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Daily oral iron supplementation during pregnancy

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Abstract

Background—Iron and folic acid supplementation has been the preferred intervention to improve iron stores and prevent anaemia among pregnant women, and it may also improve other maternal and birth outcomes.

Objectives—To assess the effects of daily oral iron supplements for pregnant women, either alone or in conjunction with folic acid, or with other vitamins and minerals as a public health intervention.

Search methods—We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (2 July 2012). We also searched the WHO International Clinical Trials Registry Platform (ICTRP) (2 July 2012) and contacted relevant organisations for the identification of ongoing and unpublished studies.

Selection criteria—Randomised or quasi-randomised trials evaluating the effects of oral preventive supplementation with daily iron, iron + folic acid or iron + other vitamins and minerals during pregnancy.

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DECLARATIONS OF INTEREST We certify that we have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of the review (e.g. employment, consultancy, stock ownership, honoraria, expert testimony).
Juan Pablo Pena-Rosas was author of an excluded study on iron and folic acid intermittent supplementation.
Disclaimer: Juan Pablo Pena-Rosas and Luz Maria De-Regil are currently staff members of the World Health Organization. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions, policy or views of the World Health Organization.

Data collection and analysis—We assessed the methodological quality of trials using standard Cochrane criteria. Two review authors independently assessed trial eligibility, extracted data and conducted checks for accuracy.

Main results—We included 60 trials. Forty-three trials, involving more than 27,402 women, contributed data and compared the effects of daily oral supplements containing iron versus no iron or placebo.

Overall, women taking iron supplements were less likely to have low birthweight newborns (below 2500 g) compared with controls (8.4% versus 10.2%, average risk ratio (RR) 0.81; 95% confidence interval (CI) 0.68 to 0.97, 11 trials, 8480 women) and mean birthweight was 30.81 g greater for those infants whose mothers received iron during pregnancy (average mean difference (MD) 30.81; 95% CI 5.94 to 55.68, 14 trials, 9385 women). Preventive iron supplementation reduced the risk of maternal anaemia at term by 70% (RR 0.30; 95% CI 0.19 to 0.46, 14 trials, 2199 women) and iron deficiency at term by 57% (RR 0.43; 95% CI 0.27 to 0.66, seven trials, 1256 women). Although the difference between groups did not reach statistical significance, women who received iron supplements were more likely than controls to report side effects (25.3% versus 9.91%) (RR 2.36; 95% CI 0.96 to 5.82, 11 trials, 4418 women), particularly at doses 60 mg of elemental iron or higher. Women receiving iron were on average more likely to have higher haemoglobin (Hb) concentrations at term and in the postpartum period, but were at increased risk of Hb concentrations greater than 130g/L during pregnancy and at term. Twenty-three studies were conducted in countries that in 2011 had some malaria risk in parts of the country. In some of these countries/territories, malaria is present only in certain areas or up to a particular altitude. Only two of these reported malaria outcomes. There is no evidence that iron supplementation increases placental malaria. For some outcomes heterogeneity was higher than 50%.

Authors' conclusions—Prenatal supplementation with daily iron are effective to reduce the risk of low birthweight, and to prevent maternal anaemia and iron deficiency in pregnancy. Associated maternal side effects and particularly high Hb concentrations during pregnancy at currently used doses suggest the need to update recommendations on doses and regimens for routine iron supplementation.

Medical Subject Headings (MeSH)

*Dietary Supplements [adverse effects]; Anemia, Iron-Deficiency [*prevention & control]; Folic Acid [*administration & dosage]; Infant, Low Birth Weight; Infant, Newborn; Iron [*administration & dosage]; Iron, Dietary [administration & dosage]; Pregnancy Complications, Hematologic [*prevention & control]; Pregnancy Outcome; Prenatal Care [methods]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy

BACKGROUND

Description of the condition

Iron deficiency is thought to be the most common nutrient deficiency among pregnant women (WHO 1992). Iron deficiency involves an insufficient supply of iron to the cells following depletion of the body's reserves. Its main causes are a diet poor in absorbable iron, an increased requirement for iron (e.g. during pregnancy) not covered through the diet, a loss of iron due to parasitic infections, particularly hookworm, and other blood losses (Crompton 2002; INACG 2002a). Chronic iron deficiency frequently turns into iron deficiency anaemia. While iron deficiency is the most common cause of anaemia, other causes such as acute and chronic infections that cause inflammation; deficiencies of folate and of vitamins B_2, B_{12}, A, and C; and genetically inherited traits such as thalassaemia and drepanocytosis (sickle-cell anaemia) may be independent or superimposed causal factors (WHO 2001; WHO 2012a). According to the most recent estimate, the global prevalence of anaemia among pregnant women is 41.8% (WHO/CDC 2008).

Diagnosis of iron deficiency and anaemia during pregnancy—Anaemia during pregnancy is diagnosed if a woman's haemoglobin (Hb) concentration is lower than 110 g/L at sea level, although it is recognized that during the second trimester Hb concentrations naturally decrease by approximately 5 g/L (WHO 2011a). Although Hb and, less frequently, hematocrit tests are used to screen for iron deficiency, low Hb or hematocrit values are not specific to iron deficiency.

Iron deficiency in non-pregnant populations can be measured quite precisely using laboratory tests such as serum ferritin, serum iron, transferrin, transferrin saturation and transferrin receptors. However, these tests are often not readily available and their results may be of limited value in some settings where different infections (e.g. malaria, HIV/AIDS, vaginosis) are highly prevalent. Furthermore, the results of those tests do not correlate closely with one another because each reflects a different aspect of iron metabolism. For example, serum ferritin concentration is an indicator of iron reserves. During pregnancy, however, serum ferritin levels as well as levels of bone marrow iron fall even in women who ingest daily supplements with high amounts of iron, which casts doubts about their true significance in pregnancy and suggests the need to review cut-off values (Puolakka 1980; Romslo 1983; Svanberg 1975). Currently, a serum ferritin concentration of less than 15 μg/L in healthy adults is an accepted cut-off of depleted iron stores, even among pregnant women (WHO 2011b). Interestingly, the nadir of maternal serum ferritin occurs by week 28, before higher iron demands are believed to occur, a decrease only partially explained by the normal plasma volume expansion that occurs during pregnancy (Taylor 1982).

The ratio of serum transferrin receptors to serum ferritin has been suggested as a good indicator of iron nutrition among pregnant and non-pregnant women (Cook 2003). Data from the United States National Health and Nutrition Examination Survey (NHANES) in 1999-2006 for 1171 pregnant women using this composed indicator showed that pregnant women in the first trimester had the highest mean total body iron compared with that of pregnant women in the second or third trimesters, and that the prevalence of iron deficiency in pregnant women increased with trimester (Mei 2011). However, the lack of a standard

soluble transferrin receptor (sTfR) assay method and a standard reference material, limit the use and comparability of this indicator with other studies. There is still a need to improve the definition of the distribution of serum transferrin receptors during pregnancy in populations with different iron status (Nair 2004) in various environments (Milman 2007).

After considering all these indicators, a World Health Organization (WHO) and Centres for Disease Control (CDC) Technical Consultation on the Assessment of Iron Status at the Population Level concluded that Hb and ferritin were the most efficient combination of indicators for monitoring change in the iron status of a population as a consequence of iron supplementation (WHO/CDC 2005). Unfortunately, only two of the very varied studies on pregnant women were included, and only one of them demonstrated changes with iron supplementation. The use of multiple indicators (Hb, ferritin and sTfRs) is useful for population-based assessments of iron-deficiency anaemia, when this is feasible.

Low and high Hb concentrations, iron status and pregnancy outcomes—The consequences of iron-deficiency anaemia are serious, and can include diminished intellectual and productive capacity (Hunt 2002), and possibly increased susceptibility to infections (Oppenheimer 2001). The lowest rates of low birthweight and premature birth appear to occur when maternal Hb levels are between 95 and 105 g/L during the second trimester of gestation (Murphy 1986; Steer 2000) and between 95 and 125 g of Hb/ L at term (Hytten 1964; Hytten 1971). However, the results of several studies suggest that near-term Hb levels below 95 g/L or even below 110 g/L may be associated with low birthweight, heavier placentas and increased frequency of premature births (Garn 1981; Godfrey 1991; Kim 1992; Klebanoff 1989; Klebanoff 1991; Murphy 1986). There is evidence that maternal Hb levels below 95 g/L before or during the second trimester of gestation are associated with increased risk of giving birth to a low birthweight infant and with premature delivery. During pregnancy, low Hb levels, indicative of moderate (between 70 and 90 g/L) or severe (less than 70 g/L) anaemia, are associated with increased risk of maternal and child mortality and infectious diseases (INACG 2002b). Favourable pregnancy outcomes occur 30% to 45% less often in anaemic mothers, and it has been estimated that their infants have less than one-half of normal iron reserves (Bothwell 1981).

Unfortunately, the time between birth and umbilical cord clamping has not been considered in the estimates of impact of maternal iron status and anaemia on the infant's iron reserves, even though late cord clamping (between one and three minutes) has been shown to improve them significantly (Chaparro 2006; Chaparro 2007; Grajeda 1997; McDonald 2008; Mercer 2001; Van Rheenen 2004) and is recommended to prevent maternal postpartum haemorrhage (WHO 2012b). Iron deficiency may adversely affect the cognitive performance, development and physical growth of infants (WHO 2001) even in the long term (Lozoff 2006). Moderate or severe iron deficiency during infancy has been shown to have irreversible cognitive effects (Gleason 2007). Studies in animal models suggest that suffering anaemia during the intrauterine period can lead to long-term chronic diseases such as hypertension, as part of a phenomenon known as fetal programming (Andersen 2006).

Haemoglobin levels greater than 130 g/L at sea level have also been associated with negative pregnancy outcomes (Hytten 1964; Hytten 1971; Murphy 1986; Scholl 1997; Steer

2000). Large epidemiologic retrospective studies (Murphy 1986; Steer 2000; Xiong 2000) and one prospective study in China (Zhou 1998) have shown that both low and high prenatal Hb concentrations are associated with increased risks for premature delivery and low birthweight. In fact, the incidence of these negative consequences increases dramatically when women's Hb levels, at sea level, are below 95 to 105 g/L at any time in pregnancy or above 130 to 135 g/L after mid-pregnancy. A randomised clinical trial in Mexico showed associations between prenatal daily iron supplement intake at recommended doses to be associated with high Hb concentrations and the risk for both low birthweight and premature delivery (Casanueva 2003a). A study (Ziaei 2007) also showed that women whose Hb concentration at gestational weeks 32 to 36 was greater than 132 g/L had more low birthweight babies and also higher blood pressure than women with lower Hb concentrations. Unfortunately, any women considered anaemic were excluded from the study. Observational studies have shown that among iron supplemented pregnant women, and particularly among those who are anaemic early in pregnancy, a failure of Hb and/or ferritin levels to decline during the second and third trimesters, and overall high ferritin levels during pregnancy, not due to infection, are associated with adverse pregnancy outcomes. However, when some confounding factors are controlled for, the association between high serum ferritin concentrations and the risk for premature delivery was not significant (Scholl 1998; Scholl 2000; Scholl 2005).

The association between iron deficiency without anaemia and adverse perinatal outcomes is less clear, although some studies have shown iron deficiency to be associated with inadequate pregnancy weight gain, decreased defence against infections, preterm delivery and low birthweight (Garn 1981; Kandoi 1991; Prema 1982; Scholl 1992).

Description of the intervention

The Institute of Medicine recommends that women consume 27 mg/day of iron during pregnancy (IOM 2001). Most women need additional iron as well as sufficient iron stores to prevent iron deficiency (Bothwell 2000), and so direct iron supplementation for pregnant women has been used extensively in most low- and middle-income countries as an intervention to prevent and correct iron deficiency and anaemia during pregnancy. It has been recommended that iron supplements also contain folic acid, an essential B-vitamin, because of the increased requirements of pregnancy, due to the rapidly dividing cells in the fetus and elevated urinary losses. Other vitamins and minerals for which deficiencies are documented, and when requirements during pregnancy are higher, this may justify their addition to the supplementation formula, although this is an ongoing area of controversy, particularly with differing conclusions on maternal and infant benefits from various reviews (Christian 2010; Bhutta 2008; Haider 2006; Shrimptom 2009).

International organisations have been advocating routine iron and folic acid supplementation for every pregnant woman in areas where anaemia is highly prevalent (Beard 2000; Villar 1997). While iron supplementation with or without folic acid has been used in a variety of doses and regimens, some current recommendations for pregnant women include the provision of a standard daily dose of 60 mg of elemental iron and 400 μg of folic acid starting as soon as possible after gestation begins -no later than the third month- and

continuing for the rest of the pregnancy. When this duration of six months of intervention cannot be achieved during pregnancy, either continued supplementation during the postpartum period or an increased dosage to 120 mg elemental iron daily during pregnancy is recommended (WHO 2006). Additionally, if iron deficiency prevalence in the country is high, or the pregnant women are anaemic (INACG 1998), the dose of 120 mg elemental iron is indicated. Recent data from national surveys from 46 countries during the years 2003 to 2009 estimated that 52% to 75% of mothers had received iron tablets during pregnancy, and that the duration of supplementation was usually short (Lutter 2011).

The dose of 60 mg of elemental iron was first established in 1959 and was based on estimated iron requirements for women during pregnancy (WHO 1959). This same dose was endorsed by subsequent expert consultations (INACG 1998; WHO 1968; WHO 2001). The use of folic acid during pregnancy was first suggested in 1967, during a technical consultation in Geneva, Switzerland. It was considered that a dose of 300 μg (0.3 mg) of folic acid per day throughout pregnancy would help prevent megaloblastic anaemia, which is associated with folate deficiency (WHO 2012a). This consultation was called three years after the start of a worldwide multi-country collaborative study in India, Israel, Mexico, Poland, South Africa, the United Kingdom, the United States of America, and Venezuela (WHO 1968). The recommended supplemental dose increased to 400 μg (0.4 mg) per day in 1998 after various studies supported its periconceptional use for prevention of neural tube defects (INACG 1998). At the time it was acknowledged that the rationale for providing folic acid supplementation after the first trimester of pregnancy would not be to prevent congenital anomalies but that the 400 μg (0.4 mg) daily dose of folic acid would provide a safe and healthy intake for women during pregnancy and lactation, although probably more than was actually required to produce an optimal Hb response in pregnant women (INACG 1998).

The tolerable upper intake level for iron has been set based on the gastrointestinal side effects associated with high levels of iron consumed on an empty stomach. Iron has the potential to cause direct erosion and irritation of the gastrointestinal mucosa, to cause oxidative damage of lipid membranes, proteins or DNA, can stimulate inflammation or, as an essential nutrient, fertilise the growth of pathogens. High-dose iron supplements are commonly associated with constipation and other gastrointestinal effects including nausea, vomiting and diarrhoea, with frequency and severity varying according to the amount of elemental iron released in the stomach. The Institute of Medicine has established the tolerable upper limit for iron during pregnancy as 45 mg/day of iron, a daily dose much lower than international recommendations (IOM 2001), although the methodology and assumptions used have been questionable (Schümann 2007). In most industrialised countries, the decision to prescribe or recommend antenatal iron with folic acid supplementation to women during pregnancy is left to the health-care personnel, and is based on the individual maternal condition. In the United States, iron supplementation as a primary prevention intervention involves smaller daily iron doses (i.e. 30 mg/day) but therapeutic doses of up to 120 mg elemental iron daily are recommended for the treatment of anaemia (CDC 1998).

Why it is important to do this review

Several studies have shown that iron supplementation, with or without folic acid during pregnancy, helps cover the iron intake gap and results in a substantial reduction in women's risk of anaemia in late pregnancy, at delivery and six weeks postpartum (Mahomed 2000a; Mahomed 1997; Villar 2003). However, the overall impact of iron supplementation interventions under field conditions has been limited, and the effectiveness of these interventions has been questioned (Beaton 1999). The limited success has been attributed to inadequate infrastructure and poor compliance (Mora 2002), although few studies have evaluated these issues adequately. The effectiveness of iron supplementation for pregnant women has been evaluated mostly in terms of improvement in Hb concentration, rather than improvements in maternal or infant health (Beaton 2000). This narrow scope may have been an important omission in most studies addressing the efficacy, effectiveness and safety of iron and iron with folic acid supplementation during pregnancy.

An additional important consideration arises when providing iron supplements to women is the presence of malaria. Approximately 40% of the world population is exposed to the parasite and it is endemic in over 100 countries (WHO 2010). Of all the complications associated with this disease, anaemia is the most common and causes the highest number of malaria-related deaths. Malaria in pregnant women increases the risk of maternal death, miscarriage, stillbirth and low birthweight with an associated risk of neonatal death (WHO 2010; WHO 2011c). Provision of iron in malaria-endemic areas has been a long standing controversy due to concerns that iron therapy may exacerbate infections, in particular malaria in childhood (Oppenheimer 2001). Although the mechanisms by which additional iron can benefit the parasite are far from clear, it is possible that lower dose supplementation might be an effective intervention to prevent anaemia and improve malaria treatment in malaria endemic areas since less iron is available for the parasite (NIH 2011). The potential interaction between malaria interventions and iron interventions in pregnancy has not been well studied. Malaria intermittent preventive treatment (IPT) is recommended for pregnant women in areas of high transmission who are particularly vulnerable to contracting malaria or suffering its consequences. A total of 35 of 45 sub-Saharan African countries had adopted IPT for pregnant women as national policy by the end of 2008 (WHO 2011c).

This review updates a previously published Cochrane Review on iron and iron + folic acid supplementation (Peña-Rosas 2009) that has clearly shown improvements on biochemical and haematological parameters, and evaluates the issues related to dose and formulation as well as the potential benefits and hazards of daily iron supplementation as a preventive intervention for women during pregnancy.

The effectiveness of different iron treatments for anaemia among pregnant women in clinical practice (Reveiz 2011) and the effects of supplementation with iron and vitamin A during pregnancy (Van den Broek 2010) are covered in other Cochrane Reviews. A planned review will assess the effectiveness of oral folate supplementation alone during pregnancy on haematological and biochemical parameters during pregnancy and on pregnancy outcomes (Haider 2008). The effects and safety of periconceptional folate supplementation for preventing birth defects (De Regil 2010) and the effects of multiple vitamin and mineral supplements during pregnancy have also been reviewed elsewhere (Haider 2006). A

separate review addresses the effectiveness of intermittent iron and folic acid supplementation regimens for women during pregnancy (Pena-Rosas 2012).

OBJECTIVES

To assess the effects of daily oral use of iron supplements by pregnant women, either alone or in conjunction with folic acid or with other vitamins and minerals as a public health intervention.

METHODS

Criteria for considering studies for this review

Types of studies—We reviewed randomised and quasi-randomised trials comparing the effects of daily oral prenatal supplements of iron, or iron + folic acid or iron + other vitamins and minerals supplements among pregnant women.

We excluded studies that assessed the effects of multiple combinations of vitamins and minerals, except studies that examined the 'additional effect' of iron or iron + folic acid supplements, i.e. when women in all arms of the trial were provided with the same other micronutrient supplements (with the exception of iron or iron + folic acid).

We have not reviewed the effects of supplementation with multiple micronutrients containing iron or iron + folic acid in comparison to supplementation with iron or iron + folic acid or in comparison to placebo or no treatment. We have excluded studies dealing specifically with iron supplementation as a medical treatment. We also excluded trials addressing the effects of intermittent (i.e. weekly, twice weekly) iron supplementation regimens in comparison to daily supplementation regimens.

Types of participants—Pregnant women of any gestational age and parity.

Types of interventions—We have included a range of interventions providing daily oral supplementation (e.g. tablets, capsules) containing iron alone, iron + folic acid or iron + other vitamins and minerals.

The oral supplements forms include tablets or capsules (WHO 2008). Tablets (soluble tablets, effervescent tablets, tablets for use in the mouth, and modified-release tablets) are solid dosage forms containing one or more active ingredients. They are obtained by single or multiple compression (in certain cases they are moulded) and may be uncoated or coated. Capsules are solid dosage forms with hard or soft shells, various shapes and sizes, that contain a single dose of one or more active ingredients. Capsules may be hard, soft, and modified-release capsules and are generally intended for oral administration.

Where data were available we planned to compare the following.

1. Any supplements containing iron versus same supplements without iron or no treatment/placebo (no iron or placebo).

2. Any supplements containing iron and folic acid versus same supplements without iron or folic acid (no iron + folic acid or placebo).
3. Supplementation with iron alone versus no treatment/ placebo.
4. Supplementation with iron + folic acid versus no treatment/ placebo.
5. Supplementation with iron + folic acid versus folic acid alone (without iron) supplementation.
6. Supplementation with iron + other vitamins and minerals supplementation versus same other vitamins and minerals (without iron) supplementation.
7. Supplementation with iron + folic acid + other vitamins and minerals versus folic acid + same other vitamins and minerals (without iron) supplementation.
8. Supplementation with iron + folic acid + other vitamins and minerals versus same other vitamins and minerals (without iron + folic acid) supplementation.

Interventions that combined daily oral iron or iron + folic acid supplementation with co-interventions such as education or other approaches were included only if the other co-interventions were the same in both the intervention and comparison groups. Studies examining supplemental iron alone or vitamins and minerals provided from supplementary food based interventions (i.e. interventions with multiple micronutrient powders, lipid based supplements, fortified complementary foods, and other fortified foods) were excluded. Likewise, regimens providing iron supplements in intermittent regimens were excluded from this review.

Types of outcome measures—Maternal, perinatal and postpartum clinical and laboratory outcomes and infant clinical and laboratory outcomes as described below.

Primary

Infant:

1. Low birthweight (less than 2500 g).
2. Birthweight (in g).
3. Premature birth (less than 37 weeks' gestation).
4. Neonatal death (within 28 days after delivery).
5. Congenital anomalies, including neural tube defects (as defined by trialists).

Maternal:

1. Maternal anaemia at term (Hb less than 110 g/L at 37 weeks' gestation or more).
2. Maternal iron deficiency at term (as defined by trialists, based on any indicator of iron status at 37 weeks' gestation or more).
3. Maternal iron deficiency anaemia at term (as defined by trialists at 37 weeks' gestation or more).

4. Maternal death (death while pregnant or within 42 days of termination of pregnancy).
5. Side effects (any reported throughout intervention period)*.
6. Severe anaemia at any time during second or third trimesters (Hb less than 70 g/L).
7. Clinical malaria (as defined by trialists).
8. Infection during pregnancy (including urinary tract infections and others as specified by trialists).

Secondary

Infant:

1. Very low birthweight (less than 1500 g).
2. Very premature birth (less than 34 weeks' gestation).
3. Hb concentration in the first six months (in g/L, counting the last reported measure after birth within this period).
4. Ferritin concentration in the first six months (in μg/L, counting the last reported measure after birth within this period).
5. Development and motor skills (as defined by trialists).
6. Admission to special care unit.

Maternal:

1. Maternal anaemia at or near term (Hb less than 110 g/L at 34 weeks' gestation or more).
2. Maternal iron deficiency at or near term (as defined by trialists, based on any indicator of iron status at 34 weeks' gestation or more).
3. Maternal iron deficiency anaemia at or near term ((Hb less than 110 g/L and at least one additional laboratory indicator at 34 weeks' gestation or more).
4. Maternal Hb concentration at or near term (in g/L, at 34 weeks' gestation or more).
5. Maternal Hb concentration within 6 weeks postpartum (in g/L).
6. Maternal high Hb concentrations at any time during second or third trimester (defined as Hb greater than 130 g/L).
7. Maternal high Hb concentrations at or near term (Hb more than 130 g/L at 34 weeks' gestation or more)
8. Moderate anaemia at postpartum (Hb between 80 and 109 g/L).
9. Maternal severe anaemia at or near term (Hb less than 70 g/ L at 34 weeks' gestation or more).
10. Severe anaemia postpartum (Hb less than 80 g/L).

11. Puerperal infection (as defined by trialists).
12. Antepartum haemorrhage (as defined by trialists).
13. Postpartum haemorrhage (intrapartum and postnatal, as defined by trialists).
14. Transfusion given (as defined by trialists).
15. Diarrhoea (as defined by trialists).
16. Constipation (as defined by trialists).
17. Nausea (as defined by trialists).
18. Heartburn (as defined by trialists).
19. Vomiting (as defined by trialists).
20. Maternal well being/satisfaction (as defined by trialists).
21. Placental abruption (as defined by trialists).
22. Premature rupture of membranes (as defined by trialists).
23. Pre-eclampsia (as defined by trialists).

* For trials reporting individual side effects separately but not specifying the number of women reporting *any* side effects, for our primary outcome, we have selected the side effect with the greatest number of women (in the intervention and control groups combined) reporting that particular problem. We did this to avoid double counting any women reporting more than one side effect.

Search methods for identification of studies

Electronic searches—We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (2 July 2012).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of EMBASE;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and EMBASE, the list of hand searched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

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Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

In addition we searched the International Clinical Trials Registry Platform (ICTRP) for any ongoing or planned trials (2 July 2012) using the search terms described in Appendix 1.

Searching other resources—For assistance in identifying ongoing or unpublished studies, we also contacted the Departments of Reproductive Health and Research and Nutrition for Health and Development from the World Health Organization (WHO), the nutrition section of the United Nations Children's Fund (UNICEF), the World Food Programme (WFP), the U.S. Centers for Disease Control and Prevention (CDC), the Micronutrient Initiative (MI), the Global Alliance for Improved Nutrition (GAIN), Hellen Keller International (HKI), and the Sight and Life.

We did not apply any language restrictions.

Data collection and analysis

Selection of studies—Two review authors independently assessed and selected the trials for inclusion in this review. We resolved any disagreement on eligibility for inclusion by discussion.

It was not possible for us to assess the relevance of the trials blinded because we knew the authors' names, institution, journal of publication and results, when we applied the inclusion criteria.

Data extraction and management—We designed a form to facilitate the process of data extraction and to request additional (unpublished) information from the authors of the original reports. We resolved any disagreements among us by discussion, and, if necessary, sought clarification from the authors of the original reports. We extracted data relating to the setting and cadre from all the included studies specifying whether the intervention was reported as being done by a physician, obstetrician, lay health worker, midwife, dietitian or a combination of health professionals. We also extracted the type of healthcare facility and the geographical location of the intervention, when this information was available.

We entered data onto Review Manager software (RevMan 2011) and checked for accuracy.

Assessment of risk of bias in included studies—Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion.

(1) Sequence generation (checking for possible selection bias): We have described for each included study the method used to generate the allocation sequence. We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
- unclear.

(2) Allocation concealment (checking for possible selection bias): We have described for each included study the method used to conceal the allocation sequence and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear.

(3) Blinding (checking for possible performance bias): We have described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or classes of outcomes and we have noted where there was partial blinding.

We assessed the methods as:

- low, high or unclear risk of bias for women;
- low, high or unclear risk of bias for clinical staff;
- low, high or unclear risk of bias for outcome assessors.

We classified blinding “inadequate” if the blinding status of a trial was unclear or the trial was open.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations): We assessed losses to follow-up and post-randomisation exclusions systematically for each trial.

We have described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We have noted whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. We assessed methods as:

- low risk of bias;

- high risk of bias; or
- unclear.

We considered follow-up to be adequate if more than 80% of participants initially randomised in a trial were included in the analysis and any loss was balanced across groups, unclear if the percentage of initially randomised participants included in the analysis was unclear, and inadequate if less than 80% of those initially randomised were included in the analysis or if loss was imbalanced in different treatment groups.

(5) Selective reporting bias: We have described for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as:

- low risk of bias (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review had been reported);
- high risk of bias (where not all the study's pre-specified outcomes had been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest were reported incompletely and so could not be used; study failed to include results of a key outcome that would have been expected to have been reported);
- unclear.

(6) Other sources of bias: We assessed whether each study was free of other problems that could put it at risk of bias. We have noted for each included study any important concerns we had about other possible sources of bias.

We assessed whether each study was free of other problems that could put it at risk of bias:

- low risk of further bias;
- high risk of further bias;
- unclear whether there is a risk of further bias.

(7) Overall risk of bias: We have made explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011) and for primary outcomes have explored the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Measures of treatment effect—For dichotomous data, we present results as summary risk ratio (RR) with 95% confidence intervals (CI).

For continuous data, we have used the mean difference (MD) if outcomes were measured in the same way between trials. We planned to use the standardised mean difference (SMD) to combine trials measuring the same outcome, but using different scales or methods.

Unit of analysis issues

Cluster-randomised trials: We included cluster-randomised trials in the analyses along with individually-randomised trials. Cluster-randomised trials are labelled with a (C). Where possible we estimated the intracluster correlation co-efficient (ICC) from trials' original data sets and reported the design effect. On the basis of this information we used the methods set out in the *Handbook* to calculate the adjusted sample sizes (Higgins 2011).

We included four cluster-randomised trials (Christian 2003 (C); Hoa 2005 (C); Menendez 1994 (C); Zeng 2008 (C)). One of these trials did not contribute data to the analysis (Hoa 2005 (C)). For the remaining three cluster-randomised trials (Christian 2003 (C); Menendez 1994 (C); Zeng 2008 (C)) data have been adjusted to take account of the design effect. In the study byChristian 2003 (C) adjusted data were provided by the author using outcome specific ICCs. For the Zeng 2008 (C) trial, we adjusted the published results and calculated an effective sample size by dividing figures by the design effect calculated using the ICC for the trial's primary outcome: birthweight ICC = 0.03. We used the same sample adjustment for all outcomes. We used the same method for the Menendez 1994 (C) trial, however in this case there was insufficient information in the study reports to allow us to calculate the design effect and so we estimated it using the ICC for Hb at term (ICC = 0.03) reported in another study with similar average cluster sizes (Winichagoon 2003). We used this same ICC for all outcomes.

Where we have identified both cluster-randomised trials and individually-randomised trials reporting data for the same outcome, we considered that it was reasonable to combine the results from both if there was little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit was considered to be unlikely.

Cross-over trials: We did not include cross-over trials.

Dealing with missing data—For included studies, levels of attrition have been noted in the Characteristics of included studies tables. The impact of including studies with high levels of missing data in the overall assessment of treatment effect have been explored by using sensitivity analysis.

When possible, we conducted an available case analysis and reinstated previously excluded cases, i.e. we attempted to include all participants randomised to each group in the analyses. The denominator for each outcome in each trial is the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity—We examined the forest plots for the analyses visually to assess any obvious heterogeneity in terms of the size or direction of treatment effect between studies. We used the I^2, and T^2 statistics and the P value of the Chi^2 test for heterogeneity to quantify heterogeneity among the trials in each analysis. The I^2 statistic quantifies inconsistency and describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance).

Assessment of reporting biases—For our primary outcomes, we investigated publication bias on outcomes with more than 10 trials by examining the funnel plots for signs of asymmetry, although we gave consideration to reasons other than publication bias that could explain the asymmetry, when present.

Data synthesis—We carried out statistical analysis using the Review Manager software (RevMan 2011).

Because of our experience in conducting other reviews in this area we anticipated high heterogeneity among trials and we pooled trial results using a random-effects model and were cautious in our interpretation of the pooled results. We have indicated in the text that the random-effects model gives the average treatment effect. For statistically significant results where there are high levels of heterogeneity ((I^2 greater than 50%), we have given the values of I^2, T^2 and the P value of the Chi^2 test for heterogeneity and have provided an estimate of the 95% range of underlying intervention effects (prediction interval (PI)).

Subgroup analysis and investigation of heterogeneity—Where more than one trial was included in a comparison, we conducted both overall analysis of the effects of various supplementation regimens on primary outcomes and subgroup analysis on the primary outcomes based on the following criteria:

1. by gestational age: early, if supplementation started before 20 weeks' gestation or prior to pregnancy; late if supplementation started at 20 weeks of gestation or later; or, unspecified or mixed gestational ages at the start of supplementation;
2. by anaemic status at start of intervention: anaemic when Hb below 110 g/L during first and third trimesters or below 105 g/L in second trimester; non-anaemic if Hb 110 g/L or above during first and third trimesters or Hb 105 g/L or above if in second trimester; or unspecified/mixed anaemic status;
3. by dose of iron: low daily dose of iron if 30 mg or less of elemental iron; medium daily dose of iron (more than 30 mg and less than 60 mg elemental iron) and higher daily dose of iron if dose is 60 mg elemental iron or more);
4. by type of formulation: slow release iron supplement (as defined by trialists) or normal release iron supplement/not specified;
5. by iron compound bioavailability in comparison to ferrous sulphate: higher bioavailability: NaFeEDTA; equivalent or lower relative bioavailability: ferrous sulphate, ferrous fumarate, ferrous gluconate; other/not specified;
6. By malaria risk setting: study carried out in malaria risk-free countries or study carried out in countries with some malaria risk or explicitly described as a malaria risk study site.

In the subgroup analyses we have provided totals and subtotals and have carried out formal tests to examine whether there was any statistical evidence of differences between subgroups and, if so we have drawn attention to this in the text. However, for some outcomes few studies contributed data, and for some outcomes, all the trials were in the

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same subgroup; as more data become available, in updates of the review, we will explore possible subgroup differences as a means of exploring heterogeneity.

Sensitivity analysis—We conducted a sensitivity analysis based on the quality of the studies. We considered a study to be of high quality if it was graded as adequate in both the randomisation and allocation concealment and in either blinding or loss to follow-up.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search—A single search was carried out for this and a related review examining intermittent iron and iron plus folic acid supplementation in pregnancy (Pena-Rosas 2012). The study flow is depicted in Figure 1. In this updated review, we have included 60 and excluded 119 trials. We confirmed that six trials are still ongoing. Forty-three trials involving more than 27,402 women contributed data for the comparisons in this review.

Studies by Chanarin 1965, Dommisse 1983, Fenton 1977,Fleming 1974, Fleming 1985, Foulkes 1982, Freire 1989, Groner 1986, Han 2011, Hoa 2005 (C), Ma 2010, Simmons 1993,Suharno 1993, Sun 2010 and Tholin 1993 were all assessed as eligible for inclusion but these studies have not contributed data to the review. We were not able to include data either because the studies did not report data on any of the review's prespecified outcomes, or the results were not presented in a way that allowed us to enter them into the analyses (e.g. results were not reported separately for randomised groups or standard deviations or standard errors were not reported for continuous outcomes). In addition, two studies that were otherwise eligible for inclusion (Butler 1968; Kuizon 1979) had such serious attrition (up to 80% for some outcomes) that we considered results were difficult to interpret, and we have not included data from these trials in the review. Details of all included studies can be found in the Characteristics of included studies tables.

In addition to the published papers, abstracts and reports identified by the search, several trial authors provided additional unpublished information for inclusion in the review, including individual patient data sets for *ad hoc* statistical analysis (Butler 1968; Eskeland 1997; Hemminki 1991; Lee 2005); some authors provided reanalysed data for this review (Christian 2003 (C); Makrides 2003; Paintin 1966) or additional information useful for description and 'Risk of bias' assessment of the studies (Cogswell 2003; Freire 1989; Harvey 2007; Siega-Riz 2001; Zeng 2008 (C); Ziaei 2007; Ziaei 2008).

For the trials contributing to the analyses, we have treated a study carried out collaboratively in two different sites as two different trials, one conducted in Rotterdam (Wallenburg 1983) and one conducted in Antwerp (Buytaert 1983). Some trials included more than two arms and are therefore, included in more than one comparison.

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Included studies—Sixty studies were included in this review.

Settings: The studies included in the review were carried out since 1936 in countries across the globe: 25 trials in Europe with 12 trials in United Kingdom (Butler 1968; Chanarin 1965; Chisholm 1966; .Chanarin 1971; Fenton 1977; Foulkes 1982; Harvey 2007; Kerr 1958; Paintin 1966; Taylor 1982 Willoughby 1967; Wills 1947); two trials in Norway (Eskeland 1997; Romslo 1983); two trials in Finland (Hemminki 1991; Puolakka 1980), two trials in Sweden (Svanberg 1975; Tholin 1993), two trials in the Netherlands.(Van Eijk 1978; Wallenburg 1983); one each in Denmark (Milman 1991); Ireland (Barton 1994); Belgium (Buytaert 1983); France (De Benaze 1989) and Italy (Tura 1989). Eleven trials were con ducted in the Americas with eight trials conducted in the United States of America (Cogswell 2003; Corrigan 1936; Groner 1986; Holly 1955; Hood 1960; Meier 2003; Pritchard 1958; Siega-Riz 2001); one in Canada (Cantlie 1971); one in Ecuador (Freire 1989) and one in Jamaica (Simmons 1993). Four trials were conducted in Africa with one trial in South Africa (Dommisse 1983), one in Nigeria (Fleming 1985); one in Gambia (Menendez 1994 (C)) and one in Niger (Preziosi 1997). Four trials were conducted in Iran (Falahi 2010; Ouladsahebmadarek 2011; Ziaei 2007; Ziaei 2008). One trial was conducted in Hong Kong (Chan 2009) and five in China (Han 2011; Liu 2000; Ma 2010; Sun 2010; Zeng 2008 (C)). Three trials were conducted in Australia (Fleming 1974; Hankin 1963; Makrides 2003). Seven trials were conducted in Asia with one trial each in Myanmar (Burma) (Batu 1976); Thailand (Charoenlarp 1988); Nepal (Christian 2003 (C)); Vietnam (Hoa 2005 (C)); Philippines (Kuizon 1979); South Korea (Lee 2005) and Indonesia (Suharno 1993).

Most included trials were published in the between years 2000-2009 and 1980-1989. Two trials were published before 1950's, three trials in the period 1950-1959, seven trials between 1960-1969, eight trials between 1970-1979, 13 trials in the period 1980-1989, nine trials between 1990-1999, 13 trials in the period 2000-2009 and only five included trials have been published since 2010 to present.

Twenty-three studies were conducted in countries that in 2011 (WHO 2011c; WHO 2011d) had some malaria risk in parts of the country, of diverse characteristics (Batu 1976; Chan 2009; Charoenlarp 1988; Christian 2003 (C); Dommisse 1983; Falahi 2010; Fleming 1985; Freire 1989; Han 2011; Hoa 2005 (C); Kuizon 1979; Lee 2005; Liu 2000; Ma 2010; Menendez 1994 (C); Ouladsahebmadarek 2011; Preziosi 1997; Simmons 1993; Suharno 1993; Sun 2010; Zeng 2008 (C); Ziaei 2007; Ziaei 2008). Only two of these reported malaria outcomes (Fleming 1985; Menendez 1994 (C)). In some of these countries/ territories, malaria is present only in certain areas or up to a particular altitude. In many countries, malaria has a seasonal pattern (WHO 2011d). These details as well as information on the predominant malaria species, status of resistance to antimalarial drugs for each country where an included study was conducted was extracted for 2011 (WHO 2011d) and provided in the notes section of the Characteristics of included studies tables. Thirty-seven of the included trials, mostly from Australia, Canada, United States of America, or countries in Europe were carried out in areas that generally are considered malaria-free.

Participants: In 23 trials it was specifically stated that all women recruited were non-anaemic at the start of supplementation (Barton 1994; Buytaert 1983; Cantlie 1971; Chisholm 1966; Cogswell 2003; De Benaze 1989; Eskeland 1997; Falahi 2010; Harvey 2007; Hemminki 1991; Liu 2000; Makrides 2003; Meier 2003; Ouladsahebmadarek 2011; Puolakka 1980; Romslo 1983; Siega-Riz 2001; Svanberg 1975; Tholin 1993; Tura 1989; Wallenburg 1983; Ziaei 2007; Ziaei 2008). For the remaining trials it was not always stated whether or not women were anaemic and some studies included some women with mild and moderate anaemia so samples were mixed in terms of women's anaemia status at the start of supplementation. In some of these trials it was specifically stated that women with severe anaemia were excluded (Batu 1976; Butler 1968; Chan 2009; Charoenlarp 1988; Kerr 1958; Paintin 1966; Willoughby 1967). Five studies specifically recruited women with mild and moderate anaemia (Hb between 80 to 110 g/L) but none of these trials contribute data to the review (Han 2011; Ma 2010; Simmons 1993; Suharno 1993; Sun 2010).

In most of the trials women began taking supplements before 20 weeks' gestation and continued taking supplements up until delivery. In 12 trials supplementation started at or after 20 weeks' gestation (Batu 1976; Chanarin 1965; Chisholm 1966; Eskeland 1997; Fleming 1974; Freire 1989; Hood 1960; Kerr 1958; Makrides 2003; Menendez 1994 (C); Paintin 1966; Preziosi 1997). In 16 studies it was not clear at what gestational age women started to take supplements or gestational ages were mixed and samples included both women who started supplements before and after the 20th week of pregnancy (Cantlie 1971; Charoenlarp 1988; Corrigan 1936; Fleming 1985; Hankin 1963; Holly 1955; Kuizon 1979; Lee 2005; Liu 2000; Ma 2010; Meier 2003; Pritchard 1958; Simmons 1993; Suharno 1993; Sun 2010; Willoughby 1967).

Interventions

Daily iron dose: The daily dose of elemental iron in some of the groups in the included trials ranged between 9-90 mg of elemental iron daily. One trial provided 9 mg elemental iron daily (Eskeland 1997); one trial provided 12 mg elemental iron (Paintin 1966); one trial provided 20 mg elemental iron daily (Makrides 2003); one trial provided 27 mg elemental iron (Eskeland 1997); six trials provided 30 mg elemental iron (Chanarin 1971; Cogswell 2003; Lee 2005; Ouladsahebmadarek 2011; Siega-Riz 2001; Zeng 2008 (C); one trial provided 40 mg elemental iron (Tura 1989); 45 mg elemental iron (De Benaze 1989); 50 mg elemental iron (Ziaei 2007, Ziaei 2008); 55 mg elemental iron (Hood 1960); 17 trials provided 60 mg elemental iron (Barton 1994; Batu 1976; Chan 2009; Christian 2003 (C); Falahi 2010; Fenton 1977; Fleming 1974; Fleming 1985; Groner 1986; Han 2011; Hoa 2005 (C); Ma 2010; Meier 2003; Menendez 1994 (C); Suharno 1993; Sun 2010; Zeng 2008 (C)); two trials provided 65 mg of elemental iron (Kuizon 1979; Taylor 1982); 66 mg elemental iron (Milman 1991); two trials provided 78 mg elemental iron (Cantlie 1971; Freire 1989); one trial provided 80 mg elemental iron (Wills 1947); nine trials provided 100 mg of elemental iron (Foulkes 1982; Hankin 1963; Harvey 2007; Hemminki 1991; Liu 2000; Preziosi 1997; Simmons 1993; Tholin 1993; Van Eijk 1978); five trials provided 105 mg of elemental iron daily (Buytaert 1983; Kerr 1958; Paintin 1966; Wallenburg 1983; Willoughby 1967); one trial provided 112 mg elemental iron (Pritchard 1958); two trials provided 120 mg of elemental iron (Charoenlarp 1988; Dommisse 1983); one trial provided

122 mg of elemental iron (Butler 1968); three trials provided 200 mg of elemental iron (Puolakka 1980; Romslo 1983; Svanberg 1975); 220 mg elemental iron (Hood 1960); 240 mg of elemental iron (Charoenlarp 1988) and 900 mg elemental iron (Chisholm 1966). One trial did not report the amount of iron as elemental iron and only referred the amount provided as a total daily dose 0.6 g of ferrous sulphate (Corrigan 1936) while another referred a dose of 1 g of iron salt daily (Holly 1955).

Folic acid daily dose: For trials providing folic acid daily as part of the intervention, the doses ranged from 10 μg (0.01 mg) folic acid to 5000 μg (5 mg) folic acid daily along with the iron. In one trial each the dosis of folic acid provided was 10 μg (0.01 mg) folic acid (Chanarin 1965); 30 μg (0.03 mg) folic acid (Chanarin 1965); 100 μg (0.1 mg) of folic acid (Willoughby 1967); 175 μg (0.17 mg) folic acid (Lee 2005); 250 μg (0.25 mg) folic acid (Hoa 2005 (C)); 300 μg (0.3 mg) of folic acid (Willoughby 1967). In three trials participants received a daily dosis pf 350 μg (0.35 mg) folic acid (Foulkes 1982; Lee 2005; Taylor 1982). In five trials the daily dose provided to participants in some of the groups were 400 μg (0.4 mg) folic acid (Christian 2003 (C); Ma 2010; Simmons 1993; Sun 2010; Zeng 2008 (C)); 450 μg (0.45 mg) folic acid (Willoughby 1967); three trials provided 500 μg (0.5 mg) folic acid daily (Chisholm 1966; Fleming 1974; Siega-Riz 2001); five trials provided participants in some of the groups with 1000 μg (1 mg) folic acid daily (Barton 1994; Batu 1976; Fleming 1985; Meier 2003; Ziaei 2007); and one trial provided participants in some of the groups 3400 μg (3.4 mg) of folic acid daily (Butler 1968). Four trials of iron and folic acid supplementation provided 5000 μg (5 mg) folic acid daily (Charoenlarp 1988; Chisholm 1966; Fleming 1974; Menendez 1994 (C).

Type of iron compounds: With the exception of six trials that explicitly described the supplements as slow or sustained release (Buytaert 1983; Hood 1960; Liu 2000; Simmons 1993; Svanberg 1975; Wallenburg 1983), all other trials appeared to be standard preparations.

Nine trials did not specify the iron compound used in the trials and described the iron daily dose only in terms of elemental iron (Barton 1994; Fleming 1985; Foulkes 1982; Hemminki 1991; Holly 1955; Makrides 2003; Ouladsahebmadarek 2011; Paintin 1966; Zeng 2008 (C)).

Most supplements used in trials were equivalent or lower, rather than high relative bioavailability iron compounds (ferrous sulphate and ferrous fumarate). Thirty-seven trials used iron supplements in one of the groups that was provided as ferrous sulphate (Batu 1976; Butler 1968; Buytaert 1983; Chan 2009; Charoenlarp 1988; Cogswell 2003; Corrigan 1936; Dommisse 1983; Falahi 2010; Fenton 1977; Fleming 1974; Freire 1989; Han 2011; Hemminki 1991; Hoa 2005 (C); Holly 1955; Hood 1960; Kerr 1958; Kuizon 1979; Lee 2005; Liu 2000; Ma 2010; Meier 2003; Menendez 1994 (C); Puolakka 1980; Romslo 1983; Siega-Riz 2001; Simmons 1993; Suharno 1993; Sun 2010; Svanberg 1975; Taylor 1982; Tholin 1993; Van Eijk 1978; Wallenburg 1983; Ziaei 2007; Ziaei 2008). Six trials used ferrous fumarate as the form of iron provided to the participants (Chanarin 1965; Chanarin 1971; Christian 2003 (C); Eskeland 1997; Groner 1986; Milman 1991). One trial used ferrous iron (Cantlie 1971).

Ferrous gluconate was used in six included trials (Chisholm 1966; Hankin 1963; Harvey 2007; Kerr 1958; Pritchard 1958; Wills 1947). Two trials used ferrous betainate hydrochloride (De Benaze 1989; Preziosi 1997), one trial used heme iron from porcine blood (Eskeland 1997), one trial used ferritin in a micro granulated gastric resistant capsule (Tura 1989), one used chelated iron aminoates (Willoughby 1967) and one study (Han 2011) used iron EDTA. Bioavailability of iron compounds is assessed in comparison (relative) to ferrous sulphate.

Supervision and co-interventions: In most of the studies women took the supplements without supervision. Some trials report that intake of the supplements was supervised in all or some of the groups (Batu 1976; Charoenlarp 1988; Preziosi 1997). In Christian 2003 (C) the intake was un-supervised but trial personnel visited women twice each week to monitor supplement intake.

Some studies included co-interventions in addition to the iron or iron + folic acid supplement. For example, in the study byCantlie 1971 participants from both groups received one tablet of multiple micronutrient supplement daily containing: 2 mg copper citrate, 6 mg magnesium stearate, 0.3 mg manganese carbonate, 1000 IU vitamin A , 500 IU vitamin D, bone flour 130 mg, 1 mg vitamin B_1, 1 mg vitamin B_2, 50 mg brewer yeast concentrate, 5 mg niacinamide, 25 mg vitamin C, 0.2 mg sodium iodide and 0.049 μg folate (naturally occurring) and in Christian 2003 (C) all participants were offered a 1000 μg retinol equivalents vitamin A supplement daily and deworming treatment (albendazole 400 mg single dose) in the second and third trimester. In Fleming 1974 all participants received 50 mg of ascorbic acid daily from the first visit until the 20th week. In Fleming 1985 the participants from the groups included in this review received chloroquine 600 mg base once, followed by proguanil 100 mg per day. In Menendez 1994 (C) all pregnant women received a weekly tablet of 5000 μg (5 mg) of folic acid but no antimalarial chemoprophylaxis. In the study by Siega-Riz 2001 folic acid supplements were prescribed for all women who had received the positive pregnancy test until the first prenatal visit. In Simmons 1993 all women received 400 μg (0.4 mg) of folic acid.

Intervention settings and health worker cadre: In the majority of these studies (52 studies, 86%), the intervention was delivered in hospital or community-based antenatal clinics usually by physicians or other healthcare professionals including midwives, dieticians or social workers. In eight of the studies the intervention was delivered by community workers, traditional birth attendants or village-based healthcare staff, and supplements were provided during visits to women's homes or in local community settings. The supplements were provided by village-based traditional birth attendants in the study by Menendez 1994 (C). In the Han 2011 trial village nurses made visits to women's homes to deliver supplements and monitor women's health. Community health or village workers were involved in delivering supplementation programmes in the trials by Charoenlarp 1988; Christian 2003 (C); Hoa 2005 (C); Ma 2010; Suharno 1993; and Sun 2010.

Comparisons: *Comparison 1*: forty-three trials that contributed data compared the effects of any daily oral supplements containing iron versus same daily oral supplements without iron. This included data from 34 trials that compared the effects of daily iron supplementation

with the effects of no iron or placebo (Batu 1976; Buytaert 1983; Chan 2009; Chanarin 1971; Charoenlarp 1988; Chisholm 1966; Cogswell 2003; Corrigan 1936; De Benaze 1989; Eskeland 1997; Falahi 2010; Hankin 1963; Harvey 2007; Hemminki 1991; Holly 1955; Hood 1960; Kerr 1958; Makrides 2003; Meier 2003; Menendez 1994 (C); Milman 1991; Ouladsahebmadarek 2011; Paintin 1966; Preziosi 1997; Pritchard 1958; Puolakka 1980; Romslo 1983; Svanberg 1975; Tura 1989; Van Eijk 1978; Wallenburg 1983; Willoughby 1967; Wills 1947; Ziaei 2008). Data from eight trials included in this comparison evaluated the effects of daily iron + folic acid supplementation with the effects of no treatment (Barton 1994; Batu 1976; Charoenlarp 1988; Chisholm 1966; Christian 2003 (C); Lee 2005; Taylor 1982; Willoughby 1967). Data from one study (Christian 2003 (C)) which met the criteria for high quality examined groups receiving daily iron + folic acid versus women receiving folic acid (without iron), with vitamin A supplementation as co-intervention. Five studies provided data comparing the effects of daily iron + folic acid with daily folic acid alone (without iron) supplementation (Batu 1976; Chisholm 1966; Christian 2003 (C); Zeng 2008 (C); Ziaei 2007). Data from four studies compared women receiving oral iron + other vitamins and minerals with women receiving other vitamins and minerals (without iron) supplementation(Cantlie 1971; Liu 2000; Ouladsahebmadarek 2011; Siega-Riz 2001). Some trials provide data from different arms of the study for different comparisons. Of all the 43 studies that provided data in this comparison, 16 trials were of high quality according to our pre-established criteria (Barton 1994; Buytaert 1983; Chisholm 1966; Christian 2003 (C); Cogswell 2003; Eskeland 1997; Harvey 2007; Hemminki 1991; Makrides 2003; Preziosi 1997; Siega-Riz 2001; Tura 1989; Wallenburg 1983; Zeng 2008 (C); Ziaei 2007; Ziaei 2008).

Comparison 2: eight trials compared the effects of daily iron + folic acid supplementation with the effects of same supplements without iron + folic acid (no iron + folic acid or placebo). Seven of them compared the effects of daily iron + folic acid supplementation with the effects of no treatment (Barton 1994; Batu 1976; Charoenlarp 1988; Chisholm 1966; Lee 2005; Taylor 1982; Willoughby 1967). Only two of these (Barton 1994; Chisholm 1966) met the criteria for high quality. No studies compared women receiving daily oral iron + folic acid + other vitamins and minerals with women receiving other vitamins and minerals (without iron + folic acid). One study (Christian 2003 (C)) included a group that compared daily iron + folic acid supplementation in comparison to no treatment, considering the vitamin A supplementation and deworming as co-interventions in the compared groups.

Comparison 3: 35 trials compared the effects of daily iron supplementation with the effects of no iron or placebo (Batu 1976; Buytaert 1983; Chan 2009; Chanarin 1971; Charoenlarp 1988; Chisholm 1966; Cogswell 2003; Corrigan 1936; Christian 2003 (C); De Benaze 1989; Eskeland 1997; Falahi 2010; Hankin 1963; Harvey 2007; Hemminki 1991; Holly 1955; Hood 1960; Kerr 1958; Makrides 2003; Meier 2003; Menendez 1994 (C); Milman 1991; Ouladsahebmadarek 2011; Paintin 1966; Preziosi 1997; Pritchard 1958; Puolakka 1980; Romslo 1983; Svanberg 1975; Tura 1989; Van Eijk 1978; Wallenburg 1983; Willoughby 1967; Wills 1947; Ziaei 2008). Of these, 12 trials were of high quality according to our pre-established criteria (Buytaert 1983; Chisholm 1966, Cogswell 2003; Christian 2003 (C);

Eskeland 1997; Harvey 2007; Hemminki 1991; Makrides 2003; Preziosi 1997; Tura 1989; Wallenburg 1983; Ziaei 2008).

Comparison 4: eight trials compared the effects of daily iron + folic acid supplementation with the effects of no treatment (Barton 1994; Batu 1976; Charoenlarp 1988; Chisholm 1966; Christian 2003 (C); Lee 2005; Taylor 1982; Willoughby 1967). Only three of them (Barton 1994; Chisholm 1966; Christian 2003 (C)) met the criteria for high quality. One study (Christian 2003 (C)) included a group that compared daily iron + folic acid supplementation in comparison to no treatment, considering the vitamin A supplementation and deworming as co-interventions in the compared groups.

Comparison 5: five studies compared the effects of daily iron + folic acid with daily folic acid alone (without iron) supplementation (Batu 1976; Chisholm 1966; Christian 2003 (C); Zeng 2008 (C); Ziaei 2007). Four of the trials met the criteria for high quality (Chisholm 1966; Christian 2003 (C) Zeng 2008 (C); Ziaei 2007). The study (Christian 2003 (C)) included a group that compared daily iron + folic acid supplementation in comparison daily folic acid alone, considering the vitamin A supplementation and de-worming as co-interventions in the compared groups.

Comparison 6: three studies compared women receiving oral iron + other vitamins and minerals with women receiving other vita-mins and minerals (without iron) supplementation (Cantlie 1971; Ouladsahebmadarek 2011; Siega-Riz 2001). One of the studies met the criteria for high quality (Siega-Riz 2001). One group in the study (Liu 2000) provided iron with vitamin C, but the comparison groups had different nutrients.

Comparison 7: no studies compared women receiving daily iron + folic acid + other vitamins and minerals versus women receiving folic acid and other vitamins and minerals (without iron).

Comparison 8: no studies compared women receiving daily oral iron + folic acid + other vitamins and minerals with women receiving same other vitamins and minerals (without iron + folic acid). See the tables of Characteristics of included studies for a detailed description of all the studies. All included studies met the pre-stated inclusion criteria.

Excluded studies—Altogether, we excluded 119 studies; some studies were excluded for more than one reason. The main reason for excluding studies was that participants in all arms of trials received iron and were therefore not eligible for any of the comparisons included in this review. This reason applied to a total of 87 trials.

- In 44 trials women received different types of iron (for example ferrous iron versus iron fumarate), or women received iron with or without other vitamins or supplements (Afifi 1978; Babior 1985; Balmelli 1974; Burslem 1968; Buss 1981; Carrasco 1962; Castren 1968; Chanarin 1968; Coelho 2000; Dawson 1987; Dijkhuizen 2004; Ekstrom 1996; Fletcher 1971; Giles 1971; Gringras 1982; Hartman-Craven 2009; Hosokawa 1989; Kaestel 2005; Kann 1988; Lira 1989; Ma 2008; Mbaye 2006; Metz 1965; Morrison 1977; Nogueira 2002; Ogunbode 1984; Ogunbode 1992; Osrin 2005; Payne 1968; Rae 1970; Ramakrishnan 2003; Rayado

1997; Rolschau 1979; Roth 1980; Rybo 1971; Saha 2007; Shatrugna 1999; Sjostedt 1977; Srisupandit 1983; Stone 1975; Trigg 1976; Weil 1977; Willoughby 1966; Willoughby 1968).

- In 34 trials both groups received iron and either different doses of iron were compared (Aaseth 2001; Ahn 2006; Brown 1972; Guldholt 1991; Horgan 1966; Madan 1999; Milman 2005; Nguyen 2008; Reddaiah 1989; Thane-Toe 1982; Thomsen 1993; Vogel 1963; Zhou 2009), or different types of regimen (for example daily versus weekly iron) (Bhatla 2009; Casanueva 2003a; Chew 1996a; Chew 1996b; Ekstrom 2002; Gomber 2002; Goonewardene 2001; Grover 1998; Liu 1996; Mukhopadhyay 2004; Mumtaz 2000; Pena-Rosas 2003; Pita Martin 1999; Quintero 2004; Ridwan 1996; Robinson 1998; Winichagoon 2003; Yecta 2011; Young 2000; Yu 1998; Zamani 2008). (Daily versus intermittent oral iron regimens in pregnancy are examined in a related Cochrane review (Pena-Rosas 2012).
- In seven trials different types of administration were compared (for example intravenous iron versus oral supplements) (Bencaiova 2007; Kumar 2005; Sinha 2011; Sood 1979; Swain 2011; Wali 2002; Zutshi 2004).
- In two trials both groups received iron and one group received an additional intervention such as education (Adhikari 2009; Sachdeva 1993).

The second most frequent reason for exclusion was that the studies were not prospective, parallel, randomised controlled trials. A total of 18 trials were excluded for this reason (Abel 2000; Angeles-Agdeppa 2003; Berger 2003; Chawla 1995; Dawson 1962; Edgar 1956; Gopalan 2004; Iyengar 1970; Kulkarni 2010; Menon 1962; Morgan 1961; Ortega-Soler 1998; Powers 1985; Roztocil 1994; Sandstad 2003; Tange 1993; Wu 1998; Young 2010).

The remaining 14 studies were excluded for other reasons: the studies by Bergsjo 1987 and Steer 1992 were not completed, and results are not available for the Hawkins 1987 trial; studies byHermsdorf 1986, Tampakoudis 1996 and Tan 1995 were reported as abstracts and there was insufficient information on methods to allow us to assess risk of bias; Cook 1990, Khambalia 2009 andPicha 1975 did not examine iron supplementation in pregnant women and Hampel 1974 recruited women, and reported outcomes at different gestational ages so we were unable to interpret results; Bokhari 2011 and McKenna 2002 looked at iron fortified food or drink; finally, Blot 1980 and Seck 2008 examined comparisons outside the scope of this review.

Risk of bias in included studies

See the ‘Risk of bias’ tables included in Characteristics of included studies for an assessment of the risk of bias for each included trial and Figure 2 and Figure 3 for an overall summary of the methodological quality of all included trials. In the description below we have summarised risk of bias only for those 43 trials contributing outcome data to the review.

In the summary of findings tables we examined risk of bias for each outcome separately, considering only those trials contributing data for each primary outcome.

Allocation

Sequence generation: We assessed 20 trials as having adequate methods for generating the randomisation sequence (Barton 1994; Buytaert 1983; Chan 2009 Charoenlarp 1988; Christian 2003 (C); Cogswell 2003; Eskeland 1997; Harvey 2007; Hemminki 1991; Kerr 1958; Lee 2005; Makrides 2003; Meier 2003; Preziosi 1997; Siega-Riz 2001; Tura 1989; Wallenburg 1983; Zeng 2008 (C); Ziaei 2007; Ziaei 2008). Eighteen trials did not report or did not state clearly the randomisation method used (Batu 1976; Chanarin 1965; Cantlie 1971; Chisholm 1966; De Benaze 1989; Holly 1955; Hood 1960; Menendez 1994 (C); Milman 1991; Ouladsahebmadarek 2011; Paintin 1966; Pritchard 1958; Puolakka 1980; Romslo 1983; Svanberg 1975; Taylor 1982; Van Eijk 1978; Willoughby 1967). Five trials were quasi-randomised using alternate sequence allocation (Chanarin 1971; Corrigan 1936; Han 2011; Hankin 1963; Wills 1947).

In three of these trials clusters rather than individual women were randomised (Christian 2003 (C); Menendez 1994 (C); Zeng 2008 (C)).

Allocation concealment: We judged that 19 trials had adequate methods of allocation concealment (Barton 1994; Buytaert 1983; Chan 2009; Chisholm 1966; Christian 2003 (C); Cogswell 2003; De Benaze 1989; Eskeland 1997; Harvey 2007; Hemminki 1991; Makrides 2003; Paintin 1966; Preziosi 1997; Siega-Riz 2001; Tura 1989; Wallenburg 1983; Zeng 2008 (C); Ziaei 2007; Ziaei 2008). The method of concealing allocation used in the remaining trials was unclear (Batu 1976; Cantlie 1971; Chanarin 1965; Charoenlarp 1988; Holly 1955; Hood 1960; Kerr 1958; Lee 2005; Meier 2003; Milman 1991; Ouladsahebmadarek 2011; Pritchard 1958; Puolakka 1980; Romslo 1983; Svanberg 1975; Taylor 1982; Willoughby 1967). Some trials used an inadequate method or did not use any allocation concealment at all (Chanarin 1971; Corrigan 1936; Han 2011; Hankin 1963; Menendez 1994 (C); Van Eijk 1978; Wills 1947).

Blinding

Blinding of participants, staff and outcome assessors: Investigators in 25 trials attempted to blind participants and staff by using placebos of similar appearance to active treatment or coded or opaque bottles although it was not always clear whether or not outcome assessment was blinded (Barton 1994; Buytaert 1983; Chanarin 1971; Charoenlarp 1988 Chisholm 1966; Christian 2003 (C); Cogswell 2003; Corrigan 1936; De Benaze 1989; Eskeland 1997; Han 2011; Harvey 2007; Hemminki 1991; Makrides 2003; Meier 2003; Milman 1991; Paintin 1966; Preziosi 1997; Siega-Riz 2001; Svanberg 1975; Tura 1989; Wallenburg 1983; Wills 1947; Ziaei 2007; Ziaei 2008). In the remaining trials blinding was either not mentioned or not attempted.

Incomplete outcome data—We judged that trials with more than 20% loss to follow-up, or with imbalanced loss to follow-up in different arms of trials were inadequate in terms of completeness of outcome data. Ten trials were assessed as having high levels of attrition, or loss was not balanced across groups and may have occurred for reasons associated with treatment (for example, if women were withdrawn from trials if they developed anaemia or experienced side effects) (Barton 1994; Cantlie 1971; Chan 2009; Christian 2003 (C);

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Cogswell 2003; Eskeland 1997; Kerr 1958; Meier 2003; Menendez 1994 (C); Siega-Riz 2001).

Selective reporting—We did not formally assess outcome reporting bias; for most of the included trials we did not have access to study protocols and assessing outcome reporting bias from published reports alone can be difficult. However, we have noted in the Characteristics of included studies tables where we suspected a problem relating to outcome reporting. Although for most outcomes too few studies contributed data to allow us to examine possible publication bias through generating funnel plots, in the data and analyses tables and in the forest plots, we have arranged studies by weight to allow us to visually examine plots to decide whether there is any evidence of a greater effect size in smaller studies.

Other potential sources of bias—We have noted other concerns about studies in the notes and other risk of bias sections of the Characteristics of included studies tables.

Effects of interventions

See: **Summary of findings for the main comparison** Any supplements containing iron versus same supplements without iron or no treatment/placebo (no iron or placebo) for women during pregnancy; **Summary of findings 2** Any supplements containing iron and folic acid versus same supplements without iron nor folic acid (no iron nor folic acid or placebo) for women during pregnancy

In this review we have included data from 43 trials, involving more than 27,402 women although in trials which included more than two treatment arms we may not have included all arms in our analyses. We have organised the summary of results by supplementation regimens compared and by primary and secondary outcomes. Most of the included studies focused on haematological indices and few reported on any of the other outcomes prespecified in the review protocol. Many of the findings showed heterogeneity that could not be explained by standard sensitivity analyses including quality assessment, and so we used a random-effects model to analyse the results.

See the Data and analyses section for detailed results on primary and secondary outcomes.

For each comparison we have indicated the number of studies contributing data to that comparison. Some studies, with more than two treatment arms are included in more than one comparison. For most outcomes only a relatively small proportion of studies included in the comparison reported data; for some outcomes a single study reported results; for this reason we have indicated for each outcome the number of studies contributing data and the number of women included in those studies. For those out comes including data from cluster-randomised trials the number included is the effective sample size; that is, sample sizes and event rates have been adjusted for cluster-trials to take account of the design effect.

(1) Any supplements containing iron versus same supplements without iron or no treatment/placebo (no iron or placebo) (43 studies)

Infant outcomes

Low birthweight (less than 2500 g): Overall, there was a statistically significant difference in the prevalence of low birthweight (less than 2500 g) between newborns of mothers in these two groups. Among 8480 women in 11 trials, 8.4% of those who took daily iron supplementation during pregnancy had a baby with birthweight below 2500 g versus 10.2% of those who received no iron or placebo (average risk ratio (RR) 0.81; 95% confidence interval (CI) 0.68 to 0.97) (Analysis 1.1). There was no clear evidence of differences between subgroups (Analysis 1.2; Analysis 1.3; Analysis 1.4; Analysis 1.5) or obvious funnel plot asymmetry (Figure 4).

Birthweight (g): We also found a significant difference in mean infant birthweight in the two groups. Among infants born to 9385 participants in 14 trials the mean difference (MD) in birthweight between those whose mothers had taken iron supplements and those whose mothers had not was 30.81 g (95% CI 5.94 to 55.68) (Analysis 1.6). We did not find evidence of subgroup differences (Analysis 1.7; Analysis 1.8; Analysis 1.9; Analysis 1.10) or obvious funnel plot asymmetry (Figure 5).

Premature birth (less than 37 weeks' gestation): Thirteen trials with 10,148 women provided data on preterm birth (before 37 week's gestation); while women receiving iron supplements were less likely to experience premature delivery the difference between groups did not reach statistical significance (average RR 0.88; 95% CI 0.77 to 1.01).There was no evidence of differences between subgroups in terms of women's gestational age or anaemia status at the start of supplementation, or for the dose of iron, however, the treatment effect appeared to be greater in non-malarial settings (Analysis 1.12; Analysis 1.13; Analysis 1.14; Analysis 1.15). Visual inspection of the funnel plot for this outcome suggested that smaller studies tended to report more pronounced treatment effects (Figure 6).

Neonatal death: Four studies with 7465 participants reported neonatal mortality and there was no clear evidence of any difference between groups (average RR 0.90; 95% CI 0.68 to 1.19) (Analysis 1.16). We did not find evidence of subgroup differences for this outcome (Analysis 1.17; Analysis 1.18; Analysis 1.19; Analysis 1.20).

Congenital anomalies: Three studies with 2702 women reported the number of infants with congenital anomalies; there was no clear evidence of any difference between groups (average RR 0.86; 95% CI 0.55 to 1.35) (Analysis 1.21).

Other primary infant outcomes: No studies reported findings for infant anaemia or infant iron-deficiency anaemia at birth or soon after.

Maternal primary outcomes

Maternal anaemia at term (Hb less than 110 g/L at 37 weeks' gestation or more): Among 2199 women in 14 trials (Batu 1976; Chanarin 1971; Chisholm 1966; Cogswell 2003; De

Benaze 1989; Eskeland 1997; Holly 1955; Liu 2000; Makrides 2003; Milman 1991; Preziosi 1997; Pritchard 1958; Puolakka 1980; Romslo 1983), 13.06% of those who received daily iron supplements during pregnancy had anaemia at term in comparison with 35.71% who did not receive iron (average RR 0.30; 95% CI 0.19 to 0.46) (Analysis 1.26). However, because the heterogeneity in study results was substantial our results have to be interpreted with caution (heterogeneity: $T^2 = 0.40$, $I^2 = 80\%$, Chi^2 test for heterogeneity $P < 0.00001$. We did not find any differences between subgroups in most of the subgroup analyses although the treatment effect appeared more pronounced in non-malarial settings (Analysis 1.27; Analysis 1.28; Analysis 1.29; Analysis 1.30). Visual inspection of the funnel plot for this outcome suggested that the treatment effect was more pronounced in smaller studies (Figure 7).

Maternal iron deficiency at term (as defined by as defined by trialists, based on any indicator of iron status at 37 weeks' gestation or more): Seven studies (1256 women) reported data for this outcome, with women in groups receiving iron as part of supplements being less likely to have iron deficiency at term (average RR 0.43; 95% CI 0.27 to 0.66) (Analysis 1.31). Subgroup analyses suggested that gestational age greater than 20 weeks, mixed or unspecified anaemia status at the start of supplementation and higher doses of iron were associated with more pronounced treatment effects (Analysis 1.32; Analysis 1.33; Analysis 1.34; Analysis 1.35).

Maternal iron deficiency anaemia at term (Hb below 110 g/L and at least one additional laboratory indicator at 37 weeks' gestation or more): Data from six trials involving 1088 women showed that 4.4% of women who received daily iron supplements and 13.2% of those who did not had iron deficiency anaemia at term (average RR 0.33; 95% CI 0.16 to 0.69). We did not find evidence of differences between subgroups (Analysis 1.37; Analysis 1.38; Analysis 1.39; Analysis 1.40).

Side effects (any): Data from 11 trials involving 4418 women suggest that women who receive daily oral iron supplementation are more likely to report side effects of any kind than women taking placebo or not taking any iron as part of supplements (25.3% versus 9.91% reporting side effects; average RR 2.36; 95% CI 0.96 to 5.82) ((Analysis 1.42). However, the heterogeneity between the treatment effects is substantial and the results have to be interpreted with caution (heterogeneity: $T^2 = 1.72$, $I^2 = 96\%$, Chi^2 test for heterogeneity $P < 0.00001$, 95% PI 0.14 to 42.28).There were no differences between subgroups in terms of women's gestational age or anaemia status at the start of supplementation. The risk of side effects appeared greater with increased doses of iron and the test for subgroup differences was close to statistical significance ($P = 0.06$, $I^2 = 64.7\%$). There also appeared to be a difference between subgroups based on malarial setting: in one trial carried out in a malarial setting there appeared to be a huge disparity between treatment groups in terms of side effects and this led to an apparent difference between subgroups (Analysis 1.43; Analysis 1.44; Analysis 1.45; Analysis 1.46). There was no obvious funnel plot asymmetry for this outcome (Figure 8).

Severe (Hb < 70/L) anaemia at any time during the second or third trimester: Nine trials with 2125 women reported results for this outcome, but estimable data were available for only three trials involving 786 women, this showed that women who received iron supplements were as likely to become severely anaemic during second and third trimesters (average RR 0.22; 95% CI 0.01 to 3.20). In many cases, women who became anaemic were treated and excluded from the analysis in the trials, independently of the group assigned, so very few cases became severely anaemic. As only three trials contributed estimable data, this result and the associated subgroup analysis have to be interpreted with caution.

Other maternal primary outcomes: There was no clear difference between groups for maternal mortality, or infection during pregnancy (Analysis 1.41; Analysis 1.53). Two studies reported on placental malaria and parasitaemia (Fleming 1985; Menendez 1994 (C)) and found no differences between groups.

Secondary infant outcomes: There was statistically significant evidence of differences between groups for the following infant secondary outcomes.

Very premature birth (less than 34 weeks' gestation): This outcome was reported in five trials with 3743 women; results suggest that babies born to mothers receiving iron were less likely to be born before 34 weeks' gestation (average RR 0.51; 95% CI 0.29 to 0.91) (Analysis 1.59).

Infant ferritin concentration at six months in µg/L: This outcome was measured in a single study with 197 participants; at six months the MD was 11.00 (95% CI 4.37 to 17.63) (Analysis 1.61).

Other infant secondary outcomes: There was no evidence of statistically significant differences between groups for the following infant secondary outcomes: very low birthweight; infant small-for-gestational age; mean Apgar score or low Apgar score at five minutes; mean infant Hb levels at three and six months; admission to special care; head circumference at birth; stunting at long-term follow-up, and breast feeding at four months (not prespecified).

No trials reported on the remaining prespecified infant secondary outcomes.

Maternal secondary outcomes: There was statistically significant evidence of differences between groups for the following maternal secondary outcomes:

Maternal Hb concentration at or near term (in g/L, at 34 weeks' gestation or more) and within six weeks postpartum period (in g/L): Haemoglobin concentration at or near term was reported in 19 studies, involving 3704 participants. There were high levels of heterogeneity for this outcome and results should be interpreted with caution. Women who received iron were on average likely to have higher Hb levels at term (MD 8.88 g/L; 95% CI 6.96 to 10.80) (heterogeneity: $T^2 = 13.92$, $I^2 = 87\%$, Chi^2 test for heterogeneity $P < 0.00001$ (Analysis 1.66).

At six weeks postpartum the difference between groups remained significant with women receiving iron as part of supplements having higher Hb levels (MD 7.61; 95% CI 5.50 to 9.72; reported in seven studies with 956 women) (heterogeneity: $T^2 = 3.09$, $I^2 = 40\%$, Chi^2 test for heterogeneity P = 0.12) (Analysis 1.67).

Maternal high Hb concentrations (Hb greater than 130 g/L) at any time during second or third trimester: There was evidence from nine studies (4869 women) with estimable data that high Hb concentrations were more likely in the second and third trimesters in women who had received iron as part of supplements (average RR 2.26; 95% CI 1.40 to 3.66). There was high heterogeneity for this outcome (heterogeneity: $T^2 = 0.44$, $I^2 = 89\%$, Chi^2 test for heterogeneity P < 0.00001, PI 0.44 to 11.54) (Analysis 1.68).

Maternal high Hb concentrations at term (defined as Hb greater than 130 g/L at 37 weeks' gestation or more): Women who received iron were at higher risk of haemoconcentration at term (RR 3.08; 95% CI 1.28 to 7.41; reported in nine studies 4850 women). Again, there was high heterogeneity for this outcome and results should be interpreted cautiously (heterogeneity: $T^2 = 1.34$, $I^2 = 96\%$, Chi^2 test for heterogeneity P < 0.00001, 95% PI 0.19 to 39.15) (Analysis 1.69).

Maternal severe anaemia at or near term (Hb less than 70 g/L at 34 weeks' gestation or more): Data from eight trials involving 1819 reported results for this outcome; in six trials no cases of severe anaemia were identified so only two trials with 494 women contributed estimable data. Results from these two trials showed no significant difference between women who receive iron or not (average RR 0.47; 95% CI 0.01 to 44.11) (Analysis 1.70).

Severe anaemia at postpartum (Hb less than 80 g/L): While eight trials reported severe anaemia in the postnatal period only two studies with estimable data for 553 women contributed to this analysis; women receiving iron as part of supplements were less at risk of severe anaemia in the weeks after the birth (average RR 0.04; 95% CI 0.01 to 0.28) (Analysis 1.71).

Transfusion provided: The number of women receiving transfusions was reported in three studies (3453 participants) with women who had iron being less likely to have a transfusion than women who had no iron as part of supplements (average RR 0.61; 95% CI 0.38 to 0.96) (Analysis 1.76).

Puerperal infection: There was a statistically significant difference between groups in the number of women reported to have puerperal infection; with women receiving iron being at reduced risk, (four studies, 4374 participants) (average RR 0.68; 95% CI 0.50 to 0.92) (Analysis 1.73).

Other secondary outcomes: There was no statistically significant evidence of differences between groups for the following secondary outcomes: ante- or post-partum haemorrhage, individual side effects, placental abruption, preterm rupture of the membranes, pre-eclampsia and moderate anaemia in the postpartum period. Several of these outcomes were reported in only a small number of studies.

No trials reported on the remaining prespecified secondary outcomes.

(2) Any supplements containing iron and folic acid versus same supplements without iron nor folic acid (no iron nor folic acid or placebo) (eight studies)

Infant primary outcomes

Low birthweight (less than 2500 g): Two trials with 1311 participants examined this outcome (Christian 2003 (C); Taylor 1982). There was no clear evidence of significant differences between infants of women receiving daily iron + folic acid supplementation versus no supplements (RR 1.07; 95% CI 0.31 to 3.74) (Analysis 2.1). Data from the same trials suggest that infant birthweight were similar in the two groups (MD 57.73; 95% CI 7.66 to 107.79) (Analysis 2.2).

Premature birth (less than 37 weeks' gestation): Three studies with 1497 women examined this outcome (Christian 2003 (C); Lee 2005; Taylor 1982). We found no evidence of differences in the numbers experiencing preterm birth between women who received daily iron and folic acid supplements and those receiving no treatment or placebo (RR 1.55, 95% CI 0.40 to 6.00). Only one of these trials met the criteria for high quality (Christian 2003 (C)) (Analysis 2.3). There were no significant differences between subgroups (Analysis 2.4; Analysis 2.5; Analysis 2.6; Analysis 2.7).

Neonatal death: Three studies reported on this outcome (Barton 1994; Christian 2003 (C); Taylor 1982); there were a total of 69 perinatal deaths, and no clear evidence of any difference between groups (average RR 0.81; 95% CI 0.51 to 1.30) (Analysis 2.8). No subgroup differences were apparent.

Congenital anomalies: One study with 1652 women reported the number of infants with congenital anomalies; and there was no clear evidence of any difference between groups (average RR 0.70; 95% CI 0.35 to 1.40) (Analysis 2.13).

Maternal primary outcomes

Maternal anaemia at term (Hb less than 110 g/L at 37 weeks' gestation or more): The data from three trials including 346 women (Barton 1994; Batu 1976; Chisholm 1966) suggest that women who routinely receive daily iron and folic acid supplementation during pregnancy are less likely to have anaemia at term than those not taking any iron and folic acid supplements at all (defined as Hb less than 110 g/L) (7.2% versus 28.3%; average RR 0.34; 95% CI 0.21 to 0.54) (Analysis 2.14). Only one study with no estimable data met the prespecified criteria for high quality. We did not identify any differences between subgroups.

Maternal iron deficiency at term (as defined by as defined by trialists, based on any indicator of iron status at 37 weeks' gestation or more): Data from one trial involving 131 women (Lee 2005) suggest that women who routinely receive daily oral supplementation with iron are less likely to have iron deficiency at term than women taking placebo or not taking any iron and folic acid supplements at all although the difference between groups did

not reach statistical significance (3.6% versus 15%; RR 0.24; 95% CI 0.06 to 0.99) (Analysis 2.19).

Maternal iron deficiency anaemia at term (Hb less than 110 g/L and at least one additional laboratory indicator at 37 weeks' gestation or more): No evidence of significant differences was found between women who received daily iron and folic acid supplements and those receiving no treatment or placebo in the single trial contributing data to this analysis (RR 0.43; 95% CI 0.17 to 1.09) (Analysis 2.20). The study contributing data did not meet prespecified criteria for high quality.

Side effects (any): One trial including 456 women (Charoenlarp 1988) suggests that women routinely receiving iron and folic acid supplementation are more likely to report any side effects; none of those receiving no supplementation reported side effects, however, the CI is very broad for this finding (RR 44.32; 95% CI 2.77 to 709.09) (Analysis 2.22). This trial did not meet criteria for high methodological quality.

Severe anaemia at any time during second and third trimester (Hb less than 70 g/L): Two studies had estimable data for this outcome; there was no evidence of a statistically significant difference between groups (RR 0.12, 95% CI 0.02 to 0.63) (Analysis 2.23).

Other outcomes: One trial with 48 women reported on infection in pregnancy (Taylor 1982); there were four events in total, two in each group (Analysis 2.29). A single study reported on maternal deaths and there were no estimable data (Analysis 2.21).

There were no data on the remaining prespecified primary outcomes.

Infant secondary outcomes: No evidence of significant differences was found between infants from these groups of women receiving daily iron + folic acid supplementation and those taking placebo or not taking any supplements at all in the following secondary outcomes: very low birth-weight (less than 1500 g), or admission to special care unit.

No trials reported on the remaining infant secondary outcomes.

Maternal secondary outcomes

Maternal Hb concentration at term (in g/L at 37 weeks' gestation or more): The data from three trials including 140 women (Barton 1994; Batu 1976; Taylor 1982) suggest that women who routinely receive daily iron and folic acid supplementation reach term with higher Hb concentration than women taking placebo or not taking any iron and folic acid supplement at all (MD 16.13 g/L; 95% CI 12.74 to 19.52) (Analysis 2.36). The effect of iron-folic acid supplementation was associated with higher Hb concentrations in the single high-quality trial (MD 17.10; 95% CI 8.44 to 25.76) (Barton 1994).

Maternal high Hb concentrations at term (defined as Hb greater than 130 g/L): No evidence of significant differences was found between women who received daily iron and folic acid supplements and those receiving no treatment or placebo (Analysis 2.39).

Maternal high Hb concentrations at any time during second or third trimesters (defined as Hb greater than 130 g/L): No evidence of significant differences was found between women who received daily iron and folic acid supplements and those receiving no treatment or placebo (RR 1.78; 95% CI 0.63 to 5.04) (Analysis 2.38).

Maternal Hb concentration within six weeks postpartum in g/L: Two studies (Christian 2003 (C); Taylor 1982) involving 459 women reported this outcome. The data from these trials suggest that women receiving daily iron + folic acid supplementation achieve a higher concentration of Hb at one month postpartum than women not taking any supplements at all (MD 10.07; 95% CI 7.33 to 12.81) (Analysis 2.37) but no firm conclusions can be drawn given the scarcity of the data.

Maternal severe anaemia at or near term (Hb less than 70 g/L at 34 weeks' gestation or more): Three trials reported severe anaemia at or near term; there were estimable data for only one trial and overall only three women were identified with severe anaemia (Analysis 2.41).

Maternal severe or moderate anaemia at postpartum (Hb less than 80 g/L): Two trials reported estimable data for moderate anaemia in the postpartum period and women receiving iron were less likely to have anaemia (RR 0.33; 95% CI 0.17 to 0.65) (Analysis 2.40). For severe anaemia in the postpartum period only one trial reported estimable data with all cases of severe anaemia occurring in the women who did not receive supplements (RR 0.05; 95% CI 0.00 to 0.76) (Analysis 2.42). The scarcity of data makes it difficult to draw any firm conclusions on these outcomes.

Other secondary maternal outcomes: No evidence of significant differences was found in the following secondary outcomes: very premature delivery, puerperal infection, antepartum haemorrhage, postpartum haemorrhage, placental abruption, and pre-eclampsia. No trials reported on the remaining maternal secondary outcomes.

(3) Supplementation with iron alone versus no treatment/placebo (35 studies)

Infant outcomes

Low birthweight (less than 2500 g): Overall, we found no statistically significant difference in the prevalence of low birthweight (less than 2500 g) between newborns of mothers in these two groups (Analysis 3.1). Among 3830 women in seven trials (Cogswell 2003; Eskeland 1997; Falahi 2010; Hemminki 1991; Makrides 2003; Meier 2003; Menendez 1994 (C)), 3.2% of those who took daily iron supplementation during pregnancy had a baby with birthweight below 2500 g versus 4.2% of those who received no iron or placebo (average RR 0.71; 95% CI 0.42 to 1.19) (Analysis 3.1). When we limited our analysis to studies meeting criteria for high quality (Cogswell 2003; Eskeland 1997; Makrides 2003; Menendez 1994 (C)), the difference in the percentage of mothers with low birthweight babies remained non-significant (data not shown). There were no significant differences between subgroups Analysis 3.2; Analysis 3.3; Analysis 3.4; Analysis 3.5).

Birthweight (g): We found no significant difference in birthweight (Analysis 3.6) in children from mothers of the two groups. Among infants born to 3953 participants in nine trials (Cogswell 2003; Eskeland 1997; Falahi 2010; Harvey 2007; Hemminki 1991; Makrides 2003; Paintin 1966; Preziosi 1997; Puolakka 1980), the MD in birth-weight between those whose mothers had taken iron supplements and those whose mothers had not was 16.43 g and was not statistically significant (95% CI -37.28 to 70.14) . When we temporarily removed from the analysis the studies that did not meet our criteria for high quality the results remained non-significant (data not shown). No subgroup differences were apparent (Analysis 3.7; Analysis 3.8; Analysis 3.9; Analysis 3.10).

Premature birth (less than 37 weeks' gestation): Seven trials with 4407 women provided data on preterm birth (before 37 weeks' gestation); while women receiving iron supplements were less likely to experience premature delivery the difference between groups did not quite reach statistical significance (average RR 0.77; 95% CI 0.60 to 1.00) (Analysis 3.11). When we temporarily removed from the analysis the one study that did not meet our criteria for high quality (Chan 2009), the results favouring women in the daily iron group reached statistical significance (average RR 0.71; 95% CI 0.53 to 0.97) (data not shown). We found no significant differences between subgroups (Analysis 3.12; Analysis 3.13; Analysis 3.14; Analysis 3.15).

Other primary infant outcomes: Only one study with 2694 participants reported neonatal mortality and there was no clear evidence of any difference between groups (Analysis 3.16). A single study with 850 women reported the number of infants with congenital anomalies; again there was no clear evidence of any difference between groups (Analysis 3.17). No studies reported findings for infant anaemia or infant iron deficiency anaemia at birth or soon after.

Maternal primary outcomes

Maternal anaemia at term (Hb less than 110 g/L at 37 weeks' gestation or more): Among 2136 women in 14 trials (Batu 1976; Chanarin 1971; Chisholm 1966; Cogswell 2003; De Benaze 1989; Eskeland 1997; Holly 1955; Liu 2000; Makrides 2003; Milman 1991; Preziosi 1997; Pritchard 1958; Puolakka 1980; Romslo 1983), 12.5% of those who received daily iron supplements during pregnancy and 34.3% who did not receive iron had anaemia at term (average RR 0.29; 95% CI 0.19 to 0.47 (Analysis 3.18). However, because the heterogeneity in study results was substantial our results have to be interpreted with caution (heterogeneity: $T^2 = 0.44$, $I^2 = 80\%$, Chi^2 test for heterogeneity $P < 0.0001$. When we temporarily removed studies from the analyses that did not meet our criteria for high quality, the difference between groups remained significant and heterogeneity was reduced although it remained over 50% (data not shown). We did not find differences between subgroups in terms of women's gestational age or anaemia status at the start of supplementation, or for the dose of iron. The treatment effect appeared more pronounced in non-malarial settings, however only two of the trials contributing data to this analysis were carried out in a malarial setting so any difference between these subgroups may have occurred by chance (Analysis 3.19; Analysis 3.20; Analysis 3.21; Analysis 3.22).

Maternal iron deficiency at term (as defined by as defined by trialists, based on any indicator of iron status at 37 weeks' gestation or more): Data from seven trials involving 1256 women (Cogswell 2003; Eskeland 1997; Falahi 2010; Makrides 2003; Milman 1991; Preziosi 1997; Tura 1989) showed that 28.5% of women who received daily iron supplements had iron-deficiency at term, compared with 51.3% of those who received no iron supplements (average RR 0.43; 95% CI 0.27 to 0.66) (Analysis 3.23). The heterogeneity between the treatment effects is high and the results should be interpreted with caution (heterogeneity: $T^2 = 0.26$, $I^2 = 85\%$, Chi^2 test for heterogeneity $P < 0.00001$). Subgroup analyses indicated that gestational age greater than 20 weeks, mixed or unspecified anaemia status at the start of supplementation, malarial setting and higher doses of iron were associated with more pronounced treatment effects (Analysis 3.24; Analysis 3.25; Analysis 3.26; Analysis 3.27).

Maternal iron deficiency anaemia at term (Hb below 110 g/L and at least one additional laboratory indicator at 37 weeks' gestation or more): Data from six trials involving 1088 women (Cogswell 2003; Eskeland 1997; Falahi 2010; Makrides 2003; Milman 1991; Tura 1989) showed that 4.4% of women who received daily iron supplements and 13.2% of those who did not, had iron-deficiency anaemia at term (RR 0.33; 95% CI 0.16 to 0.69). The heterogeneity between the treatment effects was moderate (I^2 49%) (Analysis 3.28). There were no differences identified between subgroups (Analysis 3.29; Analysis 3.30; Analysis 3.31; Analysis 3.32).

Side effects (any): Data from 10 trials involving 4232 women (Charoenlarp 1988; Cogswell 2003; De Benaze 1989; Eskeland 1997; Harvey 2007; Hemminki 1991; Hood 1960; Kerr 1958; Makrides 2003; Paintin 1966) suggest that women who receive daily oral iron supplementation are more likely to report side effects of any kind than women taking placebo or not taking any iron supplements at all (26.03% versus 8.74%; RR 2.92; 95% CI 1.10 to 7.76) (Analysis 3.34). However, the heterogeneity between the treatment effects is substantial and the results have to be interpreted with caution (heterogeneity: $T^2 = 1.79$, $I^2 = 96\%$, Chi^2 test for heterogeneity $P < 0.00001$, 95% PI 0.11 to 78.56). Side effects were increased in women who received daily higher doses of elemental iron (more than 60 mg) and where supplementation started earlier (Analysis 3.35; Analysis 3.36; Analysis 3.37; Analysis 3.38). When we restricted the analyses to those trials meeting criteria for high quality, the difference between groups did not reach statistical significance (data not shown).

Maternal severe (Hb < 70 g/L) anaemia at any time during the second or third trimester: Data from seven trials involving 1078 women was available for this outcome, although only two trials with 466 women reported estimable data which showed that women who received iron supplements were as likely to become severely anaemic during second and third trimesters (RR 0.75; 95% CI 0.02 to 29.10) as those not receiving iron. However, results are difficult to interpret as very few trials reported events, and in many cases women who became anaemic were treated and excluded from the analysis in the trials. We found no differences between subgroups (Analysis 3.40; Analysis 3.41; Analysis 3.42; Analysis 3.43).

Other maternal primary outcomes: Maternal mortality was reported in one small trial including 47 women and no events were reported (Analysis 3.33). Infection during pregnancy for 2694 women was reported by Hemminki 1991; there was no evidence of statistically significant differences between groups (Analysis 3.45).

No studies reported findings for other maternal primary outcomes: malaria.

Secondary infant outcomes

Infant ferritin concentration in the first 6 months (in g/L, counting the last reported measure after birth within this period): The MD was 11.00 μg/L; 95% CI 4.37 to 17.63 μg/L (one trial involving 197 women) (Preziosi 1997) (Analysis 3.49).

Very premature birth (less than 34 weeks' gestation): This outcome was reported in three trials, involving 690 participants; results suggest that babies born to mothers receiving iron were less likely to be born before 34 weeks' gestation (average RR 0.32; 95% CI 0.10 to 1.09) (Analysis 3.47)

Other infant secondary outcomes: We found no evidence of significant difference by treatment group in the following secondary outcomes: very low birthweight (less than 1500 g) (Analysis 3.46); infant Hb concentration in the first six months (in g/L, counting the last reported measure after birth within this period) (Analysis 3.48); admission to special care unit (Analysis 3.50).

No trials reported on the remaining infant secondary outcomes.

Maternal secondary outcomes

Maternal Hb concentration at or near term (in g/L, at 34 weeks' gestation or more): Among 1851 women who participated in 16 trials (Batu 1976; Buytaert 1983; Cantlie 1971; Chanarin 1971; Cogswell 2003; De Benaze 1989; Eskeland 1997; Falahi 2010; Makrides 2003; Milman 1991; Puolakka 1980; Romslo 1983; Tura 1989; Van Eijk 1978; Wallenburg 1983; Ziaei 2008), those who took iron supplements had a mean Hb concentration 8.95 g/L higher at term in comparison to those who took no iron supplements at all (MD 8.95; 95% CI 6.37 to 11.53 g/L) (Analysis 3.54). However, because the heterogeneity among the treatment effects found in individual studies was substantial our results have to be interpreted with caution (heterogeneity: $T^2 = 21.70$, $I^2 = 89\%$, Chi^2 test for heterogeneity $P < 0.00001$). When we restricted the analysis to studies meeting the criteria for high quality the difference between groups remained significant (data not shown).

Maternal Hb concentration within six weeks postpartum (in g/L): The data from six trials involving 659 women (Cantlie 1971; Hankin 1963; Lee 2005; Menendez 1994 (C); Milman 1991; Wills 1947) suggest that women that routinely receive daily iron supplementation have a higher concentration of Hb within six weeks postpartum than those taking placebo or not taking any iron supplements at all (MD 7.26 g/L; 95% CI 4.78 to 9.74 g/L). Heterogeneity of the results is $T^2 = 3.99$, $I^2 = 44\%$, Chi^2 test for heterogeneity $P < 0.0001$ (Analysis 3.55).

Maternal high Hb concentrations at any time during second or third trimester (Hb greater than 130 g/L): Eight trials involving 3840 women evaluated the effects of oral routine supplementation with iron alone and high Hb concentrations at any time during the second or third trimesters (Cogswell 2003; Eskeland 1997; Harvey 2007; Hemminki 1991; Holly 1955; Makrides 2003; Milman 1991; Pritchard 1958). Among women who received daily iron supplements, 17.2% were found to have high Hb concentrations at some time during their second or third trimesters, compared with 8.9% of those who received no iron supplements (average RR 1.81; 95% CI 1.21 to 2.71) (Analysis 3.56). However, because the heterogeneity between studies was substantial the results have to be interpreted with caution (heterogeneity: $T^2 = 0.20$, $I^2 = 75\%$, Chi^2 test for heterogeneity $P < 0.0005$, 95% PI 0.54 to 6.04). The difference between groups remained significant when we temporarily removed from the analysis those studies which did not meet our criteria for high quality (data not shown).

Maternal high Hb concentrations at or near term (defined as Hb greater than 130 g/L, at 34 weeks' gestation or more): Data from eight trials involving 3883 women (Chisholm 1966; Cogswell 2003; Eskeland 1997; Hemminki 1991; Holly 1955; Makrides 2003; Milman 1991; Pritchard 1958) indicated that 18.1% of women who took daily iron supplementation during pregnancy and 5.6% of those who did not had high Hb concentrations at term (average RR 3.67; 95% CI 2.23 to 6.04) (Analysis 3.57). The heterogeneity between the treatment effects was substantial and the results have to be interpreted with caution (heterogeneity: $T^2 = 0.23$, $I^2 = 63\%$, Chi^2 test for heterogeneity $P < 0.008$. The difference between groups remained significant when we restricted the analysis to studies meeting criteria for high quality (data not shown).

Transfusion provided: The data from two trials involving 2726 women (Hemminki 1991; Puolakka 1980) suggest that women that routinely receive daily iron supplementation have a lower risk of receiving transfusion in comparison with women who did not receive iron supplementation (2% versus 3.4%); RR 0.59; 95% CI 0.37 to 0.94) (Analysis 3.64).

Maternal well being/satisfaction: A maternal index of well being was measured in one trial (Hemminki 1991) through the use of a self-administered questionnaire at 36 weeks' gestation and at six weeks and six months postpartum. There were no significant differences in any of the eight health concepts measured by this methodology between the women in the iron supplemented group or those in the placebo group at 36 weeks' gestation, six weeks and six months postpartum. Another trial (Eskeland 1997) assessed maternal well being at 28 and 36 weeks' gestation, and found no differences between the iron supplemented mothers or those receiving placebo (Analysis 3.70).

Other secondary outcomes: There was no evidence of significant differences between women receiving daily iron supplementation and women receiving placebo or not taking any iron supplements at all, in the following secondary outcomes: diarrhoea, very premature delivery (less than 34 weeks' gestation), placental abruption, pre-eclampsia, moderate anaemia at postpartum, maternal severe anaemia a postpartum; puerperal infection,

antepartum haemorrhage and postpartum haemorrhage, constipation, nausea, heartburn, or vomiting. No trials reported on the remaining secondary outcomes.

(4) Supplementation with iron + folic acid versus no treatment/placebo (eight studies)

Infant primary outcomes

Low birthweight (less than 2500 g): Two studies with 1311 participants examined this outcome (Christian 2003 (C); Taylor 1982). There was no clear evidence of significant differences between infants of women receiving daily iron + folic acid supplementation versus no supplements (RR 1.07; 95% CI 0.31 to 3.74) (Analysis 4.1).

Data from the these trials suggest that infant birthweight were 57.73 g heavier 95% CI 7.66 to 107.79 g in comparison to no treatment/placebo (Analysis 4.2). One trial (Christian 2003 (C)) met our criteria for high quality.

Premature birth (less than 37 weeks' gestation): Three studies with 1497 participants examined this outcome (Christian 2003 (C); Lee 2005; Taylor 1982). We found no evidence of differences in the numbers experiencing preterm birth between women who received daily iron and folic acid supplements and those receiving no treatment or placebo. One these trials met criteria for high quality (Christian 2003 (C)). There were no subgroup differences; only two of these trials had estimable data for this outcome.

Neonatal death: Three studies with 1793 women reported on this outcome (Barton 1994; Christian 2003 (C); Taylor 1982); there was no clear evidence of any difference between groups (average RR 0.81; 95% CI 0.51 to 1.30) (Analysis 4.8).

Congenital anomalies: Only one study (1652 participants) reported data on this outcome (Christian 2003 (C)) and there appears to be no differences between the groups compared (RR 0.70, 95% CI 0.35 to 1.40) (Analysis 4.13).

No trials reported on other review primary outcomes for infants.

Maternal primary outcomes

Maternal anaemia at term (Hb less than 110 g/L at 37 weeks' gestation or more): The data from three trials including 346 women (Barton 1994; Batu 1976; Chisholm 1966) suggest that women who routinely receive daily iron and folic acid supplementation during pregnancy are less likely to have anaemia at term than those not taking any iron and folic acid supplements at all (defined as Hb less than 110 g/L) (7.2% versus 28.2%; average RR 0.34; 95% CI 0.21 to 0.54) (Analysis 4.14). Only one study with no estimable data met the prespecified criteria for high quality. There was no evidence of subgroup differences.

Maternal iron deficiency at term (as defined by as defined by trialists, based on any indicator of iron status at 37 weeks' gestation or more): Data from one trial involving 131 women (Lee 2005) suggest that women who routinely receive daily oral supplementation with iron are less likely to have iron deficiency at term than women taking placebo or not

taking any iron and folic acid supplements at all although the difference between groups did not reach statistical significance (3.6% versus 15%; RR 0.24; 95% CI 0.06 to 0.99) (Analysis 4.19).

Maternal iron deficiency anaemia at term (Hb less than 110 g/L and at least one additional laboratory indicator at 37 weeks' gestation or more): No evidence of significant differences was found between women who received daily iron and folic acid supplements and those receiving no treatment or placebo in the single trial contributing data to this analysis (RR 0.43, 95% CI 0.17 to 1.09) (Analysis 4.20). The study (131 participants) contributing data did not meet prespecified criteria for high quality.

Side effects (any): One trial including 456 women (Charoenlarp 1988) suggests that women routinely receiving iron and folic acid supplementation are more likely to report any side effects; none of those receiving no supplementation reported side effects, however the CI is very broad for this finding (RR 44.32; 95% CI 2.77 to 709.09) (Analysis 4.22). This trial did not meet criteria for high methodological quality.

Maternal severe anaemia at any time during second and third trimester (Hb less than 70 g/L): Two trials reported estimable data for this outcome and results suggest that women were less likely to be identified with severe anaemia in the group receiving iron (RR 0.12, 95% CI 0.02 to 0.63) (Analysis 4.23).

Other outcomes: One trial with 48 women reported on infection in pregnancy (Taylor 1982); there were four events in total, two in each group (Analysis 4.25). A single study reported on maternal deaths and there were no estimable data (Analysis 4.21). There were no data on the remaining prespecified primary outcomes.

Infant secondary outcomes: No evidence of significant differences was found between infants from these groups of women receiving daily iron + folic acid supplementation and those taking placebo or not taking any supplements at all in the following secondary outcomes: very low birth-weight (less than 1500 g) or admission to special care unit.

Maternal secondary outcomes

Maternal anaemia at or near term (Hb less than 110 g/L at 34 weeks' gestation or more): The data from three trials including 346 women (Barton 1994; Batu 1976; Chisholm 1966) suggest that women who routinely receive daily iron and folic acid supplementation during pregnancy are less likely to have anaemia at term than those not taking any iron and folic acid supplements at all (defined as Hb less than 110 g/L) (7.2% versus 28.2%; average RR 0.34; 95% CI 0.21 to 0.54) (Analysis 4.31). Only one study with no estimable data met the prespecified criteria for high quality.

Maternal iron deficiency at or near term (as defined by as defined by trialists, based on any indicator of iron status at 34 weeks' gestation or more): Data from one trial involving 131 women (Lee 2005) suggest that women who routinely receive daily oral supplementation with iron are less likely to have iron deficiency at term than women taking placebo or not taking any iron and folic acid supplements at all although the difference

between groups was not statistically significant (3.6% versus 15%; RR 0.24; 95% CI 0.06 to 0.99) (Analysis 4.32).

Maternal iron deficiency anaemia at or near term (Hb less than 110 g/L and at least one additional laboratory indicator at 34 weeks' gestation or more): No evidence of significant differences was found between women who received daily iron and folic acid supplements and those receiving no treatment or placebo in the single trial contributing data to this analysis (Analysis 4.33). The study contributing data did not meet prespecified criteria for high quality.

Maternal Hb concentration at or near term (in g/L at 34 weeks' gestation or more): The data from three trials including 140 women (Barton 1994; Batu 1976; Taylor 1982) suggest that women who routinely receive daily iron and folic acid supplementation reach term with higher Hb concentration than women taking placebo or not taking any iron and folic acid supplement at all (MD 16.13 g/L; 95% CI 12.74 to 19.52) (Analysis 4.34). The effect of iron-folic acid supplementation was associated with higher Hb concentrations in the single high-quality trial (MD 17.10; 95% CI 8.44 to 25.76) (Barton 1994).

Maternal high Hb concentrations at any time during second or third trimesters (defined as Hb greater than 130 g/L): No evidence of significant differences was found between women who received daily iron and folic acid supplements and those receiving no treatment or placebo (Analysis 4.36).

Maternal high Hb concentrations at term (defined as Hb greater than 130 g/L at 37 weeks' gestation or more): No evidence of significant differences was found between women who received daily iron and folic acid supplements and those receiving no treatment or placebo (Analysis 4.37).

Maternal Hb concentration within 6 weeks postpartum in g/L: Two studies (Christian 2003 (C); Taylor 1982) involving 459 women reported this outcome. The data from these trials suggest that women receiving daily iron + folic acid supplementation achieve a higher concentration of Hb within 6 weeks postpartum than women not taking any supplements at all (MD 10.07; 95% CI 7.33 to 12.81) (Analysis 4.35) but no firm conclusions can be made given the scarcity of the data.

Maternal severe anaemia at or near term (Hb less than 70 g/L at 34 weeks' gestation or more): Three trials reported severe anaemia at term, but only one study had cases (Analysis 4.39).

Maternal severe or moderate anaemia at postpartum (Hb less than 80 g/L): There was only one trial with estimable data on women with severe or moderate anaemia in the postpartum period (Analysis 4.38; Analysis 4.40). The scarcity of data makes it difficult to draw any conclusions on these outcomes.

Other secondary maternal outcomes: No evidence of significant differences was found in the following secondary outcomes: very premature delivery, moderate anaemia at term,

moderate anaemia at any time during second or third trimesters, puerperal infection, antepartum haemorrhage, post-partum haemorrhage, placental abruption and pre-eclampsia. No trials reported on the remaining maternal secondary outcomes.

(5) Supplementation with iron + folic acid versus folic acid alone (without iron) supplementation (five studies)—The study by Zeng 2008 (C) was a cluster-randomised trial and the sample size and event rate have been adjusted to take account of the design effect. In the results below we have used the effective sample size rather than the total number of women included in the study.

Infant primary outcomes

Low birthweight (less than 2500 g): Three studies with an effective sample size of 4316 contributed data to this outcome, all studies met the criteria for high quality (Christian 2003 (C); Zeng 2008 (C); Ziaei 2007). There was a slight difference between groups receiving iron and folic acid versus folic acid alone (average RR 0.84; 95% CI 0.73 to 0.95) (Analysis 5.1). These studies reported mean infant birthweight but was a difference between groups (MD 32.23; 95% CI 0.86 to 63.60) (Analysis 5.6).

Premature birth (less than 37 weeks' gestation): Three studies with an effective sample size of 4314 contributed data to this outcome; all studies met the criteria for high quality (Christian 2003 (C); Zeng 2008 (C); Ziaei 2007). There was no statistically significant difference between groups receiving iron and folic acid versus folic acid alone and no subgroup differences were apparent (average RR 0.97; 95% CI 0.78 to 1.20) (Analysis 5.11).

Neonatal death: Three studies (4771 participants) (Christian 2003 (C); Zeng 2008 (C); Ziaei 2007) contributed data; there was no clear evidence of a difference between groups (average RR 0.85; 95% CI 0.63 to 1.15) (Analysis 5.16). There were no differences between subgroups identified.

Congenital anomalies: One study with 1652 women reported the number of infants with congenital anomalies; and there was no clear evidence of any difference between groups (RR 0.70; 95% CI 0.35 to 1.40) (Analysis 5.21).

No studies reported on our remaining infant primary outcomes.

Maternal primary outcomes

Maternal anaemia at term (at 37 weeks' gestation or more): Two studies with 303 women reported on the number of women with anaemia at term (Batu 1976; Chisholm 1966). The group receiving iron and folic acid were less likely to be anaemic compared to those receiving folic acid alone (9.7% versus 30.4%; average RR 0.34; 95% CI 0.21 to 0.55) (Analysis 5.22). The result remained significant when the study that did not meet our criteria for high quality was removed (data not shown). We did not find subgroup differences.

Maternal iron deficiency anaemia at term (at 37 weeks' gestation or more): A single study (Ziaei 2007) reported on the number of women with iron deficiency anaemia at term; there were no estimable data for this outcome (Analysis 5.28).

Side effects (any): One study reported on side effects (Ziaei 2007). There were no significant differences between the compared groups (Analysis 5.30).

Maternal severe anaemia at any time during second and third trimester (Hb less than 70 g/L): Three studies reported on maternal severe anaemia in pregnancy although there were estimable data for only one (Christian 2003 (C)). In this study women receiving supplements were less likely to be identified with severe anaemia (RR 0.06; 95% CI 0.01 to 0.47) (Analysis 5.31).

Infection during pregnancy: This outcome was reported in a single study with 727 women. There was no evidence of significant differences between groups (Analysis 5.33).

Studies did not provide data on our remaining maternal prespecified outcomes (maternal iron deficiency, maternal death or clinical malaria).

Infant secondary outcomes: There was no evidence of differences between groups for very premature birth, very low birthweight. There were no data reported on our remaining infant secondary outcomes.

Maternal secondary outcomes

Maternal anaemia at or near term (at 34 weeks' gestation or more): Two studies with 303 women reported on the number of women with anaemia at term (Batu 1976; Chisholm 1966). The group receiving iron and folic acid were less likely to be anaemic compared to those receiving folic acid alone (9.7% versus 30.4%; average RR 0.34; 95% CI 0.21 to 0.55) (Analysis 5.39). The result remained significant when the study that did not meet our criteria for high quality was removed (data not shown).

Maternal iron deficiency anaemia at or near term (at 34 weeks' gestation or more): A single study (Ziaei 2007) reported on the number of women with iron deficiency anaemia at term; there were no estimable data for this outcome (Analysis 5.41).

Maternal Hb at or near term (in g/L, at 34 weeks' gestation or more): Two studies with 771 women contributed data to this outcome (Batu 1976; Ziaei 2007). The mean concentration of Hb was higher in the women receiving iron and folic acid as opposed to those receiving folic acid alone (MD 12.44; 95% CI 0.95 to 23.93). However, with only two studies contributing data this result should be treated with caution (Analysis 5.42).

Maternal high Hb concentrations at or near term (at 37 weeks' gestation or more) and during pregnancy: Two studies with 967 reported data for the number of women with high Hb concentrations at term (Chisholm 1966; Ziaei 2007). The evidence of difference between groups was not statistically significant (average RR 1.87; 95% CI 0.32 to 10.84) (Analysis 5.45).

Two studies with 1042 women reported on high Hb concentrations in the third trimester of pregnancy. Women receiving iron in addition to folic acid were more likely to have high Hb concentrations during pregnancy (RR 4.33; 95% CI 2.26 to 8.30) (Analysis 5.44).

Other outcomes: There was no evidence of significant differences between groups for the following secondary outcomes: maternal high Hb concentrations during second or third trimester, puerperal infection, antepartum haemorrhage, postpartum haemorrhage, transfusion provided, diarrhoea, vomiting, nausea or constipation, placental abruption, premature rupture of the membranes or pre-eclampsia. Studies did not report data on our remaining maternal secondary outcomes.

(6) Supplementation with iron + other vitamins and minerals supplementation versus same other vitamins and minerals (without iron) supplementation (three studies)—We have included data from three trials (Cantlie 1971; Ouladsahebmadarek 2011; Siega-Riz 2001).

Infant primary outcomes: A single study with 334 women provided data for infant primary outcomes. The study met our prespecified criteria for high quality (Siega-Riz 2001)

There was no evidence of a statistically significant differences between groups for infant birthweight or premature delivery. There were no data on perinatal death or other prespecified primary outcomes.

Maternal primary outcomes: One study provided data on side effects and no significant differences between groups were identified (Analysis 6.10). No studies provided information on maternal anaemia at term, maternal infection or any of our other prespecified maternal outcomes.

Infant secondary outcomes: There was no significant evidence that there was any difference between groups for the number of babies small-for-gestational age. There were no data reported for our remaining infant secondary outcomes.

Maternal secondary outcomes: Two studies with 809 women reported on mean maternal Hb levels at term and women receiving iron were more likely to have higher Hb levels compared with those without iron (average RR 10.85,; 95% CI 7.29 to 14.42) (Analysis 6.22). Cantlie 1971 also reported on mean maternal Hb levels in the postpartum period and women receiving iron in addition to other vitamins and minerals were more likely to have higher Hb levels compared with those receiving other vitamins and minerals without iron (MD 14.00; 95% CI 3.56 to 24.44) (Analysis 6.23).

Siega-Riz 2001 reported on side effects, there were no differences between groups in terms of the number of women suffering constipation, diarrhoea, vomiting or heartburn.

Ouladsahebmadarek 2011 reported on placental abruption, premature rupture of the membranes and pre-eclampsia for 782 women; there were no significant differences between groups for any of these outcomes (Analysis 6.39; Analysis 6.40; Analysis 6.41).

No information was reported on our remaining maternal secondary outcomes.

(7) Daily oral iron + folic acid + other vitamins and minerals supplementation versus daily oral folic acid + same other vitamins and minerals (without iron) supplementation (no studies)—No studies compared women receiving daily oral iron + folic acid + other vitamins and minerals supplementation versus daily oral folic acid + same other vitamins and minerals (without iron) supplementation.

(8) Daily oral iron + folic acid + other vitamins and minerals supplementation versus daily oral same other vitamins and minerals (without iron nor folic acid) supplementation (no studies)—No studies compared women receiving daily oral iron + folic acid + other vitamins and minerals with women receiving other vitamins and minerals (without either folic acid or iron).

DISCUSSION

Summary of main results

We have set out a summary of our main findings along with an overall assessment of the quality of the evidence in additional tables (Summary of findings for the main comparison; Summary of findings 2).

Forty-three trials compared the effects of daily oral supplements containing iron versus no iron or placebo. The majority of them (35) compared arms receiving iron alone versus no treatment and placebo. Overall, women taking iron supplements were less likely to have low birthweight newborns (below 2500 g) compared with controls (8.4% versus 10.2%). Mean birthweight was 30.81 g greater for those infants whose mothers received iron during pregnancy. Results also suggest that babies born to mothers receiving iron were less likely to be born before 34 weeks' gestation (average risk ratio (RR) 0.51; 95% confidence interval (CI) 0.29 to 0.91). For other infant outcomes there were no clear differences between groups.

Regarding maternal outcomes, women receiving iron compared with those receiving no treatment or placebo were less likely to be anaemic at term (13.06% versus 35.71%) and were less likely to have iron-deficiency (28.50% versus 51.33%) and iron-deficiency anaemia at term (4.37% versus 13.18%). At the same time, women who received iron supplements were more likely than controls to report side effects (25.30% versus 9.91%) and had increased risk of high haemoglobin (Hb) concentrations at any time during second or third trimester (RR 2.26; 95% CI 1.40 to 3.66) and at term (RR 3.08; 95% CI 1.28 to 5.41), particularly at does higher than 60 mg of elemental iron daily. Women receiving iron were on average more likely to have higher Hb levels at term and in the postpartum period. For several outcomes where there was evidence of differences between groups, the size of the treatment effect in individual studies varied considerably, and so our results should be interpreted with caution.

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Only nine trials compared the effects of daily iron + folic acid supplementation with the effects of same supplements without iron + folic acid. There were clear positive effects on maternal haematological status while the effects on infant outcomes were uncertain.

Overall completeness and applicability of evidence

This review included 60 randomised controlled trials carried out since 1936 in 27 countries across the globe. Trials were mostly conducted during the last 20 years. There was some equilibrium between the trials that included non-anaemic women and those focused on populations with high prevalence of anaemia as well among the trials assessing early or late gestational iron supplementation. Although it was not possible to extract data from all the trials, these numbers clearly reflect the wide applicability of this review.

We addressed the effects of the use of iron or iron + folic acid by pregnant women, either provided alone or in combination with other vitamins and minerals. The effects can be determined if the differences between the comparison groups relies only in the presence of iron or iron + folic acid, that is, we are estimating the effects of the addition of iron or iron + folic acid to the pregnant women independently of any other co-interventions given to both groups being compared.

Most of the trials focused primarily on maternal changes in Hb and on some haematological indices after a certain period of supplementation. The results consistently show that iron supplementation in pregnancy improves maternal haematological outcomes independently of the dosage. However, those women who consumed higher amounts of iron (60 mg of iron or more per day) tended to have higher Hb values at the end or near term of pregnancy. In some cases, women reached levels above the threshold of 130 g/L at sea level which may be associated with negative pregnancy outcomes, including preterm birth, low birth weight and pre-eclampsia. Although the clinical significance of high Hb concentration is still being debated, it seems sensible to provide supplements with lower iron concentrations to those populations with lower prevalence of anaemia and iron deficiency.

Side effects are also a clear drawback to most current iron compounds used as supplements, either alone or with folic acid. The results of this review show that women who consume daily supplements containing 60 mg of elemental iron or more report side effects, particularly diarrhoea, more frequently than those who consume lower doses per day. This concurs with the Institute of Medicine’s approach which set 45 mg of elemental iron as the upper tolerable limit per day based on the likelihood of having side effects (IOM 2001). As a result, investigators are now testing highly bioavailable iron compounds (e.g. FeNaEDTA) that may produce fewer side effects and that can be administered at low doses, but their information is still limited.

There are two important contributions of this updated review in comparison to previous versions. First, the inclusion of new trials allowed us to observe more clearly the protective effects of iron supplements on infant outcomes such as birth weight, low birth weight and premature birth and very premature birth. Second, the recent development of statistical methods to test subgroup differences when using random-effects models allowed us to examine the possible effects of the iron dosage, iron compounds, gestational age at the start

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of supplementation, anaemia status at baseline or malaria endemicity. In spite of this, in some cases the interpretation of high level of heterogeneity remained a challenge.

Quality of the evidence

The overall quality of the evidence in this review is mixed, with many studies being at risk of bias. In more than half of the included trials the methods used to conceal allocation were not described. Blinding of women, care providers and outcome assessors was not attempted in more than a third of trials although in some studies technical staff carrying out laboratory investigations were reported to be unaware of group allocation. While for some outcomes (e.g. infant birthweight), the lack of blinding may have been unlikely to have had any impact on results, for others (e.g. maternal reports of side effects to care providers), lack of blinding may represent a potentially serious source of bias. Attrition was a problem in some studies and it was not always clear that loss was balanced across groups.

The overall quality of the evidence for iron supplementation versus no iron was moderate for low birthweight, premature birth, maternal anaemia at term and maternal iron deficiency at term. The evidence was of low quality for birthweight, neonatal death, congenital anomalies, maternal death, maternal severe anaemia, and infections during pregnancy; whereas, it was of very low quality for side effects (*see* Summary of findings for the main comparison).

The overall quality of the evidence for iron + folic acid supplementation versus no iron + folic acid was high for maternal anaemia at term. The evidence was of low quality for neonatal death, maternal iron deficiency at term, maternal death at term, side effects and maternal severe anaemia at any time during the 2nd or 3rd trimesters. Evidence was of very low quality for low birth-weight, birthweight, premature birth and congenital anomalies (*see* Summary of findings 2).

Potential biases in the review process

We were aware of the possibility of introducing bias at every stage of the reviewing process. In this updated review, we tried to minimise bias in a number of ways; two review authors assessed eligibility for inclusion, carried out data extraction and assessed risk of bias. Each worked independently. Nevertheless, the process of assessing risk of bias, for example, is not an exact science and includes many personal judgements. Further, the process of reviewing research studies is known to be affected by prior beliefs and attitudes. It is difficult to control for this type of bias in the reviewing process.

While we attempted to be as inclusive as possible in the search strategy, the literature identified was predominantly written in English and published in North American and European journals. Although we did attempt to assess reporting bias, constraints of time meant that this assessment largely relied on information available in the published trial reports and thus, reporting bias was not usually apparent.

In this updated version of the review we have included ‘Summary of findings’ tables. Assessing the quality of the evidence relating to specific outcomes is a difficult process, but we attempted to produce the tables using a transparent process. Two review authors

independently assessed the evidence for each outcome for each quality domain and discussed any disagreements.

Agreements and disagreements with other studies or reviews

Iron supplementation to pregnant women has been a long standing public health intervention that has been subject to multiple reviews, some of which also include a meta-analysis. In general, those meta-analyses tend to report the results in a segmented manner. Most of them are focused only on maternal anaemia (Sloan 2002; Yakoob 2011) while others also include a few infant outcomes (Imdad 2012). This topic has also been studied from the social determinants perspective (Nagata 2011).

A recent overview of reviews on the prevention and treatment of maternal anaemia identified 11 systematic reviews assessing the effects of iron and folic acid supplementation during the antenatal period, but only five were deemed as high quality, using AMSTAR as the assessment tool for methodological quality (Parker 2012).

This Cochrane review is the most comprehensive assessment on the effects of daily iron supplementation on both maternal and infant outcomes. After two updates, there is consistent evidence that providing iron supplements to pregnant women as part of the antenatal care helps improve gestational outcomes and that these benefits can be observed at lower iron doses than usual, with less side effects.

AUTHORS' CONCLUSIONS

Implications for practice

Available data from 43 studies indicate that in comparison with receiving no iron or a placebo, women receiving daily iron supplements had:

- lower risk of anaemia at term;
- higher haemoglobin (Hb) concentrations at term and six weeks postpartum;
- lower risk of delivering low birth weight babies;
- borderline lower risk of giving birth to infants less than 34 weeks' gestation;
- higher side effects, with a dose response pattern in which women receiving 60 mg of elemental iron or more per day reported more side effects;
- higher risk of high Hb concentrations during the second and third trimesters of pregnancy. Women who received higher iron doses tended to have the highest Hb concentrations.

The lack of data impeded any evaluation of the effects of iron supplementation on maternal mortality.

Relatively few studies assessed the combined effects of iron and folic acid on maternal and infant outcomes. There were clear positive effects on maternal haematological status while the effects on infant outcomes were uncertain.

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Supplementation with iron to pregnant women may be used as a preventive strategy to improve maternal and infant outcomes in all settings, including those where malaria is endemic. In these areas, it seems sensible to complement iron and folic acid supplementation programmes with measures to prevent, diagnose and treat malaria. In order to improve the success of this intervention in public health, it is important to encourage the establishment of logistic procedures that facilitate and improve accessibility to supplements and foster compliance.

Implications for research

On the basis of the results of this review, researchers could consider investigating the following points regarding the use of iron or iron + folate supplements by pregnant women.

1. Identify the mechanisms involved in high Hb concentrations during various gestational ages and its functional consequences.
2. The effects of providing other micronutrients than iron and folic acid on maternal and infant outcomes.
3. The assessment of effectiveness, safety, and affordability of novel iron supplementation compounds for use in public health pre-pregnancy and prenatal preventive supplementation programmes.

A better documentation of haematological indicators pre and post intervention, congenital anomalies, and side and adverse effects, including malaria-related outcomes, is encouraged

DATA AND ANALYSES

Refer to Web version on PubMed Central for supplementary material.

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As part of the pre-publication editorial process, this review has been commented on by two peers (an editor and referee who is external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON

Patient or population: women during pregnancy

Settings: settings including malaria endemic areas

Intervention: any supplements containing iron versus same supplements without iron or no treatment/placebo (no iron or placebo)

Outcomes	Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Low birthweight (less than 2500 g)	**RR 0.81** (0.68 to 0.97)	8480 (11 studies)	**moderate** *1*	
Birthweight (g)	The mean birthweight (g) in the intervention groups was 30.81 (5.94 to 55.68)	9385 (14 studies)	**low** *2*	
Premature birth (less than 37 weeks of gestation)	**RR 0.88** (0.77 to 1.01)	10148 (13 studies)	**moderate** *3*	
Neonatal death (within 28 days after delivery)	**RR 0.90** (0.68 to 1.19)	7465 (4 studies)	**low** *4*	
Congenital anomalies	**RR 0.86** (0.55 to 1.35)	2702 (3 studies)	**low** *5*	
Maternal anaemia at term (Hb less than 110 g/L at 37 weeks gestation or more)	**RR 0.30** (0.19 to 0.46)	2199 (14 studies)	**moderate** *6*	
Maternal iron deficiency at term (as defined by as defined by trialists, based on any indicator of iron status at 37 weeks' gestation or more)	**RR 0.43** (0.27 to 0.66)	1256 (7 studies)	**moderate** *7*	
Maternal death (death while pregnant or within 42 days of termination of pregnancy)	Not estimable	47 (1 study)	**low** *8*	
Side effects (any reported throughout the intervention period)	**RR 2.36** (0.96 to 5.82)	4418 (11 studies)	**very low** *9*	
Maternal severe anaemia at any time during 2nd or 3rd trimester (Hb less than 70 g/L)	**RR 0.22** (0.01 to 3.20)	2125 (9 studies)	**low** *10*	
Infection during pregnancy (including urinary tract infections and others) (ALL)	**RR 1.16** (0.83 to 1.63)	3421 (2 studies)	**low** *11*	

*
The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

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Low quality: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Some of the trials contributing data had high levels of attrition and in several studies the method of allocation concealment was unclear. Low heterogeneity (16%). No serious imprecision.

[2] Some of the trials contributing data had high levels of attrition and in several studies the method of allocation concealment was unclear. There was no serious heterogeneity in the magnitude of the effect (23%) and most of the trials favoured iron supplementation. Wide confidence intervals

[3] Some of the trials contributing data had high levels of attrition and in several studies the method of allocation concealment was unclear. Nil heterogeneity (0%). No serious imprecision

[4] Some of the trials contributing data had high levels of attrition or the method of allocation concealment was unclear. Event rates in some trials were low and the 95% CI was very broad in these trials. Nil heterogeneity (0%). Some imprecision

[5] No serious risk of bias in the trials contributing data. Event rates in one study were low and the 95% CI were broad. Nil heterogeneity (0%). Some imprecision

[6] Some of the trials contributing data had high levels of attrition and in various studies the method of allocation concealment was unclear. Although the direction of the effect was the same in all these trials, the effect size varied considerably resulting in high heterogeneity (80%). No serious imprecision. Assessors refrained from downgrading due to the high magnitude of the effect.

[7] Some of the trials contributing data had high levels of attrition and in various studies the method of allocation concealment was unclear. Although the direction of the effect was the same in all these trials, the effect size varied considerably resulting in high heterogeneity (85%). No serious imprecision. Assessors refrained from downgrading due to the high magnitude of the effect

[8] A single high quality trial assessed this outcome reporting zero events for both study arms

[9] Some of the trials contributing data had high levels of attrition and in various studies the method of allocation concealment was unclear. There was serious heterogeneity in the magnitude of the effect (96%) but most of the trials favoured no intervention/placebo. Wide confidence intervals

[10] Some of the trials contributing data had high levels of attrition and in various studies the method of allocation concealment was unclear. Nil heterogeneity (0%). Wide confidence intervals

[11] Some of the trials contributing data had high levels of attrition and in various studies the method of allocation concealment was unclear

Nil heterogeneity (0%). Event rates in both studies were low and the 95% CI broad

ADDITIONAL SUMMARY OF FINDINGS

Patient or population: women during pregnancy

Settings: all settings including malaria areas

Intervention: any supplements containing iron and folic acid versus same supplements without iron nor folic acid (no iron nor folic acid or placebo)

Outcomes	Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Low birthweight (less than 2500 g)	**RR 1.07** (0.31 to 3.74)	1311 (2 studies)	**very low** [1]	
Birthweight (g)	The mean birthweight in the intervention groups was **57.73** (7.66 to 107.79)	1365 (2 studies)	**very low** [2]	
Premature birth (less than 37 weeks of gestation)	**RR 1.55** (0.40 to 6.00)	1497 (3 studies)	**very low** [3]	

Outcomes	Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Neonatal death (within 28 days after delivery)	**RR 0.81** (0.51 to 1.30)	1793 (3 studies)	**low** [4]	
Congenital anomalies	**RR 0.70** (0.35 to 1.40)	1652 (1 study)	**very low** [5]	
Maternal anaemia at term (Hb less than 110 g/L, at 37 weeks' gestation or more)	**RR 0.34** (0.21 to 0.54)	346 (3 studies)	**high** [6]	
Maternal iron deficiency at term (as defined by as defined by trialists, based on any indicator of iron status, at 37 weeks' gestation or more)	**RR 0.24** (0.06 to 0.99)	131 (1 study)	**low** [7]	
Maternal death (death while pregnant or within 42 days of termination of pregnancy)	Not estimable	131 (1 study)	**low** [8]	
Side effects (any reported throughout the intervention period)	**RR 44.32** (2.77 to 709.09)	456 (1 study)	**low** [9]	
Maternal severe anaemia at any time during 2nd or 3rd trimester (Hb less than 70 g/L)	**RR 0.12** (0.02 to 0.63)	506 (4 studies)	**low** [10]	
Infection during pregnancy (including urinary tract infections and others) (ALL)	**RR 1.00** (0.15 to 6.53)	48 (1 study)	**very low** [11]	

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] One out of the two trials was considered at high risk of bias. Low heterogeneity (29%) but inconsistency in the magnitude and direction of the effect. Wide confidence intervals

[2] One out of the two trials was considered at high risk of bias. Very low heterogeneity (2%) but inconsistency in the magnitude and direction of the effect. Wide confidence intervals.

[3] Two out of the three trials were considered at high risk of bias. Moderate heterogeneity (34%). Wide confidence intervals

[4] Two of the three trials were considered at low risk of bias. Nil heterogeneity (0%). Wide confidence intervals

[5] A single high quality trial assessed this outcome, reporting low number of events for both study arms. Wide confidence intervals

[6] Two out of three trials reported events and one was considered at high risk of bias. Nil heterogeneity (0%). No serious imprecision. Assessors refrained from downgrading due to the large magnitude of the effect

[7] A single trial (at high risk of bias) assessed this outcome, reporting low number of events for both study arms. Wide confidence intervals. Assessors refrained from downgrading due to the large magnitude of the effect

[8] A single trial (at high risk of bias) assessed this outcome reporting zero events for both study arms

[9] A single high quality trial assessed this outcome. Wide confidence intervals

[10] Three out of four trials reported events and two were considered at high risk of bias. Nil heterogeneity (0%). Wide confidence intervals. Assessors refrained from downgrading due to the large magnitude of the effect

[10] A single trial (at high risk of bias) assessed this outcome reporting low number of events for both study arms. Wide confidence intervals

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Barton 1994

Methods	RCT, 2-arm trial with individual randomisation.
Participants	97 healthy women attending prenatal care at National Maternity Hospital, Dublin, Ireland with singleton pregnancy, during their first trimester of pregnancy, and with Hb equal or higher than 140 g/L were assigned to the groups. Women were excluded if they had a recent blood transfusion, chronic respiratory disease, chronic hypertension, renal disease, diabetes mellitus, history of haematologic disorder and alcohol dependence
Interventions	Participants were randomly assigned to 1 of 2 groups: group 1: received 60 mg elemental iron and 500 μg (0.5 mg) of folic acid to be taken by mouth twice daily; group 2: placebo tablets also to be taken by mouth twice daily. Supplementation started at 12 weeks until delivery. No postpartum supplementation Setting and health worker cadre: the intervention was performed by physicians at the National Maternity Hospitalin Dublin, Ireland
Outcomes	Maternal: Hb, HCT, serum erythropoietin concentrations at baseline and at 24, 28, 32, 36 and 40 weeks; serum ferritin at baseline and at 36 weeks; number of hypertensive disorders, antepartum haemorrhage, caesarean delivery. Infant: perinatal death, birthweight below 10th percentile, Apgar score, need for neonatal resuscitation and admission to neonatal intensive care unit data recorded but not reported in paper. Cord blood values of Hb, HCT, serum ferritin, and erythropoietin concentrations
Notes	Unsupervised. No participants were withdrawn because of anaemia. Compliance not reported. Gestational age at start of supplementation: early gestational age (supplementation started before 20 weeks of gestation) (12 weeks until delivery) Anaemic status at start of supplementation: non-anaemic. Daily iron dose: higher daily dose (60 mg elemental iron or more) (120 mg elemental iron) Iron release formulation: normal release/not specified. Iron compound: not specified. Malaria setting: non-malarial setting. As of 2011: Malaria: no risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers.
Allocation concealment (selection bias)	Unclear risk	Insufficient information reported on the method used to conceal the allocation sequence
Blinding (performance bias and detection bias) All outcomes	Low risk	Reported as double blind. The placebo tablets were identical in size, colour and shape to the iron and folic acid supplements and contained the same excipients
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 5% lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Low risk	No baseline imbalance apparent.

Batu 1976

Methods	RCT, 4-arm trial with individual randomisation.
Participants	133 women referred to investigators from a population of women attending an antenatal clinic for the fist time in Yangoon (also known as Rangoon), Myanmar (Burma). Women with severe anaemia were excluded from the trial during the intervention for treatment
Interventions	Participants were randomly assigned to 1 of 4 groups starting at 22-25 weeks: group 1: 60 mg of elemental iron (as ferrous sulphate), and 1 placebo tablets twice daily; group 2: 1 tablet containing 60 mg of elemental iron (as ferrous sulphate), and 1 tablet containing 500 μg (0.5 mg) of folic acid twice daily; group 3: 2 placebo tablets twice daily; group 4: 1 placebo tablet and 1 tablet containing 500 μg (0.5 mg) of folic acid twice daily. Administration of the treatments was carefully supervised. Supplementation started at 22-25 weeks until term

	Setting and health worker cadre: the intervention was performed by physicians at an antenatal clinic in Rangoon, Burma
Outcomes	Maternal: Hb concentrations at baseline, at term (38-40th week) and 4-7 week postpartum, serum iron, serum and red cell folate activity and hypersegmented polymorph count at baseline, at 38-40th week and postpartum
Notes	Supervised. 32 women who had taken other supplements or whose Hb level at full term was not available were excluded from the analysis. 3 women from group 3 and 2 from group 4 developed severe anaemia and were also withdrawn from analysis Gestational age at start of supplementation: late gestational age (more than 20 weeks at the start of supplementation) (22-25 weeks' gestation) Anaemic status at start of supplementation: unspecified/mixed anaemia status at the start of supplementation (women with severe anaemia excluded) Daily iron dose: higher daily dose (60 mg elemental iron or more) (120 mg of elemental iron) Iron release formulation: normal release iron supplement/not specified Iron compound: ferrous sulphate Malaria setting: yes. As of 2011: Malaria risk due predominantly to *P. falciparum* exists throughout the year at altitudes below 1000 m, excluding the main urban areas of Mandalayand Yangon. Risk is highest in remote rural, hilly and forested areas. *P. falciparum* resistant to chloroquine and sulphadoxine-pyrimethamine reported. Mefloquine resistance reported in Kayin state and the eastern part of Shan state. *P. vivax* resistance to chloroquine reported. Human *P. knowlesi* infection reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated; "randomly placed in one of four treatment regimens"
Allocation concealment (selection bias)	Unclear risk	Insufficient information reported on the method used to conceal the allocation sequence
Blinding (performance bias and detection bias) All outcomes	Low risk	Participant blinded by provision of placebos. Provider/assessor not stated or unclear
Incomplete outcome data (attrition bias) All outcomes	High risk	37 women (28%) were excluded for analysis. 133 women randomised "32 women who had taken other hematinics or whose Hb level at full term was not available were excluded". 5 women developed anaemia and were given treatment. Loss was not balanced across groups
Selective reporting (reporting bias)	High risk	32 women who had taken other supplements or whose Hb level at full term was not available were excluded from the analysis. 3 women from group 3 and 2 from group 4 developed severe anaemia and were also withdrawn from analysis
Other bias	Low risk	No baseline imbalance apparent.

Butler 1968

Methods	RCT, 3-arm trial with individual randomisation.
Participants	200 women before 20th week of gestation and Hb above 100 g/L attending antenatal clinic at the Maternity Hospital in Glossop Terrace, Cardiff, United Kingdom were studied. Exclusion criteria included urinary infection and threatened miscarriage, confusion over therapy, intercurrent illness and difficult veins, intolerant to the iron form, premature labor
Interventions	Participants were randomly allocated to 1 of 3 groups: group 1: received 122 mg of elemental iron (as ferrous sulphate) daily; group 2: received 122 mg of elemental iron (as ferrous sulphate) + 3400 μg (3.4 mg) of folic acid daily; group 3: received no intervention. A group 4 was formed as some participants (n = 38) from group 3 received iron supplements for treatment of anaemia in the course of the intervention. They are excluded from the analysis. Women were supplemented from week 20 to 40 of gestation Setting and health worker cadre: the intervention was performed by obstetricians and hematologists at the antenatal clinic, Cardiff Maternity Hospital in Cardiff, United Kingdom
Outcomes	Maternal: Hb concentrations, blood and plasma volume, HCT (not reported), red cell volume, albumin and globulin fractions at weeks 20, 28, 36 and 40 of gestation and at the first postanal visit, oedema, intrapartum haemorrhage
Notes	Unsupervised. 154 women were followed through to the postnatal visit. Only 16 women (30%) in the no-treatment group remained untreated. Compliance not reported. Gestational age at start of supplementation: early gestational age (supplementation started before 20 weeks' gestation) Anaemic status at start of supplementation: mixed anaemia status (Hb above 100 g/L) Daily iron dose: higher daily dose (60 mg of elemental iron or more) (122 mg elemental iron) Iron release formulation: normal release iron supplement/not specified Iron compound: ferrous sulphate. Malaria setting: non-malarial setting. As of 2011: Malaria: no risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence	Low risk	Randomised list stratified by age, parity and initial Hb level

generation (selection bias)		
Allocation concealment (selection bias)	Low risk	The code was not opened for the iron and iron + folic acid group until the end of the investigation, thus clinical staff could not anticipate the randomisation sequence. There was no treatment for 1 group
Blinding (performance bias and detection bias) All outcomes	High risk	Participant and provider were blinded to treatment for groups 1 and 2. The control group received no treatment and did not get a placebo
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 20% were lost to follow-up to the postnatal visit. 154 women were randomised and for many outcomes there were missing data. 70% of the 54 women initially allocated to the no treatment group received iron supplements for anaemia (as there was no placebo, staff would be aware that women were not receiving supplements). Results for those women treated or not treated in the control group were reported separately. Results are therefore difficult to interpret
Selective reporting (reporting bias)	Low risk	Authors provided the full database for this review.
Other bias	Low risk	No baseline imbalance apparent.

Buytaert 1983

Methods	RCT, 2-arm trial with individual randomisation.
Participants	45 non-anaemic women with singleton pregnancy and no major illnesses attending the University Hospital Obstetric and Gynaecologic Clinic in Antwerp, Belgium
Interventions	Participants were randomly assigned to 1 of 2 groups: group 1: received 105 mg of elemental iron (as ferrous sulphate sustained release preparation) daily and group 2: received no iron supplement. Supplementation started at 14-16th week of gestation and continued until delivery Setting and health worker cadre: the intervention was performed by obstetricians at the University Hospital Obstetrical Clinic of the Erasmus University at Rotterdam, The Netherlands or the University Hospital Obstetric and Gynecologic Clinic in Antwerp, Belgium
Outcomes	Maternal: Hb, serum iron, serum transferrin and serum ferritin concentrations at 16, 28, 36 weeks, delivery and 6 weeks postpartum
Notes	Unsupervised. The randomisation was made for each clinic in Antwerp, and the results are presented separately by clinic. Compliance not reported We treated this study carried out collaboratively in 2 different sites as 2 different trials, 1 conducted in Rotterdam (Wallenburg 1983) and 1 conducted in Antwerp (Buytaert 1983). Gestational age at start of supplementation: early gestational age (supplementation started before 20 weeks' gestation) (14th-16th week) Anaemic status at start of supplementation: non-anaemic. Daily iron dose: higher dose of iron (60 mg of elemental iron or more) (105 mg elemental iron) Iron release formulation: sustained release preparation. Iron compound: ferrous sulphate. Malaria setting: non-malarial setting. As of 2011: Malaria: no risk

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random table numbers.
Allocation concealment (selection bias)	Low risk	By means of sealed envelopes.
Blinding (performance bias and detection bias) All outcomes	High risk	Participant nor provider blinded. No placebo used.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 20% lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.

Other bias	Unclear risk	No other bias apparent.

Cantlie 1971

Methods	RCT, 2-arm trial with individual randomisation.
Participants	27 apparently healthy non-anaemic pregnant women 17-35 years of age from 4 participating obstetricians' private practice clinics from Montreal, Canada in their 1-5th month of pregnancy with Hb 120 g/L or higher in first trimester and 110 g/L or higher in second trimester. Women with history of pathological blood loss or gross dietary imbalance were excluded
Interventions	Participants were randomly assigned to 2 groups: group 1 received 39 mg elemental iron (Mol-Iron®, ferrous iron) to be taken twice daily with meals (total daily 78 mg elemental iron) or group 2 who received no iron tablets. As a co-intervention, both groups received 1 tablet of multiple micronutrient supplement daily containing: 2 mg copper citrate, 6 mg magnesium stearate, 0.3 mg manganese carbonate, 1000 IU vitamin A , 500 IU vitamin D, bone flour 130 mg, 1 mg vitamin B_1, 1 mg vitamin B_2, 50 mg brewer yeast concentrate, 5 mg niacinamide, 25 mg vitamin C, 0.2 mg sodium iodide and 0.049 μg folate (naturally occurring). Duration of supplementation unclear Setting and health worker cadre: the intervention was performed by obstetricians and hematologists at the McGill University Medical Clinic, Royal Victoria Hospital in Montreal, Canada. Participant, of higher socioeconomic status, were of recruited from private obstetrical practices
Outcomes	Maternal: Hb concentration, PCV, reticulocyte count, sedimentation rate, total white blood cell and differential counts, serumiron, unsaturated and total iron binding capacity, serum B_{12}, serum and RBC folate at baseline and at 32, 36, 39th weeks and 7 days postpartum
Notes	Supervision unclear. Compliance not reported. Gestational age at start of supplementation: mixed gestational age (1-5th month of pregnancy) Anaemic status at start of supplementation: non-anaemic. Daily iron dose: higher daily dose (60 mg elemental iron or more) (78 mg elemental iron) Iron release formulation:normal release iron supplement/not specified Iron compound: Mol-Iron®, ferrous iron. Malaria setting: non-malarial setting. As of 2011: Malaria: no risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated; "divided randomly".
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	High risk	27 women were randomised. 26 mentioned in the discussion; denominators were not provided for the results
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	Women in the intervention group had higher median serum folate levels at baseline (not sig)

Chan 2009

Methods	RCT (placebo controlled) 2-arm trial, individual randomisation
Participants	1164 pregnant women with singleton pregnancies with a gestational age of 16 weeks or less able to understand English or Chinese attending their first antenatal care visit at Queen Mary Hospital, Hong Kong between April 2005 and March 2007 Exclusion criteria: women with existing diabetes, haemoglobinopathies, Hb levels < 80 g/L or >140 g/L, women with possible thalassaemia (MCV < 80), women diagnosed with gestational diabetes at booking
Interventions	Participants were randomly assigned to 1 of 2 groups: group 1: (n = 565 women) received 60 mg of elemental iron orally (as 300 mg ferrous sulphate) daily ; group 2: (n = 599 women) received daily placebo indistinguishable in appearance from the active supplements. Women in both groups were provided with a supply for 16 weeks. At 28-30 weeks further supplements were provided (up to 36 weeks) as long as women had not developed gestational diabetes mellitus or Hb level was > 140 g/L. If women in the placebo group developed anaemia (Hb < 80 g/L) they were given iron supplements as clinically indicated

	Baseline investigations included a full blood count including Hb and HCT, MCV, white cells and platelets along with serum ferritin concentration. A OGIT was carried out at baseline for women with risk factors for gestational diabetes (e.g. advanced maternal age, family history of diabetes). Otherwise women in both groups received standard antenatal care Setting and health worker cadre: the intervention was performed by physicians at a regional university teaching hospital in Hong Kong
Outcomes	Follow-up at 28 weeks and 36 weeks' gestation and delivery and 3 days pp Main outcome: development of gestational diabetes at 28 or 36 weeks. (According to WHO criteria for impaired glucose tolerance test (OGTT 2-hour value > or = 7.8 < 11.1 mmol/L) or diabetes (OGTT 2-hour value> or = 11.1 mmol) both were considered as gestational diabetes mellitus). Other maternal outcomes: Hb (g/L), serum transferrin (g/L), serum ferritin (pmol/L), compliance, glucose level, mode of delivery Neonatal outcomes: gestational age at delivery, preterm delivery, birthweight, Apgar score at 1 and 5 minutes, arterial blood pH, Hb of cord blood (g/L), ferritin of cord blood (pmol/L), jaundice, birth trauma, infection, congenital abnormality or metabolic disorder
Notes	Very high attrition (> 50% for outcomes at 36 weeks). 45.6% of controls and 43.1% of women in the study group were taking additional vitamin supplements As the results reported in the paper were not completely clear to us we preferred not to use the reported SDs and removed the information from this trial for continuous variables, while awaiting clarification from the authors Gestational age at start of supplementation: early gestational age (supplementation started before 20 weeks) (16 weeks or less) Anaemic status at start of supplementation: mixed anaemia status (Hb levels > 80 and < 140 g/L) Daily iron dose: higher dose (60 mg elemental iron). Iron release formulation:normal release iron supplement/not specified Iron compound: ferrous sulphate. Malaria setting: yes. As of 2011: Malaria risk, including *P. falciparum* malaria, exists in Yunnan and to a lesser extent in Hainan. *P. falciparum* resistance to chloroquine and sulphadoxine-pyrimethamine reported. Limited risk of *P. vivax* malaria exists in southern and some central provinces, including Anhui, Ghuizhou, Henan, Hubei, Jiangsu. There is no malaria risk in urban areas

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was carried out by a research nurse who was not involved in patient recruitment. Block randomisation with computer generation of sequence. The block size was 100
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes. The envelopes were sequentially numbered and sealed (By nurse A who did the block randomisation) and all the envelopes were accounted for. The research assistant who recruited the patients (nurse B) would sequentially open the numbered envelopes after the patient had consented to participate in the study
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Participants blinded; placebo controlled. After randomisation "The participants but not the research assistants were blinded to group assignment". Staff and research nurses were aware of the group allocation Outcomes were assessed by the principle investigator (the outcomes are mainly objective outcomes such as OGTT results, blood counts, birthweight, etc)
Incomplete outcome data (attrition bias) All outcomes	High risk	1164 women were randomised. It was stated that an ITT analysis was performed but data tables suggest there were missing data for most outcomes at 28 and 36 weeks and at delivery; e.g. at 28 weeks 90.3% attended for follow-up. Neonatal outcome data were available for 74% of those randomised. There were very high levels (> 50%) of missing data for lab values at 36 weeks
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Low risk	No baseline imbalance between groups apparent.

Chanarin 1965

Methods	Randomised controlled trial with 3 arms.
Participants	190 pregnant women before 16 week of gestational age attending antenatal clinic for the first time in St Mary's Hospital in London, England, United Kingdom were invited to participate in the study and 189 accepted
Interventions	Participants were randomly assigned to 1 of 3 groups: group 1 received 3 tablets containing 100 mg of ferrous fumarate to be taken daily (total 300 mg ferrous fumarate daily); group 2 received 3 tablets containing 100 mg of ferrous fumarate with 10 μg (0. 01 mg) folic acid (total 300 mg ferrous fumarate and 30 μg (0.03 mg) folic acid daily, or placebo (containing lactose) Setting and health worker cadre: the intervention was performed by obstetricians and pathologists at the antenatal clinic of St. Mary's Hospital in London, United Kingdom
Outcomes	The outcomes measured include full blood count at 20th, 30th, 35th and 39th week of gestation and 6th day after delivery
Notes	The paper does not report SDs in the variables measured and no data can be extracted. The trial is included but does not contribute data for the analysis Gestational age at start of supplementation: early gestational age (supplementation started before 20 weeks' gestation) Anaemic status at start of supplementation: unspecified or mixed anaemia status Daily iron dose: higher daily dose (60 mg of elemental iron or more) Iron release formulation: normal release preparation/unspecified Iron compound: ferrous fumarate. Malaria setting: non-malarial setting. As of 2011: Malaria: no risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methods not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	High risk	Participant and care provider blinded during the trial. tablets had green, red or blue labels to differentiate among the groups
Incomplete outcome data (attrition bias) All outcomes	High risk	189 women were randomised but only 154 completed the study but not all samples could be obtained from every participant. 35 women were further withdrawn from the trial. 9 participants in the placebo group and 1 in the iron + folic acid group required parenteral iron nutrition and were withdrawn from the analysis
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Chanarin 1971

Methods	Quasi RCT. 5-arm trial with individual randomisation.
Participants	251 women attending antenatal clinic at St Mary's Hospital, London, United Kingdom before 20th week of gestation
Interventions	Participants were allocated by sequence to 1 of 5 groups: group 1: oral dose of 30 mg of elemental iron (as ferrous fumarate) daily; group 2: oral dose of 60 mg of elemental iron (as ferrous fumarate) daily; group 3: oral dose of 120 mg of elemental iron (as ferrous fumarate) daily; group 4: placebo; group 5: 1 g of iron (Imferon, 4 × 250 mg) intravenously before week 20, and thereafter oral 60 mg of elemental iron (as ferrous fumarate) daily (not included in this review). Supplementation started at 20th week until 37th week. Only the data related to comparisons of group 1: oral dose of 30 mg of elemental iron daily with group 4: placebo are used in this review given that no data for the other groups could be desegregated Setting and health worker cadre: the intervention was performed by obstetricians and pathologists at the antenatal clinic of St. Mary's Hospital in London, United Kingdom
Outcomes	Maternal: full blood count, serum iron at 20, 25, 30 and 37th week. Sternal marrow aspiration at 37 weeks; antepartum haemorrhage, threatened abortion, urinary tract infection, fetal abnormalities, pregnancy hypertension, premature delivery and puerperal infection measured but not reported by groups. Infant: birthweight (not reported by groups).
Notes	Compliance not reported. Gestational age at start of supplementation: late gestational age (supplementation started at 20 week's gestation) Anaemic status at start of supplementation: unspecified/mixed anaemia status Daily iron dose: different doses in different arms of trial (group 1 lower daily dose: 30 mg; group 2 and 3 higher daily dose 60 mg or more) Iron release formulation: normal release preparation/unspecified Iron compound: ferrous fumarate. Malaria setting: non-malarial setting. As of 2011: Malaria: no risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quasi-randomised study, assignment by sequence.
Allocation concealment (selection bias)	High risk	Women were "allocated in sequence to one of five groups"; allocation order could therefore be anticipated
Blinding (performance bias and detection bias) All outcomes	Low risk	Participant and provider blinded. A placebo was provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was not clear exactly how many women were randomised; there were approximately 50 in each of 5 groups. 11 women (9 from the placebo group) were withdrawn and given treatment for anaemia "after allowance had been made for the subjects dropping out of the study… there were just under 50 subjects in each group"
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.

Other bias	Unclear risk	No other bias apparent.

Charoenlarp 1988

Methods	RCT. Series of treatment conditions.
Participants	325 pregnant women with Hb (AA) and 232 pregnant women with Hb (AE) attending midwife centres in 80 villages from the Varin Chamrab district of Ubon Province, Thailand. Chronic illness, complicated pregnancy, severe anaemia (Hb < 80 g/L), haemoglobinopathies Hb (EE) and (EF), and unwillingness to co-operate were reason for exclusion. Individuals with Hb (AA) have normal Hb genes. Individuals with Hb (AE) have a heterozygous Hb E trait with normal Hb gene (A-adults) and an abnormal Hb gene (E). This is usually a clinically insignificant condition
Interventions	Participants were divided into 2 groups according to Hb (AA) and Hb (AE) and studied separately Women from each group were randomly assigned to 1 of the following 11 interventions: group 1: placebo, supervised; group 2, 120 mg of elemental iron (as ferrous sulphate) and 5000 μg (5 mg) folic acid daily supervised; group 3, 240 mg of elemental iron (as ferrous sulphate) daily supervised; group 4: 240 mg of elemental iron (as ferrous sulphate) daily supervised; group 5: 120 mg elemental iron (as ferrous sulphate) and 5000 μg (5 mg) of folic acid, motivated but unsupervised; and group 6: 240 mg of elemental iron (as ferrous sulphate) and 5000 μg (5 mg) of folic acid daily, motivated but unsupervised. For the Hb (AE) group, women were randomly assigned to 1 of the following groups: group 7: placebo, supervised; group 8: 240 mg elemental iron (as ferrous sulphate) and 5000 μg (5 mg) of folic acid daily, supervised; group 9: 240 mg of elemental iron (as ferrous sulphate) daily, supervised; group 10: 120 mg of elemental iron (as ferrous sulphate) and 5000 μg (5 mg) of folic acid daily, motivated but unsupervised, and group 11: 240 mg of elemental iron and 5000 μg (5 mg) of folic acid daily, motivated but unsupervised. Starting and ending time of supplementation not stated. Setting and health worker cadre: the intervention was performed by community health workers under the supervision of a midwife and was delivered to the home of participants living in villages near Ubon, Thailand. Intervention was coordinated from village midwife centres
Outcomes	Maternal: Hb, serum ferritin after 10 and 15 weeks of supplementation, and side effects
Notes	Groups 1, 2, 3, 4, 7, 8, 9 supervised. Groups 5, 6, 10 and 11 motivated but unsupervised. For purposes of analysis, the groups were merged by iron alone or iron-folic acid, and included as daily higher doses in both cases. Compliance not reported. Gestational age at start of supplementation: gestational age not specified Anaemic status at start of supplementation: unspecified/mixed anaemia status Daily iron dose: higher daily dose (60 mg or more of elemental iron) Iron release formulation: normal release preparation/unspecified Iron compound: ferrous sulphate. Malaria setting: yes. As of 2011: Malaria: Malaria risk exists throughout the year in rural, especially forested and hilly, areas of the whole country, mainly towards the international borders, including the southernmost provinces. There is no risk in cities (e.g. Bangkok, Chiang Mai city, Pattaya), Samui island and the main tourist resorts of Phuket island. However, there is a risk in some other areas and islands. *P. falciparum* resistant to chloroquine and sulphadoxine-pyrimethamine reported. Resistance to mefloquine and to quinine reported from areas near the borders with Cambodia and Myanmar. *P. vivax* resistance to chloroquine reported. Human *P. knowlesi* infection reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Set of random tables.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participant and outcome assessor blinded. Provider blinding unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	Ranged from 10%-15%.
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Chisholm 1966

Methods	RCT, 6 arms.

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Participants	360 non-anaemic women attending antenatal clinic at Radcliffe Infirmary, Oxford, United Kingdom before 28th week of gestation, who had not taken iron supplements in the preceding 8 weeks and with Hb >= 102 g/L or a normal serum iron reading. Exclusion criteria: Hb < 110 g/L and serum iron less than 60 μg/L
Interventions	Participants were randomly assigned to 1 of various combinations of elemental iron as ferrous gluconate and folic acid, as follows:group 1: 900 mg elemental iron alone daily; group 2: 900 mg elemental iron and 500 μg (0.5 mg) folic acid daily; group 3: 900 mg elemental iron and 5000 μg (5 mg) folic acid daily; group 4: placebo; group 5: 500 μg (0.5 mg) folic acid daily; group 6: 5000 μg (5 mg) of folic acid daily. Iron and folic acid placebos were used. Supplementation started at 28th week until 40th week. Setting and health worker cadre: the intervention was performed by physicians at the antenatal clinic of The Radcliffe Infirmary, Oxford, United Kingdom
Outcomes	Maternal: Hb, HCT, serumiron, serum folic acid activity, serum vitamin B_{12} estimation at 28 weeks of gestation and before delivery.
Notes	Unsupervised. For purposes of this review, placebo group was the group who received neither iron nor folic acid. Groups 2 and 3 were merged for iron-folic acid comparisons. Compliance not reported. Gestational age at start of supplementation: late gestational age (from 28 weeks' gestation) Anaemic status at start of supplementation: non-anaemic. Daily iron dose: higher daily dose (60 mg or more of elemental iron) Iron release formulation: normal release preparation/not specified Iron compound: ferrous gluconate. Malaria setting: non-malarial setting. As of 2011: Malaria: no risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	External randomisation.
Allocation concealment (selection bias)	Low risk	Bottles containing the tablets had been numbered by random selection at source and the code was unknown during trial
Blinding (performance bias and detection bias) All outcomes	Low risk	Participant and provider blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up apparent.
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Christian 2003 (C)

Methods	Cluster-randomised trial with 5 treatment arms.
Participants	4998 married pregnant women (with positive pregnancy test) living in the south eastern plains district of Sarlahi, Nepal. Widows were excluded
Interventions	Participants were randomly assigned to 1 of 5 groups: group 1 received 1000 μg retinol equivalents vitamin A (control) daily; group 2 received 1000 μg retinol equivalents vitamin A and 400 μg (0.4 mg) folic acid daily; group 3 received 1000 μg retinol equivalents vitamin A, 400 μg (0.4 mg) folic acid and 60 mg elemental iron (as ferrous fumarate) daily; group 4 received 1000 μg retinol equivalents vitamin A, 400 μg (0.4 mg) folic acid, 60 mg of elemental iron (as ferrous fumarate) and 30 mg of zinc sulphate daily; and group 5 received 1000 μg retinol equivalents vitamin A, 400 μg (0.4 mg) folic acid, 60 mg elemental iron (as ferrous fumarate), 30 mg of zinc, 10 μg vitamin D, 10 mg vitamin E, 1.6 mg thiamine, 1.8 mg riboflavin, 20 mg niacin, 2.2 mg vitamin B_6, 2.6 μg vitamin B_{12}, 100 mg vitamin C, 65 μg vitamin K, 2 mg cooper, and 100 mg magnesium daily. Only groups 1, 2 and 3 are considered in this review. Supplementation started at recruitment and continued until 3 months postpartum in the case of live births of 5 weeks or more after a miscarriage or stillbirth. All participating women were offered deworming treatment (albendazole 400 mg single dose) in the second and third trimester. Supplementation lasted 257.5 days in group 1 (control) and 251.7 days in the group 3 receiving vitamin A, iron and folic acid Comparisons: group 3 vs group 1: effect of iron supplementation with folic acid; group 3 vs group 2: effect of iron supplementation alone Setting and health worker cadre: the intervention was performed by community health workers in the home of the participants in remote villages in Sarlahi, Nepal. In Nepal, 8% of women received assistance from an auxiliary nurse midwife or doctor. Dosing and supplement replenishment was done by 426 local female workers, 1 per sector, or about 40 households
Outcomes	Maternal: premature delivery, Hb and iron status at baseline in the third trimester (scheduled at 32 wk of gestation) and Hb at 6 weeks postpartum, prevalence of anaemia in third trimester and at 6-week postpartum, severe anaemia postpartum, moderate anaemia during third trimester, moderate anaemia postpartum, moderate high Hb concentrations during third trimester Infant: birthweight, prevalence of low birthweight, perinatal mortality, neonatal mortality, infant deaths, small-for-gestational age

Notes	Supplementation with 1000 μg retinol equivalents vitamin A (control) daily and deworming treatment (albendazole 400 mg single dose) in the second and third trimester at were co-interventions for purposes of the analysis Unsupervised but trial personnel visited women twice each week to monitor supplement intake. Compliance during pregnancy measured by pill count was high (median 88%) and did not vary by groups. 98% of the women accepted the albendazole treatment at both times (second and third trimesters) Approximate 50% of women started supplementation before 9 weeks of gestational age Gestational age at start of supplementation: early gestational age (supplementation started before 20 week's gestation) Anaemic status at start of supplementation:unspecified/mixed anaemia status Daily iron dose: higher daily dose (60 mg or more elemental iron) Iron release formulation: normal release preparation/not specified Iron compound: ferrous fumarate Malaria setting: yes. As of 2011: Malaria risk due predominantly to *P. vivax* exists throughout the year in rural areas of the 20 Terai districts bordering India, with occasional outbreaks of *P. falciparum* from July to October inclusive. Seasonal transmission of *P. vivax* takes place in 45 districts of the inner Terai and mid hills. *P. falciparum* resistant to chloroquine and sulphadoxine-pyrimethamine reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Cluster-randomisation.
Allocation concealment (selection bias)	Low risk	Coded.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participant, provider and outcome assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 20% losses to follow-up.
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Low risk	Baseline characteristics did not differ by treatment group in age at baseline, socioeconomic status, parity, gestational age at enrolment, previous miscarriage. The level of compliance did not differ by groups

Cogswell 2003

Methods	RCT, 2 arms with individual randomisation.
Participants	275 legally competent, non-imprisoned, non-anaemic, low-income pregnant women at < 20 weeks of gestation with ferritin levels above 20 μg/L enrolled at the Cuyahoga County, MetroHealth Center, Supplemental Nutrition Program for Women, Infants and Children in Cleveland, Ohio, USA
Interventions	Participants were randomly assigned to 1 of 2 groups: group 1 received 1 gelatin capsule containing 30 mg of elemental iron (as ferrous sulphate) daily; group 2 received 1 placebo soft gelatin capsule daily for 119 days. Supplementation started at an average of 11 weeks of gestation until delivery
Outcomes	Maternal: prevalence of anaemia at 28 and 38 weeks, side effects, compliance to treatment, maternal weight gain, iron status (MCV, Hb concentration, serum ferritin, erythrocyte protoporphyrin concentrations at 28 and 38 weeks. Infant: birthweight, birth length, proportion of low birthweight, low birthweight and premature, small-for-gestational age Setting and health worker cadre: the intervention was performed by a dietician at the Cuyahoga County, MetroHealth Medical Center, Supplemental Nutrition Program for Women, Infants and Children in Cleveland, Ohio, United States of America
Notes	Unsupervised. Women were re-evaluated at 28 weeks of gestation, and according to Hb concentrations at that time were prescribed treatment following the Institute of Medicine guidelines for iron supplementation during pregnancy. Compliance was 63.4% and 65.2% in groups 1 and 2 respectively Gestational age at start of supplementation: early gestational age (supplementation started before 20 weeks' gestation) Anaemic status at start of supplementation: non-anaemic Daily iron dose: lower daily dose (30 mg of elemental iron) Iron release formulation: normal release preparation/unspecified Iron compound: ferrous sulphate Malaria setting: non-malarial setting. As of 2011: Malaria: no risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	By computerised random numbers.

Allocation concealment (selection bias)	Low risk	Placebo controlled trial. Randomisation by study data manager. The placebo and active treatment were indistinguishable and all staff were blind to group allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	Participant and care provider blinded. Laboratory and other staff assessing outcomes blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 20% lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Corrigan 1936

Methods	Quasi-randomised trial with allocation by odd or even numbers. 2-arm trial
Participants	200 normal pregnant women attending antenatal care clinic with 3-7 months of gestational age at Boston City Hospital, Boston, USA
Interventions	Participants were assigned a number in order. Patients who had been assigned an odd number received 0.2 g of ferrous sulphate (3 tablets daily to be taken after meals - total daily dose 0.6 g); patients with even numbers received placebo that were identical in appearance and size and contained lactose but not ferrous sulphate Supplements were from recruitment until delivery. Women who took less than 1 of the 2 tablets prescribed daily were excluded Setting and health worker cadre: the intervention was performed by physicians at the antepartum clinic of Boston City Hospital, Boston, Massachusetts, United States of America
Outcomes	Number of women with anaemia at 1-week postpartum. (Figures were also provided for the mean Hb level at 1-week postpartum but no SD was provided and we were not able to include these data in the analysis)
Notes	Mean Hb in the intervention group 117 g/L and 112 g/L in the control group Gestational age at start of supplementation: mixed gestational age Anaemic status at start of supplementation: not specified. Daily iron dose: higher daily dose (60 mg or more). Iron release formulation: not specified. Iron compound: ferrous sulphate. Malaria setting: non-malarial setting. As of 2011: Malaria: no risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quasi-randomised trial, odd/even numbers.
Allocation concealment (selection bias)	High risk	Alternate allocation.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Aplacebo was provided which was identical in appearance to the active treatment but it was not clear whether investigators were aware of group allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	200 women were randomised and it was stated that women that did not comply (that took on average less than 1 of the prescribed tablets daily) or in whom sepsis or haemorrhage developed during pregnancy, birth or the early postnatal period were excluded. It was not clear how many women were excluded for these reasons and it was not clear whether or not there was any ITT analysis
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	Most of the results were provided in graphs and were not simple to interpret and we have included all of these results in the analyses Women were described as similar at baseline. The denominators for results were not clear.

De Benaze 1989

Methods	RCT, 2-arm trial with individual randomisation.
Participants	191 non-anaemic pregnant women with 12-18 weeks of gestation attending antenatal care clinic at the Maternity at Poissy Hospital, Paris, France. Exclusion criteria included women who had taken iron or folate supplements in the prior 6 months and those with language barriers for proper communication. Supplementation started at 12-18 weeks until delivery.
Interventions	Participants were randomly allocated to 1 of 2 groups: group 1: daily intake of 45 mg of elemental iron (as ferrous betainate hydrochloride) (15 mg elemental iron per tablet) and group 2: placebo tablets Setting and health worker cadre: the intervention was performed by physicians at the Maternity Ward of Poissy Hospital, Poissy, France
Outcomes	Maternal: Hb, MCV, serum iron, total iron binding capacity, transferrin saturation, serum ferritin at baseline, at 5 months, at 7 months, at delivery and 2 months postpartum
Notes	Unsupervised. Serum ferritin values presented as arithmetic and geometric means. No SD in transformed ferritin values is presented. Women in the placebo group were prescribed treatment after delivery thus not allowing comparisons at 2 months postpartum among the groups. Compliance reported as good. Gestational age at start of supplementation: early gestational age (supplementation started before 20 weeks' gestation) Anaemic status at start of supplementation: non-anaemic. Daily iron dose: medium daily dose (45 mg elemental iron). Iron release formulation: normal release preparation/not specified Iron compound: ferrous betainate hydrochloride. Malaria setting: non-malarial setting. As of 2011: Malaria: no risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised but method used unclear.
Allocation concealment (selection bias)	Low risk	Placebo controlled trial. Active and placebo tablets were in identical packaging and packages were provided randomly
Blinding (performance bias and detection bias) All outcomes	Low risk	Participant and provider blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 20% losses to follow-up.
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Dommisse 1983

Methods	RCT, 2-arm trial with individual randomisation.
Participant	146 pregnant women with less than 20 weeks of gestation who had not received iron therapy recently attending the Peninsula Maternity Service, Department of Obstetrics and Gynecology, University of Cape Town, Groote Schuur Hospital, South Africa
Interventions	Participants were randomly allocated to receive either a multivitamin tablet twice a day or a multivitamin tablet in conjunction with a standard ferrous sulphate tablet twice a day providing a total of 120 mg of elemental iron daily Setting and health worker cadre: the intervention was performed by obstetricians and professional staff at the Peninsula Maternity Service of the Department of Obstetrics and Gynecology of the University of Cape Town and Groote Schuur Hospital in Cape Town, South Africa
Outcomes	Hb, PCV, MCV, MCHC, serum iron, transferrin, red cell folate, ferritin, iron storage depletion at baseline and at 36 weeks' gestation, compliance

Notes	Mean Hb and other outcomes at term were reported, but no SDs were provided. We have therefore not been able to include data from this trial in the review Gestational age at start of supplementation: early gestational age (supplementation started before 20 weeks' gestation) Anaemic status at start of supplementation: mixed/not specified Daily iron dose: higher daily dose (60 mg or more elemental iron) Iron release formulation: normal release preparation/not specified Iron compound: ferrous sulphate. Malaria setting: yes. As of 2011: Malaria risk due predominantly to *P. falciparum* exists throughout the year in the low altitude areas of Mpumalanga Province (including the Kruger National Park), Northern Province and north-eastern KwaZulu-Natal as far south as the Tugela River. Risk is highest from October to May inclusive. Resistance to chloroquine and sulphadoxine-pyrimethamine reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly allocated."
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	High risk	146 were randomised but when compliance was assessed as poor or doubtful, the participant was excluded from the trial. 21 patients were excluded for poor or doubtful compliance and 20 patients delivered before 36th weeks' gestation. Only 105 completed the trial
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Eskeland 1997

Methods	RCT, 3-arm trial with individual randomisation.
Participants	90 healthy non-anaemic pregnant women with singleton pregnancy of less than 13 weeks, attending an inner city maternity centre in Bergen, Norway and willing to participate. Exclusion criteria: uncertain gestational age according to menstrual history, Hb concentration < 110 g/L, chronic disease or pregnancy complications (hypertension, diabetes, bleeding), multiple pregnancy, liver enzymes out of normal range and logistic difficulties foreseen at baseline (moving out of area)
Interventions	Participants were randomly allocated to 1 of the following: group 1: 3 tablets containing 1.2 mg heme iron from porcine blood and 9 mg of elemental iron (as ferrous fumarate) (Hemofer®) and 1 placebo tablet (total 27 mg elemental iron a day); group 2: 1 tablet containing 27 mg elemental iron (as iron fumarate) with 100 mg vitamin C (Collet®) and 3 placebo tablets; or group 3: 4 placebo tablets. Supplementation started at 20th week until 38-40th week. Setting and health worker cadre: the intervention was performed by midwives and physicians at an inner city maternity centre in Bergen, Norway
Outcomes	Maternal: Hb, erythrocytes count, HCT, MCV, MCH, MCHC, reticulocytes, serum iron, total iron binding capacity, serum transferrin, erythrocyte protoporphyrin at baseline and at 20, 28, 38 weeks, 8 weeks postpartum, and 6 months postpartum; pregnancy complications: hypertension, pre-eclampsia, forceps, postpartum haemorrhage, maternal well being and breastfeeding duration. Infant: birthweight and length.
Notes	Unsupervised. Only groups 1 and 3 (placebo) were included in this review. Compliance was 81% and 82% in groups 1 and 3 respectively. Gestational age at start of supplementation: late gestational age (supplementation started at or after 20 weeks' gestation) Anaemic status at start of supplementation: non-anaemic. Daily iron dose: lower daily dose (less than 30 mg elemental iron daily) Iron release formulation: normal release preparation/not specified Iron compound: iron fumarate. Malaria setting: non-malarial setting. As of 2011: Malaria: no risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated.

Allocation concealment (selection bias)	Low risk	This was a placebo controlled trial.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participant and care provider blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	23% and 21% in groups included.
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Falahi 2010

Methods	RCT-2 arms with individual randomisation
Participants	148 non-anaemic pregnant women, 20-35 years of age with gestational age less than 20 wk, primigravidae, body mass index less than 25 and less than 30 and Hb concentrations lower than 110 g/L and serum ferritin higher than 20 μg/L who visited the gynaecology centre in Khorramabad city, Lorestan Province, Western Iran. Participants who had diabetes mellitus, renal disease, coronary heart disease, or reported having used multivitamins and minerals, drugs or being on a special diet were excluded
Interventions	Participants were randomly allocated to 1 of to groups: group 1 (n = 70) received tablets containing 60 mg elemental iron (as ferrous sulphate) and group 2 (n = 78) received placebo tablets until delivery. Women who were anaemic or iron deficient were referred for medical evaluation and treated Setting and heath worker cadre: the intervention was performed by physicians at a gynaecology centre in Khorramabad city, Lorestan Province, Western Iran
Outcomes	Hb concentration, serum ferritin at baseline, week 28 and at delivery; birth weight, birth length, pregnancy duration
Notes	Gestational age at start of supplementation: early gestational age (supplementation started less than 20 weeks' gestation) Anaemic status at start of supplementation: non-anaemic. Daily iron dose: high daily dose (60 mg elemental iron daily) Iron release formulation: normal release preparation/not specified Iron compound: ferrous sulphate. Malaria setting: yes. As of 2011: Malaria risk due to *P. vivax* and *P. falciparum* exists from March to November inclusive in rural areas of the provinces of Hormozgan and Kerman (tropical part) and the southern part of Sistan-Baluchestan. *P. falciparum* resistant to chloroquine and sulphadoxine-pyrimethamine reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Low risk	This was a placebo controlled trial.
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo controlled trial. It was described as "triple-blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	148 women were randomised. It was not clear whether any women were lost to follow-up or if there were any missing data
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	Groups appeared comparable at baseline.

Fenton 1977

Methods	Quasi-randomised trial, 2 arms with individual randomisation
Participants	154 pregnant women with less than 14 weeks of gestation, and who had not received or were receiving treatment for a blood disorder at clinic in Cardiff, United Kingdom
Interventions	Participants were divided into 2 groups according to the day in which they attended the clinic in Cardiff: group 1 received 60 mg of elemental iron (as ferrous sulphate) daily and group 2 received no iron supplement Setting and health worker cadre: the intervention was performed by physicians at the Antenatal Clinic of the Welsh National School of Medicine at the University Hospital of Wales, Cardiff, United Kingdom
Outcomes	Hb concentration, MCV, serum ferritin, serumiron and total iron binding capacity were measured at 10-14 week and at term
Notes	The data in the paper are presented with no SD values. No data can be extracted from the publication for this review Gestational age at start of supplementation: early gestational age Anaemic status at start of supplementation: mixed/unspecified anaemia status Daily iron dose: higher daily dose (60 mg or elemental iron) Iron release formulation: normal release preparation/not specified Iron compound: ferrous sulphate. Malaria setting: non-malarial setting. As of 2011: Malaria: no risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	By day of clinic attendance.
Allocation concealment (selection bias)	High risk	By day of clinic attendance.
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women appear to be accounted for in the analyses; separate figures are provided for women in the control arm who received supplements
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Fleming 1974

Methods	RCT with randomisation by blocks of 50 consecutive participants into 5 arms
Participants	146 consecutive pregnant women attending a public antenatal clinic in Western Australia before the 20th week of gestation who had not received iron supplements and were willing to participate. Women with Hb < 100.0 g/L were excluded
Interventions	Participants were randomly assigned in sequences of 50 to 1 of the 5 interventions groups: group 1 received placebo; group 2 received 60 mg of elemental iron (as ferrous sulphate); group 3 received 500 μg (0.5 mg) of folic acid; group 4 received 60 mg of elemental iron (as ferrous sulphate) and 500 μg (0.5 mg) of folic acid; and group 5 received 60 mg of elemental iron (as ferrous sulphate) and 5000 μg (5 mg) of folic acid. Supplementation with iron was from 20th week of gestation until delivery. All women had received 50 mg of ascorbic acid daily from the first visit until the 20th week Setting and health worker cadre: the intervention was performed by obstetricians at a public antenatal clinic in western Australia. Patients were of a low socio-economic status
Outcomes	Hb, serum and red cell folate, serum vitamin B_{12} at first attendance, and at 20 week, 28, 35 week and at delivery, and 6 weeks postpartum; pregnancy complications, anaemia defined as Hb lower than 100 g/L, premature delivery, abortion, compliance; birthweight, placental weight, Apgar score at delivery (full outcome data were not reported for group 5, which received a higher dose of folic acid)
Notes	More than 20% of the women were lost to follow-up. We decided not to include outcome data for mean Hb at term, as the SDs provided in the paper represent a single SD for all groups and this assumes that distributions were similar in each treatment group Gestational age at start of supplementation: late gestational age (supplementation started at or after 20 weeks' gestation) Anaemic status at start of supplementation: mixed/unspecified anaemia status Daily iron dose: higher daily dose (60 mg elemental iron). Iron release formulation: normal release preparation/unspecified Iron compound: ferrous sulphate. Malaria setting: non-malarial setting. As of 2011: Malaria: no risk

Risk of bias

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk	"they were allotted according to randomised sequences of 50"
Allocation concealment (selection bias)	Unclear risk	Not clear, women were provided with colour-coded packages which identified the regimes
Blinding (performance bias and detection bias) All outcomes	Low risk	It was stated that the contents of the treatment packages were not known to women or investigators until after the completion of the trial
Incomplete outcome data (attrition bias) All outcomes	High risk	146 women randomised., 89 women completed the trial and women were removed from the trial for reasons that may have related to outcomes (e.g. women developed anaemia)
Selective reporting (reporting bias)	Unclear risk	There was high attrition in this trial and data were not reported for all treatment groups
Other bias	Unclear risk	No other bias apparent.

Fleming 1985

Methods	RCT, 5 arms with individual randomisation.
Participants	200 apparently healthy primigravidae Hausa women living in Zaria, Nigeria and planning to deliver in Zaria, with less than 24 weeks of gestation, who had not taken any antimalarial treatment or iron supplements in current pregnancy
Interventions	Participants were randomly assigned to 1 of 5 groups: group 1: received no active treatment; group 2: received chloroquine 600 mg base once, followed by proguanil 100 mg per day; group 3 received in addition to chloroquine and proguanil, 60 mg elemental iron daily; group 4 received in addition to chloroquine and proguanil, 1000 μg (1 mg) of folic acid daily, and group 5: in addition to chloroquine and proguanil received 60 mg of elemental iron and 1000 μg (1 mg) of folic acid daily Setting and health worker cadre: the intervention was performed by an obstetrician working with a Hausa-speaking social worker in Zaria
Outcomes	Full blood count, malarial parasites, serum and red cell folate, at first attendance, 28 week and 36 weeks gestational age, at delivery, and at 6 week postpartum, serumvitamin B_{12} at first attendance and at 36 weeks gestational age, Hb electrophoresis and fetal microscopy once, and bone marrow at delivery, clinical malaria
Notes	Relevant groups are: group 3 vs group 2 for comparison 2: daily oral supplementation with iron alone vs no treatment/placebo group 4 vs group 5 for comparison 4: daily oral iron + folic acid supplementation vs daily oral folic acid alone (without iron) supplementation Results were not reported separately for each randomised group and we have been unable to include data from this trial in the review Gestational age at start of supplementation: mixed gestational age (up to 24 weeks' gestation) Anaemic status at start of supplementation: mixed/unspecified anaemia status Daily iron dose: higher daily dose (60 mg elemental iron). Iron release formulation: normal release preparation/unspecified Iron compound: not clear. Malaria setting: yes. Described as a malaria endemic area: 28% of *P falciparum* in the sample and 40% of those anaemic. As of 2011: Malaria risk due predominantly to *P. falciparum* exists throughout the year in the whole country. Resistance to chloroquine and sulphadoxine-pyrimethamine reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random numbers table.
Allocation concealment (selection bias)	Low risk	Treatment allocation code; "Neither the researchers nor the patients were aware of the treatment allocated until after the completion of the study."
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and researchers blinded. Placebos were provided which were packaged so that they "could not be distinguished by sight"
Incomplete outcome data (attrition bias) All outcomes	High risk	Women that were excluded because they developed anaemia or "defaulted"; were replaced. Further loss to follow up occurred during the trial; it was not clear how many women were followed up at each data collection point. 89 out of 200 women randomised delivered in the hospital and no complete, clear data could be extracted for the outcomes of interest in this review

Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Foulkes 1982

Methods	Quasi-randomised trial, 2 arms with individual randomisation
Participants	568 apparently healthy pregnant women with less than 20 weeks of pregnancy and no prior iron supplementation
Interventions	Participants were allocated alternatively to receive 100 mg of elemental iron and 350 μg (0.35 mg) folic acid daily or no treatment
Outcomes	Ferritin and Hb concentrations were measured at baseline and at 28 and 36 weeks of gestation and 2 days postpartum. MCV and MCH were measured at 2 days postpartum. Number of women developing anaemia in the 2nd and 3rd trimester was reported (Hb < 105 g/L) Setting and health worker cadre: the intervention was performed by obstetricians at Southmead Hospital in Bristol, United Kingdom
Notes	Only means and median are presented for continuous outcomes. No SDs are reported and for ferritin concentrations no ln-transformed data are presented. Limited data were extractable from the paper and subsequent communication with the author. The paper reported the number of women developing Hb < 105 g/L from the start of supplementation to delivery. No data were extracted from this trial Gestational age at start of supplementation: early gestational age (supplementation started before 20 weeks' gestation) Anaemic status at start of supplementation: mixed/unspecified anaemia status Daily iron dose: higher daily dose (60 mg or more elemental iron) Iron release formulation: normal release preparation/unspecified Iron compound: not clear. Malaria setting: non-malarial setting. As of 2011: Malaria: no risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Alternation.
Allocation concealment (selection bias)	High risk	Alternate allocation.
Blinding (performance bias and detection bias) All outcomes	High risk	No placebos provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	537 women randomised, then 67 excluded post-randomisation for reasons that may have related to outcomes (non-compliance). Subsequent loss to follow-up was not clear as denominators were not reported in the text or figures
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Freire 1989

Methods	RCT, 2 arms with individual randomisation.
Participants	412 non-black pregnant women with 26 ± 2 weeks of gestation, who had not received iron supplements in the previous 6 months, from low SES using the prenatal unit of public obstetric hospital in Quito, Ecuador
Interventions	Participants were randomly assigned to receive 2 tablets containing 78 mg of elemental iron (as ferrous sulphate) daily or placebo during a period of 2 months Setting and health worker cadre: the intervention was performed by physicians in the Prenatal Unit of Quito's public obstetric hospital in Quito, Ecuador
Outcomes	Hb, PCV, red cell indices, serumferritin, total iron binding capacity, serumfolate, serum vitamin B_{12} at baseline and after 2 months. Prevalence of iron deficiency was estimated by response to therapy
Notes	Apart from mean Hb levels at term no other prespecified outcomes from this review are presented in the paper. No data can be extracted from this trial

	Gestational age at start of supplementation: late gestational age (supplementation started after 20 weeks' gestation) Anaemic status at start of supplementation: mixed/unspecified anaemia status Daily iron dose: high daily dose (60 mg or more elemental iron) Iron release formulation: normal release preparation/unspecified Iron compound: ferrous sulphate. Malaria setting: non-malarial setting. The study was conducted in Quito where there is no risk of malaria. As of 2011: Malaria risk - *P. vivax* (87%), *P. falciparum* (13%) - exists throughout the year below 1500 m, with moderate transmission risk in coastal provinces. There is no risk in Guayaquil, Quito and other cities of the inter-Andean region. *P. falciparum* resistance to chloroquine and sulphadoxine-pyrimethamine reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described ("randomly assigned").
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as "double-blind", placebo tablets provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	412 women were recruited and 240 followed up. Loss to follow-up was 41.7% and there were missing data for some outcomes
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Groner 1986

Methods	RCT, 2 arms, individual randomisation.
Participants	40 pregnant women attending antenatal care at the Adolescent Pregnancy Clinic and Obstetrics Clinics at the John Hopkins and Sinai Hospital in Baltimore, Maryland, USA at or before 16 weeks of pregnancy with HCT equal or above 31%. 2 women objected to the randomisation and 13 dropped out of the study. Both groups received multiple micronutrients. Supplementation lasted a month
Interventions	Participants were randomly assigned to 1 of 2 groups: group 1 (n = 16) received 60 mg of elemental iron (as ferrous fumarate) and prenatal vitamins daily; or group 2 (n = 9) received only the prenatal vitamins with no iron Setting and health worker cadre: the intervention Setting and health worker cadre: the intervention was performed by physicians at the Adolescent Pregnancy Clinic and Obstetrics Clinic of Johns Hopkins and Sinai Hospitals in Baltimore, Maryland, United States of America
Outcomes	Psychometric tests (arithmetic, total digit span, digit symbol, vocabulary and others) were performed and hematologic status was measured at baseline and after a month
Notes	Haematologic outcomes cannot be extracted from the paper. None of the other outcomes were sought Gestational age at start of supplementation: early gestational age (supplementation started before 20 weeks' gestation) Anaemic status at start of supplementation: mixed/unspecified anaemia status Daily iron dose: higher daily dose (60 mg or more elemental iron) Iron release formulation: normal release preparation/unspecified Iron compound: ferrous fumarate. Malaria setting: non-malarial setting. As of 2011: Malaria: no risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	"Each subject was handed an unlabeled bottle of capsules… The test administrator was also unaware of the content of the capsules distributed."

Incomplete outcome data (attrition bias) All outcomes	High risk	15 of the 40 women randomised were not followed up. Group size at follow up was not balanced (16 vs 9)
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Han 2011

Methods	Quasi-randomised control trial with 3 arms and individual allocation to groups by order of enrolment
Participants	153 anaemic pregnant women 12 to 24-wk gestation, age range 20-30 years, with 80≤ Hb <110 g/L, no dietary supplements use during the previous 2 months and no abnormal pregnancy response recruited from the communities of Shen county, Shandong province, China
Interventions	Participants were allocated to 1 of the 3 groups in the order of enrolment: group 1 (n = 51) was the placebo control; group 2 (n = 51) received supplement daily containing 60 mg elemental iron (as ferrous sulphate); group 3 (n = 51) received a supplement daily containing 60 mg elemental iron (as NaFeEDTA). The capsules were labelled in red, yellow and blue colour and manufactured by Hurun's company (a Chinese food-additive company, Beijing). The intervention lasted 2 months. Women were visited at home once each week by the village nurse to replenish supplements and to monitor compliance by counting and recording the number of supplements that were taken Setting and health worker cadre: the intervention was performed by village nurses in house visits to the participants in the communities of Shen county, Shandong province, China
Outcomes	Hb concentration; plasma iron; soluble transferrin receptor; total iron-binding. capacity; Malondialdehyde; superoxide dismutase; glutathione peroxidase
Notes	The participants in the placebo group in this study were given iron supplementation with NaFeEDTA or foods rich in iron, such as the hemachrome-iron from animal foodstuff, such as meat, fish and sea foods, immediately after the trial Gestational age at start of supplementation: early gestational age (supplementation started before 20 weeks' gestation) Anaemic status at start of supplementation: anaemic status. Daily iron dose: higher daily dose (60 mg or more elemental iron) Iron release formulation: normal release preparation/unspecified Iron compound: ferrous sulphate and iron EDTA. Malaria setting: yes. As of 2011: Malaria risk, including *P. falciparum* malaria, exists in Yunnan and to a lesser extent in Hainan. *P. falciparum* resistance to chloroquine and sulphadoxine-pyrimethamine reported. Limited risk of *P. vivax* malaria exists in southern and some central provinces, including Anhui, Ghuizhou, Henan, Hubei, Jiangsu. There is no malaria risk in urban areas

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Individual allocation to groups by order of enrolment.
Allocation concealment (selection bias)	High risk	The capsules were labelled in red, yellow and blue colour and manufactured by Hurun's company (a Chinese food-additive company, Beijing)
Blinding (performance bias and detection bias) All outcomes	Low risk	Trial participants and the research team were unaware of the treatment assignment. The trial was unblinded after analysis of the primary outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete data were available for 147 women, 96.1% of the original number of 153 pregnant women
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Low risk	The groups did not differ in age, gestational stage, gravidity, haematological status, levels of MDA, SOD and GSH-Px at baseline

Hankin 1963

Methods	Quasi-randomised trial, 2 arms with individual randomisation

Participants	174 primigravidae or secundigravidae at their first visit at the antenatal Clinic of Queen Elizabeth Hospital in Woodville, Australia with ability to write and speak English
Interventions	Participants were divided into a supplemented group receiving a daily dose of 100 mg of elemental iron (as ferrous gluconate) or a control group that was un supplemented. Supplementation started during 2nd trimester and ending time is unclear Setting and health worker cadre: the intervention was performed by physicians at the Queen Elisabeth Hospital in Woodville, South Australia
Outcomes	Maternal: Hb and HCT at 20-30 week, 30-40 week, at 5 days, at 6 week and at 3 months postpartum. Infant: Hb from umbilical cord, at 6 week, at 3 months and at 6 months of age (not reported)
Notes	Unsupervised. Compliance not reported. Gestational age at start of supplementation: mixed/unspecified gestational age Anaemic status at start of supplementation: mixed/unspecified anaemia status Daily iron dose: higher daily dose (60 mg or more elemental iron) Iron release formulation: normal release preparation/unspecified Iron compound: ferrous gluconate. Malaria setting: non-malarial setting. As of 2011: Malaria: no risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quasi-randomised, alternate by day of the week.
Allocation concealment (selection bias)	High risk	Alternate allocation.
Blinding (performance bias and detection bias)	High risk	Open.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 5% excluded.
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Harvey 2007

Methods	RCT, 2 arms, individual randomisation.
Participants	13 apparently healthy non-anaemic non-smokers pregnant women aged 18-40 years and < 14 weeks of gestation with singleton pregnancy recruited through local medical practitioners and the Maternity Department of the Norfolk and Norwich University Hospital, England, United Kingdom
Interventions	Participants were randomly assigned to 1 of 2 groups: group 1 received 100 mg elemental iron (as ferrous gluconate) daily after food and group 2 received a placebo. Supplementation started at 16th week of gestation until delivery Setting and health worker cadre: The intervention was performed by midwives and obstetricians at Maternity Department of the Norfolk and Norwich University Hospital in Norwich, United Kingdom
Outcomes	Maternal: Hb, serum ferritin, transferrin receptor, plasma zinc, exchangeable zinc pool, zinc excretion and zinc absorption at 16, 24 and 34 weeks of gestation. Infant: birthweight (not reported).
Notes	Unsupervised. Compliance not reported. Gestational age at start of supplementation: early gestational age (supplementation started before 20 weeks' gestation) Anaemic status at start of supplementation: non-anaemic. Daily iron dose: higher daily dose (60 mg or more elemental iron) Iron release formulation: normal release preparation/unspecified Iron compound: ferrous gluconate. Malaria setting: non-malarial setting. As of 2011: Malaria: no risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Coded bottles were provided by manufacturer.
Allocation concealment (selection bias)	Low risk	Supplied in coded opaque bottles.

Blinding (performance bias and detection bias) All outcomes	High risk	Participant blinded. Care provider and outcome assessor unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up.
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Hemminki 1991

Methods	RCT, 2 arms, individual randomisation.
Participants	2994 pregnant women with less than 16 weeks of gestation attending 15 communal maternity centres and 12 centres in 5 neighbouring communities in Tampere, Finland who consented to participate. Exclusion criteria included: chronic illness, anaemia (HCT under 0.32 or Hb < 110 g/L), late arrival, likelihood of moving away from the area before child birth, or twin pregnancies
Interventions	Participants were randomly assigned to 1 of 2 policy groups: group 1 (routine) were recommended to take 100 mg elemental iron alone (iron compounds and dosage varied as per midwife recommendation) daily after the 16th week of gestation; or group 2 (selective) who received no iron supplements. Women in the selective group who had a HCT of < 0.30 (Hb < 100 g/L) on 2 consecutive visits were provided 100 mg elemental iron (as ferrous sulphate) to be taken 1 tablet (50 mg) twice a day for 2 months or until HCT increased to 0.31 (Hb 100 g/L) Setting and health worker cadre: the intervention was performed by general practitioners, midwives and public health nurses at no-cost communal maternity centres in towns surrounding Tampere, Finland
Outcomes	Maternal: HCT at 28th and 36th week of gestation, weight increase (kg), systolic and systolic blood pressure at 36^{th} week, proteinuria, HCT at 28^{th} and 36^{th} week of gestation, overall estimation of health, symptoms of tiredness, sick days, fever, adverse effects from iron supplements, symptoms related to iron supplements, duration of first stage of labor, caesarean section, blood transfusion, fever I hospital, postpartum stay in hospital for more than 7 days, not breastfeeding in postpartum check up, spontaneous abortions, length of gestation in week, proportion of premature births Infant: birthweight, low birthweight, death, perinatal mortality, 1 min Apgar score < 7, special care unit, malformations, infections, hyperviscosity as a discharge diagnosis, weight gain, overall health
Notes	Average iron intake in the routine group was 124 mg elemental iron a day. 32 women were excluded: 20 twin pregnancies, 4 discovered not to be pregnant, and 8 for other (unintentional) reasons. Of the remaining 2912, 218 participants miscarried. Final samples were therefore 2694: 1336 women in the routine iron group and 1358 women in the selective group The limit to prescribe treatment on the selective group was changed in the middle of the study to HCT < 0.31 (Hb < 105 g/L) after the 33^{rd} week of gestation. Compliance assessed daily through self-reporting. Women in the routine group who reported not having taken the iron supplements during the preceding 2 weeks was only 8.2% at 28^{th} week of gestation and 14% at 36 weeks. It is reported that 7.4% of mothers in the selective group (i.e. no iron unless anaemic) reported having taken iron either regularly or “every now and then” in the preceding 2 weeks, at 28^{th} week of gestation, while this proportion increased to 14% in the 36^{th} week. Gestational age at start of supplementation: early gestational age (supplementation started before 20 weeks’ gestation) Anaemic status at start of supplementation: non-anaemic at the start of supplementation Daily iron dose: higher daily dose (60 mg or more elemental iron) Iron release formulation: normal release preparation/unspecified Iron compound: not clear/varied. Malaria setting: non-malarial setting. As of 2011: Malaria: no risk

Risk of bias

Bias	**Authors’ judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random codes created by computer in blocks of 10 by maternity centre
Allocation concealment (selection bias)	Low risk	Sealed numbered envelopes stored in containers from which midwives were asked to take them in order
Blinding (performance bias and detection bias) All outcomes	High risk	Neither participants nor provider blinded. Outcome assessor blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 5% lost to follow-up.
Selective reporting (reporting bias)	Low risk	There is insufficient information to permit judgement.

Other bias	Unclear risk	No other bias apparent.

Hoa 2005 (C)

Methods	Randomisation may have been by cluster (communes) rather than individual women. Block randomised trial with 4 arms
Participants	202 apparently healthy pregnant women 20-32 years of age attending health clinics from 12 communes in Dong HungDistrict, Thai Binh Province, Vietnam with 14-18 weeks of gestation who agreed to participate in the study were selected to participate
Interventions	Participants were assigned through block randomly assigned to 1 of 4 interventions: group 1 (n = 44) received 400 ml fortified milk with iron (ferrous fumarate), 17.5 mg vitamin C and 200 μg (0.2 mg) folic acid daily; group 2 (n = 41) received 400 ml of fortified milk containing 17.5 mg vitamin C and 200 μg (0.2 mg) folic acid but no iron daily; group 3 (n = 40) received 1 tablet containing 60 mg of elemental iron (as ferrous sulphate) and 250 μg (0.25 mg) folic acid daily and group 4 (n = 43) received 1 placebo tablet daily Setting and health worker cadre: the intervention was performed by community health workers working from a commune health centre operated by the National Ministry of Health in the rural delta area of the Red River in northern Vietnam (Dong Hung District, Thai Binh Province)
Outcomes	Hb at baseline, 5 , 10, 16 weeks after start of the study, total iron-binding capacity, serum transferrin saturation, anaemia, iron deficiency, weight, presence of hookworms
Notes	For purposes of this review groups 3 vs group 4 comparing iron and folic acid supplements are relevant. However, no data on outcomes of interest could be extracted from the published report. It was reported in the paper that the "decrease in haemoglobin concentration in the supplemented groups was significantly less"; and that, "the transferrin saturation level increased slightly in the supplement group" Gestational age at start of supplementation: early gestational age (supplementation started before 20 weeks' gestation) Anaemic status at start of supplementation: unspecified/mixed anaemia status Daily iron dose: higher dose (60 mg of elemental iron). Iron release formulation: normal release preparation/unspecified Iron compound: ferrous sulphate. Malaria setting: yes. As of 2011: Malaria risk due predominantly to *P. falciparum* exists in the whole country, excluding urban centres, the Red River delta, the Mekong delta, and the coastal plain areas of central Viet Nam. High-risk areas are the highland areas below 1500 m south of 18 N, notably in the 4 central highlands provinces Dak Lak, Dak Nong, Gia Lai and Kon Tum, Binh Phuoc province, and the western parts of the coastal provinces Khanh Hoa, Ninh Thuan, Quang Nam and Quang Tri. Resistance to chloroquine, sulphadoxine-pyrimethamine and mefloquine reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It was not clear whether individual women or communes were randomised "For practical reasons it was possible to implement only 1 type of intervention per commune (block randomly adjusted)"
Allocation concealment (selection bias)	Unclear risk	Little information about study methods was provided.
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo supplements were provided but it was not clear whether the health workers supervising distribution were aware of whether the women were receiving active or placebo treatment. Outcome assessment may have been partly blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up not described.
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Low risk	Groups appeared comparable at baseline.

Holly 1955

Methods	RCT, 3 arms with individual randomisation.
Participants	207 pregnant women with less than 26 weeks of gestation and Hb > 100 g/L attending antenatal care clinic in Nebraska, USA
Interventions	Participants were randomly assigned to 1 of 3 groups: group 1 received 1 g of an iron salt daily; group 2 received 0.8-1.2 g of ferrous sulphate and 60-90 mg of cobalt chloride daily, and group 3 received no treatment. Supplementation started at various times before 26th week of gestation for each of the participants until delivery Setting and health worker cadre: the intervention was performed by obstetricians at the Department of Obstetrics and Gynecology of the Univeristy of Nebraska, College of Medicine in Omaha, Nebraska, United States of America

Outcomes	Maternal: Hb, HCT, serum iron, erythrocyte protoporphyrin at 3-6 months and predelivery
Notes	Unsupervised. 3 iron compounds (n = 94) were used: ferrous gluconate (n = 40), ferrous sulphate (n = 32) and Mol-Iron® (n = 22). The iron treated groups with different iron salts were merged together by the author as iron treated group since the results were comparable. The iron and cobalt treatment group is not included in this review. Compliance not reported. Gestational age at start of supplementation: mixed gestational age at the start of supplementation (before 26 weeks) Anaemic status at start of supplementation: mixed anaemia status (Hb > 100 g/L) Daily iron dose: higher daily dose (60 mg or more elemental iron) Iron release formulation: normal release preparation/not specified Iron compound: mixed (groups merged in analysis). Malaria setting: non-malarial setting. As of 2011: Malaria: no risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	High risk	Neither participants nor provider blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up not described.
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Hood 1960

Methods	RCT, 3 arms, individual randomisation.
Participants	75 consecutive apparently healthy pregnant women with 32-34 weeks of gestation attending the maternity clinic at St Anthony's Hospital, Oklahoma City, Oklahoma, USA
Interventions	Participants were randomly divided in 3 groups: group 1 served as control and received no treatment; group 2 received 220 mg elemental iron (as ferrous sulphate) daily; and group 3 received 55 mg elemental iron (as sustained release ferrous sulphate) daily. Supplementation started at 32-34 week of gestation until delivery Setting and health worker cadre: the intervention was performed by obstetricians at the Department of Obstetrics and Gynecology of St. Anthony's Hospital in Oklahoma City, Oklahoma, United States of America
Outcomes	Maternal: Hb, HCT, incidence and severity of side effects on a weekly basis until delivery
Notes	Unsupervised. For any iron vs no treatment comparison groups were merged. Compliance not reported. Gestational age at start of supplementation: late gestational age (supplementation started after 20 weeks' gestation) Anaemic status at start of supplementation: unspecified/mixed anaemia Daily iron dose: medium dose (55 mg elemental iron) and higher dose (220 mg elemental iron) Iron release formulation: sustained release preparation and normal release preparation/not specified Iron compound: ferrous sulphate and sustained release ferrous sulphate Malaria setting: non-malarial setting. As of 2011: Malaria: no risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	High risk	Neither participant nor provider blinded. Outcome assessor unclear

Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 20% losses to follow-up.
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Kerr 1958

Methods	RCT, 4 arms with individual randomisation.
Participants	430 apparently healthy women with 24-25 weeks of singleton pregnancy and Hb equal or above 104 g/L attending antenatal clinic at Simpson Memorial Maternity Pavillion, Edinburgh, United Kingdom
Interventions	Participants were randomly allocated to 1 of 4 groups: group 1 received 35 mg of elemental iron (as ferrous sulphate) 3 times a day; group 2 received 35 mg of elemental iron (as ferrous gluconate) 3 times a day; group 3 received 35 mg of elemental iron (as ferrous gluconate) with 25 mg of ascorbic acid, 3 times a day; group 4 received placebo. Supplementation started at 24-25th week of gestation until term Setting and health worker cadre: the intervention was performed by physicians at the Simpson Memorial Maternity Pavilion in Edinburgh, United Kingdom
Outcomes	Maternal: Hb, red cell count, HCT at baseline and at 37th week
Notes	Unsupervised. Groups 1 and 2 were merged for analysis. Group 3 was not used in this review. Compliance not measured. Gestational age at start of supplementation: late gestational age (supplementation started after 20 weeks' gestation) Anaemic status at start of supplementation: unspecified/mixed anaemia status (no severe anaemia, all had Hb equal or above 104 g/L) Daily iron dose: higher iron dose (all treatment groups received more than 60 mg of elemental iron daily (105 mg)) Iron release formulation: norm,al release preparation/unspecified Iron compound: ferrous gluconate. Malaria setting: non-malarial setting. As of 2011: Malaria: no risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	By cards shuffle.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	High risk	Participant blinded. Provider blinded to treatments but not to controls. Outcome assessor unclear
Incomplete outcome data (attrition bias) All outcomes	High risk	23% of participants were lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Kuizon 1979

Methods	RCT, 4 groups (with supplementation depending on Hb levels at baseline) individual randomisation
Participants	385 pregnant women attending antenatal care at government health centres in Greater Manila area, Philippines. Mean gestation at recruitment was approximately 21 weeks until delivery. Women were assessed at baseline and women with anaemia (Hb < 120 g/L in 1st and < 110 g/L in 2^{nd} trimester) received a higher dose of supplements.
Interventions	Participants were randomly assigned to 1 of 4 groups: group 1 received placebo (anaemic and non-anaemic women received 1 placebo capsule); group 2 received 65 mg of elemental iron (as 325 mg ferrous sulphate) women received either 1 or 3 oral tablets daily; group 3 received 100 mg ascorbic acid (either 1 or 3 oral tablets daily); group 4 received 65 mg elemental oral iron (as ferrous sulphate) plus 100 mg ascorbic acid - women received either 1 or 3 tablets

	Supplementation started from recruitment in 1st and second trimester until delivery. Setting and health worker cadre: the intervention was performed by health centre staff at government health centres and maternity clinics in the greater Manila area, Manila, Phillipines
Outcomes	Mean Hb concentration at 32 and 39 weeks (for women anaemic and not anaemic at baseline) Haematiocrit at 32 and 39 weeks, serum iron at 32 and 39 weeks, transferring saturation levels at 32 and 39 weeks
Notes	Attrition in this study was very high (half of the women were lost to follow-up by 32 weeks' gestation and more than 75% by term). For this reason we have not included data from this study in our data and analyses tables Gestational age at start of supplementation: mixed gestational age at the start of supplementation (mean gestation at start of supplementation was 21 weeks) Anaemic status at start of supplementation: mixed anaemia status (dose depended on Hb level at baseline) Daily iron dose: higher daily dose (greater than 60 mg of elemental iron daily) Iron release formulation: normal release preparation/unspecified Iron compound: ferrous sulphate. Malaria setting: yes. As of 2011: Malaria risk exists throughout the year in areas below 600 m, except in the 22 provinces of Aklan, Albay, Benguet, Biliran, Bohol, Camiguin, Capiz, Catanduanes, Cavite, Cebu, Guimaras, Iloilo, Northern Leyte, Southern Leyte, Marinduque, Masbate, Eastern Samar, Northern Samar, Western Samar, Siquijor, Sorsogon, Surigao Del Norte and metropolitan Manila. No risk is considered to exist in urban areas or in the plains. *P. falciparum* resistant to chloroquine and sulphadoxine-pyrimethamine reported. Human *P. knowlesi* infection reported in the province of Palawan.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	"randomly assigned".
Blinding (performance bias and detection bias) All outcomes	High risk	Placebo was provided but women received different doses (and number of tablets). It was not clear if outcome assessment was blind
Incomplete outcome data (attrition bias) All outcomes	High risk	Very high attrition. 679 women recruited. In non-anaemic women, 189/385 followed up (49%). In anaemic group 146/294 (50%) followed up at 32 weeks by 39 weeks only 94/385 non-anaemic women followed up (24%) and 60 in anaemic group (20%)
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	High risk	The reasons for the very high levels of attrition were not explained (except that some women delivered before term). The very high loss to follow-up means that results are very difficult to interpret

Lee 2005

Methods	RCT, 5 arms with individual randomisation.
Participants	154 apparently healthy pregnant women seeking prenatal care in Gwangju, South Korea during first trimester of pregnancy who did not receive other supplements or medications throughout pregnancy and who were willing to participate
Interventions	Participants were randomly allocated to 1 of 5 groups: group 1 received 30 mg elemental iron (as ferrous sulphate) and 175 μg (0.17 mg) folic acid daily from first trimester until delivery; group 2 received 60 mg of elemental iron (as ferrous sulphate) with 350 μg (0.35 mg) of folic acid from first trimester until delivery; group 3 received 30 mg elemental iron (as ferrous sulphate) and 175 μg (0.17 mg) of folic acid from 20th week of gestation until delivery; group 4 received 60 mg elemental iron (as ferrous sulphate) and 350 μg (0.35 mg) of folic acid from 20th week of gestation until delivery; or control group with no supplement Setting and health worker cadre: the intervention was performed by physicians at a hospital and health centre in Gwangju, Korea
Outcomes	Maternal: Hb, HCT, serum ferritin, serum soluble transferrin receptor concentrations at baseline and during first, second, third trimester of pregnancy and at delivery
Notes	Unsupervised. Compliance not reported. included in comparison 3: daily iron + folic acid vs no treatment/placebo and only different groups included in the subgroup analysis by gestational age at start of supplementation (early (group 1+ group 2); late (group 3 + group 4); and by iron dose: low (group 1 + group 3); higher (group 2 + group 4) Gestational age at start of supplementation: mixed gestational ages (different arms started supplementation before or after 20 weeks' gestation) Anaemic status at start of supplementation: mixed/unspecified anaemia status Daily iron dose: mixed (with different arms receiving lower (30 mg) and higher (60 mg) of elemental iron daily Iron release formulation: normal release preparation/unspecified Iron compound: ferrous sulphate. Malaria setting: yes. As of 2011: Limited malaria risk due exclusively to *P. vivax* exists mainly in the northern areas of Gangwon-do and Gyeonggi-do Provinces and Incheon City (towards the Demilitarized Zone or DMZ)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Described as "truly random" but the method was not stated.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	High risk	Participant, provider and outcome assessor blinding unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 20% lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Liu 2000

Methods	RCT with 3-arms, and individual randomisation.
Participants	300 pregnant women with 24 - 28 weeks of gestation with no had organic disease and Hb level higher than 100 g/L who received antenatal examinations in Second Affiliated Hospital, Zhujiang Hospital, the First Military Medical University, Guangzhou, China from January 1998 to January 1999
Interventions	Participants were randomly assigned to 1 of 3 groups: group 1 received 1 table daily containing 100 mg elemental iron (as ferrous sulphate sustained-release) with 500 mg vitamin C and B-complex vitamins (amounts not reported) administered orally for 4 consecutive weeks; group 2 received conventional iron supplement (as 300 mg ferrous sulphate) administered 3 times a day to meals for 4 consecutive weeks; and group 3 did not receive any iron supplementation Setting and health worker cadre: intervention and outcome assessment were conducted by physicians from the Obstetric & Gynecology Department, Zhujiang Hospital, the First Military Medical University, Guangzhou, China
Outcomes	RBC, Hb and serum ferritin at baseline at after 4 weeks of intervention and before delivery. Anaemia, iron deficiency, fatigue, dizziness, shortness of breath, and palemucous membranes and skin, tinnitus, presence of stomatitis or glossitis, premature birth, average Apgar score, congenital malformations. Side effects reported: nausea and loss of appetite, severe gastrointestinal reactions including vomiting, abdominal pain, and diarrhoea, metallic taste in the mouth, black staining of their teeth. Blood tests and serum ferritin measurement were performed for the gravidas after 4 and 8 weeks of supplementation and before delivery. The Apgar scoring and physical examinations were performed for the newborns after delivery
Notes	Gestational age at start of supplementation: late gestational age (supplementation started at 20 weeks' gestation or later). Only groups included in the comparisons are group 2 and group 3 who did not receive supplements Anaemic status at start of supplementation: non-anaemic. Daily iron dose: high daily dose (60 mg or more mg iron daily) Iron release formulation: normal and slow release preparation for group 1 (not included in the comparisons in this review) Iron compound: ferrous sulphate. Malaria setting: yes. As of 2011: Malaria risk, including *P. falciparum* malaria, exists in Yunnan and to a lesser extent in Hainan. *P. falciparum* resistance to chloroquine and sulphadoxine-pyrimethamine reported. Limited risk of *P. vivax* malaria exists in southern and some central provinces, including Anhui, Ghuizhou, Henan, Hubei, Jiangsu. There is no malaria risk in urban areas

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as randomised but method unclear.
Allocation concealment (selection bias)	Unclear risk	There is insufficient information to permit judgement.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported in the paper.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data reported as complete for all the participants reported as randomised

Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Low risk	There were no significant differences in terms of age, gestational age, body weight, and H level among the 3 groups (all P > 0. 05)

Ma 2010

Methods	RCT with 4 arms including a placebo and individual randomisation
Participants	164 anaemic pregnant women (80 g/L , Hb ,110 g/L), 12-24 weeks gestation and 20-35 years old recruited between March 2004 and September 2006 from the community hospitals of Shen County in the central area of China
Interventions	Participants were randomly allocated to 1 of 4 groups for this 2-month intervention in the order of recruitment: group 1 (n = 41) received placebo; group 2 (n = 41) received 60 mg elemental iron (as ferrous sulphate); group 3 (n = 41) received 60 mg elemental iron (as ferrous sulphate) and 400 μg (0.4 mg) folic acid daily; and group 4 (n = 41) received 60 mg elemental iron (as ferrous sulphate), and 400 μg (0.4 mg) folic acid, 2 mg retinol and 1 mg riboflavin daily Setting and health worker cadre: In each community, a local female community health worker called ‘village nurse’ was responsible for the recruitment and distribution of the supplements. Women were recruited from the community hospitals and then home-visited once a week by the village nurse to replenish supplements and to monitor compliance by counting and recording the number of supplements that were taken. The nurse also provided counselling about the possible side effects
Outcomes	Hb, plasma iron, ferritin, folic acid, retinol riboflavin after the 2 months intervention. Other outcomes included membrane fluidity, oxidative stress markers such as GSH-Px, SOD, and MDA
Notes	This study is included but does not provide any data that can be useful; for purposes of this review Gestational age at start of supplementation: unspecified or mixed gestational ages at the start of supplementation Anaemic status at start of supplementation: anaemic. Daily iron dose: high daily dose (60 mg or more mg iron daily) Iron release formulation: normal. Iron compound: ferrous sulphate. Malaria setting: yes. Malaria as of 2011: Malaria risk, including *P. falciparum* malaria, exists in Yunnan and to a lesser extent in Hainan. *P. falciparum* resistance to chloroquine and sulphadoxine-pyrimethamine reported. Limited risk of *P. vivax* malaria exists in southern and some central provinces, including Anhui, Ghuizhou, Henan, Hubei, Jiangsu. There is no malaria risk in urban areas

Risk of bias

Bias	**Authors’ judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Quasi-randomised as participants were randomly allocated to 1 of 4 groups for this 2-months intervention in the order of recruitment: group
Allocation concealment (selection bias)	Unclear risk	Tretaments were colour coded. It was stated that the code was not revealed until after the analysis
Blinding (performance bias and detection bias) All outcomes	Low risk	It was stated that women and staff were blind to treatment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	164 women were randomised and 145 (88%) were included in the analysis
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Makrides 2003

Methods	RCT, 2 arms with individual randomisation.
Participants	430 non-anaemic pregnant women attending antenatal clinics at Women’s and Children’s Hospital in Adelaide, Australia with singleton or twin pregnancies and informed consent. Exclusion criteria: diagnosis of thalassaemia, history of drug or alcohol abuse and history of vitamin and mineral preparations containing iron prior to enrolment in study
Interventions	Participants were randomly assigned to receive 1 tablet containing 20 mg of elemental iron daily between meals from week 20 until delivery or a placebo tablet

	Setting and health worker cadre: the intervention was performed by Pediatricians and Obstetricians in a maternity hospital in Adelaide, Australia
Outcomes	Maternal: Hb concentration at 28 week, at delivery, and at 6 months postpartum; ferritin concentration at delivery and at 6 months postpartum; maternal gastrointestinal side effects at 24 and 36 weeks of gestation; serum zinc at delivery and at 6 months postpartum; maternal well being at 36 week of gestation, at 6 weeks and at 6 months postpartum; pregnancy outcomes: type of birth, blood loss at delivery, gestational age. At 4 years postpartum: general health of mothers using the SF-36, a self-administered questionnaire that assesses 8 concepts of health. Infant: birthweight, birth length, birth head circumference, Apgar scores, and level of nursery care. Follow-up at 4 years: intelligence quotient (IQ) using Stanford-Binet Intelligence Scale, child behaviour using Strength and Difficulties Questionnaire parent report form
Notes	Unsupervised but monthly phone calls to encourage compliance. If anaemia was detected in the routine 28 week blood sample or if the clinician considered her Hb too low the woman was advised to purchase and take a high-dose iron supplement (containing > 80 mg elemental iron per tablet) until the end of pregnancy. Compliance was 86% and 85% in the iron and placebo groups respectively Gestational age at start of supplementation: late gestational age (supplementation started at 20 weeks' gestation or later) Anaemic status at start of supplementation: non-anaemic. Daily iron dose: lower daily dose (less than 30 mg iron daily) (20 mg) Iron release formulation: normal release preparation. Iron compound: not clear. Malaria setting: non-malarial setting. As of 2011: Malaria: No risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence with balanced blocks and stratified for parity
Allocation concealment (selection bias)	Low risk	Opaque bottles marked with sequential numerical code prepared by the Pharmacy Department of Women's & Children's Hospital
Blinding (performance bias and detection bias) All outcomes	Low risk	Participant and care provider blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 20% lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Meier 2003

Methods	RCT, 2 arms with individual randomisation.
Participants	144 non-iron deficient adolescents 15-18 years old in their first pregnancy and adult women 19 or older in their first or greater pregnancy attending prenatal care at Marshfield Clinic, Wisconsin, USA
Interventions	Participants were randomly assigned to receive once daily 60 mg of elemental iron (as ferrous sulphate) or a placebo. All women received 1000 μg (1 mg) of folic acid daily
Outcomes	Maternal: prevalence of iron-deficiency anaemia, compliance to treatment, side effects, vomiting, nausea, constipation, diarrhoea, caesarean section, serum ferritin and Hb concentrations at 24-28 weeks' gestation and at 36-40 weeks' gestation. infant: perinatal morbidity and mortality, birthweight, birth length, Apgar scores at 1 and 5 minutes, admission to neonatal unit, prevalence of birthweight Setting and health worker cadre: the intervention was performed at multicenter clinic in central Wisconsin
Notes	Unsupervised. All adolescents and adult pregnant women who developed iron-deficiency anaemia at 24-28 weeks' gestation were offered 60 mg elemental iron 3 times a day. Compliance was assessed through pill counts and ranged from 32% to 124% (median 95.5% in iron supplemented group and 87.4% in placebo group Gestational age at start of supplementation: unspecified/mixed gestational age Anaemic status at start of supplementation: non-anaemic. Daily iron dose: higher daily dose (60 mg elemental iron daily) Iron release formulation: normal release preparation/unspecified Iron compound: ferrous sulphate. Malaria setting: non-malarial setting. As of 2011: Malaria: No risk

Risk of bias

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Stratified by age group.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participant and provider blinded. Outcome assessor unclear.
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 20% lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Menendez 1994 (C)

Methods	Cluster randomised trial, 2-arm trial.
Participants	550 multi gravidae pregnant women with less than 34 weeks of gestation attending antenatal care clinics in 18 villages near the town of Farafenni, in North Bank Division, Gambia where malaria is endemic with high transmission during 4-5 months a year
Interventions	Participants were allocated randomly by compound of residence to receive 60 mg of elemental iron (as ferrous sulphate) or placebo. All pregnant women received a weekly tablet of 5000 μg (5 mg) of folic acid but no antimalarial chemoprophylaxis. Supplementation started at 23-24 weeks until delivery. Setting and health worker cadre: the intervention was performed by traditional birth attendants in villages in the North Bank Division of The Gambia within the national village-based primary health care program
Outcomes	Maternal: Hb concentrations at baseline, 4-6 weeks before delivery and 1 week postpartum; plasma iron, total iron binding capacity, transferrin saturation, deposition of malaria pigment in placenta. Infant: birthweight within 7 days of delivery.
Notes	Unsupervised. Malaria prophylaxis is provided to primigravidae in The Gambia. 30 women with PCV less than 25% after enrolment (17 in iron group and 13 in placebo) were treated and withdrawn from study and analysis. Additionally 29 women (7 in iron and 22 in placebo group) had PCV below 25% at the second visit and were also withdrawn from study. No differences in the prevalence and severity of peripheral blood or placental malaria infection. No increase in the susceptibility to malaria infection in the 2 groups. Compliance: estimated tablet consumption was 81.1 and 81.7 tablets in the iron and placebo groups respectively Gestational age at start of supplementation: late gestational age (more than 20 week's gestation at the start of supplementation) Anaemic status at start of supplementation: unspecified/mixed anaemia status Daily iron dose: higher daily dose (60 mg daily). Iron release formulation: normal release preparation/unspecified Iron compound: ferrous sulphate. Malaria setting: high malaria risk area. As of 2011: Malaria risk due predominantly to *P. falciparum* exists throughout the year in the whole country. Resistance to chloroquine and sulphadoxine-pyrimethamine reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised but method unclear.
Allocation concealment (selection bias)	High risk	Not described. Active treatment and placebo were different colours
Blinding (performance bias and detection bias) All outcomes	High risk	Participant and provider not blinded. Outcome assessor blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 20% lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Milman 1991

Methods	RCT 2 arms with individual randomisation.
Participants	248 healthy Caucasian Danish women attending Birth Clinic in Copenhagen, Denmark within 9-18 weeks of gestation and normal pregnancy. Exclusion criteria: complicated delivery, excessive smoking (> 9 cigarettes/day)
Interventions	Participants were randomly assigned to receive 66 mg of elemental iron (as ferrous fumarate) daily (n = 121) or placebo (n = 127) until delivery. Supplementation started at 8-9th week until delivery. Setting and health worker cadre: the intervention was performed by obstetricians at the Birth Clinic of the Department of Obstetrics, Herning Hospital in Copenhagen, Denmark
Outcomes	Maternal: Hb, HCT, erythrocyte indices, iron status, serum ferritin, serum transferrin saturation, serum erythropoietin at baseline and every 4th week until delivery, and 1-8 weeks after delivery in subsample; pregnancy complications. Infant: birthweight, serum ferritin, transferrin saturation and serum erythropoietin in umbilical cord
Notes	Unsupervised. Of the 248 women, 20 placebo and 21 iron treated were excluded by the authors in some of the analysis for the following reasons: withdrawn consent, 10; uterine bleeding episodes, 5; placental insufficiency, placenta praevia and abruptio placenta, 7; preeclampsia, 3; partus prematurus, 5; excessive smoking, 3. Sample size has been adjusted for ITT. Compliance: number of tablets consumed was 159 +/− 38 and 93 +/−43 tablets in the iron treated and placebo groups respectively Gestational age at start of supplementation: early gestational age (less than 20 weeks' gestation at the start of supplementation) Anaemic status at start of supplementation: mixed anaemia status at baseline Daily iron dose: higher daily dose (60 mg or more of elemental iron daily) Iron release formulation: normal release preparation/unspecified Iron compound: ferrous fumarate. Malaria setting: non-malarial setting. As of 2011: Malaria: No risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participant and provider blinded. Outcome assessor unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 20% lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Ouladsahebmadarek 2011

Methods	RCT with 2-arms and individual randomisation
Participants	960 healthy women at first trimester of pregnancy with Hb > 120 g/L and blood pressure < 140/90 mmHg from Alzahra University dependent hospital in Vanak, Tehran, Iran
Interventions	Participants were randomly assigned to 1 of 2 groups: group 1 received daily 1 multiple micronutrient + 30 mg elemental iron from week 13 of gestation until delivery; group 2 received daily 1 daily multiple micronutrient + placebo tablet from 13 weeks of pregnancy until delivery Setting and health worker cadre: the intervention was conducted by obstetricians and gynaecologists from the Alzahra hospital, in Iran
Outcomes	Hb concentrations, HCT, serum iron, serum ferritin, total iron binding capacity at baseline and at delivery , birth weight, gestational age at birth, prematurity, Intrauterine growth retardation, 1′ Apgar score, 5 min Apgar score, admission duration in neonatal care intensive unit, premature rupture of membranes, placenta abruption, pre-eclampsia, periventricular-intraventricular haemorrhage (PIH), gestational diabetes, intrauterine fetal death (IUFD), oligohydramnios
Notes	Both groups were matched for mother's age, body mass index, parity, previous obstetric history and iron parameters Gestational age at start of supplementation: early gestational age (less than 20 weeks' gestation at the start of supplementation) Anaemic status at start of supplementation: non-anaemic status at the start of supplementation Daily iron dose: 30 mg elemental iron. Iron release formulation: normal release preparation/not specified

	Iron compound: not specified. Malaria setting: yes. As of 2011: Malaria risk due to *P. vivax* and *P. falciparum* exists from March to November inclusive in rural areas of the provinces of Hormozgan and Kerman (tropical part) and the southern part of Sistan-Baluchestan. *P. falciparum* resistant to chloroquine and sulphadoxine-pyrimethamine reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and care provider were blinded to the intervention groups. Outcome assessor not described,
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 56 loses to follow-up in the group 1 (iron) in comparison to 49 participants lost to follow-up in the placebo group. 70/480 (14.6%) were excluded in the group 1 in comparison to 108/480 (22. 5%) in the placebo group. Overall attrition was 18%
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Paintin 1966

Methods	RCT, 3 arms with individual randomisation.
Participants	180 primigravidae women with less than 20 weeks' gestation and Hb > 100 g/L attending antenatal clinic in Aberdeen Maternity Hospital, United Kingdom
Interventions	Participants were randomly assigned to 1 of 3 groups: group 1 received 3 tablets containing 4 mg elemental iron each (total 12 mg daily); group 2 received 3 tablets containing 35 mg elemental iron (total 105 mg elemental iron daily) and group 3 received placebo. Intervention was from week 20 to week 36 of gestation Setting and health worker cadre: the intervention was performed by clinic and laboratory staff of the Obstetric Medicine Research Unit of Aberdeen Maternity Hospital and Castle Terrace Antenatal Clinic in Aberdeen, United Kingdom
Outcomes	Maternal: Hb, HCT at baseline, and at weeks 20, 30, 36 of gestation and 7-13 days postpartum; plasma volume at 30 weeks, total red cell volume, serum iron and total iron binding capacity at 30 weeks, subjective health and side effects at 30 weeks
Notes	Unsupervised. Compliance estimated by measuring tablets returned. Authors report good compliance Gestational age at start of supplementation: late gestational age (20 weeks' gestation at the start of supplementation) Anaemic status at start of supplementation: unspecified/mixed anaemia status at the start of supplementation Daily iron dose: mixed doses (lower dose group - 12 mg daily; higher dose group 105 mg daily) Iron release formulation: normal release preparation/not specified Iron compound: not specified. Malaria setting: non-malarial setting. As of 2011: Malaria: No risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Low risk	Placebo controlled with sequentially numbered packages.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participant and provider blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 5%.

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Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Preziosi 1997

Methods	RCT 2 arms with individual randomisation.
Participants	197 healthy pregnant women 17-40 years of age, with 28 +/− 3 weeks of gestation attending antenatal care clinic in a Mother-Child Health Center in Niamey, Niger
Interventions	Participants were randomly assigned to 1 of 2 groups: group 1 received 100 mg of elemental iron (as ferrous betainate) daily; group 2 received placebo. Supplementation was from 28 +/− 3 weeks of gestation until delivery Setting and health worker cadre: the intervention was performed by physicians at an isolated, urban maternal and child health centre serving low- or middle-class villagers in Niger
Outcomes	Maternal: Hb concentration, MCV, HCT, erythrocyte protoporphyrin, serum iron, transferrin, total iron binding capacity, serum ferritin concentrations, at baseline and at the first stage of labor and at 3 and 6 months postpartum, prevalence of iron deficiency and iron-deficiency anaemia. Infant: birthweight and length, Hb concentration, MCV, erythrocyte protoporphyrin, serum iron, transferrin saturation, serum ferritin concentrations at birth and at 3 and 6 months; Apgar scores
Notes	Supervised by physicians who recorded tablet consumption. Compliance not reported. Gestational age at start of supplementation: late gestational age (more than 20 weeks' gestation) Anaemic status at start of supplementation: mixed anaemia status at baseline Daily iron dose: higher daily dose (more than 60 mg elemental iron daily) Iron release formulation: normal release preparation/not specified Iron compound: ferrous betainate. Malaria setting: high risk malaria setting. As of 2011: Malaria risk due predominantly to *P. falciparum* exists throughout the year in the whole country. Chloroquine-resistant *P. falciparum* reported.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	By random numbers.
Allocation concealment (selection bias)	Low risk	Packages of tablets numbered by manufacturer.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participant and provider blinded. Outcome assessor blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up not described.
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Pritchard 1958

Methods	RCT 3 arms with individual randomisation.
Participants	172 pregnant women believed to be in the second trimester of pregnancy by date of last menstrual period attending antenatal care clinic in Parland Memorial Hospital, Dallas, Texas, USA
Interventions	Participants were randomly assigned to 1 of 3 interventions: group 1 received 1000 mg of iron intramuscularly as iron-dextran; group 2 received 112 mg of elemental iron (as ferrous gluconate) daily in 3 tablets; group 3 received placebo tablets. Supplementation started during 2nd trimester until delivery. Setting and health worker cadre: the intervention was performed by physicians at a prenatal clinic in the United States of America
Outcomes	Maternal: Hb concentration at baseline and at delivery.

Notes	Unsupervised. Only groups 2 (oral iron) and 3 (placebo) were included in this review. Compliance not reported. Gestational age at start of supplementation: mixed gestational age at the start of supplementation (2nd trimester) Anaemic status at start of supplementation: mixed anaemia status at baseline Daily iron dose: higher daily dose (more than 60 mg elemental iron) Iron release formulation: normal release preparation/unspecified Iron compound: ferrous gluconate. Malaria setting: non-malarial setting. As of 2011: Malaria: No risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	High risk	Neither participant no provider blinded. Outcome assessor not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up not described (no loss to follow-up apparent)
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	High risk	No other bias apparent.

Puolakka 1980

Methods	RCT, 2 arms with individual randomisation.
Participants	32 healthy non-anaemic pregnant women attending antenatal care at maternity centres of Oulu University Central Hospital, Finland with uncomplicated pregnancy of less than 16 weeks, and no earlier haematological problems
Interventions	Participants were randomly assigned to 1 of 2 groups: group 1 received 200 mg of elemental iron (as ferrous sulphate) daily; group 2 received no treatment. Supplementation started at 16th week of gestation until 1 month postpartum Setting and health worker cadre: the intervention was performed by obstetricians at maternity centres in Oulu, Finland
Outcomes	Maternal: Hb, HCT, red cell count, leucocyte count, reticulocytes, MCV, MCH, serum iron, total iron binding capacity, transferrin, vitamin B12, whole folate, and serum ferritin concentration at baseline, and at weeks, 16, 20, 24, 28, 32, 36, 40 and 5 days, 1, 2, and 6 months postpartum. Bone marrow aspirates at 16th and 32nd week and at 2 months postpartum. Infant: birthweight, Apgar scores at 5 minutes.
Notes	Unsupervised. Compliance not reported. Gestational age at start of supplementation: early gestational age (supplementation started before 20 weeks' gestation) Anaemic status at start of supplementation: non-anaemic. Daily iron dose: higher daily dose (more than 60 mg elemental iron daily) Iron release formulation: normal release preparation/not specified Iron compound: ferrous sulphate. Malaria setting: non-malarial setting. As of 2011: Malaria: No risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	"randomly divided into two groups".
Blinding (performance bias and detection bias) All outcomes	High risk	Open.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 20% lost to follow-up. It was stated that no women discontinued the study

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Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Romslo 1983

Methods	RCT, 2 arms with individual randomisation.
Participants	52 healthy pregnant women attending outpatient Women's clinic at Haukeland Hospital, Bergen, Norway within first 10 weeks of a normal singleton pregnancy with uncomplicated delivery at 37-42 weeks
Interventions	Participants were randomly assigned to 1 of 2 groups: group 1 received 200 mg of elemental iron (as ferrous sulphate) daily; group 2 received placebo. Supplementation started at 10 weeks of gestation. Setting and health worker cadre: the intervention was performed by physicians at the outpatient clinic of the Women's Clinic, Haukeland Hospital in Bergen, Norway
Outcomes	Maternal: Hb, HCT, PCV, erythrocyte count, leucocyte count, MCV, MCH, MCHC, serumiron, iron binding capacity, erythrocyte protoporphyrin, serum ferritin at baseline and every month during 2nd trimester and every 2 weeks until delivery. Infant: birthweight and Apgar scores.
Notes	Unsupervised. Compliance measured by tablet count was 55% in the iron-treated group Gestational age at start of supplementation: early gestational age (less than 20 weeks' gestation at the start of supplementation) Anaemic status at start of supplementation: non-anaemic. Daily iron dose: higher daily dose (more than 60 mg elemental iron daily) Iron release formulation: normal release preparation/unspecified Iron compound: ferrous sulphate. Malaria setting: non-malarial setting. As of 2011: Malaria: No risk

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	"randomly divided into two groups".
Blinding (performance bias and detection bias) All outcomes	High risk	Participant blinded. Provider and outcome assessor unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 20%. (7/52 lost to follow-up).
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Siega-Riz 2001

Methods	RCT, 2 arms with individual randomisation.
Participants	429 non-anaemic iron replete women with less than 20 weeks of gestation attending who had not taken supplements containing iron in the last month, with a singleton pregnancy attending the prenatal clinic at the Wake County Human services in Raleigh, North Carolina, USA
Interventions	Participants were randomly assigned to 1 of 2 groups: group 1 received multivitamin/mineral supplements containing 30 mg of iron (as ferrous sulphate) daily or group 2 received multivitamin/mineral supplements containing 0 mg of iron (no iron) until 29 weeks of gestation. Supplementation started on average at 12 weeks. The multivitamin/ mineral supplement contained the following: 4000 IU vitamin A; 400 IU vitamin D; 70 mg vitamin C; 500 μg (0.5 mg) folic acid;1.5 mg thiamine; 1.6 mg riboflavin; 17 mg niacin; 2.6 mg vitamin B_6 ; 2.5 μg vitamin B_1; 200 mg calcium; 100 mg magnesium; 1.5 mg copper; 15 mg zinc. Folic acid supplements were prescribed for all women who had received the positive pregnancy test until the first prenatal visit Setting and health worker cadre: the intervention was performed by physicians at a clinic serving patients of a low socioeconomic group in Raleigh, North Carolina, United States of America
Outcomes	Maternal: prevalence of anaemia, iron repletion and iron-deficiency anaemia at 26-29 weeks, side effects, compliance to treatment, iron status (Hb concentration, serumferritin at 26-29 weeks, preterm delivery.

	Infant: birthweight, proportion of low birthweight, small-for-gestational age
Notes	Unsupervised. Compliance measured by pill counts and a questionnaire and was 66% in the iron group and 63% in the control group. Compliance was also measured by the Medication Event Monitoring System (MEMS) in a subsample of 100 women Gestational age at start of supplementation: early gestational age (less than 20 weeks' gestation at the start of supplementation) Anaemic status at start of supplementation: non-anaemic. Daily iron dose: lower daily dose (30 mg or less elemental iron daily) Iron release formulation: normal release preparation/unspecified Iron compound: ferrous sulphate. Malaria setting: non-malarial setting. As of 2011: Malaria: No risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	By using random number generator.
Allocation concealment (selection bias)	Low risk	Tretament provided in coded bottles by pharmacy.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participant, provider and outcome assessor blinded to treatment
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 20% lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Simmons 1993

Methods	RCT, 3 arms with individual randomisation
Participants	376 pregnant women with ages between 16-35 years, with mild anaemia (Hb concentrations between 80-110 g/L) attending 8 maternal and child health centres in Kingston, St. Andrews and Spanish Town, Jamaica, with gestational age between 14-22 weeks
Interventions	Participants were randomly assigned to 1 of 3 groups: group 1 received 1 placebo tablet daily; group 2 received 100 mg of elemental iron (as ferrous sulphate) daily; group 3 received 50 mg of elemental iron (in a gastric delivery system capsule) daily. All women received 400 μg (0.4 mg) of folic acid Setting and health worker cadre: the intervention was performed by clinic nurses and field workers at maternal and child health centres in urban areas of Jamaica
Outcomes	Hb, HCT, MCV, white cell count, serum iron, total iron binding capacity, serum ferritin, serum transferrin receptor, at baseline, at 6 weeks and at 12 weeks after start of supplementation as well as side effects
Notes	Gestational ages differed in the participants and we have not included outcome data from this trial in the review Gestational age at start of supplementation: mixed gestational age (up to 22 weeks' gestation at recruitment) Anaemic status at start of supplementation: anaemic at the start of supplementation (mild anaemia Hb 80-110 g/L) Daily iron dose: mixed dose (medium dose group - 50 mg elemental iron in gastric delivery system capsule; higher dose group 100 mg of elemental iron) Iron release formulation: gastric delivery system capsule (controlled release preparation) Iron compound: ferrous sulphate. Malaria setting: yes. As of 2011: Very limited risk of *P. falciparum* malaria may occur in the Kingston St Andrew Parish.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	By random number table.
Allocation concealment (selection bias)	Low risk	Sealed envelopes distributed to clinics (not clear if envelopes were opaque)
Blinding (performance bias and detection bias) All outcomes	High risk	Women may have been unaware of group allocation but the 2 supplements and the placebo differed in appearance and this would be apparent to staff

Incomplete outcome data (attrition bias) All outcomes	High risk	376 women were recruited. 275 women were followed up (73.1%) but laboratory results were available for 66% of the original sample
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Low risk	The 3 groups were reported to have similar characteristics at baseline

Suharno 1993

Methods	RCT 4 arms with individual randomisation.
Participants	305 women randomised and follow-up data were available for 251 pregnant women aged 17-35 years, parity 0-4 and Hb concentrations between 80 and 109 g/L from rural villages in Bogor, West Java, Indonesia. Women recruited at 16-24 weeks' gestation
Interventions	Participants were randomly allocated to 1 of 4 groups: group 1 received 2.4 mg of retinol and 1 placebo iron tablet daily; group 2 received 60 mg of elemental iron (as ferrous sulphate) and a placebo vitamin A tablet daily; group 3 received 2.4 mg of retinol and 60 mg of elemental iron (as ferrous sulphate); and group 4 received 2 placebos for 8 weeks Setting and health worker cadre: the intervention was performed by village workers among middle and low socioeconomic groups in rural villages in Bogor, West Java, Indonesia
Outcomes	Hb, HCT, serum ferritin, serumiron, total iron binding capacity, serumretinol, transferrin saturation, at baseline and after 8 weeks of supplementation (2nd and 3rd trimester)
Notes	Relevant comparison in this review: group 3 (iron + vit A) vs group 1 (vit A but no iron) for comparison 5: daily oral iron + other vitamins and minerals supplementation vs daily oral same other vitamins and minerals (without iron) supplementation group 2 (iron + placebo) vs group 4 (placebo) for comparison 2: daily oral supplementation with iron alone vs no treatment/ placebo No prespecified outcome available for extraction. No data included Gestational age at start of supplementation: mixed gestational age at the start of supplementation (16-24 weeks' gestation) Anaemic status at start of supplementation: anaemic at the start of supplementation (Hb < 110 g/L) Daily iron dose: higher daily dose (60 mg elemental iron). Iron release formulation: normal release preparation/not specified Iron compound: ferrous sulphate. Malaria setting: highmalaria risk area. As of 2011: Malaria risk exists throughout the year in all areas of the 5 eastern provinces of East Nusa Tenggara, Maluku, North Maluku, Papua and West Papua. In other parts of the country, there is malaria risk in some districts, except in Jakarta Municipality, in big cities. *P. falciparum* resistant to chloroquine and sulphadoxine-pyrimethamine reported. *P. vivax* resistant to chloroquine reported. Human *P. knowlesi* infection reported in the province of Kalimantan.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Carried out by independent researcher.
Allocation concealment (selection bias)	Low risk	"Subjects were allocated a sequential number from 1 to 305. An independent researcher randomly labelled the iron and placebo preparations" which were colour coded
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo controlled trial "the code was revealed once the data or all analyses had been entered in the computer and cleaned up"
Incomplete outcome data (attrition bias) All outcomes	Low risk	305 women were randomised and follow-up data were available for 251 (83%). Reasons for loss to follow-up were described and were similar across groups
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Low risk	Groups appeared similar at baseline.

Sun 2010

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Methods	Quasi-randomised trial with individual assignment in order of enrolment
Participants	186 anaemic pregnant women, 12 to 24-wk gestation, age between 20-30 y with Hb concentration ≥80 and < 110 g/L, no dietary supplements during the previous 2 months and no abnormal pregnancy response from the communities of Shen County in a central rural area of China
Interventions	Participants were randomly allocated in the order of enrolment to 1 of 4 groups: group 1 (n = 47) was supplemented daily with 60 mg elemental iron (as ferrous sulphate); group 2 (n = 46) received with 60 mg elemental iron (as ferrous sulphate) and 400 μg (0.4 mg) folic acid; group 3 (n = 46) with 60 mg elemental iron (as ferrous sulphate), 2 mg retinol and 400 μg (0.4 mg) folic acid, and group 4 (n = 47) was the placebo control group. The capsules were coloured red, yellow, green and blue during manufacture by Hurun (a Chinese food-additive company, Beijing). The capsules were to be taken daily for 2 months Setting and health worker cadre: the study was carried out in communities of Shen County in a central rural area of China. Women were home-visited once a week by the village nurse to replenish supplements and to monitor compliance by counting and recording the number of supplements that were taken
Outcomes	Hb concentration; plasma iron; plasma retinol and plasma folate; erythrocyte protoporphyrin; interleukin 2; lymphocyte proliferation at baseline and after 2 months intervention
Notes	Relevant comparisons for this review: group 1 (n = 47) was supplemented daily with 60 mg elemental iron (as ferrous sulphate) vs group 4 (n = 47) was the placebo control group group 2 (n = 46) received with 60 mg elemental iron (as ferrous sulphate) and 400 μg (0.4 mg) folic acid vs group 4 (n = 47) was the placebo control group Gestational age at start of supplementation: mixed gestational age at the start of supplementation (12-24 weeks' gestation) Anaemic status at start of supplementation: anaemic at the start of supplementation (Hb < 110 g/L) Daily iron dose: higher daily dose (60 mg elemental iron). Iron release formulation: normal release preparation/not specified Iron compound: ferrous sulphate. Malaria setting: yes. As of 2011: Malaria risk, including *P. falciparum* malaria, exists in Yunnan and to a lesser extent in Hainan. *P. falciparum* resistance to chloroquine and sulphadoxine-pyrimethamine reported. Limited risk of *P. vivax* malaria exists in southern and some central provinces, including Anhui, Ghuizhou, Henan, Hubei, Jiangsu. There is no malaria risk in urban areas Supported by Danone Nutrition Institute China.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as randomly assigned but method unclear. It is reported that the assignment to the groups was done in order of enrolment
Allocation concealment (selection bias)	High risk	The capsules were coloured red, yellow, green and blue during manufacture and the assignment was done in order of enrolment
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants, care providers and outcome assessors were blinded to the intervention groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low losses to followed up and they were balanced among the groups
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Low risk	There were no substantial differences between the groups in any of the baseline characteristics

Svanberg 1975

Methods	RCT, 2 arms with individual randomisation.
Participants	60 healthy primiparous women attending antenatal care clinic in Goteborg, Sweden with uncomplicated pregnancy and less than 14 weeks of gestation and with Hb concentrations above 120 g/L who had not received iron supplements in the previous 6 months or parenteral iron at any previous time. Women whose Hb concentration fell below 100 g/L during the study period were excluded and received immediate therapy
Interventions	Participants were randomly allocated to receive 200 mg of elemental iron (as a sustained release preparation of ferrous sulphate) daily or placebo from 12 weeks of gestation until 9 weeks post delivery Setting and health worker cadre: the intervention was performed by physicians at the University of Göthenburg in Sweden
Outcomes	Maternal: iron absorption measurements; Hb concentration, HCT, bone marrow haemosiderin, MCHC, total iron binding capacity, transferrin saturation at baseline, and at weeks 16, 20, 24, 28, 32, and 35; and 8-10 weeks after delivery
Notes	Unsupervised. Compliance measured by remaining pills count was 86 +/− 3%. Gestational age at start of supplementation: early gestational age (less than 20 weeks' gestation at the start of supplementation)

	Anaemic status at start of supplementation: non-anaemic. Daily iron dose: higher dose (more than 60 mg elemental iron daily) Iron release formulation: sustained release preparation of ferrous sulphate Iron compound: ferrous sulphate. Malaria setting: non-malarial setting. As of 2011: Malaria: No risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias)	Low risk	Participants blind, care provider blind and outcome assessor blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 20% lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Taylor 1982

Methods	RCT, 2 arms with individual randomisation
Participants	48 healthy pregnant women with no adverse medical or obstetric history attending antenatal care clinic in Newcastle, England, United Kingdom before 12 weeks of gestation
Interventions	Participants were randomly allocated to 1 of 2 groups: group 1 receive about 65 mg elemental iron (as 325 mg of ferrous sulphate) and 350 μg (0.35 mg) of folic acid daily from 12 weeks until delivery and group 2 received no supplements Setting and health worker cadre: the intervention was performed by physicians at the Princess Mary Maternity Hospital in Newcastle upon Tyne, United Kingdom
Outcomes	Maternal: Hb concentration, serum ferritin, MCV at 12 weeks and every 4 weeks until delivery, and at 6 days, 6 weeks and 6 months after delivery; plasma volume at 12 and 36 weeks of gestation. Infant: birthweight, infant death, admission to special care unit
Notes	Unsupervised. Compliance not reported. Gestational age at start of supplementation: early gestational age (less than 20 weeks' gestation at the start of supplementation) Anaemic status at start of supplementation: mixed/unspecified anaemia status Daily iron dose: higher daily dose (more than 60 mg elemental iron daily) Iron release formulation: normal release preparation/unspecified Iron compound: ferrous sulphate. Malaria setting: non-malarial setting. As of 2011: Malaria: No risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	"Randomly assigned".
Blinding (performance bias and detection bias) All outcomes	High risk	Open.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 20% lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Tholin 1993

Methods	RCT, 3-arm trial with individual randomisation.
Participants	83 healthy nulliparous non-vegetarian, non-anaemic pregnant women with serum ferritin concentrations above 10 μg/L
Interventions	Participants were randomly assigned to 1 of 3 groups: group 1 received 100 mg of elemental iron (as ferrous sulphate) daily; group 2 received placebo, and group 3 received dietary advice only Setting and health worker cadre: the intervention was performed by physicians at the Maternal Health Unit of Ostersund Hospital in Ostersund, Sweden
Outcomes	Blood Hb, serum ferritin and blood manganese were determined at baseline before 15th week of gestation, between 25-28 weeks, and between 35-40 weeks of gestation. Median and ranges are presented
Notes	The aim of this study was to examine the relationship between iron and zinc levels during pregnancy. No outcomes were extractable from this report for this review. Median serum zinc levels were reported by randomisation group "levels did not differ between groups". Median Hb levels were reported for women who had normal vs complicated deliveries (rather than by randomisation group. Results for mean Hb and serum ferritin levels were depicted in graphs Gestational age at start of supplementation: early gestational age at the start of supplementation (supplementation started before 20 weeks' gestation) Anaemic status at start of supplementation: non-anaemic. Daily iron dose: higher daily dose (more than 60 mg elemental iron daily) Iron release formulation: normal release preparation/unspecified Iron compound: ferrous sulphate. Malaria setting: non-malarial setting. As of 2011: Malaria: No risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as "randomly assigned".
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo controlled trial with outcome assessment by an obstetrician blind to group assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were some discrepancies in the figures reported in 2 study publications. (We have not included data from this trial in the review.)
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	High risk	Results were not simple to interpret and some results were not reported according to randomisation group

Tura 1989

Methods	RCT, 2 arms with individual randomisation.
Participants	254 non-anaemic non-iron deficient healthy pregnant women from multiple centres in Italy between 12-16 week of gestation. Exclusion criteria: acquired or congenital anaemia, haemoglobinopathies, thalassaemia, medically or surgically treated cardiopathy, abortion, hypertension, gastric resection, metabolic or endocrine disorder, hepatic or renal disease, epilepsy or another neurological disease, previously treated for cancer, alcohol or substance dependence
Interventions	Participants were randomly assigned to receive 40 mg of elemental iron (containing 250 g of ferritin in a micro granulated gastric resistant capsule) daily or no treatment from 12-16 weeks of gestation until the end of puerperium Setting and health worker cadre: The intervention was performed by physicians in health centres in Italy
Outcomes	Maternal: Hb concentration, red cell count, MCV, serumiron, total transferrin, transferrin saturation, serum ferritin at 12-16 weeks, 2 times during pregnancy, at 38-42 weeks, and at puerperium 48-52 weeks
Notes	Unsupervised. The study included another sample of women who were iron deficient and received 2 forms of iron preparation. This sample is not used in this review. Compliance reported as higher than 98.5%. Gestational age at start of supplementation: early gestational age (supplementation started before 20 weeks' gestation) Anaemic status at start of supplementation: non-anaemic. Daily iron dose: medium iron dose (more than 30 and less than 60 mg) Iron release formulation: micro granulated gastric resistant capsule Iron compound: not specified. Malaria setting: non-malarial setting. As of 2011: Malaria: No risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	By random number lists.
Allocation concealment (selection bias)	Low risk	Sealed envelopes progressively numbered.
Blinding (performance bias and detection bias) All outcomes	High risk	Open.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 20% loss to follow-up.
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Van Eijk 1978

Methods	RCT, 2 arms with individual randomisation.
Participants	30 pregnant women with uncomplicated pregnancies and deliveries attending antenatal care clinic at the University Hospital Obstetric Unit in Rotterdam, Netherlands
Interventions	Participants received 100 mg of elemental iron (as ferrous sulphate) daily or no treatment from the third month of gestation until delivery. Follow-up was until 12 weeks after delivery Setting and health worker cadre: the intervention was performed by physicians at the Univeristy Hospital Obstetrical Clinic in Rotterdam, the Netherlands
Outcomes	Maternal: Hb concentration, serum iron, serum ferritin, transferrin concentration at baseline and every 3-4 weeks until delivery, and 3 months after delivery. Infant: Hb concentration, transferrin, serum iron, serum ferritin in cord blood at term
Notes	Unsupervised. Compliance not reported. Gestational age at start of supplementation: early gestational age (supplementation started before 20 weeks' gestation) Anaemic status at start of supplementation: mixed/unspecified anaemia status Daily iron dose: higher daily dose (more than 60 mg elemental iron daily) Iron release formulation: normal release preparation/unspecified Iron compound: ferrous sulphate. Malaria setting: non-malarial setting. As of 2011: Malaria: No risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	High risk	Not used.
Blinding (performance bias and detection bias) All outcomes	High risk	Open.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 20% loss to follow-up.
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Wallenburg 1983

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Methods	RCT, 2 arms with individual randomisation.
Participants	44 non-anaemic Caucasian women with singleton pregnancy and no major illnesses attending the University Hospital Obstetrical Clinic of the Erasmus University in Rotterdam who had not received iron supplementation during their first visit
Interventions	Participants were randomly assigned to 1 of 2 groups: group 1: received 105 mg of elemental iron (as ferrous sulphate) daily in a sustained release preparation and group 2: received no iron supplement. Supplementation started at 14-16th week of gestation until delivery Setting and health worker cadre: the intervention was performed by physicians at the Antenatal Clinic of the University Hospital Dijkzigt in Rotterdam, the Netherlands
Outcomes	Maternal: Hb, serum iron, serum transferrin and serum ferritin concentrations at 16, 28, 36 weeks, delivery, 6 and 12 weeks postpartum
Notes	Unsupervised. Compliance not reported. We treated this study carried out collaboratively in 2 different sites as 2 different trials, 1 conducted in Rotterdam (Wallenburg 1983) and 1 conducted in Antwerp (Buytaert 1983). Gestational age at start of supplementation: early gestational age (supplementation started before 20 weeks' gestation) Anaemic status at start of supplementation: non-anaemic. Daily iron dose: higher daily dose (more than 60 mg elemental iron daily) Iron release formulation: normal release preparation/unspecified Iron compound: ferrous sulphate. Malaria setting: non-malarial setting. As of 2011: Malaria: No risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	By random table numbers.
Allocation concealment (selection bias)	Low risk	By means of sealed envelopes.
Blinding (performance bias and detection bias) All outcomes	High risk	Participant nor provider blinded. No placebo used.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 20% losses to follow-up.
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Willoughby 1967

Methods	RCT. 5-arm trial.
Participants	3599 pregnant women with Hb above 100 g/L at their antenatal care clinic visit at Queen's Mother's Hospital in Glasgow, Scotland, United Kingdom. Women who reported not taken the tablets regularly were excluded as well as those diagnosed with anaemia during the study
Interventions	Participants were randomly allocated to 1 of 5 interventions: group 1 received no prophylactic supplements; group 2 received 105 mg of elemental iron daily (as chelated iron aminoates); group 3 received 105 mg of elemental iron with 100 μg (0.1 mg) of folic acid; group 4 received 105 mg of elemental iron daily with 300 μg (0.3 mg) of folic acid; and group 5 received 105 mg elemental iron daily with 450 μg (0.45 mg) of folic acid. Starting and ending time of supplementation variable. Setting and health worker cadre: the intervention was performed by a team of nurses and physicians at the Antenatal Clinic of the Queen Mother's Hospital in Glasgow, United Kingdom
Outcomes	Maternal: Hb concentration at baseline and in every visit, at early puerperium and during postnatal visit; incidence of obstetric complications. incidence of megaloblastic anaemia. Infant: Hb and whole blood folate levels a 6 weeks of age. Incidence of neonatal complications
Notes	Unsupervised. Groups 3-5 were merged for the purposes of this review. Women were excluded from the trial and the analysis if they were diagnosed as anaemic. Compliance not reported. Gestational age at start of supplementation: mixed gestational age at the start of supplementation Anaemic status at start of supplementation: mixed anaemia status (Hb > 100 g/L) Daily iron dose: higher daily dose (more than 60 mg elemental iron daily) Iron release formulation: Not clear? normal release preparation/unspecified Iron compound: chelated iron aminoates. Malaria setting: non-malarial setting. As of 2011: Malaria: No risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Less than 20% losses to follow-up. However, women were excluded from the trial and the analysis if they were diagnosed as anaemic
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Wills 1947

Methods	Quasi-randomised trial with 2 arms with individual randomisation
Participants	500 pregnant women attending antenatal care clinic at the Royal Free Hospital in London, England, United Kingdom during wartime, with ages between 18-43 years. Women with severe anaemic or rheumatoid arthritis were excluded
Interventions	Participants were alternatively allocated to receive 580 mg of elemental iron (as ferrous gluconate) daily or placebo from their first visit. Supplementation starting variable and ending time unclear. Setting and health worker cadre: the intervention was performed by nurses and physicians at the Antenatal Clinic of the Obstetrical Department at the Roryal Free Hspital in London, United Kingdom
Outcomes	Maternal: Hb concentration using the Haldane method at baseline and every 4 weeks until delivery, then 1 day, 2-4 days, 5-16 days and 6 weeks postpartum; serum protein and pregnancy complications (not reported by group). Infant: birthweight (not reported).
Notes	Unsupervised. The study was conducted during wartime and a bomb incident interrupted the work allowing only a small portion of original sample studied and reported. Women were receiving special food rations. Compliance not reported. Gestational age at start of supplementation: mixed gestational age (variable) Anaemic status at start of supplementation: mixed anaemia status/unspecified Daily iron dose: higher daily dose (more than 60 mg elemental iron daily) Iron release formulation: normal release preparation/unspecified Iron compound: ferrous gluconate. Malaria setting: non-malarial setting. As of 2011: Malaria: No risk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quasirandomised, alternate.
Allocation concealment (selection bias)	High risk	Alternate allocation.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participant and care provider blinded. Outcome assessor blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 20% lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.

Other bias	Unclear risk	No other bias apparent.

Zeng 2008 (C)

Methods	Cluster-randomised trial (3 arms) Villages were assigned to interventions. Villages were stratified and there was block randomisation to ensure geographical balance in 2 participating counties
Participants	5828 eligible pregnant women with less than 28 weeks and resident in 2 poor rural counties in Shaanxi Province of north west China participated in the study. Village doctors recruited women by active surveillance. In the study areas there were no specific policies for the distribution of multiple micronutrients or iron-folic acid supplements even in disadvantaged areas although folic acid supplements were promoted to prevent NTDs. Their villages were randomly assigned for women to receive 1 of 3 groups
Interventions	Their villages were randomly assigned for participants to receive 1 of 3 groups: group 1, daily antenatal multiple micronutrients containing 30 mg elemental iron, 400 μg (0.4 mg) folic acid and 15 mg zinc, 2 mg copper, 65 μg selenium, 150 μg iodine, 800 μg vitamin A, 1.4 mg vitamin B_1 (thiamine), 1.4 mg vitamin B_2 (riboflavin), 1.9 mg vitamin B_6, 2.6 μg vitamin B_{12}, 5 μg vitamin D, 70 mg vitamin C, 10 mg vitamin E, and 18 mg niacin; group 2 who received a tablet containing 60 mg elemental iron and 400 μg (0.4 mg) of folic acid; and group 3 received a tablet containing 400 μg (0.4 mg) folic acid alone (control) Setting and health worker cadre: the intervention was performed by local maternal and child health workers in rural, antenatal clinics and local health facilities in Shaanxi Province, China
Outcomes	Birthweight within 1 hour of delivery, low birthweight, birth length, gestational age at birth, preterm delivery, small-for-gestational age babies, maternal Hb concentration in the third trimester (gestation 28-32 weeks), anaemia in the third trimester, fetal losses during pregnancy, birth outcome, delivery information, neonatal and maternal deaths; neonatal survival at the 6 weeks, perinatal deaths, neonatal deaths, stillbirths
Notes	We have included groups 2 (iron + folic acid) and 3 (folic acid alone) in the analyses In the data tables we have adjusted the raw data presented in the paper to take account of the cluster design effect. We have calculated an effective sample size by dividing figures by the design effect calculated using the ICC for the trial's primary outcome: birthweight ICC = 0.03. We have used the same sample adjustment for all outcomes 65.9 of women in group 2 (iron + folic acid) and 65.2% of women in group 3 (folic acid) started supplementation before 16 weeks of gestational age Gestational age at start of supplementation: mixed/unspecified gestational age Anaemic status at start of supplementation: mixed anaemia status Daily iron dose: higher dose group (60 mg elemental iron daily) Iron release formulation: normal release preparation/unspecified Iron compound: unspecified. Malaria setting: yes. As of 2011: Malaria risk, including *P. falciparum* malaria, exists in Yunnan and to a lesser extent in Hainan. *P. falciparum* resistance to chloroquine and sulphadoxine-pyrimethamine reported. Limited risk of *P. vivax* malaria exists in southern and some central provinces, including Anhui, Ghuizhou, Henan, Hubei, Jiangsu. There is no malaria risk in urban areas

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomisation schedule was generated off site with a pseudo-random number generator."
Allocation concealment (selection bias)	Low risk	Off-site randomisation.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Cluster trial all women in village received the same intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Total clusters (531). Total women 5828 (in 3 groups, 2 groups included in the analyses ? total randomised 3929). Overall 133 women lost to follow-up and 279 stopped taking supplements and were excluded (7% lost to follow-up) 3270 women in groups 1 and 2 had live births (3306 babies). Approximately 6% further missing data for primary outcome (infant birthweight). Further missing data for other outcomes Available case analysis for primary outcome (LBW).
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	The trial was stopped early because of funding constraints. The treatment groups appeared similar at baseline. Results were adjusted for cluster design effect.

Ziaei 2007

Methods	RCT 2 arms with individual randomisation.
Participants	750 apparently healthy non-smoking non-anaemic (with Hb higher or equal to 132 g/L) pregnant women in early stage of second trimester, BMI 19.8-26 kg/m2 and age 17-35 years with singleton pregnancy attending prenatal care in Tehran, Iran. Women with history of threatened abortion in the present pregnancy or diseases related with polycythaemia such as asthma and chronic hypertension were not included
Interventions	Participantswere randomly assigned to 1 of 2 groups: group 1 received 50 mg of elemental iron (as ferrous sulphate) + 1000 μg (1 mg) folic acid daily and group 2 received placebo and 1000 μg (1 mg) of folic acid daily Setting and health worker cadre: the intervention was performed by midwives and physicians at multiple urban clinical centres in Tehran, Iran
Outcomes	Maternal:Hb at 24-28 week, 32-36 week, premature delivery, weight gain, caesarean sections, hypertensive disorders, severe anaemia, high Hb concentrations, iron deficiency, iron-deficiency anaemia, MCV, MCH and MCHC at term, severe anaemia and high Hb concentrations at any time during 2-3 trimesters, symptomatic tract infection, puerperal infection, antepartum and postpartum haemorrhage, transfusion provided, side effects (any), diarrhoea, constipation, nausea, heartburn, vomiting, placental abruption, premature rupture of membranes Infant: birthweight, perinatal mortality rate, low Apgar at 10th minute, small-for-gestational age
Notes	Unsupervised. Supplementation started 13.07 ± 2.02 weeks' gestation for group 1 and 13.66 ± 3.45 weeks' gestation for the placebo group and lasted until after delivery. No compliance reported. Gestational age at start of supplementation: early gestational age at the start of supplementation (supplementation started before 20 weeks' gestation) Anaemic status at start of supplementation: non-anaemic. Daily iron dose: medium iron dose (50 mg elemental iron). Iron release formulation: normal release preparation/unspecified Iron compound: ferrous sulphate. Malaria setting: yes. As of 2011: Malaria risk due to *P. vivax* and *P. falciparum* exists from March to November inclusive in rural areas of the provinces of Hormozgan and Kerman (tropical part) and the southern part of Sistan-Baluchestan. *P. falciparum* resistant to chloroquine and sulphadoxine-pyrimethamine reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	By means of table of random numbers.
Allocation concealment (selection bias)	Low risk	Coded bottles.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and care provider and outcome assessor blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 5% lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Ziaei 2008

Methods	RCT 2 arms with individual randomisation
Participants	244 pregnant women 17-35 years of age attending prenatal care in Tehran, Iran, with BMI between 19.8-26 kg/m^2, and 13-18 weeks of gestation, with singleton pregnancy and non-anaemic (Hb 132 g/L or higher) and normal serum ferritin (15 μg/L or higher). Women who smoked, had history of diseases such as polycythaemia, asthma, or chronic hypertension, or a history or threatened abortion in the present pregnancy were excluded
Interventions	Participantswere randomly assigned to 1 of 2 groups: group 1 received 50 mg of elemental iron (as ferrous sulphate) daily and group 2 received placebo from 20th week of gestation until delivery. All women received 50 mg elemental iron (as ferrous sulphate) after delivery for 6 weeks Setting and health worker cadre: the intervention was performed by midwives and physicians at a prenatal clinic in Tehran, Iran
Outcomes	Maternal: Hb, HCT, serum ferritin at baseline, at time of delivery, 1 week postpartum and 6 weeks postpartum, postpartum haemorrhage, caesarean sections
Notes	Unsupervised. No compliance reported. Gestational age at start of supplementation: early gestational age (supplementation started before 20 weeks' gestation)

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	Anaemic status at start of supplementation: non anaemic. Daily iron dose: medium dose (50 mg elemental iron). Iron release formulation: normal release preparation/unspecified Iron compound: ferrous sulphate. Malaria setting: yes. As of 2011: Malaria risk due to *P. vivax* and *P. falciparum* exists from March to November inclusive in rural areas of the provinces of Hormozgan and Kerman (tropical part) and the southern part of Sistan-Baluchestan. *P. falciparum* resistant to chloroquine and sulphadoxine-pyrimethamine reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	By means of table of random numbers.
Allocation concealment (selection bias)	Low risk	Coded bottles.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and care provider blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 5% lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	No other bias apparent.

Fe: iron

GSH-Px: glutathione peroxidase

Hb: haemoglobin

HCT: haematocrit (same as PCV: packed cell volume)

ITT: intention-to-treat

MCH: mean corpuscular (or cell) haemoglobin

MCHC: mean corpuscular (or cell) haemoglobin concentration

MCV: mean corpuscular (or cell) volume

MDA: malondialdehyde

OGIT: oral glucose intolerance test

OGTT: oral glucose tolerance test

PCV: packed cell volume (same as HCT: haematocrit)

RBC: red blood cell

RCT: randomised clinical trial

SD: standard deviation

SES: socioeconomic status

SOD: superoxide dismutase

vs: versus

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aaseth 2001	67 non-anaemic pregnant women attending prenatal care clinics in Kingsvinger Hospital, in Kingsvinger, Norway were allocated to a daily regimen of either 100 mg Fe or 15 mg Fe Both groups received iron at different doses. No comparisons allowed within the scope of this review
Abel 2000	Community-based study in Vellore district, India using a pre-post experimental design measuring the impact of an iron supplementation program, helminthic treatment and education intervention in the prevalence of anaemia in the different trimesters of pregnancy

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Study	Reason for exclusion
	The same pregnant women were not followed. The type of study is not eligible for inclusion in this review
Adhikari 2009	320 pregnant women attending the Tribhuvan University Teaching Hospital, Nepal for antenatal care were randomised to 1 of 4 groups: group 1: 60 mg elemental iron daily (as ferrous sulphate); group 2: 60 mg elemental iron daily (as ferrous sulphate) with a count of unused pills at antenatal appointments; group 3: 60 mg elemental iron daily (as ferrous sulphate) with education (direct counselling and colour brochure) on iron and anaemia; group 4: 60 mg elemental iron daily (as ferrous sulphate) with pill count and education (direct counselling and colour brochure) on iron and anaemia. In this randomised trial the aim of the intervention was to increase compliance and all 4 intervention groups received daily iron supplements The type of interventions do not allow for comparisons within the scope of this review
Afifi 1978	260 pregnant women from Cairo, Egypt (formerly part of United Arab Republic) were randomly allocated to 1 of 2 groups: group 1 received 130 mg elemental iron daily (a slow release ferrous sulphate preparation, Plexafer-F®) and 360 μg (0.36 mg) folic acid; group 2 received iron (as ferrous sulphate, no dose reported) in addition to 5000 μg (5 mg) folic acid. Both groups received daily iron supplementation in different preparations The type of interventions do not allow for comparisons within the scope of this review
Ahn 2006	209 pregnant women between 18 and 45 years of age, attending outpatient obstetric clinics at North York General Hospital and the Hospital for Sick Children in Toronto, Canada were randomly assigned to receive multiple micronutrient supplements containing 60 mg of elemental iron (as ferrous fumarate) (Materna®) or another supplement (PregVit®) to be taken twice daily with the morning dose containing 35 mg of elemental iron (as ferrous fumarate) and the evening dose containing 300 mg calcium, and other vitamins and minerals. Both groups received daily iron in different doses as well as other vitamins and minerals The type of interventions do not allow for comparisons within the scope of this review
Angeles-Agdeppa 2003	744 apparently healthy pregnant (with less than 20 weeks) and non-pregnant women of reproductive age (15-49 years) from the municipalities of Calasiao, Binmaley and Santa Barbara, Philippines who were pregnant or most likely to become pregnant within the 12-month duration of the study, and who volunteered to participate in the study were provided 2 preparations of iron-folic acid supplements. Women with severe anaemia or history of malaria were excluded. Non-pregnant women were prescribed 4 capsules monthly each containing 60 mg of elemental iron and 3500 μg (3.5 mg) folic acid to be taken once weekly before bedtime (to be purchased by the women in local drugstores). Pregnant women received free of cost 4 capsules monthly each containing 120 mg of elemental iron and 3500 μg (3.5 mg) of folic acid to be taken once a week before bedtime until delivery and for 3 months thereafter. Pregnant women seen at the health centres with 20 weeks or more of gestation were advised to take their usual daily dose of iron-folic acid tablets containing 60 mg of elemental iron and 500 μg (0.5 mg) of folic acid. Women were followed for 12 months. Hb, haematocrit, mean corpuscular volume, mean corpuscular Hb concentration, serum ferritin, transferrin receptors, prevalence of iron deficiency and anaemia, compliance were assessed at baseline, 4.5, 9 and 12 months There was not randomisation and the control group was not appropriate for comparisons. The type of comparisons are not relevant for the scope of this review
Babior 1985	15 healthy pregnant women 22-32 years old, in the first trimester of pregnancy from Boston, Massachusetts, USA were randomly assigned to 3 different multiple micronutrient preparations to assess absorption of iron All women received iron in the multiple micronutrient supplements. The type of interventions is not relevant for the scope of this review
Balmelli 1974	42 pregnant women attending antenatal care clinic at the Hospital University of Berne, Switzerland were randomly assigned to one of two groups: group 1 received 37 mg elemental iron (as ferrous sulphate) and succinic acid three times daily (total daily dose of 111 mg elemental iron and 555 mg succinic acid); group 2 received 37 mg elemental iron (as ferrous sulphate) and succinic acid three times daily (total daily dose of 111 mg elemental iron and 555 mg succinic acid) and one tablet three times a day containing 100 μg (0.1 mg) folic acid and 100 μg vitamin B_{12}. Both groups received iron supplements. The type of interventions is outside the scope of this review
Bencaiova 2007	260 women with singleton pregnancy in Zurich, Switzerland, were randomised at 21-24 weeks of gestation to receive either intravenous iron group (further divided into 2 doses of 200 mg iron saccharate or 3 doses of 200 mg iron) or 80 mg elemental iron (as ferrous sulphate) daily Both groups received iron in different routes of administration. No comparisons allowed within the scope of this review
Berger 2003	864 apparently healthy married pregnant and non-pregnant nulliparous women of reproductive age planning to have a child soon from 19 rural communes of the Thanh Mien district in Hai Duong province, Vietnam were invited to participate and assigned to 1 of the following interventions according to their pregnancy status at baseline: women who were pregnant received free of charge UNICEF tablets containing 60 mg of elemental iron and 250 μg (0.25 mg) of folic acid to be taken daily and women who were non-pregnant were prescribed pink packs of tablets containing 60 mg of elemental iron and 3500 μg (3.5 mg) of folic acid that they could buy at their village from the Women's Union, to be taken once weekly. If these women became pregnant, women received red packs of tablets containing 120 mg of elemental iron and 3500 μg (3.5 mg) of folic acid free of charge to be taken once weekly. After delivery women were given tablets containing 60 mg of elemental iron and 0.5 mg of folic acid free of charge for 3 months to be taken weekly. Hb concentration, serum ferritin, and serum ferritin receptors, prevalence of anaemia and iron deficiency and compliance were measured at baseline, at 4.5, 9 and 12 months This is not a randomised study and no comparisons can be made for the aims of this review
Bergsjo 1987	Planned study registered at the Oxford Database of Perinatal Trials. Author contacted and informed the project was not completed
Bhatla 2009	109 pregnant non-anaemic women between 14 and 18 weeks (49% vegetarian) with no prior intake of iron supplements in the Department of Obstetrics and Gynaecology of the All India Institute of Medical Sciences in New Delhi, India were randomly allocated into 1 of 3 different groups: group 1 (n = 37) received the standard Government of India supply of Irofol® tablets containing 100 mg of elemental iron (as ferrous sulphate) and 500 μg (0.5 mg) folic acid (Nestor Pharmaceuticals Ltd., Faridabad, Haryana, India) to be taken once daily; group 2 (n = 36) received the standard Government of India supply of Irofol ® tablets containing 100 mg of elemental iron (as ferrous sulphate) and 500 μg (0.5 mg) folic acid and were instructed to take 2 tablets on any 1 day of the week; 1 before lunch and the other before dinner (total 200 mg elemental iron and 1000 μg (1 mg) folic acid per week) with no tablets taken during the rest of the week; and group 3 (n = 36) received Ferium® tablets iron (III)-hydroxide poly maltose complex tablets daily containing Iron (III) Hydroxide Polymaltose containing 100 mg elemental iron and 350 μg (0.35 mg) folic acid to be taken 1 tablet daily (Emcure Pharmaceuticals Ltd., Pune) All groups received health education regarding the importance of diet in pregnancy, iron-rich foods and appropriate dietary practices and were instructed to take the tablets 30 min before meals and not with tea, coffee or milk. All women were also advised to take calcium supplements after meals All groups received iron with different regimens. The type of interventions are not within the scope of this review
Blot 1980	203 pregnant women attending prenatal care clinics in Antonie Beclere Hospital, Paris, France during their 6th month visit were randomly allocated to either 105 mg of elemental iron with 500 mg of ascorbic acid or a placebo

Study	Reason for exclusion
	The intervention group received iron with ascorbic acid in comparison to placebo. The type of intervention do not allow for comparisons within the scope of this review
Bokhari 2011	33 healthy non-smokers Caucasian, primiparous, with singleton pregnancy (wk 20 to wk 30) pregnant women with pre pregnancy BMI between 19.8 and 26 not taking medicines known to influence iron status nor iron supplements and free from gastrointestinal disorders or allergies were randomised to eat 3-4 slices of iron-rich or control bread daily for 6 weeks. Women with Hb concentrations not within the normal range (below 70 g/L or over 160 g/L) were excluded. Low versus high iron fortified breads were compared. Two 24-h prompted (multiple-pass) dietary recalls were completed, and validated algorithms were used to determine the amount of 'available iron' from the diet. Findings from this study show that iron-rich staple foods can help women reach dietary targets for iron. Further research using fortified staple foods containing higher levels of iron is now warranted to establish physiological benefits. The study was excluded because food fortification is out of the scope of this review The intervention is outside of the scope of this review.
Brown 1972	109 pregnant women attending prenatal care clinics in Manchester, England, United Kingdom were randomly allocated to 1 of 3 groups: group 1 received 1 tablet daily given in 'reminder packs', group 2 received 1 tablet daily given in loose forms, or group 3 received 2 tablets daily given in loose form. Tablets contained 50 mg of elemental iron (as slow release ferrous sulphate) and 400 μg (0.4 mg) of folic acid All groups received iron daily. The type of interventions do not allow for comparisons within the scope of this review
Burslem 1968	472 pregnant women attending the booking clinic in Manchester, England, United Kingdom were alternatively allocated to 2 forms of iron: group 1 received 105 mg elemental iron (as a slow release ferrous sulphate preparation) and a tablet containing 5000 μg (5 mg) folic acid daily; group 2 received 3 tablets of combined conventional 60 mg elemental iron (as ferrous sulphate) and 1 tablet containing 5000 μg (5 mg) folic acid for a total of 180 mg elemental iron daily Both groups received daily iron supplementation in different preparations. The type of interventions do not allow for comparisons within the scope of this review
Buss 1981	18 pregnant women were randomly assigned to receive either a tablet containing 80 mg of elemental iron with a new mucous membrane vaccine (Tardyferon®) or a tablet containing 80 mg elemental iron with 350 μg (0.35 mg) folic acid (Tardyferon-Fol®) for a period of 3 months. All women received daily iron The type of interventions do not allow for comparisons within the scope of this review
Carrasco 1962	2 liquid preparations were used in this study: 1 with D-sorbitol and the other without Both preparations contained vitamin B_{12}, vitamin B_6, ferric pyrophosphate and folic acid. The type of interventions do not allow for comparisons within the scope of this review
Casanueva 2003a	120 singleton pregnant women attending the Instituto Nacional de Perinatologia in Mexico City, Mexico with Hb concentrations higher than 115 g/L at 20 weeks of gestation (equivalent to 105 g/L at sea level) were randomly were randomly assigned to 1 of 2 groups, group 1: 1 tablet containing 60 mg of elemental iron (as ferrous sulphate), 200 μg (0.2 mg) folic acid and 1 μg vitamin B_{12} given daily, and group 2: 2 tablets (total 120 mg of elemental iron (as ferrous sulphate), 400 μg (0.4 mg) folic acid, and 2 μg vitamin B_{12}) to be taken once weekly. The groups received either daily supplementation or weekly supplementation at no cost. Supplement tablets were identical in content and were to be ingested from the 20th week of pregnancy until delivery. No comparisons allowed within the scope of this review
Castren 1968	126 healthy pregnant women attending Maternity Centres of Turku, Finland were assigned to one of two groups: group 1 (n=63) received three tablets a day providing a total 120 mg elemental iron (as ferrous sulphate) daily; group 2 (n = 63) received three tablets a day providing total 120 mg elemental iron (as ferrous sulphate) + 9000 μg (9 mg) folic acid daily from their first visit at 10-20th wk of gestation until term. Both groups received iron. The type of intervention is outside the scope of this review
Chanarin 1968	206 women attending the antenatal clinic at St. Mary's Hospital, London, United Kingdom with less than 16 weeks pregnant at the first attendance. At the 20th week they were allotted to one of two groups: group 1 received tablets to be taken once daily containing 260 mg ferrous fumarate ; and group 2 received tablets to be taken daily containing 260 mg ferrous fumarate and 100 μg (0.1 mg) of folic acid. Iron deficiency was largely eliminated by giving 1 g of intravenous iron dextran as four 250-mg. doses at weekly intervals to all participants in early pregnancy. Both groups received iron. the type of comparison is not within the scope of this review
Chawla 1995	81 pregnant women with 20 +/− weeks of gestation from Ludhiana City, India were divided to 1 of 3 groups: group 1 received 60 mg of elemental iron (as ferrous sulphate) and 500 μg (0.5 mg) of folic acid daily; group 2, 60 mg of elemental iron (as ferrous sulphate) and 2,000,000 IU of vitamin A, or group 3, who did not receive any supplements. Supplementation was for a period of 15 weeks. Outcomes measured included Hb, red blood cell count, total iron binding capacity, transferrin saturation, serum iron, serum vitamin A at baseline and at 36 +/− 2 weeks of gestation. Poor methodological quality Pregnant women who were willing to go to the hospital or centre once a week to collect the iron supplements were included in the groups 1 and 2. The rest of the participants were included in the control group. This is not a randomised trial
Chew 1996a	256 clinically healthy pregnant women from low socioeconomic status attending 1 antenatal care clinic in Guatemala City, Guatemala and Hb > 80 g/L were recruited. City of Guatemala is at 1500 m above sea level, so values were adjusted by altitude subtracting 5 g/L in Hb. Participants were randomly assigned to 1 of 2 groups: group 1: daily supervised intake of 60 mg elemental iron (as ferrous sulphate) and 500 μg (0. 5 mg) folic acid; group 2: weekly supervised intake of 180 mg of elemental iron (as ferrous sulphate) and 3500 μg (3.5 mg) of folic acid in 1 intake once a week. Supplementation started at different gestational age for each participant. Average gestational age at start was 20.5 weeks until 38th week All groups received iron with different regimens. The type of interventions are not within the scope of this review
Chew 1996b	120 clinically healthy pregnant women attending 1 antenatal care clinic in Guatemala City, Guatemala with Hb >80 g/L were recruited. Women were from low SES. City of Guatemala is 1500 m above sea level, so values were adjusted by altitude subtracting 5 g/L in Hb. Participants from low SES were randomly assigned to 1 of 2 groups: group 3: daily unsupervised intake of 60 mg elemental iron (as ferrous sulphate) and 0.5 mg folic acid; or group 4: weekly unsupervised intake of 180 mg of elemental iron (as ferrous sulphate) and 3.5 mg of folic acid in 1 intake once a week. Supplementation started at an average of 20.5 weeks of gestation until 38th week All groups received iron with different regimens. The type of interventions are not within the scope of this review

Study	Reason for exclusion
Coelho 2000	100 pregnant women with 20-34 weeks of gestation attending the antenatal clinic at The Bandra Holy Family Hospital, Bandra, Mumbai India were randomly assigned to 1 of 2 groups: group 1 received 30 mg elemental iron + other essential vitamins and minerals daily; groups 2 received 116 mg elemental iron, folic acid, zinc and vitamin C daily. Outcomes included Hb concentration, maternal weight gain, infant birthweight and maternal compliance and side effects Both groups received iron supplementation Both groups received daily iron supplementation. The types of interventions do not allow for comparisons within the scope of this review
Cook 1990	200 women at Kansas University Medical Center, Kansas, USA were randomly assigned to receive 50 mg elemental iron daily given either as Gastric Delivery System (GDS) or conventional ferrous sulphate . Gastrointestinal side effects were evaluated The participants were non-pregnant women.
Dawson 1962	2498 pregnant women attending antenatal care clinic in Crumpsal Hospital, Manchester United Kingdom were grouped to receive folic acid or as controls. The assignment was not randomised. Participants whose Hb fell below 100 g/L after 28th week received oral iron if they had not previously received oral iron, had not reached the 36th wk of gestation and had a mean corpuscular Hb concentration of less than 30%. If these participants had been receiving oral iron, iron was then provided parenterally. The type of interventions and comparisons are outside the scope of this review
Dawson 1987	42 healthy women with less than 16 weeks of pregnancy entering prenatal care at the Department of Obstetrics and Gynecology, University of Texas, Texas, USA were randomly assigned to receive either a multiple micronutrient supplement containing 65 mg of elemental iron or 1 multiple micronutrient supplement with no iron, calcium, zinc and copper and pantothenic acid Both groups received different multiple micronutrient supplement formulations. No comparisons allowed within the scope of this review
Dijkhuizen 2004	170 pregnant women with less than 20 weeks' gestation from 13 adjacent villages in a rural area in Bogor District, West Java, Indonesia were randomly assigned to receive daily supplementation with B-carotene (4.5 mg), zinc (30 mg), both, or placebo containing 30 mg elemental iron and 400 μg (0.4 mg) folic acid Both groups received daily iron and folic acid. The types of interventions do not allow for comparisons within the scope of this review
Edgar 1956	179 pregnant women with Hb levels below 105 g/L and more than 16 weeks of gestation volunteered for this study and were divided into 4 supplementation groups according to the stage of pregnancy at which iron was introduced: 16th week, 20th week, 24th week, and non-supplemented controls. 37% of these women were lost to follow-up and were excluded from the final analysis This is not a randomised trial.
Ekstrom 1996	176 pregnant women attending Ilula Lutheran Health Center's antenatal service in Iringa region, Tanzania with 21-26 weeks of gestational age and Hb > 80 g/L were randomly assigned to receive 120 mg elemental iron (as ferrous sulphate in conventional form) daily or 50 mg elemental iron as gastric delivery system (GDS) daily Both groups received daily iron supplementation in different preparations. The types of interventions do not allow for comparisons within the scope of this review
Ekstrom 2002	209 apparently healthy women attending antenatal care clinics in rural areas of Mymemsingh thana, Bangladesh, with fundal height of 14-22 cm (18-24 weeks of gestation), who had not used iron supplements prior to the study. Exclusion criteria: women with Hb concentrations < 80 g/L. Each clinic was randomly assigned to 1 of 2 interventions: 60 mg of elemental iron (as ferrous sulphate) and 250 μg (0.25 mg) folic acid given in 1 tablet daily, or 120 mg of elemental iron (as ferrous sulphate) and 500 μg (0.5 mg) folic acid once a week (given in 2 tablets 1 day of the week). Supplementation continued until 6 weeks postpartum. Supplementation started at baseline for 12 weeks All groups received iron with different regimens. The type of interventions are not within the scope of this review
Fletcher 1971	643 pregnant women attending antenatal clinic in London, England, United Kingdom were randomly assigned to 1 of 2 groups: group 1 received 200 mg of ferrous sulphate daily; group 2 received 200 mg of ferrous sulphate with 5000 μg (5 mg) of folic acid daily Both groups received iron. No comparisons allowed within the scope of this review
Giles 1971	????
Gomber 2002	40 apparently healthy women with singleton pregnancy in their second trimester (between 16-24 weeks of gestation), living in urban slums, from low socioeconomic status attending Guru Teg Bahadur Hospital, Delhi, India were randomly assigned to receive 1 tablet containing 100 mg of elemental iron (as ferrous sulphate) with 500 μg (0.5 mg) folic acid daily or once a week. Weekly intake was supervised. Duration of supplementation was 100 days. Hb and haematocrit concentrations at baseline, at 4 weeks, 8 weeks and 14 weeks of supplementation, serum ferritin concentration, at baseline, at 14 weeks of supplementation and at delivery Both groups received iron and folic acid in different regimens (daily versus weekly). The type of interventions do not allow for comparisons within the scope of this review
Goonewardene 2001	92 pregnant women from 14-24 weeks of gestation attending the university antenatal clinic, in Galle, Sri Lanka were randomly assigned to 1 of 3 regimens: group 1 (n = 26) received a tablet containing 100 mg of elemental iron (as ferrous fumarate), with additional micronutrients once a week; group 2 (n = 35) received the same tablet but 3 times a week; and group 3 (n = 31) received the same supplement in a daily fashion All groups were receiving iron and multiple micronutrients with different regimens (daily, weekly, 3 times a week). The type of interventions do not allow for comparisons within the scope of this review
Gopalan 2004	900 pregnant women of poor socioeconomic status females attending government antenatal care clinics in New Delhi, India were grouped in 3 groups: group 1 (n = 300) received routine antenatal care; group 2 (n = 300) received 100 mg of elemental iron and 500 μg (0.5 mg) folic acid daily from the 20th week of gestation and group 3 (n = 300) received 100 mg of elemental iron and 500 μg (0.5 mg) folic acid daily from the 20th week of gestation and additionally 900 mg of alpha linolenic acid from the 22nd week of gestation. Outcomes assessed included birthweight, low birthweight, premature delivery The study is not reported as randomised and is excluded in the first screening for eligibility.
Gringras 1982	40 pregnant women attending antenatal care clinic in Cheschire, England, United Kingdom were given a tablet containing 47 mg of elemental iron (as ferrous sulphate) and 500 μg (0.5 mg) of folic acid daily or a tablet containing 100 mg of elemental iron (as ferrous glycine sulphate) daily Both groups received iron. No comparisons allowed within the scope of this review
Grover 1998	200 pregnant women with gestation 16-24 weeks attending for care in rural health centre in Gazipur village in East Delhi, India from Jan-Dec 1994 with Hb 70 g/L or more and no tuberculosis, chronic diseases, "toxaemia", bleeding piles were randomly assigned to 1 of 2 groups: group 1: women received 100 mg of elemental iron (as ferrous sulphate) and 500 μg

Study	Reason for exclusion
	(0.5 mg) of folic acid on alternate days: (data available for 56 women); group 2: women received 100 mg of elemental iron daily (as ferrous sulphate) and 500 μg (0. 5 mg) of folic acid (data available for 64 women) It is not clear how the doses were supplied. The type of interventions do not allow for comparisons within the scope of this review
Guldholt 1991	192 pregnant women in Horsens Hospital, Denmark were consecutively randomised to receive 1 of 2 treatments: group 1: received a daily vitamin-mineral tablet containing 15 mg of elemental iron or group 2: received a daily vitamin-mineral tablet containing 100 mg of elemental iron Both groups received iron in different doses. No comparisons allowed within the scope of this review
Hampel 1974	65 untreated and 54 treated pregnant women in West Berlin, Germany were assessed during pregnancy for Hb concentrations, iron an folate levels, total iron binding capacity, and red cell count. No data are presented for outcomes prespecified in the review Women were of different gestational age. No outcomes can be extracted from the paper
Hartman-Craven 2009	In this cross-over study 2 types of multivitamin supplements were compared: 18 healthy pregnant women 24-32 weeks' gestation attending a Toronto hospital were recruited and received 2 different supplements in a random order and followed up over 8 hours Both preparations contained iron and folic acid (although in different doses). The aim of the study was to see whether absorption was improved with a powdered preparation
Hawkins 1987	No report available of the study results.
Hermsdorf 1986	120 unselected pregnant women were given 114 mg of elemental iron daily from week 15 until delivery, or not treatment. Only an abstract with insufficient data available
Horgan 1966	42 apparently healthy pregnant women attending 2 antenatal care clinics in London, England were assigned to 1 of 3 interventions: group 1 received 200 mg ferrous sulphate with 5000 μg (5 mg) of folic acid 3 times a day; group 2 received 350 mg of ferrous aminoate with 50 μg (0.05 mg) folic acid 3 times a day; and group 3 received 200 mg of ferrous sulphate with 500 μg (0.5 mg) folic acid once a day. Intervention period was 3 weeks All groups received daily iron and folic acid. No comparisons allowed within the scope of this review
Hosokawa 1989	84 anaemic women seeking antenatal care in the Department of Obstetrics and Gynaecology of the Fukui School of Medicine Hospital, Japan were randomly assigned to receive 100 mg of elemental iron (as ferrous sulphate) daily after the evening meal, or the same dose + vitamin C for 4 weeks Both groups received daily iron. No comparisons allowed within the scope of this review
Iyengar 1970	800 pregnant women with less than 24 weeks of gestation and Hb > 85 g/L in India were assigned by rotation to 1 of 4 groups: group 1 received placebo tablets; group 2 received 30 mg of elemental iron as ferrous fumarate in a single tablet daily; group 3 received 30 mg of elemental iron (as ferrous fumarate) with 500 μg (0.5 mg) folic acid in a single tablet; and group 4 received in addition to iron and folic acid, 2 μg of vitamin B_{12} in a single tablet. Loss to follow-up was 65%. This is not a randomised trial.
Kaestel 2005	2100 pregnant women (22 +/− 7 weeks' gestation at entry) attending antenatal clinics in Bissau, Guinea-Bissau or who were identified by The Bandim Health project were randomly assigned to receive daily multi micronutrient tablet containing 1 RDA of 15 micronutrients, or daily multi micronutrients containing 2 times the RDA except for iron that was maintained at 1 RDA or a conventional prenatal daily iron (60 mg elemental iron) and 400 μg (0.4 mg) folic acid supplement In a follow-up analysis (Andersen 2010), of the previous study a two-year follow-up examined the effects of the interventions on fetal loss ans under 2 mortality. 2169 women were recruited from four suburban districts followed by the Bandim Health project in collaboration with the Danish Epidemiology Science Centre in Guinea-Bissau. Women with severe anaemia (Hb less than 70 g/L) received 60 mg elemental iron daily in addition to the intervention. All participants received impregnated bed net at inclusion ans were provided weekly anti-malarial prophylaxis with chloroquine phosphate (300 mg base) throughout pregnancy. Also women with more than 10 parasite per 200 leucocytes were offered anti-malarial treatment with chloroquine All groups receive iron and folic acid daily. No comparisons allowed within the scope of this review
Kann 1988	36 healthy non-anaemic pregnant women in second or third trimesters of gestation were randomly assigned to receive 1 of 4 groups: group 1 received a tablet (Stuartnatal® 1 + 1) containing 65 mg elemental iron, 1000 μg (1 mg) folic acid and 12 additional micronutrients daily; group 2 received a tablet (Stuart Prenatal®) containing 60 mg elemental iron, 800 μg (0.8 mg) folic acid and 11 additional micronutrients; group 3 received a tablet (Materna®) containing 60 mg elemental iron, 1000 μg (1 mg) folic acid and 17 additional micronutrients daily; and group 4 received a tablet (Natalins Rx®) containing 60 mg elemental iron, 1000 μg (1 mg) folic acid and 14 additional micronutrients daily All participants received iron and multiple micronutrients. No comparisons allowed within the scope of this review
Khambalia 2009	In this randomised trial carried out in Bangladesh childless, non-pregnant married women under 40 were randomised to receive food supplements (sprinkles) containing either iron and folic acid or folic acid alone. 272 women were randomised and women were followed up for 9 months If women became pregnant they were withdrawn from the study and ALL pregnant women received both iron and folic acid. The study was excluded as it focused on a non-pregnant population
Kulkarni 2010	This study was secondary analysis of the data from the Christian 2003 (C) study included in the review.
Kumar 2005	220 pregnant women with a singleton pregnancy and Hb between 80-110 g/L at 16-24 weeks' gestation from New Delhi, India were randomly allocated to receive daily oral iron therapy of 100 mg elemental iron (as ferrous sulphate) with 500 μg (0.5 mg) folic acid or 250 mg of iron sorbitol intramuscularly and repeated at an interval of 4-6 weeks This trial compares the effects of daily oral iron with 2 injections of high dose parenteral iron. No comparisons allowed within the scope of this review
Lira 1989	199 pregnant women with less than 16 wk gestation attending antenatal care at the Hospital clinica Universidad Catolica ein Santiago, Chile were randomly assigned to one of two groups: group 1 (n = 78) received 105 mg elemental iron (as ferrous sulphate) and 500 mg ascorbic acid; group 2 (n = 75) received 105 mg elemental iron (as ferrous sulphate), 500 mg ascorbic acid and 350 ug (0.35 mg) folic acid daily. There were 36 losses to follow-up. Both groups received iron. The type of interventions provided is outside the scope of this review
Liu 1996	395 healthy, anaemic and non-anaemic, pregnant women attending prenatal care at 2 outpatient clinics in Xianjiang, China. Women with Hb < 80 g/L were excluded. Maternal age was 25.15 ± 2.28 years. Women were randomly assigned to 1 of 3 groups: group 1: 60 mg elemental iron (as ferrous sulphate) and 250 μg (0.25 mg) of folic acid daily; group 2: 120 mg of elemental iron (as ferrous sulphate) and 500 μg (0.5 mg) of folic acid daily; group 3: 120 mg elemental iron (as ferrous sulphate) and 500 μg (0.5 mg) of folic acid once weekly

Study	Reason for exclusion
	All women randomised to treatments received iron. A control group that received no iron was composed of women who did not want to participate in the study and did not receive any iron supplements
Ma 2008	366 pregnant women between 20-35 years of age women in rural China with 12-24 wk gestation; with Hb 105 g/L or lower, all receiving 60 mg elemental iron and 400 μg (0.4 mg) folic acid were randomly assigned to one of 4 groups: group 1 (n = 93) received daily 60 mg elemental iron (as ferrous sulphate) and 400 μg (0.4 mg) folic acid; group 2 (n = 91) received daily 60 mg elemental iron (as ferrous sulphate) , 400 μg (0.4 mg) folic acid + 2000 μg retinol (as retinyl palmitate); group 3 (n = 91) received daily 60 mg elemental iron (as ferrous sulphate), 400 μg (0.4 mg) folic acid + 1.0 mg riboflavin and group 4 (n = 91) received daily 60 mg elemental iron (as ferrous sulphate), 400 μg (0.4 mg) folic acid, 2000 μg retinol (as retinyl palmitate) + 1.0 mg riboflavin. The intervention lasted 2 months. All groups received iron. The type of comparisons are outside the scope of this review
Madan 1999	109 apparently healthy pregnant women with 16-24 weeks of gestation who had not received iron supplements were randomly assigned to 1 of 3 groups: group 1 received 60 mg of elemental iron + 500 μg (0. 5 mg) of folic acid once daily; group 2 received 120 mg of elemental iron + 500 μg (0.5 mg) of folic acid once daily; group 3 received 120 mg of elemental iron twice daily + 500 μg (0.5 mg) of folic acid. Duration of supplementation was 12-14 weeks All participants received iron and folic acid daily. No comparisons are allowed within the scope of this review
Mbaye 2006	1035 pregnant women attending mother and child health clinics near the town of Farafenni, The Gambia were randomised to receive either folic acid (500-1500 μg/day) together with oral iron (47 mg of ferrous sulphate per tablet) or oral iron alone (60 mg of ferrous sulphate per tablet) daily for 14 days. All women received treatment with 3 tablets of SP (25 mg of pyrimethamine and 500 mg of sulphadoxine) Both groups received iron daily. No comparisons allowed within the scope of this review
McKenna 2002	102 healthy pregnant women attending antenatal clinics at the Royal Jubilee Maternity Hospital in Belfast, Ireland with a singleton pregnancy and Hb > 104 g/L and known gestational age of less than 20 weeks who were non-compliers with routine prescription of 200 mg of ferrous sulphate daily, were randomly assigned to receive 2 sachets of 24 mL each of Spatone® water containing 10 mg of elemental iron or placebo. Participants were instructed to take the 2 sachets daily half an hour before breakfast diluting it in orange juice. Primary outcomes were compliance and side effects. Duration of intervention was from week 22 to week 28 of gestation The intervention is not an iron supplement but an iron-fortified water product
Menon 1962	273 healthy pregnant women with 16-24 weeks of gestation and Hb concentrations at or above 105 g/L attending antenatal care clinics were divided in order in which they were registered in 3 groups: group 1 was given 5 g of ferrous sulphate daily; group 2 received 5000 μg (5 mg) of folic acid daily; and group 3 received 5 g of ferrous sulphate and 5000 μg (5 mg) of folic acid daily All participants were given 3 multivitamin tablets daily containing vitamin A, vitamin B, C and D. The study was not randomised
Metz 1965	355 Bantu and White pregnant women attending antenatal clinics at the Baragwanath and South Rand Hospitals, Johannesburg, South Africa were allocated by random numbers to one of three groups. Group 1 received 200 mg of iron by mouth; group 2 received 5000 μg (5 mg) of folic acid daily by mouth in addition to the iron, and group 3 received 50 μg of vitamin B_{12} by mouth in addition to the folic acid and iron. In the White participants supplementation was started after the 24th week while Bantu participants started after the 28th. Both groups received iron. The type of comparisons are outside the scope of this review,
Milman 2005	427 healthy Danish pregnant women living in the northeastern part of Copenhagen County, Denmark were randomly allocated to receive iron (as ferrous fumarate) in daily doses of 20 mg (n = 105), 40 mg (n = 108), 60 mg (n = 106), and 80 mg (n = 108) from 18 weeks of gestation. Hb, serum ferritin, and serum soluble transferrin receptor concentrations were measured at 18 weeks (inclusion), 32 weeks, and 39 weeks of gestation and 8 weeks postpartum All women received iron daily. No comparisons allowed within the scope of this review
Morgan 1961	356 pregnant women attending 2 different antenatal care clinics at the King Edward Memorial Hospital for Women in Subiaco, Australia received according to the clinic they visited, either no treatment or 100 mg of elemental iron (as ferrous gluconate) daily No systematic allocation was used in this open trial.
Morrison 1977	105 pregnant women attending the University Unit, Mater Misericordiae Mothers' Hospital, South Brisbane, Australia, with normal height, weight and nutrition for the Australian population and with no previous adverse medical, surgical or obstetrical history were allotted by random selection to 1 of 4 types of supplements: group 1 received 50 mg of elemental iron (as dried ferrous sulphate) daily; group 2 received 80 mg elemental iron (as dried ferrous sulphate) with 300 μg (0.3 mg) folic acid daily; group 3 received 105 mg elemental iron (as ferrous sulphate) and group 4 received 105 mg of elemental iron (as ferrous sulphate) with 300 μg (0.3 mg) of folic acid All groups received iron daily. No comparisons allowed within the scope of this review
Mukhopadhyay 2004	111 apparently healthy pregnant women with less than 20 weeks and no prior intake of iron supplements during this pregnancy with Hb equal or higher than 100 g/L and singleton pregnancy in New Delhi, India were randomly assigned to 1 of 2 groups: group 1 received 2 tablets of 100 mg elemental iron and 500 μg (0.5 mg) folic acid each (total 200 mg elemental iron and 1000 μg (1 mg) folic acid, to be taken only once a week, 1 tablet before lunch and another tablet before dinner; group 2 received 1 tablet of 100 mg elemental iron and 500 μg (0.5 mg) folic acid daily. Women were advised to take the supplements 30 minutes before the meals and not with tea, coffee or milk. Also, women were advised to take calcium supplements after meals (500 mg elemental calcium twice daily). Iron supplementation started between 14 and 20 weeks until delivery. Deworming, if required, was carried out with Mebendazole 100 mg twice a day for 3 days in the second trimester Both groups received iron and folic acid in different regimens (daily versus weekly)
Mumtaz 2000	191 anaemic pregnant women between the ages of 17-35 years of age, and uneventful obstetric history attending the Maternity wing of the Federal Government Services Hospital in Islamabad and the Maternal & Child Health Clinic at the Christian Mission Hospital in Taxila, Pakistan were randomly assigned to 1 of 2 interventions: group 1 received 40 mg elemental iron (as ferrous sulphate) with 1000 μg (1 mg) of folic acid once daily; and group 2 received 40 mg elemental iron (as ferrous sulphate) with 1000 μg (1 mg) of folic acid on 2 days of the week and placebo the rest of the days. Participants and care providers were blinded to the treatments. Outcomes measured included Hb concentration and serum ferritin at baseline and during the 3 following consecutive visits as well as compliance and weight. Change in Hb Z-scores after supplementation was the main outcome variable, in women from different gestational ages and duration of intervention Both groups received iron and folic acid in different regimens (daily versus bi-weekly)
Nguyen 2008	167 pregnant women with less than 20 weeks of gestation who called either Motherisk General Information line or the Motherisk Nausea and Vomiting of Pregnancy (NVP) Helpline (Hospital for Sick Children, Toronto) and had not started taking or had discontinued any multivitamin due to adverse events were randomly assigned to 1 of 2 groups: group 1 were provided, a small-size supplement (PregVit®), containing 35 mg elemental iron (as ferrous fumarate) and multivitamins;

Study	Reason for exclusion
	or group 2 who received high iron content, small size supplement (Orifer F®) containing 60 mg elemental iron (as ferrous sulphate) and multivitamins. Follow-up interviews documented pill intake and adverse events Participants from both groups received iron in different amounts and compounds
Nogueira 2002	74 low-income pregnant adolescents ranging from 13-18 years of age attending antenatal care at the Evangelina Rosa Maternity Hospital in Teresina, Piaui State, Brazil were distributed into 5 groups: group 1 received 120 mg elemental iron (as ferrous sulphate) and 250 μg (0.25 mg) of folic acid daily; group 2 received 80 mg elemental iron (as ferrous sulphate) and 250 μg (0.25 mg) folic acid daily; group 3 received 120 mg of elemental iron, with 5 mg of zinc sulphate and 250 μg (0.25 mg) of folic acid daily; and group 4 received 80 mg of elemental iron (as ferrous sulphate), with 5 mg of zinc sulphate and 250 μg (0.25 mg) of folic acid daily All groups received iron and 2 groups received zinc in addition to iron and folic acid. No comparisons allowed within the scope of this review
Ogunbode 1984	80 apparently healthy non-anaemic pregnant women attending University College Hospital and Inalende Maternity Hospital in Ibadan, Nigeria during the first and second trimesters of pregnancy were randomly allocated to 1 of 2 groups: group 1 (n = 39) received 1 tablet Ferrograd Folic 500 Plus® daily, a sustained-released formulation containing ferrous sulphate and folic acid (composition is not available); or group 2 (n = 41) received a capsule containing 200 mg ferrous sulphate and 5000 μg (5 mg) of folic acid. All patients were also provided 25 mg weekly of pyrimethamine throughout pregnancy as an anti-malarial agent. Patients who became anaemic during pregnancy were excluded of the study and analysis. Outcomes measured included reticulocyte count, haematocrit, anaemia, side effects Both groups received iron and folic acid supplements, thus making the comparisons not suitable for this review
Ogunbode 1992	315 apparently healthy pregnant women attending 4 prenatal care clinics in 4 geographical areas of Nigeria with mild to moderate anaemia (as defined by haematocrit between 26%-34%) and 18-28 weeks of gestation, single pregnancies, no complications and who consented to participate in the study were randomly allocated to 1 of 2 groups: group 1 (n = 159) received 1 daily capsule of a multiple micronutrient supplement Chemiron® containing 300 mg of ferrous fumarate, 5000 μg (5 mg) folic acid, 10 μg vitamin B_{12}, 25 mg of vitamin C, 0.3 mg magnesium sulphate and 0.3 mg of zinc sulphate; group 2 (n = 156) received a capsule containing 200 mg ferrous sulphate and 5000 μg (5 mg) of folic acid. All patients were also provided 600 mg of chloroquine to be taken under supervision and 25 mg weekly of pyrimethamine throughout pregnancy. Patients who became anaemic during pregnancy were excluded of the study and analysis. Outcomes measured included blood Hb, anaemia, haematocrit, serum ferritin levels, side effects. A second published study followed these same women and their infants Both groups received iron and folic acid supplements, thus making the comparisons not suitable for this review
Ortega-Soler 1998	41 healthy pregnant women, attending prenatal care clinics at Hospital Diego Paroissien in La Matanza, Province of Buenos Aires, Argentina with serum ferritin below 50 mg/mL were assigned to 1 of 2 groups: group 1 received 100 mg of elemental iron daily (as ferric maltosate), and group 2 received no treatment. Supplementation started at 21 +/− 7 weeks of gestation until birth. Maternal outcomes measured included: Hb, erythrocyte protoporphyrin, serum ferritin at baseline and term, dietary intake. The iron intake was unsupervised and compliance was not reported The trial is not randomised nor quasi-randomised so it does not fill the inclusion criteria for this review
Osrin 2005	1200 healthy pregnant women with a singleton pregnancy and less than 20 weeks' gestation attending an antenatal clinic at Janakpur zonal hospital in Nepal, were randomly assigned to receive routine 60 mg elemental iron daily and 400 μg (0.4 mg) folic acid supplements or a multiple micronutrient supplement containing 15 vitamins and minerals including 30 mg elemental iron and 400 μg (0.4 mg) folic acid Both groups received iron and folic acid. No comparisons allowed within the scope of this review
Payne 1968	200 pregnant women attending antenatal clinics in Glasgow, Scotland with less than 20 weeks' gestation, whose antenatal care was undertaken wholly by the hospital antenatal clinic and who subsequently had a normal delivery, were randomly allocated to receive 200 mg of ferrous sulphate daily or 200 mg of ferrous sulphate with 1700 μg (1.7 mg) of folic acid daily throughout pregnancy Both groups received iron. No comparisons allowed within the scope of this review
Pena-Rosas 2003	116 pregnant women of 10-30 week of gestational age attended antenatal care clinics in Trujillo, Venezuela were randomly allocated to receive a 120 mg oral dose of iron (as ferrous sulphate) and 500 μg (0.5 mg) of folic acid weekly (n = 52) or 60 mg elemental iron (as ferrous sulphate) and 250 μg (0.25 mg) folic acid and a placebo twice weekly (n = 44). Hb, HCT , serum ferritin and transferrin saturation were estimated at baseline and at 36-39 week of gestation All groups received iron and folic acid in 2 intermittent regimens with no control group. No comparisons allowed within the scope of this review
Picha 1975	In a randomised double-blind study the new effervescent iron tablet Loesferron® was tested in 57 postpartum women. The participants were not pregnant women
Pita Martin 1999	203 healthy pregnant women with normal blood pressure at first visit, attending antenatal care clinic at Diego Paroissien Hospitalin the Province of Buenos Aires, Argentina were included in the study, but in this review only 41 women who were randomised and completed the study were included in the analysis. Participants were assigned to 1 of 3 groups: group 1 received 60 mg of elemental iron (as ferrous fumarate) daily; group 2 received 60 mg elemental iron (as ferrous fumarate) every 3 days; and group 3 received no treatment. Supplementation started at 8-28 weeks until 34-37 weeks of gestation. Outcomes: maternal: Hb, haematocrit, erythroporphyrin, serum ferritin concentration at baseline and at 34-37 weeks' gestation, premature delivery, birthweight. Unsupervised. Compliance not reported Women from control group (group 3) were not assigned randomly. These women were recruited but due to delays in the acquisition of the iron tablets and the progression of their pregnancies without supplementation they were left as controls in the study
Powers 1985	Eighty-one pregnant 14-36 wk of gestation or lactating (1-20 months post partum) women with Hb less than 140 g/L living in a village in The Gambia were allocated to one of four groups: group 1 received daily placebo; group 2 received 5 mg riboflavin; group 3 received 30 mg ferrous sulphate; group 4 received 30 mg ferrous sulphate + 5 mg riboflavin. At the beginning of the study and at 3 and 6 weeks thereafter women were examined clinically and blood samples collected for haematological and biochemical measurements. This is not a randomised trial
Quintero 2004	107 healthy pregnant women with 6-20 weeks of gestation who had not received iron supplements during the current pregnancy attending 19 health units in the State of Morelos, Mexico were randomly assigned by block pairs to receive either 120 mg of elemental iron (as ferrous sulphate) in a single dose daily or once weekly. Hb concentration, prevalence of anaemia and nutrient consumption at baseline and after 10 weeks of supplementation were measured Both groups received iron in different regimens (daily versus weekly). Gestational ages were variable among the participants
Rae 1970	In this quasi-randomised trial, pregnant women attending antenatal clinic at the Department of Obstetrics and Department of Haematology, Walton Hospital, Liverpool, United Kingdom were assigned to one of two groups: group 1 received 200 mg ferrous gluconate three times a day throughout pregnancy; group 2 received 200 mg ferrous gluconate + 5000 μg (5 mg) three times a day. Both groups received iron daily. The type of comparison is outside of the scope of this review

Study	Reason for exclusion
Ramakrishnan 2003	873 pregnant women living near Cuernavaca, Morelos, Mexico with less than 13 weeks of gestation who did not use micronutrient supplements were randomly assigned to receive a daily multiple micronutrient supplement or a daily iron-only supplement. Both supplements contained 60 mg of elemental iron (as ferrous sulphate). Supplement intake was supervised by trained workers from registration until delivery by home visits 6 days a week No comparison allowed within the scope of this review.
Rayado 1997	394 healthy non-anaemic adult pregnant women with 24-32 weeks of gestation and singleton pregnancy from Fuentalabra, Spain were randomly assigned to 1 of 2 groups: group 1 received 40 mg of elemental iron (as iron mannitol albumin) daily; and group 2 received 40 mg elemental iron (as iron protein succinylate) daily Both groups received iron daily. No comparisons allowed within the scope of this review
Reddaiah 1989	110 pregnant women attending the antenatal clinic at Comprehensive Rura Health Services Project Hospital, Ballabgarh, India, with 16-24 weeks of gestation were randomly assigned to 1 of 3 groups: group 1 received 60 mg elemental iron (as ferrous sulphate) and 500 μg (0.5 mg) of folic acid daily; group 2 received 120 mg elemental iron (as ferrous sulphate) with 500 μg (0.5 mg) of folic acid daily; and group 3 received 240 mg elemental iron (as ferrous sulphate) and 500 μg (0.5 mg) of folic acid daily All groups received iron daily. No comparisons allowed within the scope of this review
Ridwan 1996	176 pregnant women with 8-24 weeks of gestation attending antenatal care at 6 health centres in West Java, Indonesia. Health centres were randomised to 1 of 2 interventions: weekly regimen, where women received 120 mg of elemental iron (as ferrous sulphate) with 500 μg (0.5 mg) of folic acid; or daily regimen where women received 60 mg of elemental iron (as ferrous sulphate) with 250 μg (0.25 mg) of folic acid daily until week 28-32 of gestation. Supplementation started at 8-24 weeks until 28-32 weeks of gestation Both groups received iron in different regimens.
Robinson 1998	680 pregnant women served by 11 health centres from 5 sub-districts on or near the western end of the island of Seramin the Province of Maluku, Indonesia were assigned to 1 of 2 interventions: group 1 received 60 mg of elemental iron (as ferrous sulphate) with 250 μg (0.25 mg) of folic acid daily by a traditional birth attendant; group 2 received 120 mg of elemental iron (as ferrous sulphate) with 500 μg (0.5 mg) of folic acid once a week by the traditional home visiting birth attendants. A control group was formed by participants receiving traditional iron supplements (60 mg elemental iron) with folic acid from health centres, self administered without incentive Groups 1 and 2 both received iron in different regimens. The control group was not assigned the traditional iron supplement
Rolschau 1979	36 pregnant women were selected consecutively, paired two and two, and allotted to two groups, one of which was supplied daily with 5000 ug (5 mg) folic acid, and the second with tablets without folic acid, from the 23rd week of pregnancy. The type of comparison is outside the scope of this review
Roth 1980	23 pregnant women were assigned to one of two groups during August 1976 and September 1977: group 1 (n = 11) received a supplement daily 'Tardyferon-Fol ®" containing 80 mg ferrous sulphate and 350 ug (0.35 mg) folic acid; group 2 (n = 12) received a supplement daily' Tardyferon®" containing 80 mg ferrous sulphate. Both groups received iron. The type of intervention is outside the scope of this review
Roztocil 1994	84 non-anaemic pregnant women at Mazarik University Brno in Czech Republic were treated from 20- 24 weeks with 1 capsule of Actiferrin Compositum®, and from 36 weeks to delivery with 2 capsules. The group was compared with 57 non-anaemic pregnant women who received no supplements. The supplement contained 34.5 mg of elemental iron (as ferrous sulphate), 500 μg (0.5 mg) of folic acid, and 0.3 mg of cyanocobalamin This is not a randomised trial. No comparisons allowed within the scope of this review
Rybo 1971	117 pregnant women between 20-29 weeks of gestation were alternatively assigned during 3 consecutive 2 weeks periods to receive daily tablets containing 200 mg of elemental iron (as ferrous sulphate), 200 mg of elemental iron (as a sustained released iron) or placebo. After each 2-week treatment period women were questioned about possible side effects. No side effects are reported by group assigned. No comparisons are allowed within the scope of this review
Sachdeva 1993	In this study carried out in rural India 66 pregnant women from low- and middle-income groups received nutritional supplements. Women in both groups received both iron and folic acid supplements. In addition, women in the experimental group received a calcium supplement, individual and group counselling and a booklet about nutrition in pregnancy All women received iron and folic acid supplements (the dose and regimen were not clear) and it was not clear that allocation to groups was random
Saha 2007	100 pregnant women aged 20-40 years at 14 to 27 weeks' gestation, with Hb < 90 g/L, and serumferritin <12 μg/L, attending the Department of Pharmacology and the Department of Obstetrics and Gynaecology at the Postgraduate Institute of Medical Education and Research, Chandigarh, India were randomly assigned to 1 of 2 groups: group 1 received 100 mg elemental iron (as iron polymaltose complex) and 500 μg (0.5 mg) folic acid daily, and group 2 received 120 mg elemental iron (as ferrous sulphate) and 500 μg (0.5 mg) folic acid daily for 8 weeks Both groups received iron and folic acid. No comparisons can be made within the scope of this review
Sandstad 2003	233 pregnant women attending their second antenatal care visit at the University Health Services of Oslo, Norway with serum ferritin concentration < 60 μg/L were randomised to 2 different iron preparations: group 1 received 1 tablet containing 60 mg of elemental iron (as ferrous sulphate) daily; group 2 received 3 tablets each containing 1.2 mg of heme iron from porcine blood plus 8 mg of elemental iron (as ferrous fumarate) per tablet (total 3.6 heme iron and 24 mg elemental iron) daily. A third group (n = 93) of pregnant women who had been given advice to take or not the iron supplements according to the centre recommendations were enrolled in the trial at 6 weeks postpartum and served as control The study groups were not randomised to the interventions and no comparisons can be made within the scope of this review
Seck 2008	221 apparently healthy pregnant women, had not used iron supplements prior to enrolment, who were 12 to 16 weeks were recruited from 6 health centres in Dakar, Senegal during their first prenatal visit, and randomly assigned to receive either a prescription to purchase iron/folic acid tablets to be taken daily, according to official policy, or to receive free tablets. Compliance was assessed 20 weeks after enrolment through interviews and pill count All women received iron. No comparisons allowed within the scope of this review

Study	Reason for exclusion
Shatrugna 1999	115 healthy pregnant women with 20-28 weeks of gestation attending the antenatal clinic of the National Institute of Nutrition, Government Maternity Hospital, India were randomly assigned to 1 of 11 different formulations and doses of iron and then undergo iron tolerance tests. They received ferrous sulphate tablets containing 60 mg, 12 mg, and 180 mg of elemental iron; formulations containing 60 mg of elemental iron as pure ferrous sulphate salt, ferrous fumarate tablets, ferrous fumarate syrup, excipients added to pure ferrous sulphate salts; powdered ferrous sulphate tablets, iron tablets distributed by the National Nutritional Anaemia Prophylaxis Programme and pure ferrous salt in gelatin capsules All women received iron. No comparisons allowed within the scope of this review
Sinha 2011	50 pregnant women between 16-20 wk of gestation with haemoglobin equal or greater than 100 g/L in Allahabad, in the north Indian state of Uttar Pradesh, India were randomly assigned to one of two groups: group 1 (n = 22): women received two doses of 400 mg iron sucrose infusion, one at 16-20 wk gestation and a second infusion at 28-32 wks gestation; group 2 (n = 28): women received 100 mg oral ferrous ascorbate daily starting at 16-20 wk gestation The type of intervention is outside the scope of this review
Sjostedt 1977	300 pregnant women attending the Maternity Welfare Center, in Oulu, Finland before the 5th month of pregnancy were randomly assigned to 1 of 3 groups: group 1 received 100 mg of elemental iron (as sustained-release tablets) daily; group 2 received 200 mg of elemental iron daily (as sustained-release tablets) and group 3 received 200 mg of elemental iron daily (as rapidly disintegrating ferrous sulphate tablets) All groups received iron in different doses and formulations
Sood 1979	151 healthy pregnant women with Hb > 50 g/L who had not received iron supplements during the last 6 months from Delhi and Vellore, India were divided in 1 of 3 strata according to Hb concentration (50-79 g/L; 80-109 g/L;110 g/L and above) and within each strata were allocated randomly to 1 of 5 interventions: group 1 received 120 mg of elemental iron (as ferrous sulphate) 6 days a week; group 2 received 100 mg of elemental iron (as iron dextran complex) intramuscular twice per week; group 3 received iron as group 1 + pteroylmonoglutamic acid 5 mg/d 6 days a week + cyanocobalamin 100 μg intramuscular once per 14 d; group 4 received 100 mg of elemental iron intramuscular + pteroylmonoglutamic acid + cyanocobalamin 100 μg intramuscular; and group 5 received iron dextran complex intramuscular in a single total dose infusion + 5 mg/d pteroylmonoglutamic acid + 100 μg intramuscular cyanocobalamin once per 14 days All groups received iron at different doses and routes. No comparisons allowed within the scope of this review
Srisupandit 1983	567 pregnant women 16-30 years of age with 18-26 wks gestation attending antenatal care clinic, in the department of Obstetrics and Gynecology of the Siriraj Hospital, Thailand were randomly assigned to one opf three groups; group 1 received 60 mg elemental iron daily; group 2 received 180 mg elemental iron daily; and group 3 received 180 mg elemental iron and 5000 ug (5 mg) folic acid daily. The intervention lasted three months. THere were 101 losses to follow-up. All participants received iron. The type of interventions is outside the scope of this review
Steer 1992	Trial abandoned. No data available.
Stone 1975	248 healthy pregnant women attending hospital antenatal clinic in London, England, were allocated randomly to receive 105 mg of elemental iron (as ferrous sulphate slow release dose) and 350 μg (0.35 mg) of folic acid daily or 80 mg of elemental iron (as ferrous fumarate) and 400 μg (0.4 mg) of folic acid daily in a standard preparation Both groups received iron in different doses and preparations. No comparisons allowed within the scope of this review
Swain 2011	100 women with uncomplicated pregnancy were assigned to received either injectable iron sucrose (400 mg diluted in 400 ml of normal saline) over 2-3 hours or to receive oral dose of 100 mg elemental iron daily. The interventions in this trial are outside of the scope of this review
Tampakoudis 1996	82 pregnant women with Hb concentrations 140 g/L or above attending clinic in Thessaloniki, Greece were randomised to receive 80 mg iron protein succinylate daily or a placebo. Serial Hb, haematocrit and serum erythropoietin were measured from maternal blood and cord blood on delivery; serum ferritin measured in frequent intervals. Abstract only available Insufficient information to assess characteristics of the trial
Tan 1995	285 healthy middle-class pregnant women with Hb concentration above 100 g/L attending antenatal clinic at the University Hospital at Kuala Lumpur, Malaysia were assigned to receive daily iron supplements or no treatment Abstract only available. No additional information was available, including doses, regimens or any other characteristics of the trial
Tange 1993	128 anaemic and non-anaemic pregnant females aged 10-19 years old, with an average gestation of 16 weeks, were grouped for 3 levels of iron supplementation: group 1 (n = 42 non-anaemic participants) received placebo (no iron); group 2 (n = 41 anaemic and non-anaemic participants) received 22 mg of elemental iron daily and group 3 (n = 45 anaemic and non-anaemic participants) received 55 mg elemental iron daily. Women were supplemented from 16 weeks until delivery. Outcomes assessed included Hb, haematocrit, red cell count, mean corpuscular volume, serum iron, serum transferring and serum, ferritin measured every 4 weeks The study is not reported as randomised and is excluded in the first screening for eligibility.
Thane-Toe 1982	135 healthy pregnant women between 22-28 weeks of gestation attending antenatal clinic in Burma, were randomly assigned to receive a daily dose of 60 mg, 120 mg or 240 mg of elemental iron (as ferrous sulphate). A control group was composed by 47 apparently healthy adults (17 males and 30 single women) Control groups are not appropriate. No comparisons allowed within the scope of this review
Thomsen 1993	52 healthy non-anaemic nulliparous women with normal singleton pregnancy and serum ferritin levels above 15 mg/L at 16th week in Herlev, Denmark were randomly assigned to receive either a daily tablet containing 18 mg elemental iron or a daily tablet containing 100 mg of elemental iron from 16 weeks until delivery. All women received 300 μg (0.3 mg) of folic acid daily. All women received iron in different doses. No comparisons allowed within the scope of this review
Trigg 1976	158 pregnant women seeking antenatal care with general practitioners in the former South-east England Faculty of the Royal College of General Practitioners, in South England, United Kingdom were assigned to one of two groups: group 1 (n = 76) received 50 mg ferrous sulphate daily to 76 pregnant women was compared with giving ferrous sulphate 50 mg daily + 500 μg (0.5 mg) folic acid. After the first test patients were randomly allocated to one of the two treatments which was either a minimum of 50 mg of ferrous sulphate daily or a minimum of 50 mg of ferrous sulphate plus 500 μg (0.5 mg) of folic acid daily, and afterwards allocation was in sequence. Both groups received iron. The type of comparison is not within the scope of this review
Vogel 1963	191 consecutive pregnant when attending antenatal care clinics and at 32 weeks of gestation were divided in 2 groups by alternate allocation by clinic: group 1 received 140 mg of elemental iron daily (as ferrous gluconate) in 4 tablets; group 2 received 150 mg elemental iron daily (as ferrous glutamate) in 3 tablets. All women received iron in different dose and number of tablets. No comparisons allowed within the scope of this review
Wali 2002	60 iron-deficient anaemic pregnant women with the gestational age of 12-34 weeks were randomly assigned to 1 of 3 groups: group 1 (n = 15) received intravenous 500 mg of iron sucrose for storage; group 2 (n = 20) received intravenous

Study	Reason for exclusion
	iron sucrose according to deficit calculated as per formula with 200 mg of iron was given for storage and group 3 received intramuscular iron Sorbitol in the dose used as practice. All groups received iron intravenous or intramuscular
Weil 1977	29 attending a clinic at University of Basel, Switzerland between May and November 1976 with 20 wk gestation were randomly assigned in one of two groups: group 1 (n = 15) received 80 mg elemental iron slow release as ferrous sulphate (Tardyferon®); group 2 (n = 14) received 80 mg elemental iron slow release as ferrous sulphate + 350 μg (0.35 mg) folic acid (gino-Tardyferon®) until term. Women who had already taken multiple micronutrient supplements containing folic acid were excluded from the study. Both groups received iron. The type of interventions is outside the scope of this review
Willoughby 1966	350 consecutive pregnant women attending antenatal care clinic were allocated to 1 of 5 groups: group 1 received no hematinic supplements; group 2 received 105 mg of elemental iron daily (as iron chelate aminoates); group 3 received 105 mg of elemental iron daily with 100 μg (0.1 mg) of folic acid; group 4 received 105 mg of elemental iron daily with 300 μg (0.3 mg) of folic acid; and group 5 received 105 mg of elemental iron daily with 450 μg (0.45 mg) of folic acid. All women received a multivitamin preparation (Vivatel®) free of folic acid This is not a randomised trial.
Willoughby 1968	68 pregnant women attending antenatal care clinic in Queen Mother's Hospital in Scotland, were randomly allocated to receive 195 mg of elemental iron alone daily or 195 mg of elemental iron in conjunction with 300 μg (0.3 mg) of folic acid daily Both groups received iron. No comparisons allowed within the scope of this review
Winichagoon 2003	484 healthy pregnant women with 13-17 weeks of gestation who had not received iron supplements before enrolling in the study, and who had a Hb concentration > 80 g/L attending antenatal care clinics at the district hospital and 7 health centres from 54 villages in the Province of Khon-Kaen in northeast Thailand The villages were grouped according to size and then randomised in 4 clusters to 1 of 3 interventions: group 1 received a daily regimen providing 60 mg of elemental iron (as ferrous sulphate) with 250 μg (0.25 mg) of folic acid daily; group 2 received 120 mg of elemental iron with 3500 μg (3.5 mg) of folic acid once a week; and group 3 received 180 mg of elemental iron (as ferrous sulphate) with 3500 μg (3.5 mg) of folic acid once a week. Supplementation started at 15 +/− 2 weeks until delivery All groups receive iron in different regimens (weekly versus daily) or doses. No comparisons allowed within the scope of this review
Wu 1998	369 pregnant women attending antenatal care at Beijing Hospital, China were divided into 2 groups according to their initial Hb concentrations. Women with Hb 110 g/L or above were randomly assigned to 1 of 2 groups: group 1 (n = 96) received 1 daily tablet of maternal supplement containing 60 mg of elemental iron in addition to other micronutrients including calcium and magnesium ; group 2 (n = 95) served as control and received no supplements. Another group of women with Hb < 110 g/L (treatment group) were randomly assigned to 1 of 3 groups: group 1 received 1 tablet of maternal supplement daily; group 2 received 0.9 g of ferrous sulphate daily; and group 3 received 1 tablet of Ferroids, a sustained released preparation daily. In the preventive group, women entered the study from 20-24 gestational weeks. In the treatment groups, women less than 36 gestational weeks were accepted. No comparisons allowed within the scope of this review This is not a randomised trial.
Yecta 2011	210 pregnant women with 17-20 weeks' gestation and singleton pregnancies, no known disease, and Hb levels higher than 110 g/L attending local public health care centres at seven prenatal healthcare clinics between September 2007 and February 2009 in the urban regions of Urmia city North West Iran were randomly assigned to one of three groups: group 1 (n=70) received two iron supplementation tablets once weekly providing 100 mg elemental iron per week (as ferrous sulfate); group 2 (n = 70) received one tablet twice weekly providing 100 mg elemental iron per week (as ferrous sulfate); and group 3 (n = 70) received one tablet daily containing 50 mg elemental iron per day (as ferrous sulfate). No additional micronutrients were supplied. Hb and serumferritin levels were measured at 20, 28, and 38 weeks. Pregnancy and birth outcomes (pregnancy termination, method of delivery, birth weight, stillbirth) were reported. All participants received iron in different regimens. The type of interventions is outside the scope of this review
Young 2000	413 healthy non-severely anaemic pregnant women attending antenatal care at Ekwendeni Hospital or its mobile clinics in northern Malawi with less than 30 weeks of gestation at their first visit, stratified by initial Hb concentration before randomisation. Supplementation starting time variable (22.2 +/− 4.8 weeks) and ending time variable (32.2 +/− 4.4 weeks of gestation). Participants were randomly assigned within each anaemia grade category to 1 of 2 interventions: group 1 received 120 mg of elemental iron (as ferrous sulphate) with 500 ?g (0.5 mg) of folic acid once a week; group 2 received 60 mg of elemental iron (as ferrous sulphate) with 250 ?g (0.25 mg) of folic acid daily. Outcomes: maternal: Hb concentration at baseline and after 8 weeks of supplementation; compliance, presence of side effects, and prevalence of anaemia All women received iron and folic acid in different regimens (daily versus weekly). No comparisons allowed within the scope of this review
Young 2010	This trial examines the relative differences in heme (animal based) and non-heme (ferrous sulphate) iron utilisation in 20 non-smoking, pregnant women (19 y or older; n = 10) and adolescents (18 years of age or younger; n = 10) from the Strong Midwifery Group and the Rochester Adolescent Maternity Program in Rochester, NY, USA and 12 healthy, nonsmoking, non-pregnant women ages 18- 27 y recruited in 2009 from Ithaca, NY, USA. Women were randomly assigned to receive both an animal-based heme meal (intrinsically labelled 58Fe pork) and labelled ferrous sulphate (57Fe) fed on alternate days The type of design and the comparisons of this study are outside the scope of this review
Yu 1998	51 healthy pregnant women with 18-22 weeks of gestation who had not taken supplements or medication in the previous 6 months attending public health centre in Ulsan, South Korea were randomly assigned to 1 of 2 groups: group 1 received 160 mg of elemental iron (as ferrous sulphate) in 1 intake once a week; group 2 received 80 mg of elemental iron (as ferrous sulphate) daily. Women with low Hb were assigned by the trialists to daily regimen. Supplementation started at 20.1 weeks and 20.2 weeks of gestation for groups 1 and 2 respectively Both groups receive iron in different regimens (weekly versus daily). No comparisons allowed within the scope of this review
Zamani 2008	152 healthy, non-anaemic pregnant women aged 18-38 years, 15-16 weeks' gestation (gestation estimated by menstrual dates and ultrasound) attending 2 clinics for prenatal care in Isfahan, Iran. ("In Iran, it is mandatory to prescribe iron (1 tablet containing 45 mg elemental iron (as ferrous sulphate) per day) and folic acid supplements to pregnant women after the 15th- 18th week of gestation"). Exclusion criteria: current anaemia (Hb < 110 g/L), past history of anaemia, thalassaemia, or other blood disorders, history of previous obstetric problems (haemorrhage, pregnancy induced hypertension, diabetes) or any other chronic systemic disorder. Participants were assigned to 1 of 2 groups: group 1 (experimental group) received 2 tablets of 45 mg elemental iron (as ferrous sulphate) taken on a single day each week. "Women in the trial group were instructed to choose any day of the week and to take 2 tablets of 45 mg elemental iron (as ferrous sulphate) each on the same day every week, 1 in the morning and 1 before dinner" i.e. 90 mg of "elemental iron (as ferrous sulphate) 1 day per week in two takes". (Supplied as 8 tablets every 4 weeks) for 16 weeks (from recruitment at 16-18 weeks); group 2 (control group) were to take 1 tablet containing 45 mg elemental iron (as ferrous sulphate) daily for 16 weeks (from recruitment at 16-18 weeks). Supplied as 28 tablets every 4 weeks

Study	Reason for exclusion
	Both groups receive iron in different regimens (weekly versus daily). No comparisons allowed within the scope of this review
Zhou 2009	180 anaemic women (Hb < 110 g/L) attending antenatal care at the Children, Youth and Women's Health Service, Adelaide, Australia with 24-32 weeks of gestation and a singleton pregnancy. Women were excluded if they were taking iron or vitamins and minerals supplements, had presumptive diagnosis of non iron-deficiency-related anaemia, history of thalassaemia, drug or alcohol abuse and/or diabetes requiring insulin or a known fetal abnormality. Women were randomly assigned to receive a daily dose of 20, 40 or 80 mg of elemental iron (as ferrous sulphate) for 8 weeks or until birth. The primary outcomes measured were Hb levels, anaemia at the end of the intervention and gastrointestinal side effects during treatment All women received iron at different doses. No comparisons allowed within the scope of this review
Zutshi 2004	200 apparently pregnant women with 24-26 weeks of gestation, with singleton pregnancy and moderate anaemia (Hb > 80 g/L and < 110 g/L) were randomly assigned to receive injectable iron-sorbitol-citrate in 3 intramuscular doses of 150 mg each at 4 weeks intervals or 100 mg of elemental iron daily. Hb concentrations were measured at baseline, every 4 weeks and at delivery. The study compares 2 routes of iron administration. Both groups receive iron. No comparisons allowed within the scope of this review

BMI: body mass index

Hb: haemoglobin

IU: international units

RDA: Recommended Dietary Allowance

Characteristics of ongoing studies *[ordered by study ID]*

Biggs 2010

Trial name or title	A randomised controlled trial to compare the impact on birthweight of daily iron-folic acid, twice weekly iron-folic acid and twice weekly multiple micronutrient supplementation for pregnant women in Ha Nam province, Vietnam
Methods	Randomised controlled trial.
Participants	Healthy pregnant women 16 weeks' gestation or less. Exclusion criteria: complicated pregnancies (e.g. twins, diabetes, other medical conditions), or Hb 80 g/L or lower
Interventions	The trial has 3 arms. Arms 1. and 2. will each receive a different intervention as follows: 1. micronutrient supplement (elemental iron 60 mg, folic acid 1.5 mg) taken orally twice weekly for the duration of pregnancy and 3 months postpartum. and 2. micronutrient supplement (multiple micronutrients - modified 2×UNIMAPP) taken orally twice weekly for the duration of pregnancy and 3 months postpartum
Outcomes	Primary: birthweight. Secondary: infant cognitive development, infant haemoglobin, infant height, maternal ferritin, maternal Hb
Starting date	28/09/2010.
Contact information	Dr. Beverley-Ann Biggs Department of Medicine Royal Melbourne Hospital Parkville, Victoria, 3050, Australia babiggs@unimelbi.edu.au
Notes	Sponsors: National Health and Medical Research Council (NHMRC) and Research and Training Center for Community Development (RTCCD)

Cogswell 2006

Trial name or title	Impact of iron/folic acid versus multi micronutrient versus folic acid supplements during pregnancy on mortality, morbidity, and complications during pregnancy, labor, and delivery: a randomised controlled trial in China
Methods	Randomised controlled trial.
Participants	Pregnant women 20 years or older who live in 1 of the study counties (Laoting, Mancheng, Fengrun, Xianghe, Yuanshi), who can follow instructions and can swallow pills
Interventions	Daily prenatal supplements that contain 400 μg (0.4 mg) folic acid alone, or daily supplements that contain 30 mg iron and 400 μg (0.4 mg) folic acid. Daily supplements that contain 30 mg iron and 400 μg (0.4 mg) folic acid or daily supplement containing 30 mg iron, 400 μg (0.4 mg) folic acid and other vitamins and minerals (UNICEF formulation)
Outcomes	Perinatal mortality, i.e., the number of stillbirths (fetal deaths of 28 weeks or more of gestation) and the number of deaths within the first 0-6 days of life per 1000 births (live births and stillbirths); gastrointestinal side effects at monthly visits

Starting date	May 2006; expected completion: December 2010.
Contact information	Mary E Cogswell, DrPH, RN 770-488-6053 MCogswell@cdc.gov Mei Zuguo, MD, MPH 770-488-5864 ZMei@cdc.gov
Notes	Principal Investigator: Mei Zuguo, MD, MPH 770-488-5864 ZMei@cdc.gov

Dibley 2012

Trial name or title	A trial to evaluate the impact of an early start to iron/folic acid supplementation in pregnancy on deaths of newborns in rural Bangladesh
Methods	Community-based cluster-randomised controlled trial. The interventions will be assigned to eligible clusters using a fixed randomisation scheme with uniform allocation ratio of treatments, stratified by Sub-Districts (upazilla) and in blocks of 5 or 10 to ensure geographic balance across each geographic area. The random allocation sequence will be generated using SAS software
Participants	32000 pregnant women registered in the 202 study clusters trained by Bangladesh Rural Advancement Committee, an NGO based in Bangladesh. Exclusion criteria: 1) clusters on the sampling frame will be excluded if there are other interventions to improve antenatal iron/folic acid distribution currently being implemented either by government or non-government sectors. 2) clusters located in areas where access is extremely difficult, for example, low land areas which are prone to flooding for extended periods of the year, will also be excluded. 3) cohort evaluation: pregnant women with more than 16 weeks of gestational age at enrolment will be excluded from 'cohort' follow-up
Interventions	Clusters will be assigned to 1 of 2 interventions: group 1: women in this group will receive a daily dose of 60 mg elemental iron + 400 μg (0.4 mg) folic acid supplementation early in pregnancy (in the first trimester) to be taken orally and sustained for at least 180 days, ensure resupply of supplements through fortnightly visits, and provide counselling in support of early uptake, continued use of the supplements until delivery, and compliance with the supplementation regimen; group 2: women receive standard treatment, the usual antenatal and postnatal care services provided by the Bangladesh Ministry of Health, which are supported by BRAC Essential Health Care Program
Outcomes	Primary: infant deaths occurring in the first month of life assessed by the data collected by the trained research field worker visits. at 4 weeks and 6 weeks after delivery Secondary: percentage of women using iron/folic acid as prescribed in the first trimester of pregnancy assessed by data collected by trained research fieldworker visits; percentage of live births with low birthweight (weighing < 2500 g) (intensive); percentage of live births with preterm delivery (intensive). Preterm delivery is defined as a birth occurring with gestational age before 37 weeks of gestation and includes early preterm delivery (< 34 weeks) based on maternal report of the date of last menstrual period; percentage of neonatal deaths attributable to preterm delivery asphyxia; percentage of neonatal deaths attributable to preterm delivery; mean marginal additional expenditure associated with early iron/folic acid supplementation, and the mean cost per neonatal death prevented referring to health service costs;
Starting date	Anticipated or actual date of first participant enrolment:1/12/2012
Contact information	Dr Tanvir Huda CHNRI Secretariat Coordinator, Centre for Child and Adolescent Health, ICDDR,B; Mohakhali, Dhaka 1212 Bangladesh Phone: +880 2 9840523-32/Ext. 3820 thuda@icddrb.org Prof Michael Dibley Sydney School of Public Health, Room: 307A, Edward Ford Building (A27), University of Sydney, NSW 2006 Australia Phone: +61 2 9351 3620 and +61 2 9351 5049 michael.dibley@sydney.edu.au
Notes	Funded by the National Health & Medical Research Council of Australia Primary sponsors: The University of Sydney, Australia and the International Centre for Diarrhoeal Disease Research, Bangladesh. Collaborator: Bangladesh Rural Advancement Committee (BRAC)

Fawzi 2010

Trial name or title	Prenatal iron supplements: safety and efficacy in Tanzania.
Methods	Randomised clinical trial.
Participants	Inclusion criteria: - at or before 19 weeks of gestation - primigravida or secundigravidae - not-anaemic (defined as Hb < 85 g/L) - not iron deficient (defined as serum ferritin < 12 μg/L) - HIV-uninfected - intend to stay in Dar es Salaam until delivery and for at least 6 weeks thereafter. Exclusion criteria: - after 19 weeks' gestation - not primigravida or secundigravidae - anaemic - iron deficient - HIV-infected - high iron stores at baseline (i.e., serum ferritin > 200 μg/L) - do not intend to stay in Dar es Salaam until delivery and for at least 6 weeks thereafter
Interventions	60 mg elemental iron (as ferrous sulphate) versus placebo.
Outcomes	Primary: incidence of placental malaria (time frame: delivery); infant birthweight (time frame: delivery); maternal Hb (time frame: 20 weeks' gestation); maternal Hb (time frame: 30 weeks' gestation); maternal Hb (time frame: 6 weeks postpartum); maternal Hb (time frame: delivery); placental malaria parasite density (time frame: delivery). Secondary: low birthweight (time frame: delivery); maternal anaemia (time frame: 20 weeks' gestation); maternal anaemia (time frame: 30 weeks' gestation); maternal anaemia (time frame: 6 weeks postpartum) ; maternal anaemia (time frame: delivery); maternal malaria infection (time frame: 20 weeks' gestation); maternal malaria infection (time frame: 30 weeks' gestation); maternal malaria infection (time frame: 6 weeks postpartum); maternal malaria infection (time frame: delivery)

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Starting date	Date of first enrolment: June 2010.
Contact information	Wafaie W Fawzi, MD, DrPh Telephone: +1 617 432-5299 mina@hsph.harvard.edu Affiliation: Harvard School of Public Health Zul Premji, MD, MSC, PhD Affiliation: Muhimbili University of Health and Allied Sciences
Notes	Scientific title: Prenatal iron supplements: safety and efficacy in Tanzania

Hemminki 2008

Trial name or title	Routine Iron Prophylaxis During Pregnancy (PROFEG).
Methods	A pragmatic randomised controlled trial with non-blind design. Total intended sample size is 4000 women. Hypothesis: group 2 will have better health outcomes. Study site: Mozambique, Maputo City
Participants	Pregnant women 18 years of age or older attending prenatal care in 2 health centres, 1 in Maputo city and 1 in Maputo province. The women are followed in prenatal visits and until delivery
Interventions	Women will be randomised individually and allocated into 2 different groups: group 1, women in the routine iron prophylaxis will receive 65 mg ferrous sulphate and 400 μg (0.4 mg) of folic acid daily; group 2, women will be screened in the antenatal visits with measurements of Hb. If Hb is lower than 90 g/L women will receive a monthly supply of 130 mg of iron to be taken daily and folic acid. If Hb is 90 g/L or higher then women receive 1 tablet containing 1 mg of folic acid
Outcomes	Primary outcomes: preterm delivery, low birthweight, malaria reactivation during pregnancy (mother) (time frame: until birth). Secondary outcome measures: perinatal mortality, complications during pregnancy and birth (time frame: pregnancy and neonatal period)
Starting date	The project consists of 3 interlinked phases: the preparatory phase, pilot study and trial as such. The research project started in April 2005 with the preparatory phase, the pilot study of the second phase tested the data collection methods and procedures in the study protocol. The third phase is currently ongoing
Contact information	Principal Investigator: Elina Hemminki Study Director: Baltazar Chilundo Elina Hemminki, Research Professor THL (National Institute for Health and Welfare) P.O.Box 30, 00271 Helsinki, Finland elina.hemminki@thl.fi Phone: +358-20-6107307 fax +358-20 6107227 http://groups.stakes.fi/thp/en Baltazar Chilundo, MD, PhD Universidade Eduardo Mondlande, Faculty of Medicine, Department of Community Health Phone: +258 84 3158350 chilubal@yahoo.com
Notes	

Mwangi 2011

Trial name or title	A randomised trial to assess the safety and efficacy or iron supplementation in Kenyan pregnant women
Methods	Randomised, placebo control double blind trial.

Participants	Pregnant women aged 15-45 years, with gestational age < 23 weeks resident in the predefined study area in Kenya Exclusion criteria • Failure to provide a blood sample. • Initial Hb concentration < 90 g/L. • Reported medical history suggestive of sickle cell anaemia, epilepsy, diabetes. • Obstetric history suggestive of eclampsia or pre-eclampsia. • Obvious mental retardation or metabolic disorder. • No written consent. • Carrying multiples. • Woman planning to leave the homestead or to be absent for prolonged periods in the course of the pregnancy or within a 1-month period thereafter. • Woman planning to deliver outside the research clinic.
Interventions	Daily supplementation with 60 mg elemental iron (as ferrous sulphate) or placebo
Outcomes	Primary: maternal Plasmodium infection at parturition. Secondary: serum non-transferrin bound iron concentration at 3 hours after ingestion of first supplement with either iron or placebo; neonatal iron stores at 1 month of age (assessed by plasma ferritin concentration, restricted to infants without inflammation); maternal iron status at 1 month after delivery (assessed by haemoglobin concentrations, prevalence of iron-deficiency anaemia (plasma ferritin concentration < 12 μg/L) and iron stores (ratio of ferritin:transferrin receptor concentrations); indicators based on ferritin and/or transferrin receptor will be restricted to those without inflammation; maternal intestinal pathogens at 1 month after delivery
Starting date	Starting date April 2011. Estimated study completion date: May 2013.
Contact information	Contact: Martin N Mwangi, MSc +254 734 018863 martinndegwa.mwangi@wur.nl Contact: Pauline EA Andang'o, PhD +254 728 485729 paulango@hotmail.com
Notes	Sponsors and Collaborators: London School of Hygiene and Tropical Medicine; University of Nairobi; Maseno University, Kenya; Wageningen University

Hb: haemoglobin

STD: sexually transmitted disease

Appendix 1. Search terms used for additional author searching

Review authors searched the WHO International Clinical Trials Registry Platform (ICTRP) for any ongoing or planned trials on 2 July 2012 using the terms "iron supplementation and pregnancy"; "iron and pregnancy"; "daily iron and pregnancy"; "iron supplements and pregnancy"; "daily supplements and pregnancy" and "anaemia and pregnancy". Duplicates were removed.

FEEDBACK

Hemminki, June 2008

Summary

My trial, Hemminki 1989a, is excluded from this review and it is not clear why. The comment in Characteristics of excluded studies is "Only women who were anaemic received iron in the unsupplemented group thus making any comparisons among the groups biased for the purposes of this review."

What bias is being referred to? Hemminki 1989a was in the previous version of this review. It was a randomised trial, analysed by intention to treat, having outcome data for all women randomised, and a high compliance (about 80% of women in both groups received the

treatment they were allocated to). The 20% of women who received iron in the non-routine supplementation group was as expected.

There are two options for dealing with women whose haemoglobin falls below a pre-specified cut-off in the non-routine supplemented group:

1. give them iron, as in my study where 20% of women in the non-routine treatment group had iron; or
2. call those who take iron non-compliant and do the analysis by intention to treat, as did some of the included studies.

What is the difference between these two strategies? They seem to me to be essentially the same.

The effect of routine iron therapy on substantive health outcomes remains unclear. It is a real pity that you have excluded Hemminki 1989a, based on criteria I consider inappropriate: it had a large number of women, several health outcomes including long term follow up, and was well conducted.

A minor issue is that it is misleading to call this trial Hemminki 1989a. Although the study design was published in 1989, the main results were not published until 1991. Hence a more appropriate study identifier would be ‘Hemminki 1991’. (Summary of feedback from Elina Hemminki, June 2008)

Reply

We agree that your trial was well conducted, had a large number of women and looked at several health outcomes including long term follow up. We did review all publications on the work you have conducted on assessing the effects of routine versus selective iron supplementation during pregnancy. This systematic review aims to assess the effectiveness and safety of daily and intermittent use of iron supplements by pregnant women, either alone or in conjunction with folic acid given as a preventive universal measure. Your trial provided 100 mg of elemental iron daily with various choice of iron compounds and dosage as determined individually by the midwives to all women in the routine iron supplementation group. For women in the “selective iron supplementation group”, treatment with iron supplements as slow release form for two months or until the hematocrit increased to 0.32 was provided only to those whose hematocrit was lower than 0.30 on two consecutive visits. Consequently, we have included your trial in the included studies and we thank you for the additional data you have provided us for this analysis. Your study compared the effects of routine versus selective iron supplementation, an issue that certainly deserves better understanding and that reflects current practices.

We have changed the study identifier to Hemminki 1991 as requested.

Contributors

Juan Pablo Pena-Rosas, MD, PhD, MPH

HISTORY

Protocol first published: Issue 2, 2004

Review first published: Issue 3, 2006

Date	Event	Description
16 June 2009	New search has been performed	Search updated. Ten new trials included (Cantlie 1971; Christian 2003 (C); Hemminki 1991; Harvey 2007; Lee 2005; Meier 2003; Mukhopadhyay 2004; Siega-Riz 2001; Ziaei 2007; Ziaei 2008). One trial included is now excluded (Ortega-Soler 1998). Twenty-seven new trials excluded.
16 June 2009	New citation required but conclusions have not changed	In this update, trials assessing the effect of iron or folic acid when given in combination with other micronutrients were included as long as both groups being compared in the daily regimens received the same other micronutrient interventions. This has resulted in four trials previously excluded now being included (Cantlie 1971; Christian 2003 (C); Hemminki 1991; Siega-Riz 2001).
20 October 2008	Feedback has been incorporated	Feedback from Elina Hemminki added with response from author
15 April 2008	Amended	Converted to new review format.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review updates part of Peña-Rosas 2009 to only evaluate the effects of oral daily iron supplementation regimens. In this update we have included 60 trials; 40 of these studies were included in the previous version of the review; but 10 had been excluded because they did not report outcomes of interest or the data reported were not extractable. In this version we include trials that comply with the eligibility criteria, even if there are no data extractable or do not report the outcomes of interest. In a previous version of this review, daily and intermittent provision of iron supplements were included. This review, however, only focuses on daily iron supplementation. The effects of intermittent iron supplementation are addressed in a separate review (Pena-Rosas 2012).

Outcomes

- Only pre-specified primary and secondary outcomes are reported. The non pre-specified outcomes that were included in previous versions were removed from this updated version and the overall number of haematological outcomes was reduced for clarity.
- We have added a description of the lay health worker setting for each trial. We have included a timeframe for haematological variables: at or near term (34 weeks or more gestational age) in addition to at term (37 weeks or more of gestational age).
- We have added the outcome ‘congenital anomalies’ instead of birth defects as this name reflects adequately a condition existing at birth and often before birth, which involves defects in or damage to a developing fetus.
- A new search was conducted (2 July 2012) and the comparisons were changed to evaluate the effects of daily tablets containing iron (alone or with any other micronutrients) versus no iron; iron alone; iron and folic acid; as well as the

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additional effects of iron alone or iron and folic acid when given in addition to other micronutrients in pregnancy.

Methods

This review uses the latest Cochrane methodological guidance (Higgins 2011), particularly on:

- the use of formal tests for subgroup analyses using random-effects models;
- the adjustment of cluster trials;
- the inclusion of 'Summary of findings' tables to assess the overall quality of the evidence for primary outcomes.

We included three additional subgroup analysis: by type of iron compound, iron compound release, and malaria setting.

WHAT'S NEW

Last assessed as up-to-date: 1 November 2012.

Date	Event	Description
1 November 2012	New citation required and conclusions have changed	This review updates part of Peña-Rosas 2009 to only evaluate the effects of oral daily iron supplementation regimens. The effects of intermittent iron supplementation regimens are evaluated in a separate review (Pena-Rosas 2012).
2 July 2012	New search has been performed	In this split review we updated the search and used the latest Cochrane methodological guidance. We included information on the health worker cadre and malaria setting. Specific changes to the previous version are described in the section Differences between protocol and review. Two new authors have contributed to this review.

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* *Indicates the major publication for the study*

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PLAIN LANGUAGE SUMMARY

Effects and safety of preventive oral iron or iron + folic acid supplementation for women during pregnancy

During pregnancy, women need iron and folate to meet both their own needs and those of the developing baby. The concern is that if pregnant women become deficient in these nutrients they are unable to supply them in sufficient quantities to their baby. Low folate before conceiving increases the risk of the baby having neural tube defects. Low iron and folate levels in women can cause anaemia, which can make women tired, faint, and at increased risk of infection.

We included 60 randomised trials in the review with 43 trials involving more than 27,402 pregnant women contributing to the analyses. The use of iron or iron and folic acid supplements was associated with a reduced risk of anaemia and iron deficiency during pregnancy and of giving birth to low birthweight babies. Daily iron supplementation was, however, associated with the women having side effects such as constipation and other gastrointestinal effects including nausea, vomiting and diarrhoea and an increased risk of high haemoglobin (Hb) concentrations at term. This may be harmful to mothers and babies and is associated with late pregnancy hypertension, pre-eclampsia and pregnancy complications. There is no evidence that iron supplementation increases placental malaria.

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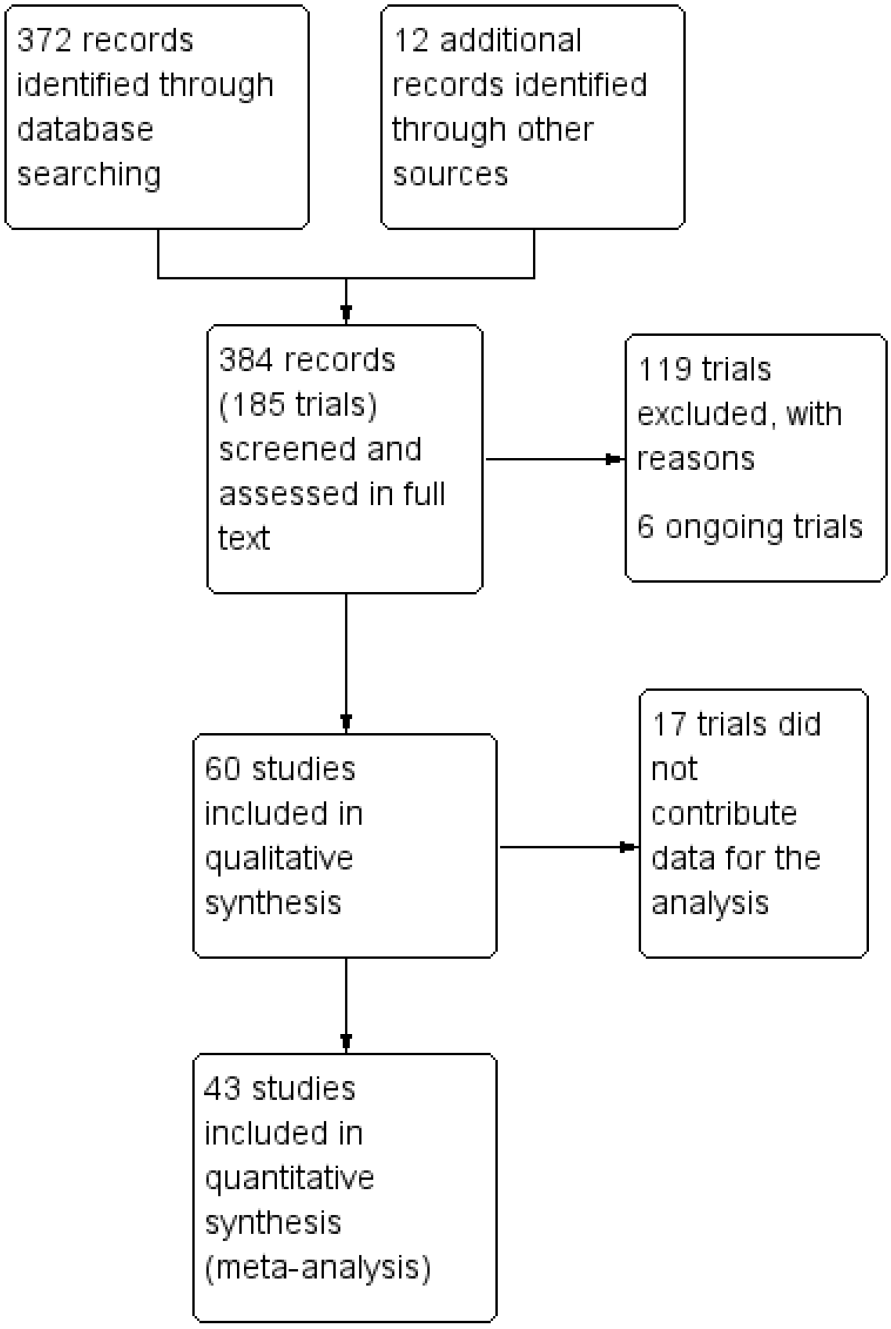

Figure 1.
Study flow diagram.

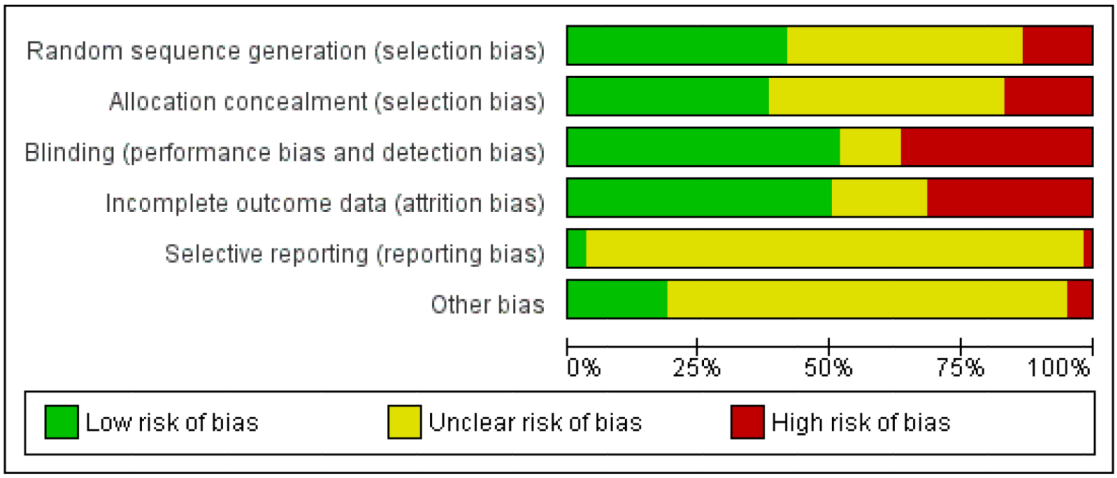

Figure 2.

'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

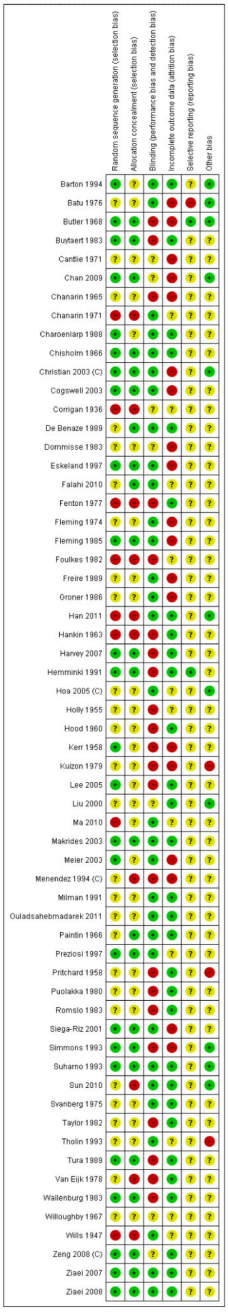

Figure 3.

'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

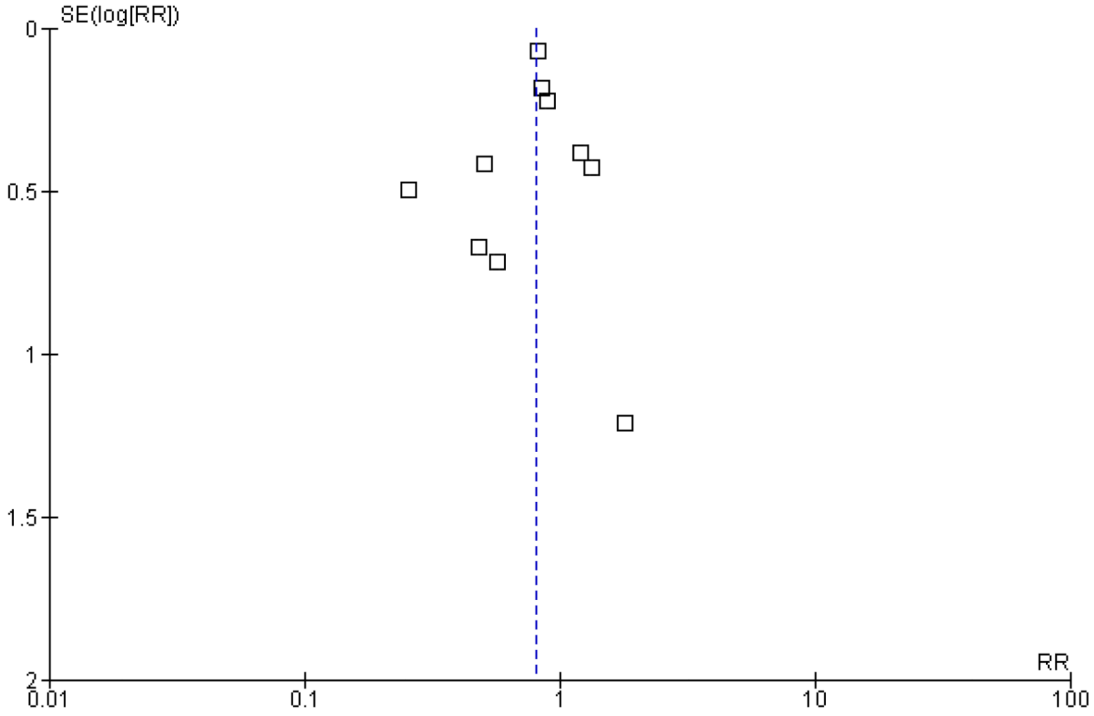

Figure 4.

Funnel plot of comparison: 1 Any supplements containing iron versus same supplements without iron or no treatment/placebo (no iron or placebo), outcome: 1.1 Low birthweight (less than 2500 g) (ALL).

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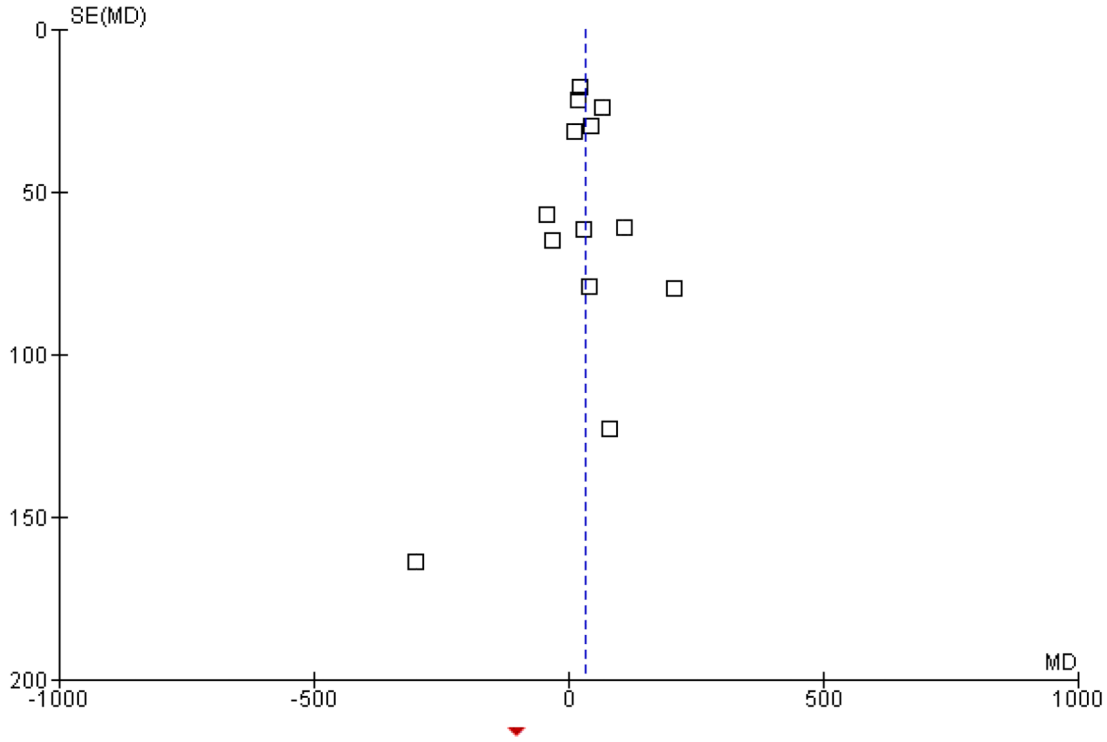

Figure 5.
Funnel plot of comparison: 1 Any supplements containing iron versus same supplements without iron or no treatment/placebo (no iron or placebo), outcome: 1.6 Birthweight (g) (ALL).

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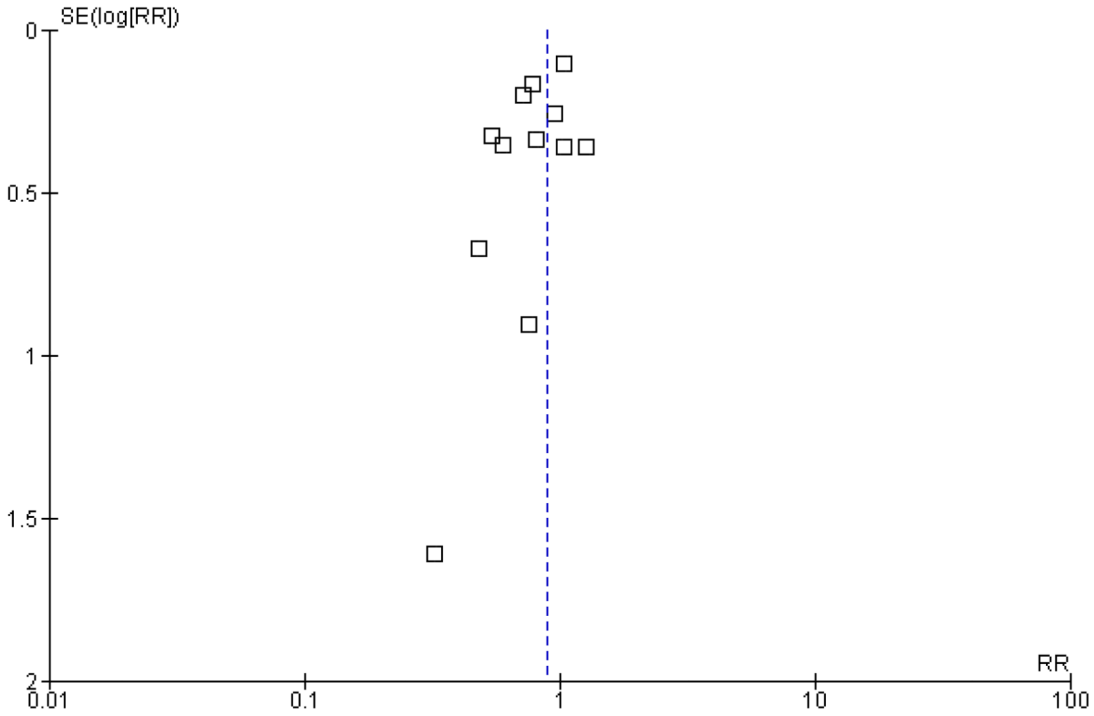

Figure 6.

Funnel plot of comparison: 1 Any supplements containing iron versus same supplements without iron or no treatment/placebo (no iron or placebo), outcome: 1.11 Premature birth (less than 37 weeks of gestation) (ALL).

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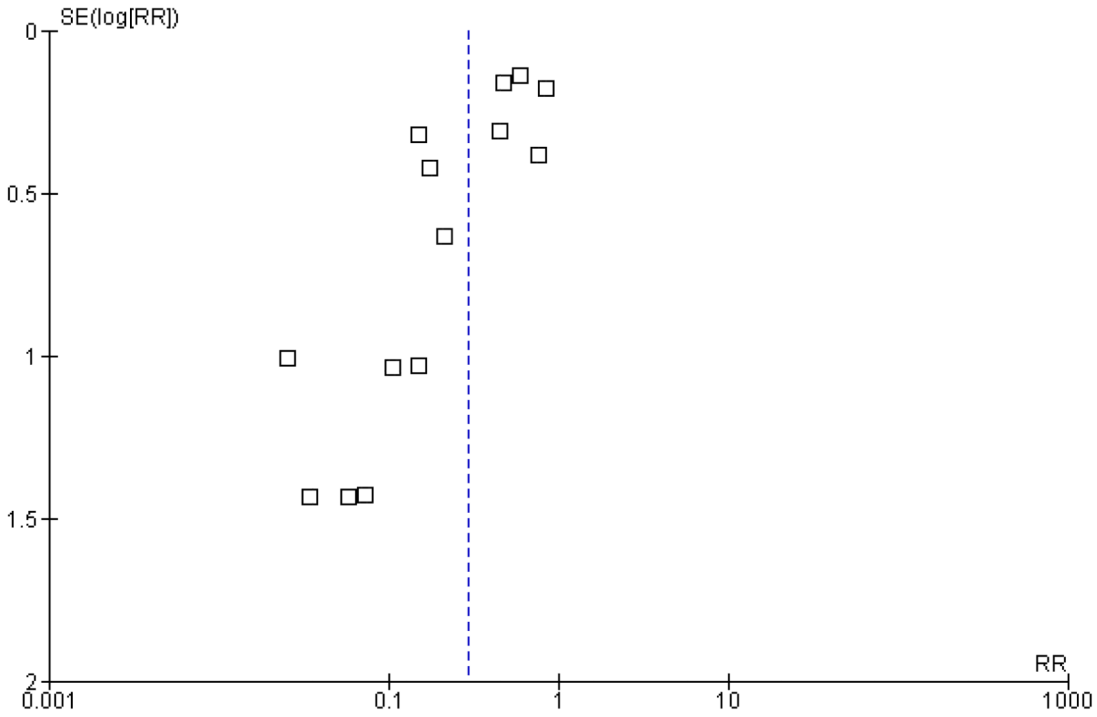

Figure 7.

Funnel plot of comparison: 1 Any supplements containing iron versus same supplements without iron or no treatment/placebo (no iron or placebo), outcome: 1.26 Maternal anaemia at term (Hb less than 110 g/L at 37 weeks' gestation or more) (ALL).

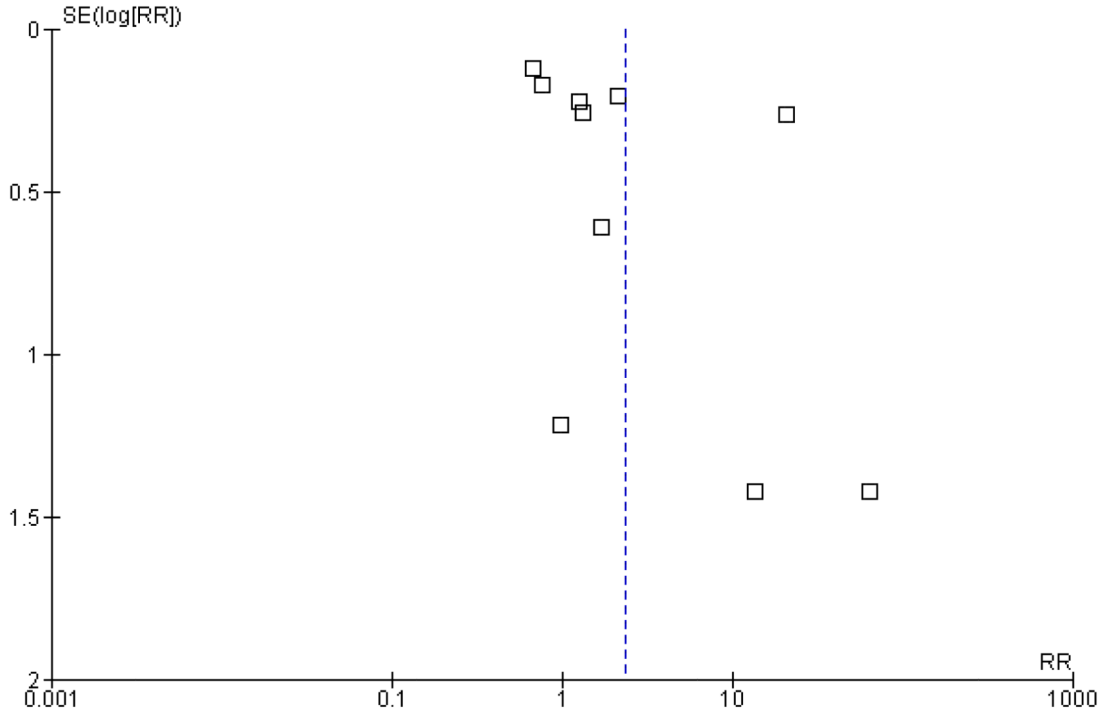

Figure 8.

Funnel plot of comparison: 1 Any supplements containing iron versus same supplements without iron or no treatment/placebo (no iron or placebo), outcome: 1.42 Side effects (any reported throughout the intervention period) (ALL).

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