N. Postpartum haemorrhage management, risks, and maternal outcomes: findings from the World Health Organization Multicountry Survey on Maternal and Newborn Health. BJOG: an international journal of obstetrics and gynaecology. 2014; 121 (Supplement 1): 41395.	Irrelevant study location.
Smith, E. R., Shankar, A., Wu, L., Aboud, S., Adu-Afarwuah, S., Ali, H., Apriatni, M., Arifeen, S., Ashorn, P., Bhutta, Z. A. and et al. Modifiers of the effect of maternal multiple micronutrient supplementation: an individual patient data meta-analysis of 17 randomized trials. FASEB journal. 2017; 31 (1).	Irrelevant study location.
Smith, E. R., Shankar, A. H., Wu, L. S. F., Aboud, S., Adu-Afarwuah, S., Ali, H., Agustina, R., Arifeen, S., Ashorn, P., Bhutta, Z. A., Christian, P., Devakumar, D., Dewey, K. G., Friis, H., Gomo, E., Gupta, P., Kaestel, P., Kolsteren, P., Lanou, H., Maleta, K., Mamadoultaibou, A., Msamanga, G., Osrin, D., Persson, L. A., Ramakrishnan, U., Rivera, J. A., Rizvi, A., Sachdev, H. P. S., Urassa, W., West, K. P., Zagre, N., Zeng, L., Zhu, Z., Fawzi, W. W. and Sudfeld, C. R. Modifiers of the effect of maternal multiple micronutrient supplementation on stillbirth, birth outcomes, and infant mortality: a meta-analysis of individual patient data from 17 randomised trials in low-income and middle-income countries. The Lancet Global Health. 2017; 5 (11): e1090-e1100.	Irrelevant study location.

Smithers, L. G., Gialamas, A., Scheil, W., Brinkman, S. and Lynch, J. W. Anaemia of pregnancy, perinatal outcomes and children's developmental vulnerability: A whole-of-population study. Paediatric and Perinatal Epidemiology. 2014. 28 (5): 381-390.	Irrelevant population; methodology suggests women may have received iron supplementation or active treatment.
Spiegler, J., Stichtenoth, G., Weichert, J., Konig, I. R., Schlaud, M., A, V. d. W., Olbertz, D., Gurth, H., Schiffmann, J. H., Bohnhorst, B., Gortner, L., Herting, E. and Gopel, W. Pregnancy risk factors for very premature delivery: What role do hypertension, obesity and diabetes play? Archives of Gynecology and Obstetrics. 2013; 288 (1): 57-64.	Unclear exposure.
Suchdev, P. S., Peña-Rosas, J. P. and De-Regil, L. M. Multiple micronutrient powders for home (point-of-use) fortification of foods in pregnant women. Cochrane Database of Systematic Reviews. 2014; 2014 (6) (CD011158).	SLR scope not aligned; irrelevant intervention.
Suchdev, P. S., Peña-Rosas, J. P. and De-Regil, L. M. Multiple micronutrient powders for home (point-of-use) fortification of foods in pregnant women. Cochrane Database of Systematic Reviews. 2015; (6).	SLR scope not aligned; majority irrelevant study locations.
Turner, S., Seybold, D., Celestine, C. and Williams, D. Incidence of anemia among obstetric patients in an Appalachian teaching clinic. Military medicine. 2012; 177 (10): 1212-1216.	Irrelevant exposure.
Tzur, T., Weintraub, A. Y., Sergienko, R. and Sheiner, E. Can anemia in the first trimester predict obstetrical complications later in pregnancy? Journal of Maternal-Fetal & Neonatal Medicine. 2012; 25 (11): 2454-7	Irrelevant study location.
Urquizu i Brichs, X., Rodriguez Carballeira, M., Garcia Fernandez, A. and Perez Picanol, E. Anaemia in pregnancy and in the immediate postpartum period. Prevalence and risk factors in pregnancy and childbirth. [Spanish]. Medicina Clinica. 2016; 146 (10): 429-435.	Non-English language.
Vandevijvere, S., Amsalkhir, S., Van Oyen, H., Ines, E. and Moreno-Reyes, R. Iron status and its determinants in a nationally representative sample of pregnant women. Journal of the Academy of Nutrition and Dietetics. 2013; 113 (5): 659-666.	Irrelevant exposure.
Veena, S. R., Gale, C. R., Krishnaveni, G. V., Kehoe, S. H., Srinivasan, K. and Fall, C. H. Association between maternal nutritional status in pregnancy and offspring cognitive function during childhood and adolescence; a systematic review. BMC Pregnancy & Childbirth. 2016; 16: 220.	SLR scope not aligned; majority included studies irrelevant.
Veltri, F., Decaillet, S., Kleynen, P., Grabczan, L., Belhomme, J., Rozenberg, S., Pepersack, T. and Poppe, K. Prevalence of thyroid autoimmunity and dysfunction in women with iron deficiency during early pregnancy: is it altered? European Journal of Endocrinology. 2016; 175 (3): 191-9.	Irrelevant outcomes.
Vogel, J. P., Souza, J. P., Mori, R., Morisaki, N., Lumbiganon, P., Laopaiboon, M., Ortiz-Panozo, E., Hernandez, B., Perez-Cuevas, R., Roy, M., Mittal, S., Cecatti, J. G., Tuncalp, O., Gulmezoglu, A. M., Maternal, W. H. O. M. S. o. and Newborn Health Research, N. Maternal complications and perinatal mortality: findings of the World Health Organization Multicountry Survey on Maternal and Newborn Health. BJOG: an international journal of obstetrics and gynaecology. 2014; 121 (Supplement 1): 76-88.	Irrelevant study location.

Vucic, V., Berti, C., Vollhardt, C., Fekete, K., Cetin, I., Koletzko, B., Gurinovic, M. and van't Veer, P. Effect of iron intervention on growth during gestation, infancy, childhood, and adolescence: A systematic review with meta-analysis. Nutrition Reviews. 2013; 71 (6): 386-401.	SLR scope not aligned; irrelevant population.
Vural, T., Toz, E., Ozcan, A., Biler, A., Ileri, A. and Inan, A. H. Can anemia predict perinatal outcomes in different stages of pregnancy? Pakistan Journal of Medical Sciences. 2016; 32 (6): 1354-1359.	Irrelevant study location.
Wainstock, T., Walfisch, A., Sergienko, R. and Sheiner, E. Maternal anemia and pediatric neurological morbidity in the offspring - Results from a population-based cohort study. Early Human Development. 2019; 128: 15-20.	Irrelevant population.
Wassef, A., Nguyen, Q. D. and St-Andre, M. Anaemia and depletion of iron stores as risk factors for postpartum depression: a literature review. Journal of Psychosomatic Obstetrics and Gynecology. 2019; 40 (1): 19-28.	SLR scope not aligned; majority irrelevant study locations.
Webb Girard, A. and Olude, O. Nutrition education and counselling provided during pregnancy: effects on maternal, neonatal and child health outcomes. Paediatric and Perinatal Epidemiology. 2012; 26 (Supplement 1): 191-204.	Irrelevant intervention.
Welten, M., Gaillard, R., Hofman, A., De Jonge, L. L. and Jaddoe, V. W. V. Maternal haemoglobin levels and cardio-metabolic risk factors in childhood: The Generation R Study. BJOG: An International Journal of Obstetrics and Gynaecology. 2015; 122 (6): 805-815.	Irrelevant outcomes.
Wetta, L. A., Szychowski, J. M., Seals, S., Mancuso, M. S., Biggio, J. R. and Tita, A. T. Risk factors for uterine atony/postpartum hemorrhage requiring treatment after vaginal delivery. American Journal of Obstetrics & Gynecology. 2013; 209 (1): 51.e1-6.	Pre-selected cohort.
Widiyanto, J. and Lismawati, G. Maternal age and anemia are risk factors of low birthweight of newborn. Enfermeria clinica. 2019; 29 (Supplement 1): 94-97.	Irrelevant study location.
Xu, F., Roberts, L., Binns, C., Sullivan, E. and Homer, C. S. E. Anaemia and depression before and after birth: a cohort study based on linked population data. BMC Psychiatry. 2018; 18 (1): 224.	Irrelevant exposure.
Yildiz, Y., Ozgu, E., Unlu, S. B., Salman, B. and Eyi, E. G. Y. The relationship between third trimester maternal hemoglobin and birth weight/length; Results from the tertiary center in Turkey. Journal of Maternal-Fetal and Neonatal Medicine. 2014; 27 (7): 729-732.	Irrelevant study location.
Yilmaz, E., Yilmaz, Z., Cakmak, B., Gultekin, I. B., Cekmez, Y., Mahmutoglu, S. and Kucukozkan, T. Relationship between anemia and depressive mood in the last trimester of pregnancy. Journal of Maternal-Fetal and Neonatal Medicine. 2017; 30 (8): 977-982.	Irrelevant study location.
Young, M. F., Oaks, B. M., Tandon, S., Martorell, R., Dewey, K. G. and Wendt, A. S. Maternal hemoglobin concentrations across pregnancy and maternal and child health: a systematic review and meta-analysis. Annals of the New York Academy of Sciences. 2019.	Irrelevant publication type.
Yuce, T., Aker, S. S., Seval, M. M., Kalafat, E. and Soylemez, F. Obstetric and neonatal outcomes of adolescent pregnancy. Northern Clinics of Istanbul. 2015; 2 (2): 122-127.	Irrelevant study location.

Appendix 3 — Summary of individual studies

Question 1 (What are the maternal and infant outcomes associated with untreated ID, with or without mild or moderate anaemia in pregnancy?)

Table 35. Beckert 2019

Study Reference	Beckert 2019[28]
Study Design	Design Retrospective cohort study. Objective To describe the adverse maternal and neonatal outcomes in women diagnosed with anaemia during pregnancy. Dates 1st January 2007 to 31st December 2012. Country United States. Setting Californian hospitals.
Methods	Duration of follow-up Unclear; anaemia diagnosis occurred during pregnancy, outcomes measured during pregnancy, or at/shortly after birth. Definition of anaemia The presence of an ICD-9 diagnostic code for anaemia, recorded during a hospital admission during pregnancy, or in the birth hospital discharge record. Outcomes Outcomes obtained from a hospital discharge database maintained by the California Office of Statewide Health Planning and Development. Adverse obstetric outcomes included: hypertension, diabetes, fibroids, previous preterm birth, previous poor pregnancy outcome, placental abruption, placental insufficiency, chorioamnionitis, **blood transfusion**, hysterectomy, admission to the intensive care unit, or unplanned operation following pregnancy. Additional adverse neonatal outcomes included small or large for gestational age (**SGA**, <10th percentile and LGA, >90th percentile, respectively), **preterm** (<37 weeks' gestation) or early term (37 and 38 weeks' gestation) birth, and **infant death in the first year** (obtained from linked death certificates or hospital discharge status).
Population Characteristics	Patient recruitment and eligibility **Recruitment** Sample drawn from California live born infants, linked to a hospital discharge database maintained by the California Office of Statewide Health Planning and Development .

Study Reference **Beckert 2019[28]**

Inclusion
Singleton births with gestations between 22 and 42 weeks, and birth weights within 3 SD of the mean for sex and gestational age.

Exclusion
Infants with chromosomal abnormalities or major structural birth defects.

Other
NA.

Sample size
N in database = 2,960,504
N included in analysis = 2,869,415

Maternal Demographics

Parameter	Anaemia (n=284,780)	No anaemia (n=2,584,635)
Maternal age, n (%)		
<18 years	11,168 (3.9)	71,918 (2.8)
18–34 years	227,533 (79.9)	2,052,518 (79.4)
>34 years	46,059 (16.2)	460,113 (17.8)
Missing	20 (0.0)	86 (0.0)
Ethnicity, n (%)		
White non-Hispanic	59,414 (20.9)	688,430 (26.6)
Hispanic	142,302 (50.0)	1,256,700 (48.6)
Black	29,006 (10.2)	124,498 (4.8)
Asian	30,338 (10.7)	326,953 (12.7)
Other	23,720 (8.3)	188,054 (7.3)
Iron status		
Anaemia, n (%)	284,780 (100)	2,584,635 (0)
Iron-deficient anaemia, n (%)	NR	NR
Iron-deficient, n (%)	NR	NR
Iron supplement use, n (%)	NR	NR
Haemoglobin levels, g/dL	NR	NR
Serum ferritin, µg/L	NR	NR
Obstetric History		
Nulliparous, n (%)	119,947 (42.1)	1,023,342 (39.6)
Parous, n (%)	NR	NR
Gestational age, weeks	NR	NR
Previous poor pregnancy outcome, n (%)	6,443 (2.3)	34,205 (1.3)
Pre-pregnancy BMI, n (%)		
Underweight	14,466 (5.1)	125,743 (4.9)
Normal	124,852 (43.8)	1,189,811 (46.0)
Overweight	68,505 (24.1)	613,189 (23.7)
Obese	58,419 (20.5)	481,935 (18.7)

Study Reference	Beckert 2019[28]

	Missing	18,538 (6.5)	173,957 (6.7)
	Maternal education, n (%)		
	<12 years	73,715 (25.9)	611,265 (23.7)
	12 years	78,762 (27.7)	654,521 (25.3)
	>12 years	121,825 (42.8)	1,224,319 (47.4)
	Missing	10,478 (3.7)	94,530 (3.7)
	Smoked, n (%)	17,056 (6.0)	112,293 (4.3)
	Employment status	NR	NR

Adverse Maternal and/or Neonatal Outcomes

Maternal Outcomes

Outcome	Anaemia (n=284,780)	No anaemia (n=2,584,635)	Adjusted RR (95% CI)[a]
Maternal blood transfusion, n (%)	20,167 (7.1)	9,548 (0.4)	6.8 (6.7, 6.9)

[a]Adjusted for race, age, timing of entry into prenatal care, number of prenatal care visits, healthcare insurance plan, participation in supplemental nutrition programme, BMI, drug use, smoking, parity and interpregnancy interval.

Neonatal Outcomes

Outcome	Anaemia (n=284,780)	No anaemia (n=2,584,635)	Adjusted RR (95% CI)[a]
SGA at birth, n (%)	22,936 (8.1)	215,610 (8.3)	0.9 (0.9, 0.9)
Preterm birth (32–36 weeks' gestation), n (%)	21,069 (7.4)	148,662 (5.8)	1.0 (1.0, 1.1)
Very premature birth (<32 weeks' gestation), n (%)	4,349 (1.5)	18,978 (0.7)	1.1 (1.1, 1.1)
Infant death within 1 year, n (%)	1,049 (0.4)	5,498 (0.2)	1.0 (1.0, 1.1)

[a]Adjusted for maternal characteristics (race, age, timing of entry into prenatal care, number of prenatal care visits, healthcare insurance plan, participation in supplemental nutrition programme, BMI, drug use, smoking, parity and inter-pregnancy interval) and significant obstetric outcomes. SGA at birth and infant death within 1 year also adjusted for gestational age.

Authors' Conclusions	The diagnosis of anaemia in pregnancy carries a higher risk of complications for the mother, and a higher risk of preterm birth for the infant.

Abbreviations: CI: confidence interval; BMI: body mass index; ICD: International Classification of Diseases; LGA: large for gestational age; NA: not applicable; NR: not reported; RR: risk ratio; SD: standard deviation; SGA: small for gestational age.

Table 36. Bencaiova 2014

Study Reference	Bencaiova 2014[14]
Study Design	Design Prospective longitudinal study. Objective To investigate the relationship between haemoglobin concentration and serum ferritin, and adverse outcomes in pregnancy. Dates

Study Reference	Bencaiova 2014[14]
	Not specified. Country Switzerland. Setting Department of Obstetrics, University Hospital of Zurich.
Methods	Duration of follow-up Haematological status and serum ferritin examined between 16- and 20-weeks' gestation and before delivery; outcomes measured at birth. Definition of anaemia and ID Anaemia defined as haemoglobin <11.0 g/dL based on CDC criteria and centre experience. IDA defined as haemoglobin <11.0 g/dL and serum ferritin ≤15 µg/L (**Note**: Women with haemoglobin 10.0 to 11.0 g/dL received oral iron supplementation, and women with haemoglobin <10.0 g/dL were treated directly with IV iron in the anaemia clinic if consent was given; the IDA cohort is therefore not relevant to this review) . Iron depletion defined as a serum ferritin <20 µg/L. Outcomes Maternal outcomes: PPH, defined as a haemoglobin decrease >3.0 g/dL on the second day after birth. Other outcomes reported included placenta praevia and placenta accrete/increta/percreta. Neonatal outcomes: Low birth weight, defined as birth weight <2,500 g; preterm birth, defined as birth <37 completed weeks' gestation. Other outcomes reported included IUGR, preterm premature rupture of fetal membranes (PPROM) and macrosomia.
Population Characteristics	Patient recruitment and eligibility **Recruitment** Not specified. **Inclusion** Not specified. **Exclusion** Chronic renal disease and malignancies, and having a blood transfusion at least 3 months before enrolment in the study. **Other** All women had singleton pregnancies. Sample size N included in study = 382 N with non-anaemic ID = 123 Maternal Demographics

Parameter	Non-anaemic ID (n=123)	Normal (n=189)
Maternal age, mean years (SD)	29.7 (5.7)	30.8 (5.9)
Origin of mother		
Europe + North America, n (%)	37 (30.1)	76 (40.2)

Study Reference **Bencaiova 2014[14]**

Former Yugoslavia, n (%)	49 (39.8)	50 (26.5)
Lower income countries	37 (30.1)	63 (33.3)
Iron status		
Anaemia, n (%)	0 (0)	0 (0)
Iron-deficient anaemia, n (%)	0 (0)	0 (0)
Iron-deficient, n (%)	123 (100)	0 (0)
Iron supplement use, n (%)[a]	NR	NR
Haemoglobin levels, g/dL	NR	NR
Serum ferritin, µg/L	NR	NR
Obstetric History		
Parity, mean (SD)	1.9 (0.9)	1.7 (1.0)
Gestational age at enrolment, mean weeks (SD)	16.4 (1.3)	16.2 (1.2)
BMI, kg/m^2	23.5 (5.5)	24.2 (5.1)
Maternal education level	NR	NR
Smoking status	NR	NR
Employment status	NR	NR

[a]Women with haemoglobin 10.0 to 11.0 g/dL received oral iron supplementation. Women with haemoglobin <10.0 g/dL were treated directly with IV iron in the anaemia clinic if consent was given.

Adverse Maternal and/or Neonatal Outcomes

Maternal Outcomes

Relevant adverse maternal outcomes to be extracted, including but not limited to:

Outcome	Non-anaemic ID (n=123)	Normal (n=189)
PPH, n (%)	7 (5.7)	21 (11.1)
P value (versus normal)	0.11	NA

Neonatal Outcomes

Relevant adverse neonatal outcomes to be extracted, including but not limited to:

Outcome	Non-anaemic ID (n=123)	Normal (n=189)
Low birth weight, n (%)	7 (5.7)	19 (10.1)
P value (versus normal)	0.211	NA
Preterm birth (<37 weeks' gestation)	7 (5.7)	18 (9.5)
P value (versus normal)	0.287	NA
Neonatal death	0 (0)	1 (0.5)
P value (versus normal)		NA
Admission to NICU	0 (0)	1 (0.5)
P value (versus normal)	1	NA

Study Reference	Bencaiova 2014[14]
Authors' Conclusions	Mild anaemia and depleted iron stores, detected early in pregnancy, were not associated with adverse maternal and perinatal outcomes in iron supplemented women.

Abbreviations: BMI: body mass index; CDC: Centre for Disease Control; ID: iron deficiency; IDA: iron deficiency anaemia; IUGR: intrauterine growth restriction; IV: intravenous; NICU: neonatal intensive care unit; SD: standard deviation; PPH: postpartum haemorrhage; PPROM: preterm premature rupture of fetal membranes; NA: not applicable.

Table 37. Beta 2013

Study Reference	Beta 2013[15]
Study Design	Design Case-control study. Objective To investigate risk factors associated with spontaneous early preterm birth. Dates February 2008 to December 2009. Country Poland. Setting Not reported. Data from maternity records.
Methods	Duration of follow-up Follow-up until birth; unclear date follow-up began. Definition of anaemia Anaemia defined as haemoglobin <11 g/dL, according to WHO definitions. Outcomes Preterm birth, defined as spontaneous birth before 34 weeks' gestation.
Population Characteristics	Patient recruitment and eligibility **Recruitment** Data derived from retrospective analysis of medical records. **Inclusion** Singleton pregnancies delivering a phenotypically normal neonate at or after 23 weeks' gestation. **Exclusion** Pregnancies with major fetal abnormalities. Medically indicated preterm birth. **Other** NA Sample size

Study Reference **Beta 2013[15]**

N screened = 2,528
N included in analysis = 1,865

Maternal Demographics

Parameter	Spontaneous early preterm (n=31)	Birth ≥37 weeks' gestation (n=1,834)
Maternal age, median years (IQR)	31 (28–35)	30 (27–33)
Ethnicity, n (%)		
Caucasian	31 (100)	1,834 (100)
Iron status		
Anaemia, n (%)	11 (35.4)*	886 (16.1)*
Iron-deficient anaemia, n (%)	NR	NR
Iron-deficient, n (%)	NR	NR
Iron supplement use, n (%)	NR	NR
Haemoglobin levels, g/dL	NR	NR
Serum ferritin, µg/L	NR	NR
Obstetric History		
Nulliparous, n (%)	18 (58.1)	1,060 (57.8)
Parous (previous caesarean), n (%)	4 (12.9)	205 (11.2)
Parous (previous birth 23–34 weeks' gestation), n (%)	5 (16.1)*	35 (1.9)*
Gestational age, weeks	NR	NR
Pre-pregnancy BMI, kg/m^2	NR	NR
Maternal education level	NR	NR
Smoking, n (%)	2 (6.5)	112 (6.1)
Employment status	NR	NR

*p<0.05.

Adverse Maternal and/or Neonatal Outcomes

Neonatal Outcomes
Univariate logistic regression analysis showed that women with anaemia, diagnosed during pregnancy, have an increase in the risk of spontaneous preterm birth.

Outcome	Spontaneous early preterm (n=31)	Birth ≥37 weeks' gestation (n=1,834)
Very premature birth (<34 weeks' gestation), n (%)	11 (35.4)	886 (16.1)
Odds ratio (95% CI; p)[a]	2.754 (1.805, 4.488; p<0.001)	

[a]Univariate logistic regression analysis.

Authors' Conclusions Maternal anaemia, diagnosed during pregnancy, is associated with an increase in the risk of spontaneous preterm birth.

Abbreviations: BMI: body mass index; CI: confidence interval; IQR: interquartile range; NA: not applicable; NR: not reported; WHO: World Health Organisation.

Table 38. Biguzzi 2012

Study Reference	Biguzzi 2012[27]
Study Design	Design Retrospective cohort study. Objective To define the prevalence of PPH and associated risk factors after vaginal birth in a large obstetric unit in Northern Italy, in order to identify women at risk for PPH and to develop a risk model that could improve the capability of PPH prediction. Dates July 2007 to September 2009. Country Italy. Setting Obstetric Unit of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico in Milan.
Methods	Duration of follow-up Haemoglobin levels measured within 1 month of birth; outcomes measured in the postpartum period. Methods for haemoglobin and iron measurement NR. Outcomes PPH, defined as ≥500 mL blood loss, according to the original WHO criteria.
Population Characteristics	Patient recruitment and eligibility **Recruitment** Eligible individuals interviewed and recruited. **Inclusion** Women who underwent vaginal birth in the study centre. **Exclusion** Age <18 years, caesarean section, birth before 37 weeks' gestation, twin pregnancy, lack of proficiency in Italian language, refusal to provide consent. **Other** Deliveries that occurred on Friday afternoon were not included in the study because of the impossibility to approach the puerperae on Monday morning (minimum hospitalization after birth being 2 days). Sample size N screened = 8,530 N eligible = 6,035

Study Reference Biguzzi 2012[27]

N included in analysis = 6,011

Maternal Demographics

Parameter	Blood loss ≥500 mL (n=1,435)	Blood loss <500 mL (n=4,576)
Maternal age, median years (range)	34 (18, 45)	34 (18, 47)
Ethnicity, n		
Caucasian	1,232	4,074
Hispanic	116	333
Asian	77	145
African	10	24
Iron status		
Anaemia, n (%)	NR	NR
Iron-deficient anaemia, n (%)	NR	NR
Iron-deficient, n (%)	NR	NR
Iron supplement use, n (%)	NR	NR
Haemoglobin levels, mean g/dL (range)	11.9 (7.8, 16.5)	12.0 (7.3, 15.8)
Serum ferritin, µg/L	NR	NR
Obstetric History		
Nulliparous, n	984	2,328
Primiparous, n	376	1,698
Multiparous, n	75	550
Gestational age, weeks	NR	NR
Pre-pregnancy BMI, kg/m²	NR	NR
Maternal education level	NR	NR
Smoking status	NR	NR
Employment status	NR	NR

Adverse Maternal and/or Neonatal Outcomes

Maternal Outcomes

The odds of PPH decreased approximately 16% per 1 g/dL increment in antenatal haemoglobin in a multivariate analysis (OR 0.84; 95% CI 0.78 to 0.90; p<0.0001).[a]

[a]The OR for each variable was adjusted for the presence of all other variables in a multiple logistic regression model. Information on all putative risk factors complete in 4,748 women (79%).

Authors' Conclusions Low ante-partum haemoglobin is a new potentially modifiable risk factor for PPH.

Abbreviations: BMI: body mass index; CI: confidence interval; NR: not reported; OR: odds ratio; PPH: postpartum haemorrhage.

Table 39. Crispin 2019

Study Reference	Crispin 2019[19]
Study Design	Design Retrospective cohort study with comparison following a quality improvement intervention and a validation study. Objective To determine the optimum approach and timing to screen for ID in pregnancy. Dates July 2014 to June 2016. Validation study 1996 to 2014. Country Australia. Setting Centenary Hospital for Women and Children, Canberra.
Methods	Duration of follow-up First trimester, second trimester and after pregnancy. Definitions of ID and mild or moderate anaemia A transferrin saturation of <20% or a ferritin concentration of <30 µg/L were used as cut-of values for ID. Estimates of iron replete haemoglobin ranges were determined by non-parametric derivation of the 95% range in women where all ferritin readings performed were >30 µg/L. Anaemia was defined as <110 g/L during trimesters 1 and 3, and <105 g/L in the second trimester. Laboratory results from the pathology database. However, there was no standardised approach to screening for or treating ID, so iron studies were performed at the discretion of the treating clinicians, and the laboratory reported ID when the ferritin was<10 µg/L. Outcomes Relevant outcomes of interest covered perinatal bleeding, gestational age at birth and birth weight.
Population Characteristics	Patient recruitment and eligibility **Recruitment** The study retrospectively evaluated women who had antenatal care through the hospital. **Inclusion** Only women who had antenatal care through the hospital, with bloods tests performed there during pregnancy were included. **Exclusion** Premature deliveries (< 250 days gestation) were excluded. **Other** A validation cohort study was carried out because the initial study suggested that ferritin was predictive of anaemia in the first, but not the second trimester. It consisted of all pregnant women with a ferritin measurement and recorded gestational age in the laboratory information system, between 1996 to 2014. Cases overlapping with the first study cohort were excluded. Sample size N screened = 4,102 N eligible = 3,885

Study Reference **Crispin 2019[19]**

N trimester 1 ferritin = 146
N trimester 2 ferritin = 285
N validation cohort = 1,767

Predictive value for markers of ID

Parameter	Trimester 1		Trimester 2	
	Pre-birth anaemia N=146	Normal Hb at birth N=187	Pre-birth anaemia N=285	Normal Hb at birth N=249
Haemoglobin g/L, median (95% range)	–	133 (109, 150)	–	122 (99, 139)
Pre-intervention				
Ferritin < 30 µg/L, n (%) [N=77]	5 (6.5)	19 (24.7)	8 (9.6)	51 (61.4)
Ferritin ≥ 30 µg/L, n (%)[N=77]	2 (2.6)	51 (66.2)	3 (3.6)	21 (25.3)
Transferrin saturation <20%, n (%) [N=32]	4 (12.5)	3 (9.4)	4 (12.9)	12 (38.7)
Transferrin saturation ≥20%, n (%) [N=32]	1 (3.1)	24 (24)	2 (6.5)	13 (41.9)
Anaemia, n (%) [N=270]	5 (1.9)	6 (2.2)	12 (1.8)	22 (3.4)
Normal haemoglobin, n (%) [N=270]	22 (8.1)	237 (88.8)	44 (6.8)	575 (88.1)

Adverse Maternal and/or Neonatal Outcomes

Exploration of pregnancy outcomes demonstrated no association between ID or anaemia and birth weights, there was no difference in the amount of perinatal bleeding recorded between anaemic and non-anaemic women, and there was no difference in the gestational age at birth.

Anaemia Outcomes

Outcome	With condition		Without condition		
	Median	Range	Median	Range	
Estimated perinatal blood loss (m/L)					
Trimester 1	300	100–1,500	350	50–3,200	P=0.438
Trimester 2	416	50–3,000	400	100–2,700	P=0.21
Gestational age at birth (days)					
Trimester 1	278	216–293	277	145–296	P=0.57
Trimester 2	274	206–296	274	216–293	P=0.61
Birth weight (g)					
Trimester 1	3,290	890–4,230	3,380	360–5,450	P=0.06
Trimester 2	3,325	940–5,320	3,200	1,400–4,918	P=0.16

Iron Depleted Outcomes

Outcome	With condition		Without condition		
	Median	Range	Median	Range	
Estimated perinatal blood loss (m/L)					
Trimester 1	350	100–2,000	300	100–3,000	P=0.13
Trimester 2	350	100–2,700	400	50–3,000	P=0.21

Study Reference	**Crispin 2019[19]**					
	Gestational age at birth (days)					
	Trimester 1	278	217–293	278	172–293	P=0.63
	Trimester 2	274	206–296	216	216–293	P=0.61
	Birth weight (g)					
	Trimester 1	3,427	890–4,675	3,360	600–4,918	P=0.25
	Trimester 2	3,325	940–5,320	3,200	1,400–4,918	P=0.16
Authors' Conclusions	This study supports changes to currently accepted patient blood management paradigms. Ideally the findings should be confirmed in a prospective cohort of women where iron supplementation is not routine. The results demonstrate that it would be feasible to show the predictive value of ferritin with a high power with a relatively small population if all had iron studies performed. Testing for iron deficiency with a serum ferritin in early pregnancy, before second trimester, may be recommended to appropriately detect and target iron deficiency. This may be preferred to universal iron replacement therapy to avoid unnecessary side effects in a significant proportion of women who may not benefit. Either should be preferred over a strategy relying on haemoglobin alone, which fails to detect a majority of cases and may leave women at risk of anaemia prior to birth.					

Abbreviations: Hb: haemoglobin; ID: iron deficiency.

Table 40. Ehrenthal 2012

Study Reference	**Ehrenthal 2012[25]**
Study Design	Design Retrospective cohort study. Objective To identify potentially modifiable risk factors for transfusion in pregnant women. Dates January 2000 to July 2008. Country United States. Setting Obstetric facility at a large regional community hospital.
Methods	Duration of follow-up Unclear. Data extracted from the obstetric record, which serves as the hospital record for the patients' labour and birth course, and outcome measured in the perinatal period. Definition of anaemia Anaemic defined as haemoglobin ≤10.5 and >9.5 g/L, severe anaemia as haemoglobin ≤9.5 g/L. The 10.5 g/dL is aligned to the ACOG definition of anaemia; severe anaemia was added as a category because the researchers anticipated a non-linear association of haemoglobin with odds of transfusion. Blood was routinely drawn on admission to labour and birth. Outcomes Perinatal transfusion of blood products, identified by linking the obstetric data file to the blood bank data base.
Population Characteristics	Patient recruitment and eligibility **Recruitment**

Study Reference **Ehrenthal 2012[25]**

All women giving birth within the study period at a large regional community hospital evaluated for inclusion.

Inclusion
All women delivering at 20 or more completed gestational weeks with a birth weight of ≥350 g; both caesarean and vaginal births included.

Exclusion
Missing data for maternal race/ethnicity, parity, age, gestational age at birth, birth weight, a complete blood count within 7 days before birth, or if the birth weight fell outside of the standard range for the gestational age, suggesting data entry error.
Medical diagnosis of thalassemia or sickle cell crisis, or if the platelet count at presentation was <100,000/µL.

Other
NR.

Sample size
N screened = 60,916
N excluded (with reason) = 35 (birth weight outside range), 1,188 (missing blood count within 7 days before birth), 411 (diagnosis of sickle cell crisis or thalassemia, or platelet count <100,000/µL)
N included in analysis = 59,282

Maternal Demographics

Parameter	Cohort (n=59,282)
Maternal age (years), n (%)	
<20	5,256 (8.9)
20–34	44,279 (74.7)
≥35	9,745 (16.4)
Ethnicity, n (%)	
White	36,994 (62.4)
Black	13,214 (22.3)
Hispanic	5,498 (9.3)
Asian	2,569 (4.3)
Other	1,007 (1.7)
Iron status, n (%)	
Anaemia (haemoglobin ≤10.5 and >9.5 g/L	4,729 (8.0)
Severe anaemia (haemoglobin ≤9.5 g/dL	1,693 (2.9)
Obstetric History, n (%)	
Nulliparous	24,507 (41.3)
Term birth	52,910 (89.3)
Preterm birth	6,372 (10.7)
Multiple gestation	1,250 (2.1)
Pre-pregnancy BMI, kg/m^2	NR
Maternal education level	NR
Smoking status	NR

<table>
<tr><td>Study Reference</td><td colspan="2">Ehrenthal 2012[25]</td></tr>
<tr><td></td><td>Employment status</td><td>NR</td></tr>
<tr><td>Adverse Maternal and/or Neonatal Outcomes</td><td colspan="2">Maternal Outcomes
Anaemia at entry for birth is significantly associated with perinatal transfusion, in women undergoing both vaginal and caesarean birth; anaemic women with caesarean birth have a greater odds of perinatal transfusion compared with anaemic women undergoing vaginal births.

<table>
<tr><th></th><th rowspan="2">Perinatal transfusion (n/N)</th><th colspan="2">Adjusted OR (95% CI)[a]</th></tr>
<tr><th></th><th>Vaginal birth (n=41,578)</th><th>Caesarean section (n=17,704)</th></tr>
<tr><td>No anaemia (haemoglobin >10.5 g/dL)</td><td>374/52,860</td><td>–</td><td>–</td></tr>
<tr><td>Anaemia (haemoglobin ≤10.5 and >9.5 g/L</td><td>100/4,729</td><td>2.09 (1.37, 3.19)</td><td>3.08 (2.29, 4.15)</td></tr>
<tr><td>Severe anaemic (haemoglobin ≤9.5 g/dL</td><td>140/1,693</td><td>7.58 (5.09, 11.30)</td><td>13.3 (9.9, 17.7)</td></tr>
</table>
[a]Multivariate regression, adjusted for gestational age at birth, marital status and year.</td></tr>
<tr><td>Authors' Conclusions</td><td colspan="2">Potentially modifiable factors most strongly associated with risk for transfusion were antenatal anaemia and cesarean section, and their co-occurrence was synergistic.</td></tr>
</table>

Abbreviations: ACOG: American College of Obstetricians and Gynecologists; BMI: body mass index; CI: confidence interval; OR: odds ratio.

Table 41. Gaillard 2014

<table>
<tr><td>Study Reference</td><td>Gaillard 2014[16]</td></tr>
<tr><td>Study Design</td><td>Design:
Prospective cohort study.

Objective:
To determine sociodemographic and lifestyle-related risk factors of maternal anaemia and elevated haemoglobin levels in early pregnancy, and to examine trimester specific maternal, placental and fetal consequences of maternal anaemia and elevated haemoglobin levels during pregnancy.

Dates:
Not reported.

Country:
Netherlands.

Setting:
Rotterdam.</td></tr>
<tr><td>Methods</td><td>Duration of follow-up
Not specified. Haemoglobin measured at enrolment (gestational age 14.4 weeks, IQR 12.5, 17.5 weeks); outcome measures recorded up to birth.

Definitions of anaemia</td></tr>
</table>

Study Reference	Gaillard 2014[16]

Anaemia defined as haemoglobin ≤11 g/dL or haematocrit ≤33%, according to the WHO criteria. Maternal haemoglobin and haematocrit concentrations were measured in fresh ethylenediamine tetra acetic acid plasma samples using venous blood samples.

Outcomes

Relevant neonatal outcomes included: preterm birth (<37 weeks' gestation), low birth weight (<2,500 g) and SGA at birth (<5th percentile of gestational age and sex adjusted birth weight). Information about offspring sex, gestational age, weight, length and head circumference at birth was obtained from medical records.

Population Characteristics

Patient recruitment and eligibility

Recruitment:
The cohort study was completed in Rotterdam where there are 4 hospitals with maternal and childcare services, and a tertiary hospital for neonatal care. It is not stated whether all women participating in the study were enrolled from these locations.

Inclusion:
Mothers providing written consent.

Exclusion:
Mothers without information on either haemoglobin or haematocrit levels in the first 32 weeks of pregnancy and pregnancies leading to induced abortions, fetal death, twin pregnancies and loss to follow-up.

Other:
NR.

Sample size
N screened/invited = 8,880
N eligible = 7,317
N excluded = 1,357 (no information on haemoglobin or haematocrit levels in first 32 weeks of pregnancy), 26 (induced abortion), 65 (fetal death), 77 (twin pregnancies), 38 (loss to follow up)

Maternal Demographics

Parameter	Cohort (n=7,317)
Mean maternal age (SD), years	29.7 (5.3)
Ethnicity, n (%)	
Dutch or other European	3,842 (56.8)
Non-European	2,928 (43.2)
Folic acid supplement use, n (%)	
No use	1,573 (29.1)
First 10 weeks use	1,664 (30.8)
Preconception use	2,169 (40.1)
Haematological measurements	
Haemoglobin levels (g/dL), mean (SD)	12.0 (1.0)
Haematocrit levels (g/dL), mean (SD)	36 (2.7)
Mean corpuscular volume (fl), mean (SD)	87.9 (5.0)
Obstetric History, n (%)	
Primiparous	4,021 (54.9)

Study Reference	Gaillard 2014[16]		
	Gestational age at intake (weeks), median (IQR)	14.4 (12.5, 17.5)	
	Mean pre-pregnancy BMI (kg/m^2), mean (SD)	23.6 (4.4)	
	Maternal education level, n (%)		
	No education or primary school	783 (11.8)	
	Secondary school	3,053 (45.9)	
	Higher education	2,813 (42.3)	
	Smoking habits, n (%)		
	None	4,645 (74.5)	
	Yes	1,590 (25.5)	
	Dietary intake (kcal), mean (SD)	2,039 (564)	
	Alcohol consumption, n (%)		
	None	3,153 (50.2)	
	Yes	3,124 (49.8)	
	Employment status	NR	
Adverse Maternal and/or Neonatal Outcomes	Neonatal outcomes The risk of preterm birth (anaemic: 60/998; non-anaemic: 260/5,288) and SGA at birth (anaemic: 54/982; non-anaemic: 241/5,239) was increased in women with anaemia, compared to those without anaemia; this was not significant. The risk of low birth weight (anaemic: 47/983; non-anaemic: 241/5,251) was reduced in women with anaemia, compared to those without anaemia; this was not significant. RRs were adjusted for gestational age at enrolment and at blood sampling, maternal age, BMI, parity, ethnicity, education, alcohol consumption during pregnancy, smoking during pregnancy, folic acid supplement use and multivitamin use. Observed associations were attenuated after adjustment for confounding factors.		
Authors' Conclusions	Maternal haemoglobin levels during pregnancy are influenced by sociodemographic and lifestyle-related risk factors. Elevated maternal haemoglobin levels, but not maternal anaemia, is associated with increased risk of adverse and fetal outcomes. Associations between lower haemoglobin levels and adverse birth outcomes attenuated after adjustment for confounding factors. It has been suggested that only severe anaemia, but not mild anaemia, is associated with an increased risk of adverse pregnancy outcomes. Among the study population, few severe anaemia cases were present.		

Abbreviations: BMI: body mass index; CI: confidence interval; IQR: interquartile range; kcal: kilocalories; NR: not reported; RR: risk ratio; SD: standard deviation; SGA: small for gestational age; WHO: World Health Organisation.

Table 42. Haider 2013

Study Reference	Haider 2013[12]
Study Design	Design: SLR and meta-analysis. Objective: To summarise evidence on the associations of maternal anaemia and prenatal iron use with maternal haematological and adverse outcomes; and to evaluate potential exposure-response relations of iron dose, duration of use and haemoglobin concentration in the prenatal period with pregnancy outcomes.

Study Reference	Haider 2013[12]
	Dates: PubMed = 1966–31/05/2012. Embase = 1974–31/05/2012. Countries: **High income:** Ireland, UK, Netherlands, Canada, Hong Kong, USA, France, Norway, South Korean, Australia, Denmark, Finland, Sweden, Italy, Hungary, Belgium, French Guiana, Finland, Israel, Germany, Wales. **Low/middle income:** Burma, Thailand, Nepal, Iran, Nigeria, Ecuador, Vietnam, China, Gambia, UAE, Uganda, Niger, Jamaica, India, Indonesia, Sierra Leone, Sri Lanka, Benin, Latin American countries, Zimbabwe, Peru, Pakistan, Papua New Guinea.
Methods	Definitions of ID and mild or moderate anaemia **RCTs (haematological outcomes):** Anaemia defined as haemoglobin <110 g/L. ID defined as serum ferritin <12 µg/L. IDA defined as haemoglobin <110 g/L and serum ferritin <12 µg/L. **Observational studies:** Anaemia defined as haemoglobin <100 g/L to <115 g/L; where haemoglobin not available, estimated by dividing haematocrit by 3 and multiplying by ten. Outcomes Relevant maternal outcomes included: infection during pregnancy and postpartum. Other outcomes included GDM, maternal malaria and parasitaemia and placental malaria. Relevant neonatal outcomes included: preterm birth (birth of a neonate <37 weeks' gestation), low birth weight (birth weight <2,500 g), SGA at birth (birth weight below the 10th centile of the gestational age and sex), perinatal mortality (stillbirths and neonatal deaths before 7 days of life) and neonatal mortality (death of a neonate in the first month of life). Other neonatal outcomes included mean duration of gestation (weeks), mean birth weight (g), mean birth length (cm) and stillbirth (death of a foetus after 28 weeks' gestation).
Population Characteristics	Study eligibility **Recruitment:** Comprehensive systematic literature searches of PubMed and Embase. **Inclusion:** • Randomised trials in pregnant women of daily oral iron (supplementation and fortification) or iron and folic acid use compared with placebo, no iron or no iron and folic acid. • Trials (both cluster and individual) examining maternal haematological, morbidity and birth outcomes. • Prospective cohort studies that allowed examination of the association of baseline anaemia with specified birth outcomes. **Exclusion:** • Trials of multiple vitamins and minerals, unless they examined the additional effect of iron or iron with folic acid in which all treatment groups received similar vitamins and minerals. • Trials evaluating different doses of iron, unless they presented a placebo, no iron or no iron and folic acid comparison group . • Cross-sectional and case-control studies. • Quasi-randomised study designs. • Studies in HIV infected women or those with haemoglobinopathies.

Study Reference	Haider 2013[12]

Other:

- No language or publication restrictions.

Sample size

N screened = 13,668.
Titles and abstracts reviewed = 10,821.
Full texts reviewed = 1,048.
N excluded = Duplicates pre-abstract review (n=2,847), inclusion/exclusion criteria (n=891), foreign language where no translator available (n=11), full text not available (n=1) and published only as an abstract (n=5).

Study characteristics

	Randomised control trials (n=48)	Observational studies (n=44)
Population		
Pregnant women, n	17,793	1,851,682
Pregnant women in high income, n (n trials)	4,861 (27)	650,126 (22)
Pregnant women in low/middle income, n (n trials)	12,932 (21)	1,201,556 (22)
Trial focus		
Daily iron use vs no iron/placebo, trial n	34	NA
Iron + folic acid vs folic acid, trial n	4	NA
Iron with folic acid vs placebo or no treatment, trial n	14	NA
Iron + micronutrients vs micronutrients, trial n	10	NA
Iron fortification vs no fortification, trial n	2	NA
Anaemia assessment		
Haemoglobin measure in first or second trimester, n	NA	17
Haemoglobin measure in the third trimester, n	NA	9
Haemoglobin measure each trimester, n	NA	5
Haemoglobin measure at first antenatal visit, n	NA	8
Time of haemoglobin measure not specified, n	NA	10

Adverse Maternal and/or Neonatal Outcomes

Anaemia and birth outcomes

- Prenatal anaemia significantly increased the risk of low birth weight compared with no anaemia; but the association was not significant when adjusted estimates were pooled (aOR 1.13; 95% CI 0.94 to 1.35; I^2 = 86%; 9 studies). **For high income countries only: aOR 1.21; 95% CI 0.95 to 1.53; p = 0.12; 6 studies**.

Study Reference	Haider 2013[12]
	• There was a significantly higher risk of preterm birth in the anaemic group (aOR 1.28; 95% CI 1.11 to 1.48; I^2 = 83%; 13 studies). **For high income countries only: aOR 1.26; 95% CI 1.02 to 1.57; p<0.001; 12 studies.** Significantly higher odds of preterm birth with first or second trimester anaemia (aOR 1.21; 95% CI 1.13 to 1.30; I^2=0%; 7 studies) but not with third trimester anaemia (aOR 1.20; 95% CI 0.80 to 1.79; I^2=90%; 6 studies). • There was a significantly higher risk of stillbirth in the anaemic group (OR 1.19; 95% CI 1.09 to 1.29; I^2=24%; 12 studies); however adjusted estimates could not be pooled because only 2 studies presented them. • Anaemia was marginally associated with the duration of gestation (p=0.05) but not with birth weight; associations with SGA births and perinatal mortality were not significant (p>0.05).
Authors' Conclusions	Cohort studies indicate a higher risk of preterm birth with first or second trimester anaemia and with lower mean haemoglobin concentrations.

Abbreviations: aOR: adjusted odds ratio; CI: confidence interval; GDM: gestational diabetes mellitus; HIV: human immunodeficiency virus; ID: iron deficiency; IDA: iron deficiency anaemia; OR: odds ratio; RCTs: randomised controlled trials; NA: not applicable; SGA: small for gestational age; SLR: systematic literature review; UAE: United Arab Emirates; UK: United Kingdom; USA: United States of America.

Table 43. Khambalia, 2015

Study Reference	Khambalia, 2015[31]
Study Design	Design: Record-linkage cohort study. Objective: To examine the association between iron biomarkers and the risk of total (<37 weeks' gestation), early (<34 weeks' gestation) and moderate-to-late (34 to 36 weeks' gestation) spontaneous preterm birth (sPTB). Dates: January to October 2007. Country: Australia. Setting: Pregnant women who attended first trimester Down's syndrome screening and had their results analysed by Pathology North, a state-wide public screening service in New South Wales.
Methods	Definition of ID ID defined as serum ferritin <12 µg/l or sTfR (≥21 nmol/l). Serum samples were thawed and analysed for the levels of serum ferritin, sTfR and C-reactive protein (CRP). Serum ferritin was measured using a solid-phase direct sandwich enzyme-linked immunosorbent assay (ELISA) method (Calbiotech, Inc.). sTfR level was measured using an ELISA method

Study Reference	Khambalia, 2015[31]

(Quantikine IVD, Human sTfR Immunoassay; R&D Systems). CRP level was measured using the quantitative sandwich enzyme immunoassay technique (Quantikine™; R&D Systems, Inc).

Outcomes

sPTB, defined as births <37 weeks' gestation after the onset of spontaneous labour or preterm premature rupture of the membranes. This was subdivided into early (<34 weeks' gestation) and moderate-to-late (23 to 36 preterm births).

Laboratory records and the results of each woman's iron biomarker analyses were linked to electronic birth and hospital records, sourced from the New South Wales Perinatal Data Collection and New South Wales Admitted Patient Data Collection respectively, to obtain pregnancy and birth information. Reporting in both datasets has high specificity (>99%).

Population Characteristics

Patient recruitment and eligibility

Recruitment:
A sample of pregnant women attending Down's syndrome screening who had serum samples available.

Inclusion:
Women with a singleton infant, with a birth weight of at least 400 g or at least 20 weeks' gestation, who attended first trimester Down's syndrome screening and had results analysed by the specified pathology service.

Exclusion:
Details not reported.

Other:
Only deidentified data was provided to the researchers.

Sample size

N included = 2,254.

Maternal Demographics

Parameter	Serum ferritin quartiles			
	<15 µg/l (n=580)	15–24 µg/l (n=536)	25–42 µg/l (n=578)	≥43 µg/l (n=560)
Maternal age (years), *n (%)*				
<25,	78 (13.6)	49 (9.2)	41 (7.2)	27 (4.9)
25–34	342 (59.5)	344 (64.5)	391 (68.5)	353 (63.8)
≥35	155 (27.0)	140 (26.3)	139 (24.3)	173 (31.3)
Country of birth, *n (%)*				
Australia	373 (64.3)	343 (64.0)	362 (62.6)	344 (61.4)
New Zealand, North and South Americas	18 (3.1)	15 (2.8)	19 (3.3)	17 (3.0)
Europe	46 (7.9)	30 (5.6)	43 (7.4)	38 (6.8)
Middle East and Africa	26 (4.5)	32 (6.0)	19 (3.3)	29 (5.2)
South and Southeast Asia	56 (9.7)	58 (10.8)	59 (10.2)	61 (10.9)
Northeast Asia	41 (7.1)	41 (7.7)	54 (9.3)	47 (8.4)
Other	20 (3.5)	17 (3.2)	22 (3.8)	24 (4.3)
Smoking during pregnancy, n (%)	39 (6.8)	31 (5.8)	44 (7.7)	35 (6.3)

Study Reference	Khambalia, 2015[31]				
	Socioeconomic disadvantage quintiles, n (%)				
	1 (most disadvantage)	119 (20.5)	113 (21.2)	110 (19.3)	130 (23.3)
	2	115 (19.8)	84 (15.7)	99 (17.4)	91 (16.3)
	3	133 (22.9)	126 (23.6)	116 (20.4)	107 (19.2)
	4	102 (17.6)	111 (20.8)	115 (20.2)	116 (20.8)
	5 (least disadvantage)	111 (19.1)	100 (18.7)	130 (22.8)	114 (20.4)
	Biochemical indices				
	sTfR (nmol/l), median (IQR)	15.6 (12.2, 19.5)	14.5 (11.6, 18.3)	15.0 (12.0, 18.0)	15.3 (12.5, 18.4)
	CRP (mg//), median (IQR)	7 (3, 14)	7 (3, 14)	8 (3, 16)	8 (3, 18)
	Obstetric History, n (%)				
	Nulliparous	268 (46.2)	292 (54.5)	315 (54.5)	340 (60.7)
	Gestational diabetes	2 (0.3)	17 (3.2)	18 (3.1)	17 (3.0)
	Hypertensive disorders in pregnancy	23 (4.0)	24 (4.5)	17 (2.9)	25 (4.5)
	Gestational age at blood sampling, weeks, n (%)				
	9–10	41 (12.1)	36 (11.0)	52 (14.2)	64 (16.1)
	11	115 (34.0)	125 (38.2)	139 (37.9)	145 (36.4)
	12–14	182 (53.9)	166 (50.8)	176 (48.0)	189 (47.5)
Adverse Maternal and/or Neonatal Outcomes	Neonatal Outcomes				
	Outcome	Preterm birth (<37 weeks' gestation)	Term birth (≥37 weeks' gestation)	Unadjusted OR; 95% CI	
	Serum ferritin (<12 µg/l), n (%)	30 (17.1)	402 (19.3)	0.86; 0.57, 1.30	
	sTfR (≥21 nmol/l), n (%)	29 (16.6)	318 (15.3)	1.10; 0.73, 1.67	
Authors' Conclusions	Serum ferritin concentrations in early pregnancy are significantly elevated in pregnant women with subsequent spontaneous preterm labour or premature rupture of the membrane. There was no significant association identified between ID (defined as serum ferritin <12 µg/l or sTfR ≥21 nmol/l) and preterm birth.				

Abbreviations: CI: confidence interval; C-reactive protein: CRP; ELISA: enzyme-linked immunosorbent assay; ID: iron deficiency; IQR: interquartile range; OR: odds ratio; sPTB: spontaneous preterm birth; sTfR: soluble transferrin receptor.

Table 44. Khambalia 2016

Study Reference	Khambalia 2016[29]
Study Design	Design Retrospective cohort study.

Study Reference	Khambalia 2016[29]
	Objective The aims of this study are to examine the prevalence of ID in women in the first trimester of pregnancy using various measures of iron status of serum ferritin, serum transferrin receptor, total body iron and C reactive protein, and assess risk factors of ID and associations between ID and pregnancy and birth outcomes. Dates January to October 2007. Country Australia. Setting First trimester screening clinic and hospital.
Methods	Duration of follow-up Exposure measured during first trimester Down Syndrome screening; outcomes measured at birth. Definition of ID Three established definitions used: serum ferritin <12 µg/L, serum transferrin receptor ≥21.0 nmol/L, and total body iron <0 mg/kg. Outcomes Relevant outcomes included PPH, preterm birth, SGA at birth and admission to NICU or special care nursery. Birth data was sourced from the New South Wales Perinatal Data Collection and hospitalization data from the New South Wales Admitted Patients Data Collection. PPH was defined as blood loss of ≥500 ml following vaginal birth or ≥750 ml following caesarean section, and where a diagnosis of PPH was recorded in the medical record. Preterm birth (<37 weeks' gestation), infant birth weight and infant admission to a neonatal intensive or special care unit were identified from PDC data. SGA was defined, respectively, as those infants in the ≤10th percentile birth weight distribution for gestational age and infant sex.
Population Characteristics	Patient recruitment and eligibility **Recruitment** Random sample of pregnant women who attended first trimester Down Syndrome screening and had their results screened by Pathology North, a state-wide public screening service in New South Wales, Australia. **Inclusion** NR. **Exclusion** Women with a twin pregnancy, medical abortion, infant with a major congenital anomaly or an undetectable ferritin and serum transferrin concentration. **Other** NR. Sample size N excluded = 122 N included in analysis = 4,420 N serum ferritin measurements = 3,795

Study Reference **Khambalia 2016[29]**

Maternal Demographics

Parameter	Iron deficient (serum ferritin <12 µg/L) (n=742)	Iron replete (serum ferritin ≥12 µg/L) (n=3,053)
Maternal age ≤25 years, n (%)	90 (13.0)	185 (6.6)
Ethnicity, n (%)	NR	NR
Iron status		
Iron-deficient (serum ferritin <12 µg/L), %	742 (100)	0 (0)
Inflammation (CRP >0.5 mg/dL)	475 (66.2)	1,932 (64.8)
Obstetric History		
Multiparous, n (%)	397 (57.2)	1,305 (46.2)
Gestational age at testing ≥ 12 weeks, n (%)	198 (47.3)	965 (51.1)
Pre-pregnancy BMI, kg/m^2	NR	NR
Maternal education level	NR	NR
Smoking status		
Smoked during pregnancy, n (%)	45 (6.5)	158 (5.6)
Employment status	NR	NR

Maternal Outcomes

Results from univariate analysis indicate no significant association between ID and PPH in pregnant women.

Outcome	Iron deficient (serum ferritin <12 µg/L) (n=742)	Iron replete (serum ferritin ≥12 µg/L) (n=3,053)	P value
PPH, n (%)	20 (2.7)	120 (3.9)	>0.05

Adverse Maternal and/or Neonatal Outcomes

Neonatal Outcomes

Results from univariate analysis indicate no significant association between ID and preterm birth, SGA birth or admission of neonates to NICU or special care nursery in pregnant women.

Outcome	Iron deficient (serum ferritin <12 µg/L) (n=742)	Iron replete (serum ferritin ≥12 µg/L) (n=3,053)	P value
Preterm birth (<37 weeks' gestation), n (%)	28 (4.0)	112 (4.0)	>0.05
SGA at birth, n (%)	46 (6.6)	213 (7.6)	>0.05
Admitted to NICU or special care nursery, n (%)	35 (15.6)	117 (14.7)	>0.05

Authors' Conclusions Nearly 1 in 5 Australian women begin pregnancy with ID. Further investigation of excess maternal weight and inflammation in the relationships between ID and gestational diabetes mellitus and large for gestational age infants is needed. Univariate analysis indicated no significant association between ID and PPH, preterm birth, SGA at birth or admission of neonates to NICU or special care nursery.

Abbreviations: BMI: body mass index; CRP: C-reactive protein; ID: iron deficiency; NICU: neonatal intensive care unit; NR: not reported; PPH: postpartum haemorrhage; SD: standard deviation; SGA: small for gestational age.

Table 45. Nyflot 2017

Study Reference	Nyflot 2017[24]
Study Design	Design Case-control study. Objective To evaluate risk factors for severe PPH, taking into consideration pre-pregnancy, antenatal and intrapartum variables. Dates 1st January 2008 to 31st December 2011. Country Norway. Setting Hospital based (Ullevaal and Rikshopitalet University Hospitals, Drammen Hospital).
Methods	Duration of follow-up Beginning of pregnancy (anaemia defined as that at the start of pregnancy) until the postpartum period. Definition of anaemia Haemoglobin ≤9.0 g/dL, recorded at start of pregnancy. Outcomes Severe PPH, defined as blood loss ≥1,500 mL or the need for blood transfusion for excessive bleeding at the time of birth. Blood transfusion for excessive bleeding was defined as a blood transfusion given for a likely PPH ≥1500 mL due to clinical symptoms and signs of anaemia or hemodynamic decompensation after birth. Determined using birth suite records and hospital databases.
Population Characteristics	Patient recruitment and eligibility **Recruitment** Review of birth suite records and hospital databases. **Inclusion** Pregnant women living in the metropolitan area of the Oslo and Buskerud municipality admitted to the study centres. Cases: Severe PPH. Controls: No severe PPH from the same period of time and source population as the cases. **Exclusion** Cases: Women who received a blood transfusion because of postpartum anaemia, without evidence of excessive haemorrhage. **Other** The control population was weighted according to the total number of deliveries in each hospital during the study period. If a woman had more than 1 birth, the second and subsequent pregnancies were excluded to limit repeated correlated measurements. Sample size

Study Reference **Nyflot 2017[24]**

N source population = 43,105
N included in analysis = 3,123
N cases = 1,064
N controls = 2,059

Maternal Demographics

Parameter	Severe PPH (n=1,064)	Controls (n=2,059)
Maternal age (years), median (IQR)	32 (29, 36)	32 (29, 35)
Ethnicity, n (%)		
Europe/USA/Oceania	838 (78.8)	1,682 (81.7)
Middle East/North Africa	50 (4.6)	122 (5.9)
Latin America	14 (1.3)	22 (1.1)
Asia	99 (9.3)	151 (7.3)
Sub-Saharan Africa	63 (5.9)	82 (4.0)
Iron status, n (%)		
Anaemia	74 (7.0)	38 (1.9)
Obstetric History, n (%)		
Nulliparous	622 (58.5)	1,007 (48.9)
Previous severe PPH	66 (6.2)	21 (1.0)
Previous caesarean	126 (11.8)	221 (10.7)
Multiple pregnancy	94 (8.8)	52 (2.5)
Pre-pregnancy BMI (kg/m^2), median (IQR)	23.1 (21.0, 26.1)	22.8 (20.8, 25.7)
Maternal education level	NR	NR
Smoking status	NR	NR
Employment status	NR	NR

Adverse Maternal and/or Neonatal Outcomes

Maternal Outcomes

PPH

In a multivariate logistic model, anaemia diagnosed at the start of pregnancy was a strong independent risk factor for severe PPH.

Outcome	Severe PPH (n=1,064)	Controls (n=2,059)	Adjusted OR (95% CI)	P value
Anaemia (≤9.0 g/dL)	74 (7.0)	38 (1.9)	4.27 (2.79, 6.54)	<0.001

Authors' Conclusions Women with increased risk of severe PPH can be identified when antepartum and intrapartum variables, including anaemia, are considered.

Abbreviations: BMI: body mass index; CI: confidence interval; IQR: interquartile range; NR: not reported; OR: odds ratio; PPH: postpartum haemorrhage.

Table 46. Orlandini 2017

Study Reference	Orlandini 2017[26]
Study Design	Design Retrospective cohort study. Objective To evaluate the relationship between maternal mild anaemia in the third trimester of pregnancy, fetal birth weight and fetal gender in healthy women with uncomplicated gestations. Dates 1st January 2014 to 30th June 2015. Country Italy. Setting Hospital.
Methods	Duration of follow-up Third trimester to birth. Anaemia definition Haemoglobin <11.0 g/dL in the third trimester (evaluated between 35 and 36 weeks' gestation) of pregnancy, as per the WHO definition. Outcomes Emergency caesarean section, PPH, fetal birth weight and fetal gender.
Population Characteristics	Patient recruitment and eligibility **Recruitment** NR. **Inclusion** Inclusion criteria were spontaneous conception and gestational age at hospital admission ≥37 weeks' gestation. **Exclusion** Pre-gravidic diseases (hypertensive disorders, diabetes, haematological pathologies, inflammatory bowel diseases), obstetric complications until birth (hypertensive disorders, gestational diabetes, intrauterine growth retardation), fetal malformations, and cigarette smoking. **Other** 42 single pregnancies excluded due to presence of maternal anaemia in the first trimester of gestation. Sample size N screened = 1,691 N included in analysis = 1,131 Maternal Demographics

Parameter	Haemoglobin ≤11 g/dL (n=156)	Haemoglobin ≥11.1 g/dL (n=975)	P value
Maternal age (years), mean (SD)	32.24 (6.07)	32.42 (5.99)	Non-significant
Ethnicity, n (%)	NR	NR	NR

Study Reference	Orlandini 2017[26]			
	Iron status			
	Anaemia, n (%)[a]	156 (100)	0 (0)	–
	Haemoglobin in third trimester (g/dL), mean (SD)	10.45 (0.55)	12.16 (0.76)	<0.0001
	MCV in third trimester (fL), mean (SD)	85.52 (5.50)	88.70 (4.33)	<0.0001
	Obstetric History			
	Nulliparous, n (%)	54 (34.6)	465 (47.7)	0.002
	Multiparous, n (%)	102 (65.4)	510 (52.3)	
	Pre-pregnancy BMI (kg/m^2), n (%)			
	<18.5	9 (5.8)	89 (9.1)	Non-significant
	18.5–25	116 (74.3)	735 (75.4)	
	>25 and <30	24 (15.4)	121 (12.4)	
	>30	7 (4.5)	30 (3.1)	
	Maternal education level	NR	NR	NR
	Smoking status	NR	NR	NR
	Employment status	NR	NR	NR
	[a]Within the anaemic group, all women showed a mild anaemia, defined as haemoglobin ≥9 g/dl and ≤11 g/dl.			
Adverse Maternal and/or Neonatal Outcomes	Maternal Outcomes			
	Outcome	Haemoglobin ≤11 g/dL (n=156)	Haemoglobin ≥11.1 g/dL (n=975)	P value
	Emergency caesarean section	25	69	0.006
	PPH	1	13	Non-significant
	The rate of emergency caesarean section was significantly higher (p=0.003) in those carrying male than those carrying female foetuses.			
Authors' Conclusions	The present study showed that maternal mild anaemia in the third trimester of gestation correlates with a higher fetal birth weight. Women with mild anaemia underwent more frequently to emergency caesarean section during labour with respect to spontaneous birth, and, among anaemic women, male fetuses are more likely to be associated with higher rates of emergency caesarean section, confirming that they appear more vulnerable than their sisters.			

Abbreviations: BMI: body mass index; MCV: mean cell volume; NR: not reported; PPH: postpartum haemorrhage; SD: standard deviation; WHO: World Health Organisation.

Table 47. Petty 2018

Study Reference	Petty 2018[17]
Study Design	Design: Retrospective cross-sectional chart review.

Study Reference	Petty 2018[17]
	Objective: To determine if antenatal anaemia is associated with postpartum red blood cell (RBC) transfusion. Dates: 1st December 2015 to 31st September 2016. Country: United States. Setting: A regional tertiary care maternity hospital.
Methods	Duration of follow-up Anaemia determined using the antenatal haemoglobin concentration that was measured closest to the time of parturition; outcomes recorded at birth or in the postpartum period. Definition of anaemia Anaemia was defined as haemoglobin <11.0 g/dL, according to the WHO criteria. Outcomes Association between anaemia and risk of postpartum RBC transfusion. RBC transfusion defined as the administration of allogenic RBC units from the blood bank. Reinfusion of intrapartum cell salvage was not counted as an allogenic RBC transfusion. Both groups of women were stratified by the number of RBC units they received in the postpartum period (between birth and maternal discharge): any quantity of RBC units, not more than 2 units, or more than 2 units.
Population Characteristics	Patient recruitment and eligibility **Recruitment:** NR. **Inclusion:** Women who gave birth in the maternity hospital between specified dates, and for whom antenatal haemoglobin concentration measurement was available. **Exclusion:** Deliveries where an antenatal haemoglobin concentration measurement was not available. **Other** NR. Sample size N screened/invited = 8,100 N eligible = 8,039 N excluded (with reason) = 61 (absence of third trimester haemoglobin measurement) N included in analysis = 8,039 Maternal Demographics

Parameter	No antenatal anaemia (n=6,477)	Antenatal anaemia (n=1,562)
Maternal age, years	NR	NR

Study Reference	Petty 2018[17]

Ethnicity, n (%)	NR	NR
Iron status	NR	NR
Haemoglobin levels (g/dL), mean (SD)	11.9 (0.74)	9.2 (1.3)
Obstetric History	NR	NR
Pre-pregnancy BMI, kg/m^2	NR	NR
Maternal education level	NR	NR
Smoking status	NR	NR
Employment status	NR	NR

Adverse Maternal Outcomes

Maternal Outcomes

Outcome	No antenatal anaemia (n=6,477)	Antenatal anaemia (n=1,562)	OR; 95% CI (p value)
At least 1 RBC transfusion during postpartum period, n (%)	49 (0.76)	57 (3.6)	4.97;3.38, 7.31 (0.0001)
Received not more than 2 RBC units in the postpartum period, n (%)	31 (0.48)	43 (2.8)	5.89; 3.70, 9.37 (0.0001)
Received more than 2 RBC units in the postpartum period, %	18 (0.28)	14 (0.90)	3.25; 1.61, 6.54 (0.001)

Outcome	Caesarean birth and no antenatal anaemia (n=1,818)	Caesarean birth and antenatal anaemia (n=490)	OR; 95% CI (p value)
Received at least 1 RBC unit, n (%)	24 (1.32)	31 (6.3)	5.05; 2.93, 8.69 (0.0001)
Outcome	Vaginal birth and no antenatal anaemia (n=4,621)	Vaginal birth and antenatal anaemia (n=1,062)	OR; 95% CI (p value)
Received at least 1 RBC unit, n (%)	25 (0.54)	25 (2.4)	4.43; 2.54, 7.75 (0.0001)

Authors' Conclusions	There is a strong association between antenatal anaemia and receiving a postpartum RBC transfusion, regardless of mode of birth (caesarean or vaginal). However, the overall rate of receiving a postpartum RBC transfusion remains low.

Abbreviations: BMI: body mass index; CI: confidence interval; NR: not reported; OR: odds ratio; RBC: red blood cell; SD: standard deviation; WHO: World Health Organization;

Table 48. Räisänen, 2013

Study Reference	Räisänen, 2013[22]
Study Design	Design: Retrospective population-based case-control study.

Study Reference	Räisänen, 2013[22]
	Objective: To identify risk factors of preterm birth (<37 weeks' gestation) among singleton births. Dates: 1987 to 2010. Country: Finland. Setting: Singleton births obtained from the Finnish Medical Birth Register, a clinical record from all obstetric units in Finland. This was supplemented with data from the Population Register Centre on live births and data compiled by Statistics Finland.
Methods	Duration of follow-up Outcomes recorded at birth. Definition of anaemia Anaemia defined as haemoglobin <100 g/L. Outcomes Association between anaemia and preterm birth assessed using data collected from the Medical Birth Register and tested using multivariable logistic regression. Extremely preterm defined as birth at <28 weeks' gestation; very preterm as 28 to 31+6 weeks' gestation; moderately preterm as 32 to 36+6 weeks' gestation; term as ≥37 weeks' gestation.
Population Characteristics	Patient recruitment and eligibility **Recruitment:** Total population of singleton births between 1987 to 2010 in Finland, obtained from the Medical Birth Register. **Inclusion:** All singleton births where information on gestational age was available. **Exclusion:** Births where information on gestational age was missing, non-singleton births. **Other:** NR. Sample size N eligible and enrolled = 1,390,742 N excluded = 8,754 (information on gestational age missing) Maternal Demographics

Parameter	Extremely preterm (n=4,452)	Very preterm (n=6,213)	Moderately preterm (n=54,177)	Term (n=1,338,438)
Maternal age (years), mean (SD)	30.1 (6.0)	29.8 (5.9)	29.4 (5.7)	29.1 (5.3)
Ethnicity, n (%)	NR	NR	NR	NR

Study Reference	Räisänen, 2013[22]				
	Iron status				
	Anaemia, %	1.1	0.8	0.6	0.6
	Obstetric History				
	Primiparous, %	43.2	48.3	49.0	40.4
	Number of miscarriages, mean (SD)	0.50 (0.99)	0.39 (0.81)	0.31 (0.72)	0.26 (0.61)
	Number of prior terminations, mean (SD)	0.19 (0.56)	0.17 (0.53)	0.14 (0.45)	0.12 (0.41)
	Pre-pregnancy BMI (kg/m^2), mean (SD)	25.0 (5.7)	24.8 (5.3)	24.4 (5.1)	24.2 (4.7)
	Maternal education level	NR	NR	NR	NR
	Smoking status				
	Non-smoking, %	78.3	78.2	81.4	84.7
	Quit smoking, %	3.8	4.2	3.7	3.5
	Smoking, %	18.0	17.7	14.9	11.8
	Socio-economic status				
	"Upper white-collar", %	5.2	5.6	6.1	6.6
	"Lower white-collar", %	29.3	31.2	32.3	32.6
	"Blue-collar", %	14.3	14.6	14.4	13.7

Adverse Maternal Outcomes

Maternal Outcomes

Outcome	Extremely preterm (n=3,079)	Very preterm (n=4,757)	Moderately preterm (n=44,390)
Adjusted OR (95% CI) for anaemia	2.48 (1.82, 3.38)	1.48 (1.08, 2.04)	0.99 (0.88, 1.12)

Authors' Conclusions	Anaemia was associated with a high risk of extremely preterm singleton birth and a moderate risk of very preterm singleton birth.

Table 49. Räisänen 2014

Study Reference	Räisänen 2014[21]
Study Design	Design: A population-based cross-sectional study. Objective: To identify risk factors for, and consequences of, physician-diagnosed major depression during pregnancy. Dates:

Study Reference	Räisänen 2014[21]
	2002 to 2010. Country: Finland. Setting: Data gathered from 3 Finnish health registers (the Finnish Medical Birth Register, the Hospital Discharge Register and the Register of Congenital Malformations).
Methods	Definition of anaemia Haemoglobin levels ≤100 g/L. Outcomes **Primary:** Physician-diagnosed major depression during pregnancy, treated in specialised healthcare centres and defined by ICD-10 codes F31.3, F31.5 and F32 to 34. **Secondary:** Relevant adverse outcomes included: admission to neonatal intensive care (having spent at least 24 hours in a unit), early neo-natal death (death during first 7 postnatal days), preterm birth (<37 weeks' gestation), low birth weight (<2,500 g), and SGA at birth (sex-specific and parity-specific birth weight >2 standard deviations below the mean weight based on a national 2013 reference). Stillbirth (fetal death at any point from the 22nd gestational week onwards, or at any point after the foetus attained 500g) was also reported. Apgar scores <7 at 5 min and infant's vein pH <7.15 were considered low. **Methods to derive outcomes:** Data available from the Medical Birth Register, the Hospital Disease Register or the Register of Congenital Malformations.
Population Characteristics	Patient recruitment and eligibility **Recruitment:** All singleton births in Finnish hospitals from 2002–2010. Data on prior history of depression available since 1996 for inpatient visits and since 1998 for outpatient visits. **Inclusion:** Singleton births in Finnish hospitals. **Exclusion:** Multiple births (for example, twins) as these carry a higher risk of complications. **Other:** NA. Sample size N screened/invited = 527,705 N excluded (with reason) = 15,767 (multiple births) N eligible/enrolled = 511,938 Maternal Demographics

Parameter	No major depression during pregnancy (n=507,818)	Major depression during pregnancy (n=4120)

Study Reference	**Räisänen 2014[21]**				
	History of depression prior to pregnancy	No (n=493,037)	Yes (n=14,781)	No (n=2,189)	Yes (n=1,931)
	Maternal age (years), mean (SD)	29.6 (5.4)	27.6 (6.0)	28.4 (6.2)	28.7 (6.6)
	Ethnicity, n (%)	NR	NR	NR	NR
	Anaemia, %	1.6	2.6	3.5	2.8
	Obstetric History				
	Nulliparous, %	42.0	45.1	45.5	50.0
	Parous %	58.0	54.9	54.5	50.0
	Gestational age (weeks), mean (SD)	39.8 (1.8)	39.7 (1.9)	39.4 (2.0)	39.5 (2.0)
	Previous adverse pregnancy outcomes				
	Prior miscarriages, %	20.7	23.6	23.3	23.2
	Prior terminations, %	12.2	22.4	19.8	21.7
	Prior caesarean section, %	10.6	10.5	10.3	10.2
	Pre-pregnancy BMI, kg/m^2	NR	NR	NR	NR
	Maternal education level	NR	NR	NR	NR
	Smoking status				
	Non-smoking, %	83.2	63.4	66.1	59.5
	Quit smoking during first trimester, %	3.7	6.9	6.5	8.3
	Smoking after first trimester, %	10.5	26.7	25.1	29.3
	Missing information, %	2.6	2.9	2.3	3.0
	Socioeconomic status				
	"Upper white-collar", %	8.6	3.7	4.0	3.8
	"Lower white-collar", %	34.5	25.8	27.9	25.5
	"Blue-collar", %	14.2	16.0	14.9	15.3
	Other, %	25.7	31.0	31.9	30.0
	Missing, %	17.2	23.6	21.3	25.3

Study Reference	Räisänen 2014[21]
Adverse Maternal and/or Neonatal Outcomes	Maternal Outcomes An increased prevalence of major depression during pregnancy was associated with anaemia, when using women with no major depression during pregnancy (with or without a history of depression prior to pregnancy) as a reference group: **aOR[a] = 1.49; 95% CI 1.22 to 1.81**. [a]Adjusted by history of depression prior to pregnancy, maternal age, parity, smoking status, marital status, socioeconomic status, prior miscarriages, prior terminations, IVF, anaemia, gestational diabetes, pre-existing diabetes, fear of childbirth and fetal sex.
Authors' Conclusions	Physician-diagnosed major depression, treated in specialised centres, was associated with anaemia. Outcomes of pregnancies among women affected by major depression during pregnancy were worse than in unaffected women

Abbreviations: aOR: adjusted odds ratio; BMI: body mass index; CI: confidence interval; ICD: International Classification of Diseases; IVF: in vitro fertilisation; NA: not applicable; NR: not reported; SD: standard deviation; SGA: small for gestational age.

Table 50. Rukuni, 2016

Study Reference	Rukuni, 2016[23]
Study Design	Design: Retrospective cohort study. Objective: To estimate the incidence and clinical outcomes of antenatal anaemia in the Grampian region of Scotland. Dates: 1995 to 2012. Country: Scotland. Setting: Aberdeen Maternal and Neonatal Databank data collected from the University of Aberdeen Maternity Hospital, a tertiary maternity hospital for the NHS Grampian region and the only maternity unit for the city of Aberdeen.
Methods	Follow-up Data collected from the first antenatal visit through to the postpartum period. Definition of anaemia Defined as haemoglobin ≤10 g/dL. Antenatal anaemia was identified at any time before birth, although the specifics of how it was tested for were not discussed. This value is lower than NICE guidance: <11 g/dL in first trimester, 10.5 g/dL after second trimester and <10 g/dL in the postpartum period. Results should therefore be interpreted as the outcomes of more severe anaemia. Outcomes Relevant adverse maternal outcomes included: • PPH (blood loss at birth ≥500 ml, derived from the reported clinical estimate of blood loss at birth)

Study Reference **Rukuni, 2016[23]**

- Transfusion (no definition provided)

Additional maternal outcomes included: gestational hypertension, postpartum infection, pre-eclampsia, eclampsia, antepartum haemorrhage, obstetric haemorrhage and maternal death.

Relevant neonatal outcomes included:

- Neonatal unit admission (no definition provided)
- Preterm birth (gestational age at birth <37 weeks)
- Low birth weight (<2,500 g)
- Very low birth weight (<1,500 g)
- Early neonatal death (no definition provided)

Stillbirth was also reported.

Data for all outcomes was acquired from the AMND retrospectively.

Population Characteristics

Patient recruitment and eligibility

Recruitment:
Data acquired from the AMND retrospectively.
Inclusion:
Singleton pregnancy recorded in the AMND between study dates.
Exclusion:
Abortions, non-singleton births and pregnancies occurring after 2012.
Other:
NA.

Sample size

N included in database = 82,545
N excluded = abortions (n=205), multiple pregnancies (n=1,541) and pregnancies after 2012 (n=377)
N enrolled/ included in analysis = 80,422

Maternal Demographics

Parameter	Antenatal anaemia (n=7,475)	No antenatal anaemia (n=72,947)
Mean maternal age, years	28.2	29.2
Ethnicity, n (%)		
White	6,829 (91.36)	67,321 (92.29)
Black, Asian and minority ethnic groups	583 (7.80)	5,155 (7.07)
Missing	63 (0.84)	6 (0.01)
Obstetric History, n (%)		
Nulliparous	2,778 (37.16)	36,176 (49.59)
Parous	4,697 (62.84)	36,765 (50.40)
Missing	0	6 (0.01)
Median BMI, kg/m^2	23.5	24.5
Scottish Index of Multiple Deprivation, n (%)		

Study Reference	**Rukuni, 2016[23]**		
	First decile (most deprived)	1,111 (14.86)	12,690 (17.40)
	Second decile	1,041 (13.93)	11,762 (16.12)
	Third decile	1,009 (13.50)	11,809 (16.19)
	Fourth decile	467 (6.25)	5,379 (7.37)
	Fifth decile	661 (8.84)	6,124 (8.40)
	Sixth decile	679 (9.08)	6,342 (8.69)
	Seventh decile	445 (5.95)	3,669 (5.03)
	Eighth decile	731 (9.78)	5,511 (7.55)
	Ninth decile	48 (6.5)	3,523 (4.83)
	Tenth decile	705 (9.43)	4,308 (5.91)
	Smoking status, n (%)		
	Smokers	2,114 (28.28)	19,074 (26.15)
	Non-smokers	5,195 (69.50)	52,302 (71.70)
	Missing	166 (2.22)	1,571 (2.15)

Adverse Maternal and/or Neonatal Outcomes

Maternal Outcomes

Odds of adverse maternal outcomes with antenatal anaemia, using unexposed (no antenatal anaemia) as a reference.

Outcome	Adjusted OR[a] (95% CI; p value)
PPH (>500 ml)	0.92 (0.86, 0.98; p=0.007)
Maternal transfusion	1.87 (1.65, 2.13; NR)

[a]Adjusted for age, parity, smoking status, ethnicity, socio-economic status, BMI and chronic kidney disease

Neonatal Outcomes

Odds of adverse neonatal outcomes with antenatal anaemia, using unexposed (no antenatal anaemia) as a reference.

Outcome	Adjusted OR[a] (95% CI; p value)
Preterm birth (<37 weeks' gestation)	0.97 (0.88, 1.07; p=0.554)
Low birth weight (<2500 g)	0.77 (0.69, 0.86; NR)
Very low birth weight (<1500 g)	0.81 (0.62, 1.06; NR)
Special baby care/neonatal intensive care unit	1.01 (0.94, 1.09; NR)
Early neonatal death	1.17 (0.76, 1.79; NR)

[a]Adjusted for age, parity, smoking status, ethnicity, socio-economic status, BMI and chronic kidney disease

Authors' Conclusions	The incidence of severe antenatal anaemia is decreasing within the studied Scottish population. Severe antenatal anaemia was associated with a higher odds of antepartum haemorrhage, postpartum infection, transfusion and stillbirth. Contrary to other studies, results indicated a reduced odds of PPH and low birth weight.

Abbreviations: AMND: Aberdeen Maternal and Neonatal Databank; BMI: body mass index; CI: confidence interval; NA: not applicable; NICE: National Institute for Health and Care Excellence; NHS: National Health Service; NR: not reported; PPH: postpartum haemorrhage.

Table 51. Smith 2019

Study Reference	Smith 2019[18]
Study Design	Design Retrospective cohort study. Objective To quantify the association of anaemia with maternal and perinatal morbidity and mortality in British Columbia, Canada. Dates 2004 to 2016. Country Canada. Setting Pregnancies and births obtained from the British Columbia Perinatal Data Registry.
Methods	Duration of follow-up Anaemia measurements taken in the third trimester, or based on ICD10 codes from the birth admission but before birth; maternal outcomes measured up to and including the postpartum period. Definition of anaemia Third trimester haemoglobin <11 g/dL, or diagnosis of anaemia made during the birth admission but before birth (ICD10 codes D50–64 and O99.0 for anaemia). Outcomes Relevant maternal outcomes cover caesarean birth, antepartum transfusion and intrapartum–postpartum transfusion. Relevant neonatal outcomes cover preterm birth (<37 weeks' gestation), very premature birth (<32 weeks' gestation), SGA at birth, special care nursery admission and perinatal death. All diagnoses and procedures recorded in the database were based on physician notes, as recorded in the medical charts.
Population Characteristics	Patient recruitment and eligibility **Recruitment** Data obtained from British Columbia Perinatal Data Registry. **Inclusion** All pregnant women in British Columbia who had a live birth or stillbirth at or after 20 weeks' gestation between 2004 and 2016. **Exclusion** NR. **Other** NR. Sample size N included in analysis = 515,270 N no anaemia (haemoglobin >11 g/dL) = 449,364 N mild anaemia (haemoglobin 9 to 10.9 g/dL) = 60,590 N moderate anaemia (haemoglobin 7–8.9 g/dL) = 2,195

Study Reference **Smith 2019[18]**

N severe anaemia (haemoglobin <7 g/dL) = 127
N unspecified (diagnosis of anaemia) = 2,994

Maternal Demographics

Parameter	No anaemia (haemoglobin >11 g/dL; n=449,364)	Mild anaemia (haemoglobin 9–10.9 g/dL; n=60,590)	Moderate anaemia (haemoglobin 7–8.9 g/dL; n=2,195)
Maternal age (years), n			
<20	12,288	1,977	122
20–24	57,402	7,877	378
25–29	124,268	15,452	564
30–34	152,909	19,715	676
35–39	83,677	12,388	370
≥40	18,815	3,181	85
Ethnicity, n (%)	NR	NR	NR
Iron status	NR	NR	NR
Obstetric History			
Nulliparous, n	210,026	26,994	764
Multiparous, n	239,318	33,594	1,431
Gestational age, weeks	NR	NR	NR
Previous caesarean, n	66,182	9,502	444
Previous perinatal death, n	4,796	683	42
Pre-pregnancy BMI, kg/m^2	NR	NR	NR
Maternal education level	NR	NR	NR
Smoking status, n			
Current smoker	39,570	5,138	195
Past smoker	36,434	4,735	122
Never smoker	373,360	50,717	1,878
Employment status	NR	NR	NR

Adverse Maternal and/or Neonatal Outcomes

Maternal Outcomes

Women with mild and moderate anaemia have significantly increased odds of requiring caesarean section, antepartum transfusion or intrapartum–postpartum transfusion than non-anaemic women.

Outcome	No anaemia (haemoglobin >11 g/dL; n=449,364)	Mild anaemia (haemoglobin 9–10.9 g/dL; n=60,590)		Moderate anaemia (haemoglobin 7–8.9 g/dL; n=2,195)	
	n	n	Adjusted OR (95% CI)	n	Adjusted OR (95% CI)
Caesarean section	136,853 (30.5)	19,998 (33.0)	1.17 (1.14, 1.19)	872 (39.7)	1.86 (1.67, 2.08)
Antepartum transfusion	34 (0.01)	18 (0.03)	2.17 (1.28, 3.66)[a]	28 (1.28)	94.2 (60.2, 147.5)[a]

Study Reference	Smith 2019[18]

Intrapartum–postpartum transfusion	2,284 (0.51)	643 (1.06)	2.45 (1.74, 3.45)	173 (7.88)	21.3 (12.2, 37.3)

Models adjusted for maternal age, parity, pre-pregnancy weight, smoking, previous caesarean birth, alcohol use, pre-existing hypertension, chronic diseases and in vitro fertilization (not adjusted for nonindependence of outcomes among deliveries to the same woman). [a]Adjusted ORs not estimated for antepartum transfusion, as too few events were observed relative to the number of variables in the regression model; unadjusted ORs therefore reported.

Neonatal Outcomes

Women with mild and moderate anaemia have significantly increased odds of preterm birth, very premature birth and requirement for neonatal admission to NICU compared to non-anaemic women. Odds of perinatal death and SGA live birth are significantly reduced in women with mild anaemia compared with non-anaemic women; contrastingly, women with moderate anaemia have an increased odds of SGA at birth (non-significant) and perinatal mortality (significant, unadjusted) compared with non-anaemic women.

Outcome	No anaemia (haemoglobin >11 g/dL; n=449,364)	Mild anaemia (haemoglobin 9–10.9 g/dL; n=60,590)		Moderate anaemia (haemoglobin 7–8.9 g/dL; n=2,195)	
	n	n	Adjusted OR (95% CI)	n	Adjusted OR (95% CI)
Preterm birth (<37 weeks' gestation)	42,507 (9.38)	6,745 (10.9)	1.09 (1.05, 1.12)	470 (20.6)	2.26 (2.02, 2.54)
Very premature birth (<32 weeks' gestation)	6,680 (1.47)	1,247 (2.01)	1.30 (1.21, 1.39)	134 (5.86)	3.95 (3.23, 4.83)
SGA live birth (less than 10th centile)	31,329 (6.92)	3,860 (6.24)	0.83 (0.80, 0.86)	190 (8.34)	1.13 (0.97, 1.33)
NICU (special care nursery) admission	31,884 (7.03)	5,336 (8.61)	1.21 (1.17, 1.25)	372 (16.2)	2.52 (2.22, 2.85)
Perinatal death	3,076 (0.67)	267 (0.43)	0.61 (0.53, 0.70)	31 (1.34)	1.99 (1.37, 288)[a]

[a]Adjusted ORs not available, therefore unadjusted OR reported.

Authors' Conclusions	Maternal anaemia in pregnancy represents a common and potentially reversible risk factor associated with antepartum, intrapartum, and postpartum maternal morbidity and perinatal morbidity and mortality.

Abbreviations: BMI: body mass index; CI: confidence interval; ICD: International Classification of Diseases; NICU: neonatal intensive care unit; NR: not reported; OR: odds ratio; SGA: small for gestational age.

Table 52. Wiegersma 2019

Study Reference	Wiegersma 2019[30]
Study Design	Design Retrospective, register-based cohort study (the Stockholm Youth Cohort). Registers contain routinely collected health and sociodemographic data crosslinked via each resident's national identification number.

Study Reference	Wiegersma 2019[30]
	Objective To examine the association between prenatal anaemia diagnoses in mothers and offspring risk of autism spectrum disorder, attention deficit/hyperactivity disorder, and intellectual disability. Dates January 1, 1987 to December 31, 2010 (cohort contains individuals born from January 1, 1984, to December 31, 2011, residing in Stockholm County at any point from January 1, 2001, to December 31, 2011). Country Sweden. Setting Stockholm County.
Methods	Duration of follow-up NR. Data analysis was performed from January 15, 2018, to June 20, 2018, on individuals born from January 1, 1987, to December 31, 2010. Definitions of ID and mild or moderate anaemia International Classification of Diseases (ICD)-coded diagnosis of anaemia complicating pregnancy or IDA registered up to 1 calendar year before the birth of the index person was used to define the anaemia group. The rationale for using up to 1 calendar before the birth was because anaemia diagnosis during the periconceptual period likely indicates exposure to ID during early gestation. Outcomes • Caesarean birth. • Mother hospitalised for infection during pregnancy. • Size for gestational age. • Gestational age at birth (categorical), with the preterm category split into induced and spontaneous. Other outcomes reported but not extracted: • The primary objective of the study: explore maternal anaemia and later development of intellectual disability, autism spectrum disorder, and attention deficit/hyperactivity disorder, and whether there is an association with the timing of the first recorded anaemia diagnosis. Additional neonatal outcomes: low Apgar score.
Population Characteristics	Patient recruitment and eligibility **Recruitment** Non-adopted individuals born 1987 to 2010 in Sweden and their mothers. **Inclusion** Complete record in the Medical Birth Register and were residing in Stockholm County for more than 4 years through 2016. **Exclusion** Individuals affected by a study outcome who were also affected by a congenital disorder known to be associated with intellectual disability (for example, Down syndrome); incomplete record. Sample size N screened/invited = 736,196 (individuals born); 384,232 (mothers) N included in analysis = 532,232 (individuals born); 299,768 (mothers)

Study Reference **Wiegersma 2019[30]**

Maternal Demographics

Parameter	Anaemia (n=31,018)	No anaemia (n=501,214)
Maternal age, n (%)		
<25	3,933 (12.7)	75,180 (15.0)
25–29	8,245 (26.6)	148,240 (29.6)
30–34	11,188 (36.1)	173,187 (34.6)
35–39	6,135 (19.8)	86,675 (17.3)
≥40	1,517 (4.9)	17,932 (3.6)
Ethnicity, n (%)		
Mother born outside Sweden	8,877 (28.6)	123,716 (24.7)
Iron status	NR	NR
Obstetric History, n (%)		
Nulliparous	17,320 (55.8)	224,443 (44.8)
Singleton	28,699 (92.5)	488,961 (97.6)
Maternal BMI (kg/m^2), n (%)		
Normal (18.5–25)	15,685 (50.6)	252,748 (50.4)
Underweight (<18.5)	800 (2.6)	13,399 (2.7)
Overweight (25–30)	5,579 (18.0)	71,039 (14.2)
Obese (>30)	2,170 (7.0)	23,675 (4.7)
Missing	6,784 (21.9)	140,353 (28.0)
Maternal education level, n (%)		
Highest parental education level		
≤9 years	1,599 (5.2)	29,014 (5.8)
10–12 years	10,999 (35.5)	191,079 (38.1)
>12 years	17,760 (57.3)	272,670 (54.4)
Missing	660 (2.1)	8,451 (1.7)
Smoking status	NR	NR
Employment status	NR	NR

Adverse Maternal and/or Neonatal Outcomes

Maternal Outcomes

Outcome	Anaemia (n=31,018)	No anaemia (n=501,214)
Caesarean birth, n (%)	10,433 (33.6)	78,225 (15.6)
Mother hospitalised for infection during pregnancy, n (%)	2,373 (7.7)	17,229 (3.4)

Neonatal Outcomes

Outcome	Anaemia (n=31,018)	No anaemia (n=501,214)
Size for gestational age, n (%)		
SGA	684 (2.2)	11,761 (2.4)
Missing because of multiple birth	2,319 (7.5)	12,253 (2.4)

Study Reference	Wiegersma 2019[30]

Gestational age at birth, n (%)		
Preterm (induced)	1,879 (6.1)	11,948 (2.4)
Preterm (spontaneous)	852 (2.8)	14,898 (3.0)

	Anaemia diagnosed at ≤30 weeks' gestation	Anaemia diagnosed at >30 weeks' gestation
Odds of preterm birth vs non-anaemic mothers, OR (95% CI)	7.10 (6.28, 8.03)	–
Odds of post term birth vs non-anaemic mothers, OR (95% CI)	–	1.56 (1.49, 1.62)
Odds of SGA at birth vs non-anaemic mothers, OR (95% CI)	2.81 (2.26, 3.50)	–
Odds of SGA at birth vs non-anaemic mothers, OR (95% CI)	–	1.76 (1.66, 1.87)

Authors' Conclusions

The authors did not summarise conclusions related to the outcomes of interest to this rapid review. The authors concluded:

'In this study, anaemia diagnosed at 30 weeks or less of pregnancy was associated with modestly increased offspring risk of autism spectrum disorder and attention-deficit/hyperactivity disorder and greater risk of intellectual disability, suggesting that exposure to anaemia earlier in gestation may be negatively associated with neurodevelopment in the child. Given that ID and anaemia are common among women of childbearing age, our findings appear to emphasize the importance of early screening for iron status and nutritional counselling in antenatal care.'

Abbreviations: BMI: body mass index; CI: confidence interval; ICD: International Classification of Diseases; ID: iron deficiency; IDA: iron deficiency anaemia; OR: odds ratio.

Question 2 (What are the benefits and harms of treating pregnant women for IDA to pregnant women and their infants?)

Table 53. Arora 2015

Study Reference	Arora 2015[7]
Study Design	Design Retrospective review of birth records. Objective To identify characteristic risk factors of preterm birth in Central and Eastern Europe and explore the differences from other developed countries. Dates 1st January 2007 to 31st December 2009 (1 centre, University of Pecs Medical School contributed data for 2007–2008 only). Country Czech Republic, Hungary, Romania, Slovakia, and Ukraine.

Study Reference	Arora 2015[7]
	Setting University Hospital, Hradec Kralove (Czech Republic), Budapest Semmelweis University and University of Pecs Medical School, a regional tertiary center for preterm birth (Hungary), Carol Davila University of Medicine and Pharmacy (Romania), Slovak Medical University Hospital (Slovakia), and Danylo Halytskyy Lviv National Medical University (Ukraine).
Methods	Duration of follow-up Until birth. Method of assigning treatment arm Not applicable; retrospective analysis of birth records. Iron supplementation (n=NR) Received iron supplementation. No iron supplementation (n=NR) Did not receive iron supplementation. Outcomes Preterm or term birth, defined as birth at <37 weeks' gestation or >37 weeks' gestation, respectively.
Population Characteristics	Patient recruitment and eligibility **Recruitment** Not applicable. Clinical data was sourced from medical records. **Inclusion** Singleton deliveries (vaginal or caesarean). **Exclusion** Not reported. **Other** Slovakia and Czech Republic representative of high income countries. Sample size N included in analysis = 37,661. N included from Slovakia = 7,256. N included from Czech Republic = 5,483. Maternal Demographics

	Slovakia		Czech Republic	
Parameter	Preterm births (N=353)	Term births (N=6,903)	Preterm births (N=585)	Term births (N=4,898)
Maternal age, mean years (SD)	29.65 (5.64)	29.67 (4.94)	30.40 (5.45)	30.28 (4.81)
Ethnicity, n (%)	NR	NR	NR	NR
Iron status				
Anaemia, %	56.9	35.1	7.4	11.1

Study Reference	Arora 2015[7]				
	Iron-deficient anaemia, %	NR	NR	NR	NR
	Iron-deficient, %	NR	NR	NR	NR
	Iron supplement use, %	57.5	40.7	7.9	11.1
	Haemoglobin levels, g/dL	NR	NR	NR	NR
	Serum ferritin, µg/L	NR	NR	NR	NR
	Obstetric History				
	Nulliparous, %	NR	NR	NR	NR
	Parous, %	NR	NR	NR	NR
	Gestational age, weeks	NR	NR	NR	NR
	Pre-pregnancy BMI, mean kg/m^2 (SD)	22.6 (4.52)	22.8 (4.0)	23.1 (4.7)	27.1 (5.0)
	Maternal education level	NR	NR	NR	NR
	Smoking status				
	History of smoking, %	10.8	8.5	21.2	10.9
	Current smoking, %	17.1	7.8	10.2	7.8
	Employment status	NR	NR	NR	NR
Adverse Maternal and/or Neonatal Outcomes	Neonatal Outcomes Slovakia: Of individuals with preterm and term births, 60.3% and 38.6% used iron, respectively. Iron use was a significant risk factor for preterm birth, with an adjusted RR of 0.4 (95% CI 0.2 to 0.9; p=0.02). Czech Republic: Of individuals with preterm and term births, 7.9% and 11.1% used iron, respectively. **Note:** For both populations, it is unclear whether individuals who received iron were also those who had anaemia.				
Authors' Conclusions	Iron use is a risk factor for preterm birth.				

Abbreviations: BMI: body mass index; CI: confidence interval; NR: not reported; RR: risk ratio; SD: standard deviation.

Table 54. Pels 2015

Study Reference	Pels 2015[6]
Study Design	Design Retrospective case-control study. Objective To assess the safety and efficacy of IV ferric carboxymaltose (FCM) in pregnant women. Dates 2010 to 2012. Country Netherlands. Setting

Study Reference	Pels 2015[6]
	Department of Obstetrics and Gynecology of the Academisch Medisch Centrum in Amsterdam.
Methods	Duration of follow-up NR (until birth). Method of assigning treatment arm NA Case (n=64) IV FCM given as a single infusion over at least 15 minutes. Median dose 1000 mg (IQR 1000 to 1500). Majority (51/64) received a single dose of FCM, 6/64 received 2 doses of FCM, 3/64 received 3 doses. Control (n=64) No treatment Outcomes Assessed pregnancy outcomes were hospital admission (before birth, for other reasons than FCM administration), intensive care unit admission, intrauterine growth restriction (IUGR), hypertension/preeclampsia, placental abruption, major adverse outcomes (maternal or fetal), minor maternal adverse outcomes, Hb at birth (g/dL), need for RBC transfusion, gestational age at birth, mode of birth, estimated blood loss during birth, fetal weight (g), and neonatal Apgar score. Major maternal adverse outcomes were defined as death, stroke, neurological symptoms, severe preeclampsia, Hemolysis Elevated Liver enzymes Low Platelets (HELLP) syndrome, and birth before 34 weeks of gestation. Major adverse fetal outcomes were defined as death, respiratory problems (requiring intubation), NICU admission, pneumonia, morbidity requiring surgery, birth problems, and Apgar score <7.
Population Characteristics	Patient recruitment and eligibility **Recruitment** Patients were identified by searching the digital records of the Department of Obstetrics and Gynaecology for women who received FCM treatment and/or delivered a baby between 2010 to 2012. **Inclusion** Case group: all women who received at least 1 administration of FCM during their pregnancy. Control group: pregnant women who were either non-anaemic or had anaemia to a lesser degree not necessitating IV iron treatment. **Exclusion** Case group: women treated with FCM in the postpartum period. **Other** The control group was matched to the case group for birth period, type of comorbidity, age, parity, and number of foetuses. Definition of anaemia Anaemia during advanced gestation defined as haemoglobin <9.7 g/dL. Sample size N screened = 85 cases. N excluded (with reason) = 21 cases (3 not pregnant during treatment with FCM, 18 received FCM postpartum). N included in analysis = 128 (64 cases, 64 controls).

Study Reference **Pels 2015[6]**

Maternal Demographics

Parameter	Case group (n=64)	Control group (n=64)	P value
Maternal age, median years (range)	27 (17–39)	28 (17–40)	0.71
Ethnicity, n (%)			
Caucasian	5 (8)	22 (34)	0.00
African descent	38 (59)	15 (23)	0.00
Other	11 (17)	16 (25)	0.00
Unknown	10 (16)	11 (17)	0.00
Iron status			
Anaemia, n (%)	64 (100)	NA	NR
Haemoglobin, g/dL, median (IQR)[a]	8.44 (7.7, 8.9)	10.8 (9.8, 11.8)	NR
Comorbidities			
Hypothyroidism, n (%)	2 (3)	1 (2)	NR
Sickle cell anaemia, n (%)	2 (3)	1 (2)	NR
Alpha thalassemia, n (%)	0	1 (2)	NR
HIV infection, n (%)	1 (2)	1 (2)	NR
IL-12 receptor deficiency, n (%)	0	1 (2)	NR
Rheumatoid arthritis	1 (2)	0	NR
Obstetric History			
Gestational age, median days (IQR)[b]	244 (224–256)	NA	NR
Parity, median (range)	1 (0–4)	1 (0–4)	0.87
Pre-pregnancy BMI, kg/m^2	NR	NR	NR
Maternal education level, n (%)			
Lower education	13 (20)	10 (16)	0.18
Middle education	21 (33)	12 (19)	0.18
Higher education	7 (11)	12 (19)	0.18
Unknown education	23 (36)	29 (46)	0.18
Smoking status	NR	NR	NR
Employment status	NR	NR	NR

[a]Median haemoglobin at first FCM administration in case group; median haemoglobin at birth in control group. [b]Gestational age at first treatment.

Adverse Maternal and/or Neonatal Outcomes

No statistically significant pregnancy outcomes were seen between groups. There were also no reported treatment-related adverse outcomes or serious treatment-related adverse outcomes amongst the case group (those treated with FCM).

Maternal Outcomes

Outcome	Case (n=64)	Control (n=64)	P value

Study Reference	Pels 2015[6]

Transfusion (n=125), n (%)	2 (3)	3 (5)	0.20
Primary caesarean (n=126), n (%)	9 (14)	12 (19)	0.29
Secondary caesarean (n=126), n (%)	5 (8)	8 (13)	0.29

Neonatal Outcomes

Outcome	Case (n=64)	Control (n=64)
Very premature birth (<34 weeks' gestation) (n=128), n	5	5
Admission to NICU (n=128), n	0	2

Authors' Conclusions	Maternal and fetal outcomes were similar between the case and the control group.

Abbreviations: BMI: body mass index; FCM: ferric carboxymaltose; Hb: haemoglobin; HELLP: Hemolysis Elevated Liver enzymes Low Platelets; ICU: intensive care unit; IQR: interquartile range; IUGR: intrauterine growth restriction; IV: intravenous; NA: not applicable; NICU: neonatal intensive care unit; NR: not reported; RBC: red blood cell.

Table 55. Rukuni 2015

Study Reference	Rukuni 2015[13]
Study Design	Design Structured review and gap analysis. Objective To appraise the evidence against the UK NSC criteria as to whether a national screening programme could reduce the prevalence of IDA and/or ID in pregnancy and improve maternal and fetal outcomes. Dates Medline 1946 to August 2014; Embase 1974 to August 2014; Cochrane Library 2014. Country NA. Setting NA.
Review Characteristics	Study eligibility Literature searches of Medline, Embase and the Cochrane Library. **Inclusion** • Studies published in English. Definitions of ID and mild or moderate anaemia (if applicable) Definition of anaemia not reported within the study eligibility criteria, although a summary of guidelines for the management of anaemia in the UK is provided.

Study Reference	Rukuni 2015[13]
	Sample size N studies = NR
Methods	Intervention and comparators None specified. Outcomes Outcomes of interest to the review not reported.
Adverse Maternal and/or Neonatal Outcomes	A systematic review and meta-analysis of 48 randomised trials and 44 cohort studies (Haider 2013) has reported that prenatal iron in the context of maternal anaemia increases maternal haemoglobin reduces ID and reduces low birth weight. These effects showed a linear dose–response relationship at doses of 66 mg/day or higher. Only a small number of trials reported effects on other outcomes such as stillbirth, neonatal mortality, gestational diabetes and maternal infections in pregnancy, which precluded meta-analysis. A Cochrane review of treatments for iron deficiency anaemia in pregnancy (Reveiz 2011) included 23 trials using different combinations of intravenous, oral and intramuscular iron. Oral iron therapy was associated with higher rates of withdrawal from studies due to side effects and associated poor compliance. Intravenous iron led to greater improvements in haematological indices, fewer problems with gastrointestinal side effects and better compliance; the trials did not assess clinical consequences. However, it should be noted that IV iron use is only recommended in the second trimester for safety reasons.
Authors' Conclusions	Further evidence is required to ensure that the benefits of treating pregnant women for IDA outweigh the harms to them and their infants.

Abbreviations: ID: iron deficiency; IDA: iron deficiency anaemia; IV: intravenous; NA: not applicable; NR: not reported; UK NSC: United Kingdom National Screening Committee.

Table 56. USPSTF SLR (Cantor 2015, McDonagh 2015)

Study Reference	USPSTF SLR[13, 40]
Study Design	Design Systematic review and meta-analysis. Update to a 2006 systematic review by the US Preventive Services Task Force (USPSTF) on screening and supplementation for IDA in pregnancy. Objective To examine evidence from US-relevant populations on the effectiveness of routine supplementation and screening for IDA in pregnancy. Dates MEDLINE and the Cochrane Library (1996 to August 2014) and reference lists of relevant systematic reviews to identify studies published since 1996. Country Studies conducted in the US and those conducted in countries with 'high' or 'very high' human development based on the United Nations Human Development Index. Setting English-language trials and controlled observational studies about effectiveness of screening and routine supplementation for IDA in developed countries.

Study Reference	USPSTF SLR[13, 40]
Review Characteristics	Search strategy The Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and Ovid MEDLINE (1996 to August 2014) were searched. Reference lists of relevant systematic reviews were also searched to identify studies published before 1996, the year that the prior reviews concluded. Study eligibility Abstracts were selected for full-text review if they included asymptomatic pregnant women receiving screening or supplementation for IDA, were relevant to a key question, and met predefined inclusion criteria. Studies using iron supplementation and treatment regimens commonly used in clinical practice in the United States and those conducted in countries with 'high' or 'very high' human development based on the United Nations Human Development Index were the main focus. This included randomised, controlled trials; nonrandomised, controlled trials; and cohort studies for all key questions. **Exclusion** When good- and fair-quality studies were available, poor-quality studies were excluded. Definitions of mild or moderate iron deficiency and anaemia (if applicable) Outcomes included iron status based on hematologic indices, including ferritin levels. Sample size N articles identified = 1431 N relevant to key questions = 283 N included studies = 12 (14 publications) N benefits and harms of treating iron deficiency anaemia = 0
Methods	Duration of follow-up NA. Method of assigning treatment arm NA. Outcomes Key Question 3: What Are the Benefits of Treatment of Iron Deficiency Anaemia in Pregnant Women on Maternal and Infant Health Outcomes?
Adverse Maternal and/or Neonatal Outcomes	No relevant studies were identified.
Authors' Conclusions	No studies met the inclusion criteria for any of the key questions on benefits and harms of screening for IDA in pregnancy, benefits and harms of screen-detected treatment, or the association between a change in maternal iron deficiency or IDA status and improvement in new born and peripartum outcomes in US-relevant populations. Rigorous studies are needed to fully understand the short- and long-term effect of routine iron supplementation and screening for IDA in pregnancy on women and their infants.

Abbreviations: IDA: iron deficiency anaemia; NA: not applicable; US: United States; USA: United States of America; USPSTF: US Preventive Services Taskforce.

Question 3 (What are the benefits and harms of screening for IDA during pregnancy?)

Table 57. Rukuni 2015

Study Reference	Rukuni 2015[13]
Study Design	Design Structured review and gap analysis. Objective To appraise the evidence against the UK NSC criteria as to whether a national screening programme could reduce the prevalence of IDA and/or ID in pregnancy and improve maternal and fetal outcomes. Dates Medline 1946 to August 2014; Embase 1974 to August 2014; Cochrane Library 2014. Country NA. Setting NA.
Methods	Index test/comparator None specified. Reference standard None specified. Outcomes Outcomes of interest to the review not reported.
Review Characteristics	Study eligibility Literature searches of Medline, Embase and the Cochrane Library. **Inclusion** • Studies published in English. Definitions of ID and mild or moderate anaemia (if applicable) Definition of anaemia not reported within the study eligibility criteria, although a summary of guidelines for the management of anaemia in the UK is provided. Sample size N studies = NR
Adverse Maternal and/or Neonatal Outcomes	No screening programmes or randomised trials of screening for ID and/or IDA in pregnancy were identified. Evaluations of screening programmes for IDA in infants and adolescents in the USA reported little benefit. No relevant data to address Criterion 13 of the UK NSC criteria were identified.

Study Reference	Rukuni 2015[13]
Authors' Conclusions	The lack of data from high quality RCTs indicating that a screening programme for IDA would be effective at reducing morbidity or mortality represents a major gap in the evidence. Further work is required to investigate the association between antenatal anaemia and clinical outcomes to develop more effective strategies to further reduce the incidence of antenatal anaemia.

Abbreviations: ID: iron deficiency; IDA: iron deficiency anaemia; NA: not applicable; NR: not reported; RCT: randomised control trial; UK NSC: United Kingdom National Screening Committee; USA: United States of America.

Table 58. USPSTF SLR (Cantor 2015, McDonagh 2015)

Study Reference	USPSTF SLR[39, 40])
Study Design	Design Systematic review and meta-analysis. Update to a 2006 systematic review by the US Preventive Services Task Force (USPSTF) on screening and supplementation for IDA in pregnancy. Objective To examine evidence from US-relevant populations on the effectiveness of routine supplementation and screening for IDA in pregnancy. Dates MEDLINE and the Cochrane Library (1996 to August 2014) and reference lists of relevant systematic reviews to identify studies published since 1996. Country Studies conducted in the US and those conducted in countries with 'high' or 'very high' human development based on the United Nations Human Development Index. Setting English-language trials and controlled observational studies about effectiveness of screening and routine supplementation for IDA in developed countries.
Review Characteristics	Search strategy The Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and Ovid MEDLINE (1996 to August 2014) were searched. Reference lists of relevant systematic reviews were also searched to identify studies published before 1996, the year that the prior reviews concluded. Study eligibility Abstracts were selected for full-text review if they included asymptomatic pregnant women receiving screening or supplementation for IDA, were relevant to a key question, and met predefined inclusion criteria. Studies using iron supplementation and treatment regimens commonly used in clinical practice in the US and those conducted in countries with 'high' or 'very high' human development based on the United Nations Human Development Index were the main focus. This included randomised, controlled trials; nonrandomised, controlled trials; and cohort studies for all key questions. **Exclusion** When good- and fair-quality studies were available, poor-quality studies were excluded. Definitions of mild or moderate iron deficiency and anaemia Outcomes included iron status based on hematologic indices, including ferritin levels. Sample size N articles identified = 1431

Study Reference	USPSTF SLR[39, 40])
	N relevant to key questions = 283 N included studies = 12 (14 publications) N screening for iron deficiency anaemia = 0
Methods	Intervention and comparators NA. Outcomes Key Question 1: What Are the Benefits of Screening for Iron Deficiency Anaemia in Asymptomatic, Pregnant Women on Maternal and Infant Health Outcomes?
Adverse Maternal and/or Neonatal Outcomes	No randomised trial or observational study compared clinical outcomes between pregnant women who were screened or not screened for iron deficiency anaemia.
Authors' Conclusions	No studies met the inclusion criteria for any of the key questions on benefits and harms of screening for IDA in pregnancy, benefits and harms of screen-detected treatment, or the association between a change in maternal iron deficiency or IDA status and improvement in new born and peripartum outcomes in US-relevant populations. Rigorous studies are needed to fully understand the short- and long-term effect of routine iron supplementation and screening for IDA in pregnancy on women and their infants.

Abbreviations: IDA: iron deficiency anaemia; NA: not applicable; US: United States; USA: United States of America; USPSTF: US Preventive Services Taskforce.

Appendix 4 — Appraisal for quality and risk of bias

Question 1 (What are the maternal and infant outcomes associated with untreated ID, with or without mild or moderate anaemia?)

Table 59. ROBINS-I assessments for non-RCTs evaluating the adverse effects of IDA in pregnancy

Question	Beckert 2019[28]	Bencaiova 2014[14]	Beta 2013[15]	Biguzzi 2012[27]	Crispin 2019[19]	Ehrenthal 2012[25]
BIAS DUE TO CONFOUNDING						
1.1 Is there potential for confounding of the effect of intervention in this study?	PY Significant differences in baseline characteristics that could have affected maternal outcomes observed between anaemic and non-anaemic groups.	Y Factors that could impact upon iron/anaemia status were part of exclusion criteria. Women received iron supplementation or IV iron dependent on haemoglobin status.	PY Women with previous pre-term birth included; other significant differences between study groups in baseline characteristics also present.	PY Serious maternal illness (including bleeding disorders) not excluded.	PY No women with potentially confounding factors were excluded from the study.	Y Adjustments were not made for key variables including parity and multiple births.
1.2 If Y/PY to 1.1: Was the analysis based on splitting participants' follow up time according to intervention received? 1.3 If Y/PY to 1.1: Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	PN Time between exposure and outcome unknown. NI The authors were not able to elucidate whether treatment was attempted, therefore it is unclear whether women were supplemented and potentially able to switch exposure groups.	PN Time between exposure and outcome unknown. NI Anaemic women were eligible to receive iron supplementation, and it is therefore possible that they were able to switch between exposure groups.	PN Time between exposure and outcome unknown. NI It is not reported whether women received iron supplementation, and whether women therefore switched exposure over time.	PN Time between exposure and outcome unknown. NI It is not reported whether women received iron supplementation, and whether women therefore switched exposure over time.	PN Time between exposure and outcome unknown. NI No discontinuation from exposure or switches are likely, although women may have received oral iron supplementation; the study reports that baseline iron use was unknown.	PN Time between exposure and outcome unknown. NI Unclear whether women received iron supplementation, which could influence exposure, and if this varied over time.

Question	Beckert 2019[28]	Bencaiova 2014[14]	Beta 2013[15]	Biguzzi 2012[27]	Crispin 2019[19]	Ehrenthal 2012[25]
1.4 Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Y Covariates that could have affected the outcome were controlled for.	PN Statistical analyses to adjust for confounding do not appear to have been undertaken.	N Statistical analyses did not include techniques to adjust to confounding.	Y Potential risk factors for PPH were controlled for.	N Covariates that could have affected the outcome were not controlled for.	PN Authors adjusted for some potential covariates, but a number of relevant variables were not adjusted for.
1.5 If Y/PY to 1.4 Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	PY Data was extracted from medical records.	NA	NA	PY Data extracted from medical records.	NA	PY Data recorded through direct entry by nursing staff during the women's hospitalisations.
1.6 Did the authors control for any post-intervention variables that could have been affected by the intervention?	Y Obstetric outcomes were controlled for in analysis of neonatal outcomes.	N No variables were controlled for.	N No variables were controlled for.	Y Post-exposure risk factors controlled for, including factors related to birth approach (including induction, vacuum, retained placenta)	N Covariates that could have affected the outcome were not controlled for.	PY Gestational age at birth was controlled for.
1.7 Did the authors use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding?	NA	NA	NA	NA	NA	NA
Risk of bias judgement	Moderate	Critical	Critical	Moderate	Critical	Serious
BIAS IN PARTICIPANT SELECTION						
2.1 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	Y Women included on the basis of birth within certain period of pregnancy and certain neonatal characteristics.	N Prospective study; haematological status determined after enrolment.	Y Women with induced births were excluded.	Y Inclusion criteria included vaginal birth at ≥37 weeks' gestation.	N Women included retrospectively based on having had blood tests performed.	PY Some inclusion criteria based on post-exposure characteristics such as birth weight and gestational age at birth.

Question	Beckert 2019[28]	Bencaiova 2014[14]	Beta 2013[15]	Biguzzi 2012[27]	Crispin 2019[19]	Ehrenthal 2012[25]
2.2 If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention? and, 2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	PN Unlikely that presence of chromosomal abnormalities and abnormally small/large infants would be associated with anaemia or outcomes reported.	NA	PY Selection was based on an outcome of interest possibly associated with anaemia.	PY Women were selected based on preterm birth and caesarean section; it is possible that these outcomes may be influenced by low haemoglobin.	NA	PN It is unlikely that anaemia would be associated with birth <20 weeks' gestation or a birth weight <350 g.
2.4 Do start of follow-up and start of intervention coincide for most participants?	PN Unclear how long women would have had anaemia, but likely some had it for longer than others.	PN Majority of women had anaemia assessed at specified timepoints, although unclear how long women had anaemia for. Outcomes measured at birth in all women.	PN Unclear how long women would have had anaemia, but likely some had it for longer than others.	PN Unclear how long women would have had prenatal anaemia, but likely some had it for longer than others.	PN Unclear how long women would have had ID, but likely some had it for longer than others.	PN Unclear how long women would have had anaemia for before measurement.
2.5 If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	N No adjustment techniques appear to have been used.	N No adjustment techniques appear to have been used.	N No adjustment techniques appear to have been used.	N No adjustment techniques appear to have been used.	N No adjustment techniques were used.	N No adjustment techniques appear to have been used.
Risk of bias judgement	Low	Low	Moderate	Moderate	Low	Low
BIAS IN THE CLASSIFICATION OF INTERVENTIONS						
3.1 Were intervention groups clearly defined?	PY Diagnosis of anaemia based on ICD codes.	Y IDA, iron depletion and anaemia clearly defined.	Y Anaemia clearly defined.	N Haemoglobin measured on a continuous scale.	Y Anaemia and cut off for ID clearly defined.	Y Anaemia clearly defined based on haemoglobin levels.
3.2 Was the information used to define intervention groups recorded at the start of	PN	PN	PN	PN	PN	PN

Question	Beckert 2019[28]	Bencaiova 2014[14]	Beta 2013[15]	Biguzzi 2012[27]	Crispin 2019[19]	Ehrenthal 2012[25]
the intervention?						
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	PN Anaemia status determined either prenatally or in the birth admission, likely to have occurred before outcomes were measured.	PN Anaemia status determined either prenatally or in the birth admission, likely to have occurred before outcomes were measured.	PN Anaemia was diagnosed during pregnancy, and therefore likely to have occurred prior to outcome measurement..	PN Haemoglobin measured within 1 month of birth, and therefore likely to have occurred prior to outcome measurement.	N Blood tests were performed during pregnancy, and occurred prior to outcome measurement.	N Unlikely that knowledge of perinatal transfusion would have influenced determination of haemoglobin levels.
Risk of bias judgement	Low	Low	Low	Moderate	Low	Low
BIAS DUE TO DEVIATIONS FROM INTENDED INTERVENTIONS						
4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	NA	NA	NA	NA	NA	NA
4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome?	NA	NA	NA	NA	NA	NA
4.3. Were important co-interventions balanced across intervention groups?	NA	NA	NA	NA	NA	NA
4.4. Was the intervention implemented successfully for most participants?	NA	NA	NA	NA	NA	NA
4.5. Did study participants adhere to the assigned intervention regime?	NA	NA	NA	NA	NA	NA
4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate	NA	NA	NA	NA	NA	NA

Question	Beckert 2019[28]	Bencaiova 2014[14]	Beta 2013[15]	Biguzzi 2012[27]	Crispin 2019[19]	Ehrenthal 2012[25]
analysis used to estimate the effect of starting and adhering to the intervention?						
Risk of bias judgement	Not assessed; relevant details (such as use of iron supplementation) captured under confounding domain.	Not assessed; relevant details (such as use of iron supplementation) captured under confounding domain.	Not assessed; relevant details (such as use of iron supplementation) captured under confounding domain.	Not assessed; relevant details (such as use of iron supplementation) captured under confounding domain.	Not assessed; relevant details (such as use of iron supplementation) captured under confounding domain.	Not assessed; relevant details (such as use of iron supplementation) captured under confounding domain.
BIAS DUE TO MISSING DATA						
5.1 Were outcome data available for all, or nearly all, participants?	PY Implied, although not confirmed.	PY Implied, although not confirmed.	Y Inclusion criteria related to outcomes of interest.	N Data for all outcomes available for 79% women.	NI Values not reported for outcomes.	PY If there was no record of transfusion likely to be recorded as a non-event in study.
5.2 Were participants excluded due to missing data on intervention status?	N Exposure status available for all women.	N Exposure status available for all women.	PN Likely assumed absence of anaemia on records signified no anaemia.	Y Women were only included in the analysis if they had complete data	PY	PY Women were excluded if they were missing a 'complete blood count' drawn in the 7 days prior to birth.
5.3 Were participants excluded due to missing data on other variables needed for the analysis?	PN Evidence of some missing baseline data, however it is implied all included in analysis.	PN Implied, although not confirmed.	PN Implied, although not confirmed.	Y Women were only included in the analysis if they had complete data	PN	Y Cases were excluded if they had missing data for maternal race/ethnicity, parity, age, gestational age at birth, and birth weight.
5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	NA	NA	NA	NA	PN Proportion of women with missing ferritin/Hb measurements not similar across exposures.	NI
5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing	NA	NA	NA	NA	PN	N Women with missing data were excluded from the study cohort outright, and it does not

Question	Beckert 2019[28]	Bencaiova 2014[14]	Beta 2013[15]	Biguzzi 2012[27]	Crispin 2019[19]	Ehrenthal 2012[25]
data?						appear that any sensitivity analyses, for example, were conducted.
Risk of bias judgement	Low	Low	Low	Moderate	Serious	Serious
BIAS IN MEASUREMENT OF OUTCOMES						
6.1 Could the outcome measures have been influenced by knowledge of the intervention received?	N Outcomes were objective and not likely to have been influenced by knowledge of exposure.	N Outcomes were objective and not likely to have been influenced by knowledge of exposure.	N Outcomes were objective and not likely to have been influenced by knowledge of exposure.	N Outcomes were objective and not likely to have been influenced by knowledge of exposure.	N Outcomes were objective and not likely to have been influenced by knowledge of exposure.	N Outcomes were objective and not likely at have been influenced by knowledge of exposure.
6.2 Were outcome assessors aware of the intervention received by study participants?	PY Not reported, although likely as recorded on birth records.	PY Not reported, although likely as recorded on medical records.	PY Not reported, although likely as recorded on medical records.	PY Not reported, although likely as recorded on medical records.	PN Women were retrospectively evaluated for anaemia and ID.	PY Not reported, although likely as recorded on medical records.
6.3 Were the methods of outcome assessment comparable across intervention groups?	Y Outcomes were objective and likely to have been assessed consistently.	Y Outcomes were objective and likely to have been assessed consistently.	Y Outcomes were objective and likely to have been assessed consistently.	Y Outcomes were objective and likely to have been assessed consistently.	Y Outcomes were objective and likely to have been assessed consistently.	Y Outcomes were assessed based on the blood bank database.
6.4 Were any systematic errors in measurement of the outcome related to intervention received?	PN Outcomes were objective and likely to have been assessed consistently.	PN Outcomes were objective and likely to have been assessed consistently.	PN Outcomes were objective and likely to have been assessed consistently.	PN Outcomes were objective and likely to have been assessed consistently.	N	PN Outcomes were objective and likely to have been assessed consistently.
Risk of bias judgement	Low	Low	Low	Low	Low	Low
BIAS IN SELECTION OF THE REPORTED RESULT						
Is the reported effect estimate likely to be selected, on the basis of the results, from... 7.1. ... multiple outcome measurements within the	N Multiple outcome measurements not relevant to the outcomes recorded.	N Multiple outcome measurements not relevant to the outcomes recorded.	N Multiple outcome measurements not relevant to the outcomes recorded.	N Multiple outcome measurements not relevant to the outcomes recorded.	N Multiple outcome measurements not relevant to the outcomes recorded.	N Multiple outcome measurements not likely.

Question	Beckert 2019[28]	Bencaiova 2014[14]	Beta 2013[15]	Biguzzi 2012[27]	Crispin 2019[19]	Ehrenthal 2012[25]
outcome domain?						
7.2 ... multiple analyses of the intervention-outcome relationship?	PN Multiple analyses with adjustment for different variables presented, but these seem reasonable in the context of the study.	PN Unlikely multiple exposure definitions used, unlikely for there to be multiple interpretations of outcome.	PN Unlikely that multiple analyses were undertaken, although some analyses (multivariate) could have been considered.	PN Potential to analyse haemoglobin level in different ways, but unlikely.	N Unlikely multiple exposure definitions used, unlikely for there to be multiple interpretations of outcome.	PN Unlikely that multiple definitions of anaemia considered.
7.3 ... different subgroups?	N No subgroups were reported.	N It does not appear that subgroups other than those reported would have been recorded.	N No subgroups were reported.	N No subgroups were reported.	N No subgroups were reported.	PN aOR not reported for the overall study population.
Risk of bias judgement	Low	Low	Low	Low	Low	Low
OVERALL BIAS	Moderate	Critical	Critical	Moderate	Critical	Serious

Table 59 continued. ROBINS-I assessments for non-RCTs evaluating the adverse effects of IDA in pregnancy

Question	Gaillard 2014[16]	Khambalia 2015[31]	Khambalia 2016[29]	Nyflot 2017[24]	Orlandini 2017[26]	Petty 2018[17]
BIAS DUE TO CONFOUNDING						
1.1 Is there potential for confounding of the effect of intervention in this study?	PN A comprehensive range of potential confounding factors was measured and adjusted for during statistical analysis. Nevertheless, residual confounding may still have been present.	PY Observational design means residual confounding may have been present. Because no association was found between ID in the first trimester and pre-term birth, multivariate analyses were not performed. The study did not consider iron supplementation.	Y Over 50% of women had elevated CRP, and ID could therefore be a result of inflammation in these women.	Y Differences between cases and controls in key baseline variables, including parity. Case-control study, with controls selected to match cases.	PY Significant differences in parity between 2 exposure groups.	Y Only bivariate statistical analyses completed. Potential sources of confounding were not accounted for.

Question	Gaillard 2014[16]	Khambalia 2015[31]	Khambalia 2016[29]	Nyflot 2017[24]	Orlandini 2017[26]	Petty 2018[17]
1.2 If Y/PY to 1.1: Was the analysis based on splitting participants' follow up time according to intervention received? 1.3 If Y/PY to 1.1: Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	N Women were followed and measurements taken up until the point of birth. NI Information on maternal iron or ferritin intake was not available. Instead, multivitamin use was used as a proxy. It is possible that after detection of anaemia, women may have received iron supplements, affecting the observed associations.	N All women were followed to the point of birth. NI Iron supplementation was not considered in the study. In addition, serum ferritin levels were only measured during the first trimester. It is possible that women identified as iron deficient in first trimester may have received supplementation.	PN Time between exposure and outcome unknown. NI No information was available on iron supplement use, which could result in switches between exposures.	PN Time between exposure and outcome unknown. NI No information was available on iron use, which could result in switches between exposures.	PN Time between exposure and outcome unknown. NI No information was available on iron supplement use, which could result in switches between exposures.	PN Time between exposure and outcome unknown. NI Unclear whether individuals received iron supplementation; switches may have been possible to/from iron supplementation, which was not considered in the analysis.
1.4 Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	PY Covariates that could have affected the outcome were controlled for in the analysis.	PN Some covariates that could have affected the outcome were controlled for. Others (such as iron supplement use) were not.	PN Some variables were adjusted for in multivariate analyses; outcomes of interest were not included in multivariate analyses, and relevant results therefore reflect unadjusted multivariate analyses.	Y Risk factors were adjusted for.	N Statistical analyses did not include techniques to adjust for confounding.	N Covariates that could have affected the outcome were not controlled for in the analysis.
1.5 If Y/PY to 1.4 Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	PY Extensive details were provided on how covariates were measured. Some information relied on self-reporting and multivitamin use was considered a proxy for iron supplementation use.	PY Those confounding domains included in the analysis were taken from datasets where reporting had a high specificity (>99%).	NA	PY Data was extracted from medical records.	NA	NA

Question	Gaillard 2014[16]	Khambalia 2015[31]	Khambalia 2016[29]	Nyflot 2017[24]	Orlandini 2017[26]	Petty 2018[17]
1.6 Did the authors control for any post-intervention variables that could have been affected by the intervention?	Y Maternal smoking and alcohol consumption were assessed by questionnaire repeatedly during pregnancy and controlled for.	PY Some data collected from the New South Wales Perinatal Data Collection and Admitted Patients Data Collection systems may have been recorded after the serum blood samples that were analysed for serum ferritin levels.	N Considering the relevant results, no variables were controlled for.	PY Conditions associated with pregnancy, such as gestational diabetes were controlled for.	N No variables were controlled for.	N No variables were controlled for in the analysis.
1.7 Did the authors use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding?	NA	NA	NA	NA	NA	NA
Risk of bias judgement	Moderate	Serious	Critical	Moderate	Critical	Critical
BIAS IN PARTICIPANT SELECTION						
2.1 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	PY Women that were lost to follow-up (n=38), missing haemoglobin/haematocrit measures (n=1,357), fetal death (n=65) and pregnancies leading to induced abortions (n=26) were excluded in the analysis.	PY Study inclusion criteria included a minimum birth weight or minimum gestational period prior to birth; both would have been recorded after development of ID. More generally, the study provides very little information on inclusion or exclusion criteria.	PY Women had to attend first trimester Down Syndrome screening to be eligible (where blood samples were taken), but otherwise were selected randomly. Women were excluded for medical abortions or infants with major congenital anomaly, which may have occurred after the first trimester.	Y Selection based on presence or absence of severe PPH.	PY Inclusion criteria included gestational age at admission to hospital.	N Only those records where an antenatal haemoglobin concentration measurement was available were included.

Question	Gaillard 2014[16]	Khambalia 2015[31]	Khambalia 2016[29]	Nyflot 2017[24]	Orlandini 2017[26]	Petty 2018[17]
2.2 If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention? and, 2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	PY Fetal death, abortion, or loss to follow-up may have been associated with maternal anaemia. PY Fetal death, abortion, or loss to follow-up may have been associated with adverse pregnancy outcomes.	PN Birth weight <400g or birth before 20 weeks' gestation unlikely to be associated with ID.	N Unlikely that medical abortion or presence of congenital anomaly associated with exposure or reported outcomes.	Y Evidence indicates that PPH may be influenced by anaemia. The criteria for selection was the outcome of interest for cases. Controls were a random sample of all deliveries without severe PPH from the same source population and period of time.	PY Some evidence suggests that preterm birth can be associated with anaemia.	NA
2.4 Do start of follow-up and start of intervention coincide for most participants?	PN At enrolment, maternal haemoglobin was measured. However, it is likely that some women may have been anaemic for a longer period than others.	PN Unclear how long those women with low serum ferritin levels had been iron deficient.	PN Unclear how long women had ID before first trimester reading.	PN Unclear how long women would have had anaemia for before measurement.	PN Unclear how long women would have had anaemia for before measurement.	PN Unclear how long women would have had anaemia, but likely some had it for longer than others.
2.5 If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	N No techniques were used to adjust for selection bias.	N No techniques were used to adjust for selection bias.	N No adjustment techniques appear to have been used.	PN No adjustment techniques appear to have been used.	N No adjustment techniques appear to have been used.	N Adjustment techniques were not used to account for selection bias.
Risk of bias judgement	Moderate	Serious	Low	Moderate	Moderate	Low
BIAS IN THE CLASSIFICATION OF INTERVENTIONS						
3.1 Were intervention groups clearly defined?	Y Anaemia was clearly defined using both haemoglobin and haematocrit levels.	Y ID was clearly defined.	Y ID defined according to serum ferritin levels.	Y Anaemia clearly defined based on haemoglobin levels.	Y Anaemia clearly defined based on haemoglobin levels.	Y Anaemia and non-anaemia were clearly defined.
3.2 Was the information used to define intervention groups	PN	PN	PN	PN	PN	PN

Question	Gaillard 2014[16]	Khambalia 2015[31]	Khambalia 2016[29]	Nyflot 2017[24]	Orlandini 2017[26]	Petty 2018[17]
recorded at the start of the intervention?						
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	N There were clear definitions used for each exposure group. Outcomes were recorded prospectively.	N Classification as iron deficient would not have an impact on whether a birth is defined as preterm.	N ID determined using an objective approach, although measurement occurred after birth (measurements taken from stored blood samples taken in first trimester).	N Anaemia status determined at the start of pregnancy, whereas outcome recorded in postpartum period.	N Anaemia status determined at the start of pregnancy, whereas outcomes recorded at birth or in postpartum period.	PN Subsequent receipt of a red blood cell transfusion should not have affected whether a woman was classified as being anaemic.
Risk of bias judgement	Low	Low	Low	Low	Low	Low
BIAS DUE TO DEVIATIONS FROM INTENDED INTERVENTIONS						
4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	PN Iron supplementation was assessed using multivitamin use as a proxy.	NI No information on iron supplementation provided in the paper.	NA	NA	NA	NI Unclear whether individuals received iron supplementation.
4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome?	PN Adjustment for multivitamin use during assessment of associations did not strongly affect observed outcomes.	NA	NA	NA	NA	NI
4.3. Were important co-interventions balanced across intervention groups?	NA	NA	NA	NA	NA	NA
4.4. Was the intervention implemented successfully for most participants?	PY Most women received the required antenatal haemoglobin or haematocrit measurements to participate (7,317/8,880 =82.4%).	Y All women enrolled had serum samples tested for serum ferritin levels.	NA	NA	NA	Y Most women (99.2%) received an antenatal haemoglobin concentration measure.

Question	Gaillard 2014[16]	Khambalia 2015[31]	Khambalia 2016[29]	Nyflot 2017[24]	Orlandini 2017[26]	Petty 2018[17]
4.5. Did study participants adhere to the assigned intervention regime?	NA	NA	NA	NA	NA	NA
4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	NA	NA	NA	NA	NA	NA
Risk of bias judgement	Not assessed; relevant details (such as use of iron supplementation) captured under confounding domain.	Not assessed; relevant details (such as use of iron supplementation) captured under confounding domain.	Not assessed; relevant details (such as use of iron supplementation) captured under confounding domain.	Not assessed; relevant details (such as use of iron supplementation) captured under confounding domain.	Not assessed; relevant details (such as use of iron supplementation) captured under confounding domain.	Not assessed; relevant details (such as use of iron supplementation) captured under confounding domain.
BIAS DUE TO MISSING DATA						
5.1 Were outcome data available for all, or nearly all, participants?	Y Data from 7,316 out of 7,317 women was included in the presented outcome assessments.	Y All women had outcome data (timing of birth) recorded.	Y Outcomes were known to be reliably reported in birth and/or hospital records; not otherwise specified.	Y Women selected on the basis of outcome.	PY Implied, and not otherwise specified.	PY Likely that non-receipt of RBC transfusion recorded based on absence from medical records; missing outcome data would not be identified.
5.2 Were participants excluded due to missing data on intervention status?	Y Women missing haemoglobin or haematocrit measures in the first 32 weeks of pregnancy were excluded (n=1,357).	NI It is not stated whether samples that could not be tested for serum ferritin were excluded.	N Women grouped according to exposure status.	NI Unclear from article.	N Women grouped according to exposure.	Y Women without an antenatal haemoglobin measurement were not included.
5.3 Were participants excluded due to missing data on other variables needed for the analysis?	PN	NI	N No other variables needed for relevant analyses; more broadly, not reported otherwise.	NI Unclear from article.	NI Unclear from article.	PN No variables other than RBC transfusion and exposure included in analysis.
5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons	NI Not possible to outline how many mothers	NA	NA	NA	NA	NI

Question	Gaillard 2014[16]	Khambalia 2015[31]	Khambalia 2016[29]	Nyflot 2017[24]	Orlandini 2017[26]	Petty 2018[17]
for missing data similar across interventions?	missing haemoglobin measures were anaemic. There was no information provided on loss to follow-up and other reasons for exclusion.					
5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	N	NA	NA	NA	NA	N No specific analyses presented to explore the effect of missing data.
Risk of bias judgement	Moderate	Moderate	Low	Moderate	Moderate	Moderate
BIAS IN MEASUREMENT OF OUTCOMES						
6.1 Could the outcome measures have been influenced by knowledge of the intervention received?	PN Although those recording outcome measures may have been aware that their patient was anaemic, this should not have influenced how outcomes were measured. The recording of certain lifestyle factors, such as smoking and anaemia, may have been influenced by knowledge of exposure status.	N The outcome of preterm birth could not have been influenced by knowledge of first trimester serum ferritin levels.	N Knowledge of exposure was not known at time of birth.	PN Unlikely that the clinician's estimate of blood loss would be influenced by knowledge that the woman is anaemic.	N Outcomes were objective and not likely at have been influenced by knowledge of exposure.	PY The use of red blood cell transfusion and the number of units used may have been linked with a woman's haemoglobin concentration.
6.2 Were outcome assessors aware of the intervention received by study participants?	PY It is possible that those recording certain outcomes in this analysis were aware that the participant was anaemic.	PN Unlikely that those classifying a birth as preterm were aware of first trimester serum ferritin levels.	PN ID may have been reported on hospital records, and therefore available to outcome assessors, but study values recorded after outcomes.	PY Not reported, although likely as recorded on medical records.	PY Not reported, although likely as recorded on medical records.	PY It is likely that those delivering a red blood cell transfusion were aware that their patient was classified as anaemic.
6.3 Were the methods of outcome assessment comparable across intervention groups?	Y	Y	Y Outcomes were objective and likely to have been assessed consistently.	PY Blood loss was visually estimated by the attending physician or	Y Outcomes were objective and likely to have been assessed	Y Outcomes were objective and likely to have been assessed

Question	Gaillard 2014[16]	Khambalia 2015[31]	Khambalia 2016[29]	Nyflot 2017[24]	Orlandini 2017[26]	Petty 2018[17]
				midwife. Possibility of systematic under/over estimation based on clinician but unlikely that this would occur between comparison groups.	consistently.	consistently.
6.4 Were any systematic errors in measurement of the outcome related to intervention received?	N	N	PN Outcomes were objective and likely to have been assessed consistently.	PN Unlikely that maternal anaemia would affect clinician estimate of blood loss.	PN Outcomes were objective and likely to have been assessed consistently.	N Outcomes were objective and likely to have been assessed consistently.
Risk of bias judgement	Low	Low	Low	Moderate	Low	Moderate
BIAS IN SELECTION OF THE REPORTED RESULT						
Is the reported effect estimate likely to be selected, on the basis of the results, from... 7.1. ... multiple outcome measurements within the outcome domain?	N	N	PN Unlikely that multiple outcome measurements available in medical records, and outcome measures were objective.	PN An additional sensitivity analysis was conducted using a more limited outcome definition and reported in the publication.	PN Unlikely to have multiple outcome measurements for PPH and emergency caesarean.	PN Unlikely to have multiple outcome measurements for the outcomes of interest.
7.2 ... multiple analyses of the intervention-outcome relationship?	N	N	PN Reported results for all definitions of ID included in study.	PN Unlikely that multiple definitions of anaemia considered.	PN Unlikely that multiple definitions of anaemia considered.	PN Unlikely that multiple definitions of anaemia considered.
7.3 ... different subgroups?	N	N	N No subgroups, other than those for which results were reported, were implied.	N No subgroups were reported.	N No subgroups were reported.	PN No subgroups were reported.
Risk of bias judgement	Low	Low	Low	Low	Low	Low
OVERALL BIAS	Moderate	Serious	Critical	Moderate	Critical	Moderate

Table 59 continued. ROBINS-I assessments for non-RCTs evaluating the adverse effects of IDA in pregnancy

Question	Räisänen 2013[22]	Räisänen 2014[21]	Rukuni 2016[23]	Smith 2019[18]	Wiegersma 2019[30]
BIAS DUE TO CONFOUNDING					
1.1 Is there potential for confounding of the effect of intervention in this study?	PY Potential confounding controlled for during statistical analysis. Certain relevant covariates may have been missed.	PY Potential sources of confounding (such as smoking and parity) were adjusted for during statistical analysis. BMI was not included in this.	PY Sources of confounding were adjusted for during statistical analysis. However, the impact of treatment was not accounted for.	PY No women excluded from study, and not able to exclude women who contributed more than 1 birth. Key factors like parity, weight, smoking appear to be relatively consistent across study group.	Y No specific eligibility criteria were applied around conditions or behaviours that could affect iron status and/or presence of anaemia.
1.2 If Y/PY to 1.1: Was the analysis based on splitting participants' follow up time according to intervention received? 1.3 If Y/PY to 1.1: Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	PN Time between exposure and outcome unknown. NI Unclear whether individuals received iron supplementation; switches may have been possible to/from iron supplementation.	PN Time between exposure and the outcome (birth) was unknown. Women could not be split according to follow up time. NI Switches between exposures may have been possible from iron supplementation. This was not considered in the paper.	PN Time between exposure and outcome unknown. NI Switches may have occurred from treatment of ID. However, the proportion of women classified as anaemic and receiving iron supplementation was not presented and this was not accounted for in the analysis.	PN Time between exposure and outcome unknown. NI Study did not have access to information on treatments for anaemia, therefore unclear whether women received iron and potentially switched between exposures.	PN Time between exposure and outcome unknown. NI No information provided regarding whether women received iron treatment and potentially switched between exposures.
1.4 Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	PY Covariates that could have affected the outcome were controlled for in the analysis; unlikely that all possible confounders (iron supplementation, previous preterm birth) were controlled for.	PY Covariates that could have affected the outcome were controlled for using appropriate statistical methods. Some relevant covariates (for example, BMI) were not included.	PY Covariates that could have affected the outcome were controlled for. However, the impact of treatment on outcomes was not considered.	PY Analyses adjusted for several variables. However, for a few outcomes the number of events was too low to adjust against all variables so only unadjusted odds reported.	N For the outcomes of interest to this review, covariates that could have affected the outcome were not controlled for; the use of iron supplements was not reported or controlled for, and it was unclear whether the dates of births were comparable within the dataset (for example, were births earlier in the time frame of database coverage more likely to have been to anaemic mothers?).

Question	Räisänen 2013[22]	Räisänen 2014[21]	Rukuni 2016[23]	Smith 2019[18]	Wiegersma 2019[30]
1.5 If Y/PY to 1.4 Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	PY Data was extracted from the Finnish Medical Birth Register.	PY Data was extracted from the Finnish Medical Birth Register. Some information (for example, smoking status) was self-reported and therefore subject to social desirability bias.	PY Data was extracted from the Aberdeen Maternity and Neonatal Databank. Some values were self-reported and may have been subject to desirability bias (for example, smoking).	PY Data was extracted from medical records.	NA
1.6 Did the authors control for any post-intervention variables that could have been affected by the intervention?	Y Limited post-exposure variables were controlled for; these could have been affected by anaemia (for example, SGA at birth).	N Only pre-exposure variables were controlled for in the analysis.	N Only pre-exposure variables were controlled for.	N No post-exposure variables were adjusted for.	N For the outcomes of interest to this review, post-exposure variables that could have affected the outcome were not controlled for.
1.7 Did the authors use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding?	NA	NA	NA	NA	NA
Risk of bias judgement	Moderate	Serious	Moderate	Moderate	Critical
BIAS IN PARTICIPANT SELECTION					
2.1 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	N All singleton births in Finland between 1987 to 2010 were included.	PN All singleton births in Finland between 2002 to 2010 were included; multiple births were excluded, which may have been observed after onset of anaemia (timings unknown).	PN Selection of women was completed retrospectively, and diagnosis of anaemia did not influence selection; multiple births and abortions were excluded, which may have been observed after onset of anaemia (timings unknown).	PY Women required to have had given birth at >20 weeks' gestation to be included in study.	N

Question	Räisänen 2013[22]	Räisänen 2014[21]	Rukuni 2016[23]	Smith 2019[18]	Wiegersma 2019[30]
2.2 If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention? and, 2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	NA	NA	NA	PN Unlikely that birth >20 weeks' gestation would be influenced by anaemia or the outcomes of interest.	NA
2.4 Do start of follow-up and start of intervention coincide for most participants?	PN It was unclear how long women had anaemia, likely some had it for longer than others.	PN Data from the Medical Birth Register could not be used to determine how long women had been anaemic. It is likely some had anaemia longer than others.	PN Unclear how long women included in the study were anaemic, but it is likely that some had it for longer than others at the point of diagnosis.	PN Unclear how long women would have had anaemia for before measurement in third trimester or during birth admission.	PN Unclear how long women would have had anaemia, but likely some had it for longer than others.
2.5 If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	N Adjustment techniques were not used to account for selection bias.	N Adjustment techniques were not used to account for selection bias.	N Adjustment techniques were not used to account for selection bias.	N No adjustment techniques appear to have been used.	N No adjustment techniques appear to have been used.
Risk of bias judgement	Low	Low	Low	Low	Low
BIAS IN THE CLASSIFICATION OF INTERVENTIONS					
3.1 Were intervention groups clearly defined?	Y Anaemia and non-anaemia were clearly defined.	Y Anaemia clearly and appropriately defined.	Y Anaemia and non-anaemia were clearly defined.	PY Anaemia clearly defined based on haemoglobin levels, although women with anaemia based on diagnostic codes had non-specific severity.	PY Anaemia and ID were defined by the presence or absence of the relevant ICD-10 code.
3.2 Was the information used to define intervention groups recorded at the start of the intervention?	PN	PN	PN	PN	NA
3.3 Could classification of	N	PN	N	N	PN

Question	Räisänen 2013[22]	Räisänen 2014[21]	Rukuni 2016[23]	Smith 2019[18]	Wiegersma 2019[30]
intervention status have been affected by knowledge of the outcome or risk of the outcome?	Classification of a pregnancy being preterm should not have affected whether a woman was classified as being anaemic.	Physician-diagnosed depression should not have affected whether a woman was classified as being anaemic.	The occurrence of an adverse maternal or neonatal outcome should not have affected whether a woman was classified as being anaemic.	Anaemia status determined in the third trimester, or in the birth admission but before admission.	Anaemia and ID were coded in the Medical Birth Register as part of routine care.
Risk of bias judgement	Low	Low	Low	Low	Low
BIAS DUE TO DEVIATIONS FROM INTENDED INTERVENTIONS					
4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	NI Unclear whether individuals received iron supplementation.	PN There was no mention of oral iron administration. Previous studies in Finland have noted that oral iron administration (60-100 mg/day) is recommended if Hb is below 10-11 g/dL. However, the proportion of women receiving oral iron administration was not presented.	NI The proportion of women classified as anaemic and receiving iron supplementation was not presented.	NA	NA
4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome?	NI	PY If women classified as anaemic were receiving oral iron, then this should have been balanced between multiparous and nulliparous groups; this would likely not have been balanced between groups defined by anaemia, and may have affected the observed effect of exposure on outcomes.	NI	NA	NA
4.3. Were important co-interventions balanced across intervention groups?	NA	NA	NA	NA	NA
4.4. Was the intervention implemented successfully for most participants?	NA Study did not state how many women had a haemoglobin	PY Although it was not explicitly stated, data appeared to	Y All women included in the analysis had a haemoglobin	NA	NA

Question	Räisänen 2013[22]	Räisänen 2014[21]	Rukuni 2016[23]	Smith 2019[18]	Wiegersma 2019[30]
	concentration measure available.	suggest that all women included in the analysis had a haemoglobin concentration measure.	concentration measure.		
4.5. Did study participants adhere to the assigned intervention regime?	NA	NA	NA	NA	NA
4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	NA	NA	NA	NA	NA
Risk of bias judgement	Not assessed; relevant details (such as use of iron supplementation) captured under confounding domain.	Not assessed; relevant details (such as use of iron supplementation) captured under confounding domain.	Not assessed; relevant details (such as use of iron supplementation) captured under confounding domain.	Not assessed; relevant details (such as use of iron supplementation) captured under confounding domain.	Not assessed; relevant details (such as use of iron supplementation) captured under confounding domain.
BIAS DUE TO MISSING DATA					
5.1 Were outcome data available for all, or nearly all, participants?	Y Women grouped according to outcome data.	Y Women grouped according to outcome data.	Y <1% of both exposed unexposed women did not have data on haemorrhage. Missing neonatal outcome data was similar between groups.	Y Likely that outcome data available for all women; if not recorded on medical records, would have been a non-event in study.	PY There was some missing data for some outcomes (for example, SGA at birth), but this was explained.
5.2 Were participants excluded due to missing data on intervention status?	N Only those records where gestational age was missing were excluded.	N Only those women that were not classified as 'singleton' birth were excluded.	N Only multiple pregnancies, abortions, and pregnancies outside of the study period were excluded.	N Women grouped according to exposure.	NI The authors did not report excluding individuals based on missing data on anaemia status.
5.3 Were participants excluded due to missing data on other variables needed for the analysis?	PN	N Not stated but can be inferred from the publication.	N Not stated but can be inferred from the publication.	NI Unclear from article.	NA
5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	NA	NA	NA	NA	NA
5.5 If PN/N to 5.1, or Y/PY to	NA	NA	NA	NA	NA

Question	Räisänen 2013[22]	Räisänen 2014[21]	Rukuni 2016[23]	Smith 2019[18]	Wiegersma 2019[30]
5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?					
Risk of bias judgement	Low	Low	Low	Low	Low
BIAS IN MEASUREMENT OF OUTCOMES					
6.1 Could the outcome measures have been influenced by knowledge of the intervention received?	N It is unlikely that outcome measurements would have been influenced by the knowledge that a woman was anaemic.	N It is highly unlikely that a physician-diagnosis of major depression would be influenced by knowledge that a woman was anaemic.	PN It is unlikely that outcome measurements would have been influenced by the knowledge that a woman was anaemic.	N Outcomes were objective and not likely at have been influenced by knowledge of exposure.	PN The outcome data used for analysis was documented in the Medical Birth Register as part of routine care, and the outcomes of interest are objective.
6.2 Were outcome assessors aware of the intervention received by study participants?	PN Those recording details of the birth are unlikely to know the woman's haemoglobin concentration during pregnancy.	PN It is unlikely that those physicians making a diagnosis of 'major depression' would know the woman's haemoglobin concentration.	PN Those recording details of the birth are unlikely to know the woman's haemoglobin concentration during pregnancy.	PY Not reported, although likely as recorded on medical records.	PY The outcome data used for analysis was documented in the Medical Birth Register as part of routine care.
6.3 Were the methods of outcome assessment comparable across intervention groups?	Y Outcomes were objective and likely to have been assessed consistently.	Y Outcomes were objective and likely to have been assessed consistently.	Y Outcomes were objective and likely to have been assessed consistently.	Y Outcomes were objective and likely to have been assessed consistently.	Y The outcome data used for analysis was documented in the Medical Birth Register as part of routine care, and as such was the same for all mother-infant dyads in the data set.
6.4 Were any systematic errors in measurement of the outcome related to intervention received?	N Outcomes were objective and likely to have been assessed consistently.	N Outcomes were objective and likely to have been assessed consistently.	N Outcomes were objective and likely to have been assessed consistently.	PN Outcomes were objective and likely to have been assessed consistently.	N It is very unlikely that outcomes were misclassified due a systematic error related to the ICD-10 coding of anaemia and ID.
Risk of bias judgement	Low	Low	Low	Low	Low
BIAS IN SELECTION OF THE REPORTED RESULT					
Is the reported effect estimate likely to be selected, on the	PN Unlikely to have multiple	N Unlikely to have multiple	PN Unlikely to have multiple	PN Unlikely that multiple	NI

Question	Räisänen 2013[22]	Räisänen 2014[21]	Rukuni 2016[23]	Smith 2019[18]	Wiegersma 2019[30]
basis of the results, from... 7.1. ... multiple outcome measurements within the outcome domain?	outcome measurements for the outcomes of interest.	outcome measurements for the outcomes of interest.	outcome measurements for the outcomes of interest.	outcome measurements available in medical records.	
7.2 ... multiple analyses of the intervention-outcome relationship?	PN Unlikely that multiple definitions of anaemia considered.	N Unlikely that multiple definitions of anaemia considered	PN Unlikely that multiple definitions of anaemia considered	PN Unlikely that multiple definitions of anaemia considered, unlikely that multiple outcome measurements recorded in medical records.	N No analyses of the outcomes of interest were performed, aside from providing the raw proportions of individuals affected.
7.3 ... different subgroups?	PN No subgroups were reported.	N No subgroups were reported.	PN No subgroups were reported.	N No subgroups were reported.	NA
Risk of bias judgement	Low	Low	Low	Low	Low
OVERALL BIAS	Moderate	Moderate	Moderate	Moderate	Critical

Table 60. AMSTAR-2 assessment for SLR evaluating the adverse effects of IDA in pregnancy

Question	Haider 2013[12]
Did the research questions and inclusion criteria for the review include the components of PICO? (Yes/No)	Y
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? (Yes/Partial Yes/No)	N Although the authors state that they followed the Cochrane Collaboration's method for this review, it is not explicitly stated that research questions and study methods were planned ahead of conducting the review. In addition, there is no mention of PROSPERO registration or a reference to a published trial protocol.
Did the review authors explain their selection of the study designs for inclusion in the review? (Yes/No)	Y Justifications were provided for their selection of RCT and prospective cohort studies. In line with recommendations, study types were assessed and combined independently.
Did the review authors use a comprehensive literature search strategy? (Yes/Partial Yes/No)	Y Search strategy appears sufficient and is presented in the publication for review.
Did the review authors perform study selection in duplicate? (Yes/No)	Y

Did the review authors perform data extraction in duplicate? (Yes/No)	Y
Did the review authors provide a list of excluded studies and justify the exclusions? (Yes/Partial Yes/No)	Y Justifications were provided for exclusion of papers. Excluded studies were listed in a supplement.
Did the review authors describe the included studies in adequate detail? (Yes/Partial Yes/No)	Y Details of included studies were provided within a supplement.
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? (Yes/Partial Yes/No)	Partial Y The method used to assess risk of bias in RCT trials was systematic and covered key domains. However, a specifically designed and tested rating instrument would have been preferable. In addition, a more in-depth assessment of cohort study quality would have been desirable. Authors mention that they assessed methodological quality by comparing crude and adjusted estimates, but an exploration of sample selection, exposure and outcome measurement and selective reporting would have been desirable.
Did the review authors report on the sources of funding for the studies included in the review? (Yes/No)	N
If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results? (Yes/No/No meta-analysis conducted)	Y Details of how the meta-analysis was performed were comprehensive. Pooled estimates were reported separately for different study types. Meta-analysis of the cohort data used confounder-adjusted estimates, rather than unadjusted estimates, where possible.
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? (Yes/No/No meta-analysis conducted)	Y Authors presented key outcomes using all available data and only using data acquired from studies designated as high quality.
Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review? (Yes/No)	Y
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? (Yes/No)	Y The presence of heterogeneity was assessed by using the Q statistic with its p value and I^2 statistic. If Q p value was below 0.10 and I^2 exceeded 50%, heterogeneity was considered to be substantial and a random effects model was presented. Sources of heterogeneity were further investigated using meta-regression.
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? (Yes/No/No meta-analysis conducted)	Y Publication bias assessed by visual inspection of funnel plots for asymmetry and through Begg's rank correlation and Egger's linear regression tests.
Did the review authors report any potential sources of conflict of interest, including any funding they received for the review? (Yes/No)	N

Question 2 (What are the benefits and harms of treating pregnant women for IDA to pregnant women and their infants?)

Table 61. ROBINS-I assessments for non-RCTs evaluating the adverse effects of treatment for IDA in pregnancy

Question	Arora 2015 [7]	Pels 2015 [6]
BIAS DUE TO CONFOUNDING		
1.1 Is there potential for confounding of the effect of intervention in this study?	NI Information on potentially confounding variables not provided for individuals based on use of iron. No information provided for any inclusion/exclusion criteria, other than singleton birth.	Y Controls were either non-anaemic or anaemic to a lesser extent than cases.
1.2 If Y/PY to 1.1: Was the analysis based on splitting participants' follow up time according to intervention received? 1.3 If Y/PY to 1.1: Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	N Women may have been able to switch between intervention groups (choosing/not choosing to take iron). It is unclear whether any switches would have occurred due to related factors that are prognostic for the outcome.	N No switches or discontinuation possible; women either did or did not receive intervention. Iron was given as discrete doses (rather than long-term administration).
1.4 Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	PN Multivariate analyses performed. However, key covariates that may have affected the association between anaemia and preterm birth were not controlled for (for example, parity or ethnicity).	N Statistical analyses did not include techniques to adjust to confounding.
1.5 If Y/PY to 1.4 Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	NA	NA
1.6 Did the authors control for any post-intervention variables that could have been affected by the intervention?	PY Preeclampsia may have been measured post-intervention and was controlled for in multivariate logistic regression.	N No variables were controlled for.
1.7 Did the authors use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding?	NA	NA
Risk of bias judgement	Serious	Critical
BIAS IN PARTICIPANT SELECTION		
2.1 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	N All singleton births included.	N Selection was based on the presence or absence of intervention.

Question	Arora 2015 [7]	Pels 2015 [6]
2.2 If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention? and, 2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	NA	NA
2.4 Do start of follow-up and start of intervention coincide for most participants?	PN Gestational age at intervention not a specified eligibility criterion, and not reported; the length of treatment duration is also unclear.	PN Gestational age at intervention was not a specified eligibility criterion, and not reported.
2.5 If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	N No adjustment techniques appear to have been used.	N No adjustment techniques appear to have been used.
Risk of bias judgement	Moderate	Serious
BIAS IN THE CLASSIFICATION OF INTERVENTIONS		
3.1 Were intervention groups clearly defined?	N Definitions of anaemia and iron usage not provided.	Y Women either did or did not receive the intervention.
3.2 Was the information used to define intervention groups recorded at the start of the intervention?	NI	Y
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	N Outcome was at birth, intervention defined as being administered during pregnancy.	N Outcome was at birth, intervention defined as being administered during pregnancy.
Risk of bias judgement	Serious	Low
BIAS DUE TO DEVIATIONS FROM INTENDED INTERVENTIONS		
4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	NI Deviations from treatment beyond expectations in clinical practice unlikely to have arisen.	NI Deviations from treatment beyond expectations in clinical practice unlikely to have arisen.
4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome?	NA	NA
4.3. Were important co-interventions balanced across intervention groups?	NI	NI No information given on nutritional supplementation (for

Question	Arora 2015 [7]	Pels 2015 [6]
		example, iron, folic acid).
4.4. Was the intervention implemented successfully for most participants?	PY All cases received the intervention/exposure. Adherence to iron use unclear, although likely to be representative of expected real-world usage.	Y All cases received the intervention.
4.5. Did study participants adhere to the assigned intervention regime?	PY All cases received the intervention/exposure. Adherence to iron use unclear, although likely to be representative of expected real-world usage.	Y All cases received the intervention.
4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	NA	NA
Risk of bias judgement	Low	Low
BIAS DUE TO MISSING DATA		
5.1 Were outcome data available for all, or nearly all, participants?	Y Preterm or term birth recorded for all included women.	Y For relevant outcomes, data was available for more than 95% of women.
5.2 Were participants excluded due to missing data on intervention status?	NI Unclear how the analysis dealt with missing data for anaemia or iron use status.	N Intervention status was available for all women.
5.3 Were participants excluded due to missing data on other variables needed for the analysis?	N Women were not excluded on the basis of missing baseline characteristics.	N Women were not excluded on the basis of missing baseline characteristics.
5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	NA	NA
5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	NA	NA
Risk of bias judgement	Moderate	Low
BIAS IN MEASUREMENT OF OUTCOMES		
6.1 Could the outcome measures have been influenced by knowledge of the intervention received?	N Outcomes were objective and not likely to have been influenced by knowledge of intervention/exposure.	N Outcomes were objective and not likely at have been influenced by knowledge of intervention.
6.2 Were outcome assessors aware of the intervention	PY	PY

Question	Arora 2015 [7]	Pels 2015 [6]
received by study participants?	Not reported, although likely as recorded on birth records.	Not reported, although likely as recorded on birth records.
6.3 Were the methods of outcome assessment comparable across intervention groups?	Y Outcomes were objective and likely to have been assessed consistently.	Y Outcomes were objective and likely to have been assessed consistently.
6.4 Were any systematic errors in measurement of the outcome related to intervention received?	PN Outcomes were objective and likely to have been assessed consistently.	PN Outcomes were objective and not likely at have been influenced by knowledge of intervention.
Risk of bias judgement	Low	Low
BIAS IN SELECTION OF THE REPORTED RESULT		
Is the reported effect estimate likely to be selected, on the basis of the results, from... 7.1. ... multiple outcome measurements within the outcome domain?	N Multiple outcome measurements not relevant to the outcomes recorded.	N Multiple outcome measurements not relevant to the outcomes recorded.
7.2 ... multiple analyses of the intervention-outcome relationship?	N Unlikely to have multiple definitions of anaemia and iron use, and multiple interpretations of outcomes not relevant.	N Unlikely to have multiple definitions of anaemia and intervention, and multiple interpretations of outcomes not relevant.
7.3 ... different subgroups?	N No subgroups were reported.	N No subgroups were reported.
Risk of bias judgement	Low	Low
OVERALL BIAS	Serious	Critical

Table 62. AMSTAR-2 assessment for SLR evaluating the benefits and harms of treatment for IDA in pregnancy

Question	Rukuni 2015[13]	USPSTF SLR (Cantor 2015[39] and McDonagh 2015[40])
Did the research questions and inclusion criteria for the review include the components of PICO? (Yes/No)	N The eligibility criteria for the review were not clear.	Y
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? (Yes/Partial Yes/No)	N However, the authors state that relevant aspects of the PRISMA guidelines were followed.	N Although the authors stated that they used methods developed by the USPSTF to determine the scope and key review questions, it is not explicitly stated that research questions and study methods were planned ahead of conducting the review. In addition, there is no mention of registering the review on a database like PROSPERO, or

		reference to a published trial protocol.
Did the review authors explain their selection of the study designs for inclusion in the review? (Yes/No)	N The authors did not specify the study designs to be included in the review.	N The review authors provided a description of the inclusion and exclusion criteria used; these were appropriate for the review objectives and questions. However, an explanation for these criteria were not provided.
Did the review authors use a comprehensive literature search strategy? (Yes/Partial Yes/No)	Y The search strategy appears sufficient and an example is presented in the supplementary for the review.	Y Search strategy appears sufficient and is presented in the report for review.
Did the review authors perform study selection in duplicate? (Yes/No)	Not reported	Y At least 2 reviewers independently evaluated each study to determine inclusion and eligibility.
Did the review authors perform data extraction in duplicate? (Yes/No)	Not reported	Y One investigator abstracted details about each article. A second investigator reviewed data abstraction for accuracy.
Did the review authors provide a list of excluded studies and justify the exclusions? (Yes/Partial Yes/No)	N A list of excluded studies was not provided.	Y Excluded studies are available in Appendix 4 of the report; these are categorised by the rationale for exclusion.
Did the review authors describe the included studies in adequate detail? (Yes/Partial Yes/No)	N Details of included studies were minimal.	Y
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? (Yes/Partial Yes/No)	NR It is not clear whether the authors assessed the risk of bias for included studies.	Y Two investigators independently applied criteria developed by the USPSTF to rate the quality of each study as good, fair or poor. Details of the quality assessment criteria are presented in Appendix 5 of the report.
Did the review authors report on the sources of funding for the studies included in the review? (Yes/No)	N	Y Details of the funding source for the included studies are presented in Appendix B1.
If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results? (Yes/No/No meta-analysis conducted)	No meta-analysis conducted.	Y Both Mantel-Haenszel random and fixed effects models were fitted. Statistical heterogeneity was assessed using the I^2 statistics.
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? (Yes/No/No meta-analysis conducted)	No meta-analysis conducted.	Y In consideration of methodological shortcomings in the studies and differences across studies in design, interventions, patient populations and other factors, meta-

		analysis was not attempted for all outcome measures.
Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review? (Yes/No)	N	Y
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? (Yes/No)	N	Y
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? (Yes/No/No meta-analysis conducted)	No meta-analysis conducted.	Y Publication bias was not formally assessed with graphical or statistical methods because of the small number of studies identified and differences in study design, populations and outcomes assessed; this was judged to be an adequate approach.
Did the review authors report any potential sources of conflict of interest, including any funding they received for the review? (Yes/No)	N	Y

Question 3 (What are the benefits and harms of screening for IDA during pregnancy?)

The 2 studies included under this question (Rukuni 2015 and the USPSTF SLR) are appraised in Table 62.

Appendix 5 — UK NSC reporting checklist for evidence summaries

All items on the UK NSC Reporting Checklist for Evidence Summaries have been addressed in this report. A summary of the checklist, along with the page or pages where each item can be found in this report, is presented in Table 63.

Table 63. UK NSC reporting checklist for evidence summaries

	Section	Item	Page no.
1.	TITLE AND SUMMARIES		
1.1	Title sheet	Identify the review as a UK NSC evidence summary.	1
1.2	Plain English summary	Plain English description of the executive summary.	5
1.3	Executive summary	Structured overview of the whole report. To include: the purpose/aim of the review; background; previous recommendations; findings and gaps in the evidence; recommendations on the screening that can or cannot be made on the basis of the review.	6–13
2.	INTRODUCTION AND APPROACH		
2.1	Background and objectives	Background – Current policy context and rationale for the current review – for example, reference to details of previous reviews, basis for current recommendation, recommendations made, gaps identified, drivers for new reviews Objectives – What are the questions the current evidence summary intends to answer? – statement of the key questions for the current evidence summary, criteria they address, and number of studies included per question, description of the overall results of the literature search. Method – briefly outline the rapid review methods used.	14–18
2.2	Eligibility for inclusion in the review	State all criteria for inclusion and exclusion of studies to the review clearly (PICO, dates, language, study type, publication type, publication status etc.) To be decided *a priori*.	19–24

2.3	Appraisal for quality/risk of bias tool	Details of tool/checklist used to assess quality, for example, QUADAS 2, CASP, SIGN, AMSTAR.	25
3.	SEARCH STRATEGY AND STUDY SELECTION (FOR EACH KEY QUESTION)		
3.1	Databases/ sources searched	Give details of all databases searched (including platform/interface and coverage dates) and date of final search.	25
3.2	Search strategy and results	Present the full search strategy for at least 1 database (usually a version of Medline), including limits and search filters if used. Provide details of the total number of (results from each database searched), number of duplicates removed, and the final number of unique records to consider for inclusion.	75–92
3.3	Study selection	State the process for selecting studies – inclusion and exclusion criteria, number of studies screened by title/abstract and full text, number of reviewers, any cross checking carried out.	19–24
4.	STUDY LEVEL REPORTING OF RESULTS (FOR EACH KEY QUESTION)		
4.1	Study level reporting, results and risk of bias assessment	For each study, produce a table that includes the full citation and a summary of the data relevant to the question (for example, study size, PICO, follow-up period, outcomes reported, statistical analyses etc.). Provide a simple summary of key measures, effect estimates and confidence intervals for each study where available. For each study, present the results of any assessment of quality/risk of bias.	Study level reporting: 93–144 Quality assessment: 145–172
5.	QUESTION LEVEL SYNTHESIS		
5.1	Description of the evidence	For each question, give numbers of studies screened, assessed for eligibility, and included in the review, with summary reasons for exclusion.	Question 1: 27–33 Question 2: 56–58 Question 3: 68–69
5.2	Combining and presenting the findings	Provide a balanced discussion of the body of evidence which avoids over reliance on 1 study or set of studies. Consideration of 4 components should inform the reviewer's judgement on whether the criterion is 'met', 'not met' or 'uncertain': quantity; quality; applicability and consistency.	Question 1: 34–51 Question 2: 58–65 Question 3: 69–70

5.3	Summary of findings	Provide a description of the evidence reviewed and included for each question, with reference to their eligibility for inclusion. Summarise the main findings including the quality/risk of bias issues for each question. Have the criteria addressed been 'met', 'not met' or 'uncertain'?	Question 1: 51–55 Question 2: 65–67 Question 3: 70–71
6.	REVIEW SUMMARY		
6.1	Conclusions and implications for policy	Do findings indicate whether screening should be recommended? Is further work warranted? Are there gaps in the evidence highlighted by the review?	72–74
6.2	Limitations	Discuss limitations of the available evidence and of the review methodology if relevant.	74

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