Effects of routine oral iron supplementation with or without folic acid for women during pregnancy (Review)

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ABSTRACT

Background
It has been suggested that routine intake of supplements containing iron or combination of iron and folic acid during pregnancy improves maternal health and pregnancy outcomes.

Objectives
To assess the efficacy, effectiveness and safety of routine antenatal daily or intermittent iron supplementation with or without folic acid during pregnancy on the health of mothers and newborns.

Search strategy
We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (June 2005). Additionally, we contacted relevant organizations for the identification of ongoing and unpublished studies.

Selection criteria
All randomised or quasi-randomised trials evaluating the effect of routine supplementation with iron or combination of iron and folic acid during pregnancy.

Data collection and analysis
We assessed trials for methodological quality using the standard Cochrane criteria. Two authors independently assessed the trials for inclusion and one author extracted data. We collected information on randomisation method, allocation concealment, blinding and loss to follow up. The primary outcomes included maternal and infant clinical and laboratory outcomes.

Main results
Forty trials, involving 12706 women, were included in the review. Overall, the results showed significant heterogeneity across most prespecified outcomes. Heterogeneity could not be explained by standard sensitivity analyses including quality assessment; therefore, all results were analysed assuming random-effects. Very limited information related to clinical maternal and infant outcomes was available in the included trials.

The data suggest that daily antenatal iron supplementation increases haemoglobin levels in maternal blood both antenatally and postnatally. It is difficult to quantify this increase due to significant heterogeneity between the studies. Women who receive daily antenatal iron supplementation are less likely to have iron deficiency and iron-deficiency anaemia at term as defined by current cut-off values. Side-effects and haemoconcentration are more common in women who receive daily iron supplementation. No differences were evident between daily and weekly supplementation with regards to gestational anaemia; haemoconcentration during pregnancy appears less frequent with the weekly regimen. The clinical significance of hemoconcentration defined as haemoglobin greater than 130 g/L remains uncertain.

Authors' conclusions
Further studies are needed to assess the effects of routine antenatal supplementation with iron or a combination of iron and folic acid on clinically important maternal and infant outcomes.

PLAIN LANGUAGE SUMMARY

There is not enough evidence to determine with confidence if routine daily or intermittent iron or iron-folic acid supplementation in pregnancy improves functional and health outcomes for women and babies

During pregnancy, the mother and the baby need iron and folate to meet maternal needs and for the baby to develop properly. There is concern that the mother may become deficient in these nutrients and unable to sufficiently supply them to her baby. Low iron and folate levels can cause anaemia, which can make women tired, faint and be at increased risk of infection. These deficiencies could impact the mother and her pregnancy and the baby. The review of 44 trials, involving 12706 women, on routine antenatal iron or combination of iron with folic acid found insufficient data to evaluate these outcomes. Laboratory tests were reported but their functional significance is uncertain. More research is needed on preventive programs, particularly in income-poor countries.

BACKGROUND

Iron-deficiency anaemia, the late manifestation of chronic iron deficiency, is thought to be the most common nutrient deficiency among pregnant women (WHO 1992) although in pregnancy iron status is often difficult to measure. Iron deficiency is caused by an insufficient supply of iron to the cells following depletion of the body's reserves (Viteri 1998). The main causes of iron deficiency are a diet poor in absorbable iron, an increased requirement for iron (e.g. pregnancy) or a loss of iron due to parasitic infections, particularly hookworm, or other blood losses (Crompton 2002; INACG 2002a).

Although haemoglobin and haematocrit are commonly used to screen for iron deficiency, their low values are not specific to iron deficiency. While iron deficiency is the most common cause of anaemia, other causes such as acute and chronic infections that cause inflammation; deficiencies of folate, vitamin C, vitamin B12 and vitamin A; and genetically inherited traits such as thalassaemia and drepanocytosis may be independent or superimposed causal factors (WHO 2001). Anaemia in pregnancy is diagnosed if haemoglobin (Hb) concentration is lower than 110 g/L during the first and third trimesters or lower than 105 g/L during the second trimester, according to recommended U.S. Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) cut-off points. Readers should be aware of the limitations of cut-off points to define anaemia or haemoconcentration rather than defining these conditions by distributions analysis and the effect of haemoglobin on functional outcomes during pregnancy. Iron-deficiency anaemia is defined as anaemia accompanied by depleted iron stores and signs of a compromised supply of iron to the tissues (WHO 2001).

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 have limitations in their interpretation in some settings and conditions, particularly where different infections are present (malaria, HIV/AIDS, vaginosis, and others) and during pregnancy. Each test does not correlate closely with one another because each reflects a different aspect of iron metabolism. Serum ferritin concentration is an indicator of iron reserves. In pregnancy, however, serum ferritin levels as well as bone marrow iron fall even in women ingesting 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). In spite of this, a serum ferritin concentration of less than 12 µg/litre in adults is accepted to indicate depleted iron stores, even during pregnancy. Interestingly, the nadir of maternal serum ferritin occurs by week 28, before higher iron demands are believed to occur and the fall is only partially explained by the normal plasma volume expansion (Taylor 1982). Other indicators of iron status are also distorted during pregnancy even among women who are administered supplements containing 200 mg of iron daily (Puolakka 1980). Recently it has been suggested that the ratio of serum transferrin receptors to serum ferritin, a seemingly good estimator of iron nutrition in non-pregnant adults, could be used also in pregnancy to estimate iron nutritional status. However, this ratio does not seem to differentiate clearly between an iron-deficient and an iron-sufficient population of pregnant women (Cook 2003). An important consistent finding in all the above mentioned studies is the preventive effect that iron supplementation on the indicators of iron nutritional status during pregnancy, when compared with unsupplemented women (Hb, iron and ferritin declined less, and lower serum transferrin and erythrocyte protoporphyrins increased less).

Recently, a WHO and 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 of iron status as a consequence of intake of iron supplements in populations (WHO/CDC 2005). Unfortunately, only two very differing studies on pregnant women were included and only one of them demonstrated changes with iron supplementation. The use of multiple indicators (Hb, ferritin and serum transferrin receptors) is useful for population-based assessments of iron-deficiency anaemia, when this is feasible. There seems to be a need to evaluate the evidence to better understand the observed changes in iron nutrition and its indicators occurring during preg-

nancy under different circumstances. These studies should also assess the functional significance of iron nutritional status in terms of maternal health and pregnancy outcomes (i.e. birthweight, premature delivery, new born vitality, etc.) in different populations.

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). 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 maternal and child mortality and infectious diseases (INACG 2002b). The lowest incidence of low birthweight and prematurity appears to occur when Hb levels are between 95 g/L and 105 g/L during the second trimester of gestation (Steer 2000) and between 95 and 125 g of Hb/L at term (Hytten 1964; Hytten 1971; Murphy 1986). However, 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 prematurity (Garn 1981; Godfrey 1991; Kim 1992; Klebanoff 1989; Klebanoff 1991; Murphy 1986). There is little doubt that unfavourable effects in terms of low birthweight and premature delivery occur when haemoglobin falls below 95 g/L before or during the second trimester of gestation. Favourable pregnancy outcomes occur 30% to 45% less often in anaemic mothers, and probably 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. Delayed cord clamping can provide significant iron reserves to the infant (Mercer 2001; van Rheenen 2004). Iron deficiency affects adversely the cognitive performance and development and physical growth of these infants (WHO 2001). High haemoglobin levels (greater than 130 g/L) 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 antenatal haemoglobin concentrations are associated with increased risk of premature delivery and low birthweight. In fact, the incidence of these negative consequences increases dramatically when haemoglobin levels, at sea level, are below 95 to 105 or above 130 to 135 g/L at any time in pregnancy. A prospective study in Mexico has shown associations between prenatal daily iron supplement intake at recommended doses, high haemoglobin concentrations and the risk of both low birthweight and premature delivery (Casanueva 2003a). Observational studies have shown that among iron supplemented pregnant women, a failure of ferritin levels to decline during the 2nd and 3rd trimesters and overall high ferritin levels during pregnancy, not due to infection, are also thought to be deleterious for pregnancy outcomes, particularly for women who are anaemic early in pregnancy. However, when some confounding factors are controlled for, the association between high serum ferritin concentrations and the risk of premature delivery remains high but is no longer significant (Scholl 1998; Scholl 2000; Scholl 2005).

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

Interventions to control iron deficiency and iron-deficiency anaemia include iron supplementation and iron fortification, health and nutrition education, control of parasitic infections and improvement of sanitation (INACG 1977). Delayed clamping of the umbilical cord also is an effective preventive measure for iron deficiency in infancy and young children (Mercer 2001; van Rheenen 2004).

Some authors suggest that the amount of iron that can be absorbed from diet alone is insufficient to cover the increased iron requirements during pregnancy except when women can draw enough iron from pre-pregnancy iron reserves. The Institute of Medicine recommends a dietary allowance of 27 mg/day of iron for women during pregnancy (IOM 2001). Most women would need additional iron as well as sufficient iron stores to prevent iron deficiency (Bothwell 2000). Thus, direct iron supplementation has been extensively used 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. The rationale for this combination lies in the need of folic acid to cover the increased requirements of pregnancy, due to the rapidly dividing cells in the fetus and elevated urinary losses.

There is evidence to show that iron supplementation with or without folic acid during pregnancy results in a substantial reduction of women with haemoglobin levels less than 100 g/L in late pregnancy, at delivery and six weeks postpartum (Mahomed 2000; Mahomed 1997; Villar 2003). However, the overall impact of iron supplementation interventions under field conditions has been limited and its effectiveness questioned (Beaton 1999). The failure has been attributed to inadequate infrastructure and poor compliance (Mora 2002) although few studies have evaluated this issue adequately. The effectiveness of this intervention has been evaluated mostly in terms of improvement in haemoglobin concentration, rather than 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 antenatal iron and iron with folic acid supplementation during pregnancy.

International organizations have been advocating routine iron and folic acid supplementation for every pregnant woman in areas of high anaemia prevalence (Beard 2000; Villar 1997). While iron supplementation with or without folic acid has been used in a variety of doses and regimens, current international recommendations

for populations include the provision of a daily dose of 60 mg of iron for pregnant, non-anaemic women if supplementation for more than six months is possible and an increased dose of 120 mg of iron daily if the duration of supplementation is shorter, if iron deficiency prevalence in women of a given country is high, and if pregnant women are anaemic (INACG 1998). This supplement should include 400 µg of folic acid or lower doses if this amount is not available. Gastrointestinal side-effects have been selected as the critical adverse effect on which to base the tolerable upper intake level for iron, as gastrointestinal distress is observed commonly in women consuming high levels of supplemental iron on an empty stomach. High-dose iron supplements are commonly associated with constipation and other gastrointestinal effects including nausea, vomiting and diarrhea, 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 based on gastrointestinal side-effects as 45 mg/day of iron (IOM 2001). This is the level likely to pose no risk of adverse effects for almost all individuals in the general population (IOM 2001). In most industrialized 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 in 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) (CDC 1998).

Less frequent regimens of supplementation, such as weekly or twice weekly with iron alone or in conjunction with folic acid, have been evaluated in the last decade as a promising innovative regimen. The weekly iron administration is based on two lines of evidence: (1) daily iron supplementation, by maintaining an iron-rich environment in the gut lumen and in the intestinal mucosal cells, produces oxidative stress, reduces the long-term iron-absorption efficacy and is prone to increasing the severity and frequency of undesirable side-effects (Srigirihar 1998; Srigiridhar 2001; Viteri 1997; Viteri 1999a); (2) the concept that exposing intestinal cells to supplemental iron less frequently, every week based on the rate of mucosal turnover that occurs every five to six days in the human, may improve absorption capacity. Additionally, compliance could increase due to fewer side-effects and the costs of supplementation may be favourable if provided outside of the medical context (Viteri 1995; Viteri 1999b). However, some authors have questioned this belief indicating that the main reason for the poor compliance with the programs is the unavailability of iron supplements for the targeted women (Galloway 1994). Recently, other potentially detrimental effects (i.e. lower birthweight and premature delivery) have been associated with excess iron intake (i.e. cell damage from the production of reactive oxygen species) and with higher levels of haemoglobin concentrations late during the second trimester and early into the third trimester but not at term (Casanueva 2003b).

This review combines and updates the two currently published Cochrane Reviews on iron and iron and folic acid supplementation (Mahomed 2000; Mahomed 1998) that have clearly shown improvements on biochemical and haematological parameters and evaluates the issues related to alternative doses, periodicity as well as the potential benefits and hazards of these interventions.

OBJECTIVES

To assess the efficacy, effectiveness and safety of daily or intermittent routine supplementation of pregnant women with iron alone or in conjunction with folic acid.

The effectiveness of different treatments for iron-deficiency anaemia in pregnancy (Cuervo 2003) and the effects of supplementation with iron and vitamin A (Van den Broek 2002) are covered in other Cochrane Reviews. The effectiveness of vitamin C is covered in another Cochrane Review (Rumbold 2005). The effects of supplementation with folic acid alone (Mahomed 1998) or its effectiveness on the prevalence of neural tube defects periconceptionally is also evaluated elsewhere (Lumley 2003). The effects of a combination of iron and folic acid with multiple vitamin and mineral supplementation are also being reviewed elsewhere (Bhutta 2004). Studies examining the 'additional effect' of iron rather than iron versus a placebo provided with other micronutrients were excluded in this review and are expected to be analyzed in the multiple vitamin and mineral supplementation during pregnancy review (Bhutta 2004). It is possible that interactions between iron and other nutrients would increase or decrease the effects of iron.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised and quasi-randomised trials comparing any form of routine oral iron with or without folic acid supplements with no treatment/placebo or intermittent supplementation regimens. Studies reporting combinations with other vitamins and minerals and studies dealing with this intervention for anaemic women as a medical treatment were excluded.

Types of participants

Pregnant women of any gestational age, parity and number of fetuses.

Types of intervention

Daily routine oral supplementation with iron or iron-folic acid compared to no supplementation/placebo.

Daily routine oral supplementation with iron or iron-folic acid compared to routine intermittent (weekly and twice weekly) regimens.

Intermittent oral iron or iron-folic acid supplementation compared to no supplementation/placebo.

Types of outcome measures

The outcomes of this review were maternal and perinatal and infant postpartum clinical and laboratory outcomes. The following outcomes were sought for this review.

Primary

Infant

Low birthweight (less than 2500 g)
Birthweight (g)

Maternal

Premature delivery (less than 37 weeks' gestation)
Haemoglobin concentration at term in g/L
Anaemia at term (Hb less than 110 g/L) (not prespecified)
Haemoconcentration at term (defined as Hb greater than 130 g/L)
Haemoconcentration at any time during 2nd or 3rd trimesters (defined as Hb greater than 130 g/L)
Iron deficiency at term (based on two or more laboratory indicators)
Iron-deficiency anaemia at term (Hb less than 110 g/L and at least one additional laboratory indicator)
Side-effects (any)

Secondary

Infant

Very low birthweight (less than 1500 g)
Perinatal mortality
Hb concentration at one month in g/L
Ferritin concentration at one month
Hb concentration at three months in g/L
Ferritin concentration at three months
Hb concentration at six months in g/L
Ferritin concentration at six months
Long-term infant developmental (as defined by trial authors)
Admission to special care unit

Maternal

Very premature delivery (less than 34 weeks' gestation)
Severe anaemia at term (Hb less than 70 g/L)
Moderate anaemia at term (Hb greater than 70 g/L and less than 110 g/L)
Severe anaemia at any time during 2nd or 3rd trimesters (Hb less than 70 g/L)
Moderate anaemia at any time during 2nd or 3rd trimesters (Hb greater than 70 g/L and less than 110 g/L)
Infection during pregnancy (including urinary tract infections and others as specified by trial authors)
Puerperal infection (as defined by trial authors)
Antepartum haemorrhage (as defined by trial authors)
Postpartum haemorrhage (intrapartum and postnatal, as defined by trial authors)
Transfusion given (as defined by trial authors)
Haemoglobin concentration within one month postpartum
Severe anaemia postpartum (Hb less than 80 g/L)
Moderate anaemia at postpartum (Hb greater than 80 g/L and less than 100 g/L)
Diarrhoea
Constipation
Nausea
Heartburn
Vomiting
Maternal death (any known)
Maternal wellbeing/satisfaction (as defined by trial authors)
Placental abruption (as defined by trial authors)
Premature rupture of membranes (as defined by trial authors)
Pre-eclampsia (as defined by trial authors)

Other outcomes reported by trial authors were recorded and labelled as 'not prespecified'.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

We searched the Cochrane Pregnancy and Childbirth Group Trials Register by contacting the Trials Search Co-ordinator (June 2005).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:
(1) quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
(2) monthly searches of MEDLINE;
(3) handsearches of 30 journals and the proceedings of major conferences;
(4) weekly current awareness search of a further 37 journals.

Details of the search strategies for CENTRAL and MEDLINE, 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 "Search strategies for identification of studies" section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities above are given a code (or codes) depending on the topic. The codes are linked to review topics. The Trials Search Co-ordinator searches the register for each review using these codes rather than keywords.

Additionally, we contacted the Iron Deficiency Project Advisory Service (IDPAS), Micronutrient Initiative (MI), International Anaemia Consultative Group (INACG), WHO Maternal and Reproductive Health and WHO Nutrition Division for the identification of ongoing and unpublished studies.

METHODS OF THE REVIEW

We assessed trials for methodological quality using the criteria in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2005) for adequacy of allocation concealment: adequate (A), unclear (B), inadequate (C) or that allocation concealment was not used (D). We also collected information on blinding of outcome assessment and loss to follow up and incorporated them in the additional table of methodological quality. Blinding is A when both the participant and care provider/assessor are blind to the treatment, B when either the participant or care provider/assessor is blind to the treatment and C when it is unclear or is open. Follow up was considered A - adequate when more than 80% of participants were included in the analysis, B - if unclear, and C - if less than 80% of those initially randomised were included in the analysis.

Two independent authors assessed the eligibility of identified studies. The contact authors extracted data from the reports. We assessed the number of losses to follow up and postrandomisation exclusions systematically for each trial. We included quasi-randomised studies and conducted a sensitivity analysis. We also included cluster-randomised studies and adjusted their samples sizes (Higgins 2005) if sufficient information was available to allow for this. The intracluster correlation coefficients were estimated from original data provided by the authors when available and was estimated for each outcome. Authors of the original reports were contacted for additional data as required for the subgroup analysis.

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 entered data onto the Review Manager computer software (RevMan 2003). Any discrepancies between the authors in either the decision to include or exclude studies or in data extraction were resolved by discussion and we requested clarification from the authors of the original reports when necessary. For dichotomous data we used relative risk and for continuous data we used weighted mean difference, unless the trials reported the outcomes on different scales that could not be converted to a common scale. In this case, we used the standard mean difference.

We tested for heterogeneity between the trials using the I-square statistic test available in RevMan 2003. Given the high heterogeneity among trials, the results were pooled using a random-effects model. Because of the high heterogeneity we were cautious in the interpretation of the pooled results.

Sensitivity analysis

In the presence of significant heterogeneity, a sensitivity analysis was conducted based on the quality of the studies. A study was considered of high quality if it was graded as adequate or A in the randomisation and allocation concealment and at least adequate (one additional grade A) in either the blinding or the loss to follow-up study characteristics. We conducted an available case analysis and avoidable exclusions were reinstated when possible.

Supplementation regimens were defined as follows: daily, when the person is advised to take every day the dose of iron or iron-folic acid provided either as a single or repeated dose; intermittent, any dose of iron or iron-folic acid ingested less frequently than daily (alternate days, twice a week or weekly).

We aimed to conduct a total of eight comparisons: (1) any iron alone compared to no intervention/placebo; (2) daily iron alone compared to no intervention/placebo; (3) intermittent iron alone compared to no intervention/placebo; (4) intermittent iron alone compared to daily iron alone; (5) any iron-folic acid compared to no intervention/placebo; (6) daily iron-folic acid compared to no intervention/placebo; (7) intermittent iron-folic acid compared to no intervention/placebo; (8) intermittent iron-folic acid compared to daily iron-folic acid. However, to avoid repetitive data and due to the fact that there were no studies in many of the comparisons, we were able to conduct the following four comparisons:

(1) daily iron alone compared to no intervention/placebo;
(2) intermittent iron alone compared to daily iron alone;
(3) daily iron-folic acid compared to no intervention/placebo;
(4) intermittent iron-folic acid compared to daily iron-folic acid.

We conducted analysis with all studies and then a subgroup analysis on the primary outcomes based on the following criteria:
(1) early gestational age (supplementation started before 20 weeks' gestation or prepregnancy);
(2) late gestational age (supplementation started at 20 weeks or more of gestation);
(3) unspecified/mixed gestational ages at the start of supplementation;
(4) anaemic (Hb below 110 g/L during first and third trimesters or below 105 g/L in second trimester) at start of supplementation;
(5) non-anaemic (Hb 110 g/L or above during first and third trimesters or Hb 105 g/L or above if in second trimester) at start of supplementation;
(6) unspecified/mixed anaemic status at start of supplementation;
(7) daily low dose (60 mg elemental iron or less);
(8) daily higher dose (more than 60 mg elemental iron).

DESCRIPTION OF STUDIES

Our search strategy identified 151 references corresponding to 122 trials. Of these, 40 trials were included, 69 trials were excluded, 12 trials are awaiting assessment and one trial is still ongoing. The trial in Guatemala included two sub-studies and thus was included as two separate trials: one with supervised intake (Chew 1996a) and one with unsupervised intake (Chew 1996b). One study was carried out collaboratively in two different sites and thus was cited as two different trials (Wallenburg 1983) conducted in Rotterdam and (Buytaert 1983) conducted in Antwerp. One trial in China

included three comparison groups: one with weekly doses of iron, another with daily doses and a control group. However since the allocation of the control group was not randomised this study was included only in the comparisons for intermittent versus daily iron supplementation in this review (Liu 1996).

Twenty nine trials evaluated supplementation with iron alone compared to no treatment or placebo (Batu 1976; Butler 1968; Buytaert 1983; Chanarin 1971; Charoenlarp 1988; Chisholm 1966; Cogswell 2003; De Benaze 1989; Eskeland 1997; Hankin 1963; Holly 1955; Hood 1960; Kerr 1958; Makrides 2003; Menendez 1994; Milman 1991; Ortega-Soler 1998; Paintin 1966; Pita Martin 1999; Preziosi 1997; Pritchard 1958; Puolakka 1980; Romslo 1983; Svanberg 1975; Tura 1989; Van Eijk 1978; Wallenburg 1983; Willoughby 1967; Wills 1947). Of these, only seven trials were of high quality according to our pre-established criteria (Buytaert 1983; Cogswell 2003; Eskeland 1997; Makrides 2003; Preziosi 1997; Tura 1989; Wallenburg 1983).

Two studies evaluated intermittent supplementation with iron alone compared to daily supplementation with iron alone (Pita Martin 1999; Yu 1998) and no study evaluated intermittent supplementation with iron alone compared to no treatment or placebo. None of these met the pre- established criteria for high quality.

Eight trials evaluated daily iron supplementation with folic acid compared to no treatment (Barton 1994; Batu 1976; Butler 1968; Charoenlarp 1988; Chisholm 1966; Liu 1996; Taylor 1982; Willoughby 1967). These same trials also evaluated daily iron and folic acid compared to no treatment. Only one of them (Barton 1994) met the criteria for high quality.

Seven trials evaluated intermittent supplementation with iron and folic acid compared to daily supplementation with iron and folic acid (Chew 1996a; Chew 1996b; Ekstrom 2002; Liu 1996; Ridwan 1996; Robinson 1998; Winichagoon 2003). One trial met the pre-established criteria of high quality (Chew 1996a).

See table of 'Characteristics of included studies' for a detailed description of the studies. All included studies met the prestated criteria for inclusion in this review.

METHODOLOGICAL QUALITY

Sixteen trials adequately randomised the participants to the treatment groups (Barton 1994; Butler 1968; Buytaert 1983; Charoenlarp 1988; Chew 1996a; Chew 1996b; Cogswell 2003; Ekstrom 2002; Eskeland 1997; Kerr 1958; Makrides 2003; Preziosi 1997; Ridwan 1996; Tura 1989; Wallenburg 1983; Young 2000). Eighteen trials did not report or did not state clearly the randomisation method used (Batu 1976; Chisholm 1966; De Benaze 1989; Holly 1955; Hood 1960; Liu 1996; Menendez 1994; Milman 1991; Ortega-Soler 1998; Paintin 1966; Pritchard 1958; Puolakka 1980; Romslo 1983; Svanberg 1975; Taylor 1982; Van Eijk 1978; Willoughby 1967; Winichagoon 2003) and six trials were quasi-randomised using alternate or sequence allocation (Chanarin 1971; Hankin 1963; Pita Martin 1999; Robinson 1998; Wills 1947; Yu 1998). Three trials used cluster randomisation (Ekstrom 2002; Ridwan 1996; Winichagoon 2003).

Thirteen trials reported using sealed envelopes or opaque bottles when doing the allocation of the women to treatment groups (Barton 1994; Butler 1968; Buytaert 1983; Chisholm 1966; Cogswell 2003; De Benaze 1989; Eskeland 1997; Liu 1996; Makrides 2003; Paintin 1966; Preziosi 1997; Tura 1989; Wallenburg 1983). The remaining studies were unclear in their method of concealment of allocation (Batu 1976; Charoenlarp 1988; Holly 1955; Hood 1960; Kerr 1958; Milman 1991; Pritchard 1958; Puolakka 1980; Robinson 1998; Romslo 1983; Svanberg 1975; Taylor 1982; Willoughby 1967; Young 2000). Some trials used an inadequate method or did not use any allocation concealment at all (Chanarin 1971; Chew 1996a; Chew 1996b; Ekstrom 2002; Hankin 1963; Menendez 1994; Ortega-Soler 1998; Pita Martin 1999; Ridwan 1996; Van Eijk 1978; Wills 1947; Winichagoon 2003; Yu 1998). However it is clear that the studies evaluating intermittent compared to daily supplementation regimens would pose an extreme effort to keep the participants blinded as to what treatment they were receiving. Adherence would be obscured if daily placebo for six days and iron plus folic acid once a week were assigned.

See table of 'Methodological quality assessment of included trials' (Table 01) for a summary of the trials quality.

RESULTS

Forty trials involving 12706 women were included in the review. The summary results are organized by comparisons and by primary and secondary outcomes. Most of the studies focused on haematological indices and few reported other outcomes prespecified in the protocol. Overall, the results showed significant heterogeneity across all the prespecified outcomes. Heterogeneity could not be explained by standard sensitivity analyses including quality assessment, therefore, all results were analysed by random-effects.

See 'Graphs and tables' for detailed results on primary and secondary outcomes.

(1) Daily iron alone compared to no intervention/placebo

Infant outcomes

Evidence of significant differences was found in the following outcomes.

Infant ferritin concentration at three months in ug/L: weighted mean difference (WMD) 19.0; 95% confidence interval (CI) 2.75 to 35.25 (one trial involving 197 women) (Figure 01:25) and at six months in ug/L: WMD 11.0; 95% CI 4.37 to 17.63 (one trial involving 197 women) (Figure 01:27).

Infant Hb concentration at six months in g/L: WMD -5.0; 95% CI -9.11 to -0.89 (one trial involving 197 women). This result goes in the opposite direction than was expected (Figure 01:26).

There was no evidence of significant difference found in:
low birthweight (less than 2500 g) (Figure 01:01), birthweight (Figure 01:03), very low birthweight (less than 1500 g) (Figure 01:20), or infant Hb concentration at three months in g/L (Figure 01:24). The data from three trials with 1147 women (Cogswell 2003; Makrides 2003; Menendez 1994) suggest that women who take daily iron supplementation during pregnancy are as likely as women not receiving iron supplements to have a baby with birthweight below 2500 grams (4% versus 6.6%; relative risk (RR) 0.59; 95% CI 0.23 to 1.49). However, the heterogeneity between the treatment effects is substantial (I-square greater than 50%) (Figure 01:01). When selecting only high-quality studies (Cogswell 2003; Makrides 2003) the effect remains not significant. Similarly, the data from five trials (Cogswell 2003; Eskeland 1997; Makrides 2003; Preziosi 1997; Puolakka 1980) with 925 women suggest that there is not any effect in birthweight of newborns born to women who had taken daily supplementation with iron alone during pregnancy as compared to those taking placebo or not taking any supplements at all (WMD 22.49; 95% CI -99.35 to 144.34) (Figure 01:03). Heterogeneity between the treatment effects is substantial (I square greater than 50%) and the results have to be interpreted cautiously.

No trials reported on the remaining outcomes.

Maternal outcomes

Evidence of significant differences was found in the following outcomes.

Haemoglobin concentration at term in g/L

The data from 15 trials involving 1516 women (Batu 1976; Butler 1968; Buytaert 1983; Chanarin 1971; Cogswell 2003; De Benaze 1989; Eskeland 1997; Makrides 2003; Milman 1991; Ortega-Soler 1998; Puolakka 1980; Romslo 1983; Tura 1989; Van Eijk 1978; Wallenburg 1983) suggest that women who take daily supplementation with iron during pregnancy reach term with 7.53 g/L higher concentration of haemoglobin than women taking placebo or not taking any iron supplements at all (WMD 7.53; 95% CI 4.40 to 10.66) (Figure 01:07). However, the heterogeneity between the treatment effects is substantial (I-square greater than 50%) and the results have to be interpreted with caution. The difference was slightly higher among those receiving a higher dose of iron and those starting supplementation after 20 weeks of gestation (Figure 01:08). The effect of daily iron supplementation did not change significantly after including only high-quality trials (Buytaert 1983; Cogswell 2003; Eskeland 1997; Makrides 2003; Tura 1989) (WMD 4.72; 95% CI 0.95 to 8.49) and heterogeneity remained high.

Anaemia at term (Hb less than 110 g/L) (not prespecified)

Data from 13 trials including 1696 women (Batu 1976; Chanarin 1971;Chisholm 1966; Cogswell 2003; De Benaze 1989; Eskeland 1997; Holly 1955; Makrides 2003; Milman 1991; Preziosi 1997; Pritchard 1958; Puolakka 1980; Romslo 1983) suggest that women who receive routine daily supplementation with iron during pregnancy are less likely to have anaemia at term than those taking placebo or not taking any iron supplements at all, as indicated by a Hb less than 110 g/L (10.9% versus 32.6%; RR 0.26; CI 0.16 to 0.43 (Figure 01:09)). However, the heterogeneity between the treatment effects is substantial (I-square greater than 50%) and the results have to be interpreted with caution. The sensitivity analysis when selecting only the four high-quality studies involving a total of 787 women (Cogswell 2003; Eskeland 1997; Makrides 2003; Preziosi 1997) shows that women who take daily iron supplementation during pregnancy are less likely to have anaemia at term (16.2% versus 31.3%; RR 0.56; 95% CI 0.40 to 0.78). The heterogeneity I-square was reduced to 24.1% (not shown).

Haemoconcentration at term (defined as Hb greater than 130 g/L)

Data from eight trials involving 1222 women (Butler 1968; Chisholm 1966; Cogswell 2003; Eskeland 1997; Holly 1955; Makrides 2003; Milman 1991; Pritchard 1958) suggest that women who routinely take daily iron supplementation during pregnancy are almost three times more likely to have haemoconcentration at term than those taking placebo or not taking any iron supplements at all (defined as an Hb higher than 130 g/l) (32.7% versus 10.4%; RR 3.01; 95% CI 1.46 to 6.19) (Figure 01:10). The heterogeneity between the treatment effects is substantial (I-square greater than 75.8%) and the results have to be interpreted with caution (Figure 01:10). This effect was similar for any gestational age at start of supplementation and lower or higher doses of iron provided. The effect was no longer significant when a sensitivity analysis was conducted with three high-quality trials involving a total of 590 women (Cogswell 2003; Eskeland 1997; Makrides 2003) (28.6% versus 14.8%; RR 1.15; 95% CI 0.05 to 24.75) and the heterogeneity increased (I-square = 85.4%) (not shown).

Haemoconcentration at any time during 2nd or 3rd trimesters (defined as Hb greater than 130 g/L)

The effects of oral routine supplementation with iron alone and haemoconcentration at any time during the second or third trimesters was evaluated in six trials including 1133 women (Cogswell 2003; Eskeland 1997; Holly 1955; Makrides 2003; Milman 1991; Pritchard 1958). The data from these trials suggest that women who routinely receive daily iron supplementation during pregnancy are more likely to present haemoconcentration at any time during the second or third trimesters than those taking placebo or not taking any iron supplements at all, according to the definition used here. (30.9% versus 15.4%; RR 1.90; 95% CI 1.07 to 3.35) (Figure 01:12). However, the heterogeneity between the treatment effects is substantial (I-square = 79.6%) and the results have to be interpreted with caution (Figure 01:12). When only three trials of high quality were included (Cogswell 2003; Eskeland 1997; Makrides 2003) the effect was no longer significant

(RR 1.60; 95% CI 0.85 to 2.99) and the heterogeneity remained high (77%).

Iron deficiency at term (based on two or more laboratory indicators)
Data from six trials involving 1108 women (Cogswell 2003; Eskeland 1997; Makrides 2003; Milman 1991; Preziosi 1997; Tura 1989) 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 supplements at all (30.7% versus 54.8%; RR 0.44; 95% CI 0.27 to 0.70) (Figure 01:14). The heterogeneity between the treatment effects is substantial (I-square greater than 50%) and the results have to be interpreted with caution (Figure 01:14). Five of the trials were of high quality.

Iron-deficiency anaemia at term (Hb below 110 g/L and at least one additional laboratory indicator)
Data from five trials involving 940 women (Cogswell 2003; Eskeland 1997; Makrides 2003; Milman 1991; Tura 1989) suggest that women who routinely receive daily iron supplementation are less likely to have iron-deficiency anaemia at term than women taking placebo or not taking any iron supplements at all (4.9% versus 15.5%; RR 0.33; 95% CI 0.16 to 0.69) (Figure 01:16). The heterogeneity between the treatment effects was small (I-square less than 50%) (Figure 01:16). These results were similar for the different subgroups including those who start supplementation early in the gestation and those who are non-anaemic at start, and in any iron dose. The effect was similar (5.6% versus 15.2%); when only four trials of high quality involving 820 women (Cogswell 2003; Eskeland 1997; Makrides 2003; Tura 1989) were compared: RR 0.39; 95% CI 0.20 to 0.74 and a test of heterogeneity (I-square = 40.4%) (not shown).

Side-effects (any)
Data from six trials involving 1099 women (Charoenlarp 1988; Cogswell 2003; De Benaze 1989; Eskeland 1997; Hood 1960; Kerr 1958) 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 (26.4% versus 11.9%); (RR 1.90; 95% CI 1.09 to 3.33)) (Figure 01:18). However, the heterogeneity between the treatment effects is substantial (I-square greater than 50%) and the results have to be interpreted with caution (Figure 01:18). When only the two high-quality trials involving 520 women were included (Cogswell 2003; Eskeland 1997), the effect is no longer significant (28.7% versus 21.9%); RR 1.31; 95% CI 0.94 to 1.82 (data not shown) with no heterogeneity (I-square = 0%).

Maternal haemoglobin concentration within one month postpartum in g/L
The data from four trials involving 833 women (Hankin 1963; Menendez 1994; Milman 1991; Wills 1947) suggest that women that routinely receive daily iron supplementation have a higher concentration of haemoglobin after one month postpartum than those taking placebo or not taking any iron supplements at all (WMD 6.10 g/L; 95% CI 3.70 to 8.49 g/L). The I-square statistic show that heterogeneity of the results is less than 50% (Figure 01:40). None of the trials met the criteria for high quality.

There was no evidence of significant difference between women receiving daily iron supplementation and women receiving placebo or not taking any iron supplements at all, in the following outcomes.
Premature delivery (less than 37 weeks' gestation) (Figure 01:05), very premature delivery (less than 34 weeks' gestation) (Figure 01:30), placental abruption (Figure 01:50), pre-eclampsia (Figure 01:52), severe anaemia at term (Figure 01:31), at any time during 2nd or 3rd trimesters (Figure 01:33) or postpartum (Figure 01:41), moderate anaemia at term (Figure 01:32), at any time during 2nd or 3rd trimesters (Figure 01:34) and in the postpartum (Figure 01:42), puerperal infection (Figure 01:36), antepartum haemorrhage (Figure 01:37) and postpartum haemorrhage (Figure 01:38), transfusion given (Figure 01:39), diarrhoea (Figure 01:43), constipation (Figure 01:41), nausea (Figure 01:45), heartburn (Figure 01:46), vomiting (Figure 01:47), maternal death (Figure 01:48), pre-eclampsia (Figure 01:52) or maternal wellbeing/satisfaction (Figure 01:49).

No trials reported on the remaining outcomes.

(2) Intermittent iron alone compared to daily iron alone

Infant outcomes
No evidence of significant differences was found between these groups of infants in birthweight (Figure 02:03). Only one study (Pita Martin 1999) with 41 women provided data for this outcome.

No trials reported on the remaining outcomes.

Maternal outcomes
No evidence of significant differences was found between these groups of women in the following outcomes.
Premature delivery (less than 37 weeks' gestation) (Figure 02:05), haemoconcentration at any time during 2nd or 3rd trimesters (defined as Hb greater than 130 g/L) (Figure 02:12), or moderate anaemia at any time during 2nd or 3rd trimesters (Figure 02:34). The effect of the intervention on severe anaemia at any time during second or third trimesters could not be estimated (Figure 02:33).

No trials reported on the remaining outcomes.

(3) Daily iron-folic acid compared to no intervention/placebo

Infant outcomes
No evidence of significant differences was found between infants from these groups of women receiving daily iron an folic acid supplementation and those taking placebo or not taking any supplements at all in the following outcomes.
Low birthweight (less than 2500 g) (Figure 03:01), birthweight (g) (Figure 03:03), very low birthweight (less than 1500 g) (Figure 03:20), perinatal mortality (Figure 03:21) or admission to special care unit (Figure 03:29).

No trials reported on the remaining outcomes.

Maternal outcomes

Evidence of significant differences was found in the following outcomes.

Haemoglobin concentration at term in g/L

The data from four trials including 179 women (Barton 1994; Batu 1976; Butler 1968; 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 (WMD 12.00 g/L; 95% CI 2.93 to 21.07). However, the heterogeneity between the treatment effects is substantial (I-square greater than 50%) and the results have to be interpreted with caution (Figure 03:07). The effect of iron-folic acid supplementation did not change significantly after including only the one high-quality trial (WMD 17.10; 95% CI 8.44 to 25.76) (data not shown). The subgroup analysis provided similar results (Figure 03:08).

Anaemia at term (Hb less than 110 g/L) (not prespecified)

The data from two trials including 346 women (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 supplements at all (defined as Hb less than 110 g/L) (8.2% versus 35.5%; RR 0.27; 95% CI 0.12 to 0.56) (Figure 03:09). However, the heterogeneity between the treatment effects is substantial (I-square greater than 50%) and the results have to be interpreted with caution. No studies met the prespecified criteria for high quality.

Side-effects (any)

One trial including 456 women (Charoenlarp 1988) suggest that women routinely receiving iron and folic acid supplementation are more likely to report any side-effects in comparison to none from those receiving no supplementation (RR 44.32; 95% CI 2.77 to 709.09) (Figure 03:18). The scarcity of data makes it difficult to draw any conclusion.

Haemoglobin concentration within one month postpartum in g/L

One study (Taylor 1982) involving 45 women reported this outcome. The data from this trial suggest that women receiving daily iron and folic acid supplementation achieve a higher concentration of haemoglobin at one month postpartum than women not taking any supplements at all (WMD 10.40; 95% CI 4.03 to 16.77) (Figure 3:40) but no firm conclusions can be made given the scarcity of the data.

No evidence of significant differences was found in the following outcomes.

Premature delivery (less than 37 weeks' gestation) (Figure 03:05), very premature delivery (Figure 03:30), antepartum haemorrhage(Figure 03:37), postpartum haemorrhage (Figure 03:38), placental abruption (Figure 03:50), pre-eclampsia (Figure 03:52), haemoconcentration at term (defined as Hb greater than 130 g/L) (Figure 03:08), severe anaemia at any time during 2nd or 3rd trimesters (Figure 03:33) or severe anaemia at term (Figure 03:31), moderate anaemia at any time during 2nd or 3rd trimesters (Figure 03:34) or at term (Figure 03:32), infection during pregnancy (Figure 03:35), or puerperal infection (Figure 03:36).

No trials reported on the remaining outcomes.

(4) Intermittent iron-folic acid compared to daily iron-folic acid

Infant outcomes

Evidence of significant differences was found in the following outcome.

Infant ferritin concentration at six months in ug/L

One study (Winichagoon 2003) including involving 88 women reported this outcome (Figure 04:27). The data from this trial suggest that the infants from women receiving intermittent iron and folic acid supplementation achieve a higher concentration of serum ferritin at six months (WMD 0.09; 95% CI 0.05 to 0.13) (Figure 4:27) but no firm conclusions can be made given the scarcity of the data.

No evidence of significant differences was found in the following outcomes.

Low birthweight (less than 2500 g) (Figure 04:01), birthweight (Figure 04:03) and very low birthweight (less than 1500 g) was not estimable (Figure 04:20).

The data from three trials (Chew 1996a; Chew 1996b; Winichagoon 2003) involving 650 women suggest that women who take intermittent iron and folic acid supplementation during pregnancy are as likely to have a baby with birthweight below 2500 grams (4.8% versus 5.4%; RR 0.99; 95% CI 0.50 to 1.97) (Figure 04:01) and that there is no significant effect in birthweight of newborns born from women who had taken daily supplementation with iron and folic acid during pregnancy or from those being supplemented intermittently (WMD -8.36; 95% CI -73.56 to 56.85) (Figure 04:03).

No trials reported on the remaining outcomes.

Maternal outcomes

Evidence of significant differences was found in the following outcomes.

Haemoconcentration at any time during 2nd or 3rd trimesters (defined as Hb greater than 130 g/L)

Five trials recorded this outcome (Ekstrom 2002; Liu 1996; Ridwan 1996; Robinson 1998; Winichagoon 2003) but only four trials including 1031 women reported cases. The data from these four trials suggest that women who routinely receive intermittent iron and folic acid supplementation during pregnancy are less likely to have haemoconcentration at any time during the second or third trimesters as those receiving the daily regimen (7.75% versus 19.31%; RR 0.41; 95% CI 0.21 to 0.80) (Figure 04:12). None of the trials met the criteria for high quality.

Vomiting

The data from four trials including 774 women (Chew 1996a; Chew 1996b; Ekstrom 2002; Robinson 1998) suggest that women who routinely receive intermittent iron and folic acid supplementation during pregnancy are more likely to report vomiting during pregnancy as a side-effect as compared to those receiving the daily regimen (15.7% versus 8.94%; RR 1.69; 95% CI 1.15 to 2.47 (four trials including 774 women) (Figure 04:47).

There was no evidence of significant difference in the following outcomes
Haemoglobin concentration at term in g/L (Figure 04:07), anaemia at term (Hb less than 110 g/L) (Figure 04:09), haemoconcentration at term (Figure 04:11), iron-deficiency anaemia at term (Hb below 110 g/L and at least one additional laboratory indicator) (Figure 04:16), severe anaemia at any time during 2nd or 3rd trimesters (Figure 04:33), severe anaemia at term (Figure 04:31) or postpartum (Figure 04:41), moderate anaemia at term (Figure 04:32), at any time during 2nd or 3rd trimesters (Figure 04:34) and postpartum (Figure 04:42), side-effects (any) (Figure 04:18), diarrhoea (Figure 04:43), constipation (Figure 04:44), nausea (Figure 04:45), or heartburn (Figure 04:46).

No trials reported on the remaining outcomes.

DISCUSSION

This review addresses only supplementation with iron or a combination of iron and folic acid. Exclusion of the additional effects of other micronutrients in antenatal supplements allowed us to focus on the effects of iron and folic acid. Possible synergistic effects of additional supplements are being addressed by other systematic Cochrane Reviews (Bhutta 2004).

The number of women in each study and even when all studies were combined did not allow firm conclusions about events that are infrequent but important. Also, the great majority of studies with daily iron supplementation were carried out in industrialized/high-income countries, with minor representation from African, Asian and Latin American countries. On the other hand, intermittent iron and folic acid antenatal supplementation trials came from developing countries.

Unfortunately, there is very limited information relating to clinical outcomes in the included studies. Most studies chose to focus mostly on haematological indices after a certain period of supplementation. Outcome data at term or postpartum are very scanty, except for maternal haematology.

The interpretation of the data in the presence of significant heterogeneity remains a challenge. Pooling the results may also not be a good way to understand the effects. For example in the United States study (Cogswell 2003) non iron deficient non-anaemic women were enrolled before 20 week of gestation and were randomly assigned to receive 30 mg of iron or placebo only until 28 week of gestation. From 28 to 38 week of gestation, the women received different interventions according to the Institute of Medicine guidelines for iron supplementation during pregnancy, regardless of initial assignment. Most women received some iron supplementation throughout pregnancy. The Australia study (Makrides 2003) evaluated the effects of supplementing pregnant women with a low dosage (20 mg/d) of iron from 20 week until delivery. Therefore these two studies provided low doses of iron supplementation during different periods of pregnancy.

Women receiving iron alone or iron with folic acid had higher haemoglobin concentration at term than women who had no supplements. This was the case whether supplementation started early or at any time in pregnancy, whether women were anaemic or non-anaemic at the start of supplementation. In most cases available, iron dosage was high. There were no data for supplementation with low-dose iron in combination with folic acid.

The data available do not allow us to differentiate between iron dosage and the women's haematological condition at the start of supplementation because non-anaemic women received low doses of iron while women with no predetermined haematological condition received high doses of iron.

There are no studies that compare intermittent iron alone with non-supplemented women because all the studies with intermittent supplementation have been carried out in developing countries whose legislature requires mandatory antenatal supplementation with iron. Also, there are only very few cases that allow a comparison between the effects of intermittent iron alone with daily iron alone because common supplementation practice in those regions of the world include iron with folic acid tablets.

Adverse effects

Side-effects are a clear drawback to most current iron compounds used as supplements either alone or with folic acid. The results of this review confirm that daily iron doses are associated with a higher risk for side-effects, as has been recognized for many years.

The search for highly bioavailable iron compounds that produce less side-effects and that can be administered at low doses or intermittently (please *see* below) is evident. The intermittent supplemented group showed a significantly higher risk for vomiting because the dose administered weekly was twice or three times higher than the daily dose, although it was given only once weekly. Most iron and iron and folic acid supplementation regimens have involved doses that surpass the upper tolerable level of 45 mg/day.

Similar to the debate on the best indicators for iron deficiency and anaemia during pregnancy, there is a debate on the benefits of routine daily iron supplementation during pregnancy at the currently high-levels recommended by various agencies. It appears that small daily doses as recommended by the US Food and Nutrition Board, the U.S. Centers for Disease Control and Prevention and the Institute of Medicine (Anderson 1991; CDC 1998; IOM 1993) as well as weekly dosing are essentially as efficacious as daily iron at current doses in preventing significant anaemia at term, defined

as that having health and functional consequences. The risk for haemoconcentration in the 2nd and/or 3rd trimester is lower with intermittent supplementation, either low daily iron supplements or weekly iron supplementation appear safer. Unfortunately, the studies exploring the risk for haemoconcentration as well as those exploring iron deficiency and iron-deficiency anaemia at term with daily iron supplementation are confounded by the fact that low iron doses were administered to non-anaemic women and high iron doses were administered to women with undefined anaemia at the start of supplementation.

This review suggests that haemoconcentration at term as well as in/or during the 2nd and 3rd trimester of pregnancy is associated with daily iron supplementation, particularly when doses are high and started early in pregnancy . Haemoconcentration secondary to excessive erythropoiesis during pregnancy in association with iron supplementation has been previously suggested by researchers in Newcastle and others (Hytten 1971; Hytten 1985; Lund 1961; Letsky 1991; Mahomed 1989). Low haemoglobin levels but also high haemoglobin levels have been associated with low birthweight (Garn 1981; Huisman 1986; Koller 1979; Murphy 1986; Scanlon 2000; Steer 1995; Zhou 1998). Further associations were reported between preterm birth and low haemoglobin during the first and second trimesters, and low birthweight due to intrauterine growth retardation and high haemoglobin concentrations also during the first two trimesters (Scanlon 2000). Haemoglobin levels during the 3rd trimester had erratic consequences regarding birthweight. Importantly, the odds ratios for small-for-gestational-age babies were lower when haemoglobin concentrations were low-normal or low (Z scores < -1 and > -2, and < -2 and > -3 for haemoglobin, respectively) during the 2nd and 3rd trimesters.

It would appear that the normal haemodilution reaching a nadir during the second and early third trimester of pregnancy favours the uneventful course of pregnancy and fetal growth and well-being, resulting in normal newborns. In many instances antenatal iron supplementation at doses currently recommended for developing nations (60 mg to 300 mg of iron/day) and commonly prescribed by obstetricians in industrial societies may annul the normal haemodilution and even produce abnormally elevated haemoglobin levels in pregnancy (Scanlon 2000). Whether high doses of iron during pregnancy increase the risk of low birthweight and premature delivery is not yet clear. It is not only important to explore that possible association but also to refute other possible adverse consequences of high iron supplementation doses besides haemoconcentration and possible poor placental perfusion such as oxidative stress, as suggested by different studies (Casanueva 2003b). This issue merits research because the literature abounds in data suggesting that haemoconcentration increases the risk of low birthweight.

Presently, most researchers associate high haemoglobin levels during pregnancy with plasma volume depletion, pre-eclampsia, eclampsia, pregnancy complications and low birthweight (Gallery 1979; Goodlin 1981; Koller 1979; Silver 1998). Reduced plasma volume appears to precede late pregnancy hypertension and low birthweight (Gallery 1979; Huisman 1986). The most recent trial that studied both plasma and red blood cell volumes simultaneously showed that both plasma and red cell volumes were reduced, plasma volume reduction averaging 16% was present only in pre-eclampsia (hypertension with albuminuria) but not in non-albuminuric gestational hypertension and was associated with a greater risk of small-for-gestational-age babies (Silver 1998). Other studies involving low birthweight babies where maternal plasma volume was measured failed to demonstrate a level of haemoconcentration that resulted in haemoglobin levels greater than or equal to 135 g/L (Gallery 1979; Hytten 1971; Hytten 1985; Koller 1979; Letsky 1991; Poulsen 1990). These results may suggest that, in otherwise normal pregnant women, haemoconcentration defined as haemoglobin greater than 135 g/l cannot be wholly explained by reduction in maternal plasma volume.

Can haemoconcentration of the levels reported in the studies included in this review result in hyperviscosity, poor placental perfusion and placento/fetal hypoxia? This seems possible based on the data presented by some authors (Erslev 2001; LeVeen 1980). On the one hand, blood viscosity increases essentially in a linear form by about 45% (from 3.2 to 4.3 units relative to H_2O) between a haematocrit of 30% and 47% (corresponding to haemoglobin concentrations of 89 and 140 g/L) but oxygen transport declines only by about 4% between the optimum at haematocrit of 30 % to that of 45% (corresponding to haemoglobin concentration of 134 g/L) (LeVeen 1980).

The direct evidence that daily iron supplementation increases the risk of low birthweight and premature delivery is still lacking. Further studies are needed to explore the mechanisms involved.

AUTHORS' CONCLUSIONS

Implications for practice

Antenatal supplementation with iron or with iron and folic acid results in a substantial reduction in the prevalence of haemoglobin levels below 10 or 10.5 g/L at term or near term. There are not enough data to determine that routine supplementation with iron alone or in combination with folic acid had any substantial benefits or adverse effects on maternal and fetal health and pregnancy outcomes (premature delivery and low birthweight) among populations where anaemia is common. Weekly supplementation appears to be as effective as daily in preventing low haemoglobin levels. Routine daily or weekly antenatal iron or iron plus folic acid supplementation may be of benefit, especially where pre-gestational iron deficiency and anaemia are prevalent. There is not enough evidence to suggest a change in current recommended iron and folic acid doses with either modality of supplementation.

Implications for research

This review has identified the following recommendations for research.

(1) It is important to establish a solid basis for defining desirable ranges of iron nutrition and haematological conditions in pregnancy leading to safe and desirable outcomes of clinical relevance.

(2) Understand the mechanisms involved in haemoconcentration and its functional consequences.

(3) Establish effective and safe doses (healthwise and functionwise) of supplemental iron with folic acid and possibly other nutrients using daily and intermittent preventive supplementation, considering early nutritional and haematological status of the mothers, in industrial settings as well as in the developing world.

(4) Find effective, safe and affordable iron compounds that have reduced or no side-effects for use in public health antenatal supplementation programs that have been proven safe.

(5) Lastly, there is a clear need to carry out much larger multicenter studies to define effective and safe antenatal supplementation strategies and modalities. This research should focus in populations where gestational anaemia and iron deficiency are highly prevalent by current standards and where routine antenatal supplementation with iron and folic acid is the norm, independent of iron status and anaemia at the start of supplementation. Supplementation strategies with different iron doses and starting supplementation before gestational week 20 or at this or later pregnancy stages as well as daily or weekly modality of administration should be explored. In this case the intermittent schedule should be compared to the daily regimen. The influence of altitude should be included in these studies.

POTENTIAL CONFLICT 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).

Fernando Viteri was involved in some included studies with intermittent iron supplementation. Juan Pablo Pena-Rosas was author of an excluded study on iron and folic acid intermittent supplementation.

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** Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	Barton 1994
Methods	Randomisation: (A) adequate by means of computer-generated numbers. Allocation concealment: (A) adequate. Blinding: (A) adequate. Participant and care provider blinded. Loss to follow-up: (A) adequate. Less than 5%.
Participants	97 healthy women with singleton pregnancy, during their first trimester of pregnancy, and with haemoglobin 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.

Characteristics of included studies (*Continued*)

Interventions	Women were randomly assigned to one of two groups: group 1: received iron and folic acid tablets, one tablet to be taken by mouth twice daily (each tablet contained 0.5 mg of folic acid and 60 mg elemental iron); group 2: placebo tablets also to be taken by mouth twice daily. Supplementation started at 12 weeks until delivery. No postpartum supplementation.
Outcomes	Maternal: haemoglobin, haematocrit, serum erythropoietin concentrations at baseline and at 24, 28, 32, 36 and 40 wk; serum ferritin at baseline and at 36 wk; number of hypertensive disorders, antepartum haemorrhage, cesarean 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 haemoglobin, haematocrit, serum ferritin, and erythropoietin concentrations.
Notes	Unsupervised. No participants were withdrawn because of anaemia. Compliance not reported.
Allocation concealment	A – Adequate

Study	**Batu 1976**
Methods	Randomisation: (B) method not stated. Allocation concealment: (B) unclear. Blinding: (B) participant blinded. Provider/assessor not stated or clear. Loss to follow up: (C) 37 women (28%) were excluded for analysis.
Participants	133 women referred to investigators from a population of women attending an antenatal clinic for the fist time in Rangoon. Women with severe anaemia were excluded from the trial during the intervention for treatment.
Interventions	Women were randomly assigned to one of four groups starting at 22-25 weeks of gestation: group 1: one ferrous sulphate tablet containing 60 mg of elemental iron, and one placebo tablets twice daily; group 2: one tablet containing 60 mg of elemental iron as ferrous sulphate, and one tablet containing 0.5 mg of folic acid twice daily; group 3: two placebo tablets twice daily; group 4: one placebo tablet and one tablet containing 0.5 mg of folic acid twice daily. Administration of the treatments was carefully supervised. Supplementation started at 22-25 weeks of gestation until term.
Outcomes	Maternal: haemoglobin concentrations at baseline, at term (38-40th wk) and 4-7 wk postpartum, serum iron, serum and red cell folate activity and hypersegmented polimorph count at baseline, at 38-40th wk 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. Three women from group 3 and two from group 4 developed severe anaemia and were also withdrawn from analysis.
Allocation concealment	B – Unclear

Study	**Butler 1968**
Methods	Randomisation: (A) adequate by means of a randomised list stratified by age, parity and initial haemoglobin level. Allocation concealment: (A) adequate. Numbered bottles of tablets and code was broken after study completed for group 1 and 2. Blinding: (C) inadequate. participant and provider were blinded to treatment for groups 1 and 2. The control group did not get a placebo. Loss to follow up: (C) More than 20% were lost to follow up to the postnatal visit.
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, England, 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	Women were randomly allocated to three groups: group 1: received 122 mg of elemental iron as ferrous sulphate daily; group 2: received 122 mg of elemental iron as ferrous sulphate plus 3.4 mg of folic acid

	daily; group 3: no treatment. A group 4 was formed as some subjects (n = 38) from group 3 received iron supplements for treatment of anemia in the course of the intervention. They are excluded for analysis. Women were supplemented from week 20 to week 40 of gestation.
Outcomes	Maternal: haemoglobin concentrations, blood and plasma volume, haematocrit (not reported), red cell volume, albumin and globulin fractions, oedema, intrapartum haemorrhage.
Notes	Unsupervised. One hundred and fifty-four women were followed through to the postnatal visit. Only 16 women (30%) in the no treatment group remained untreated. Compliance not reported.
Allocation concealment	A – Adequate

Study	**Buytaert 1983**
Methods	Randomisation: (A) by random table numbers. Allocation concealment: (A) adequate by means of sealed envelopes. Blinding: (C) inadequate. Participant nor provider blinded. No placebo used. Loss to follow-up: (B) unclear.
Participants	45 non-anaemic women with singleton pregnancy and no major illnesses attending the University Hospital Obstetric and Gynaecologic Clinic in Antwerp.
Interventions	Women were randomly assigned to one of two 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 and continued until delivery.
Outcomes	Maternal: haemoglobin, 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.
Allocation concealment	A – Adequate

Study	**Chanarin 1971**
Methods	Randomisation: (C) quasi-randomised study, assignment by sequence. Allocation concealment: (C) inadequate. Blinding: (A) adequate. Participant and provider blinded. Loss to follow up: (A) less than 20%.
Participants	251 women attending antenatal clinic at St Mary's Hospital before 20th week of gestation.
Interventions	Women were allocated by sequence to one of five groups: group 1: oral dose of 30 mg of elemental iron daily; group 2: oral dose of 60 mg of elemental iron daily; group 3: oral dose of 120 mg of elemental iron daily; group 4: placebo; group 5: 1 gram of iron (Imferon, 4 x 250 mg) intravenously before week 20, and thereafter oral 60 mg of elemental iron as ferrous fumarate daily (not included in this review). Oral elemental iron provided as ferrous fumarate. 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.
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.
Allocation concealment	C – Inadequate

Characteristics of included studies (*Continued*)

Study	**Charoenlarp 1988**
Methods	Randomisation: (A) adequate, using a set of random tables. Allocation concealment: (B) unclear. Blinding: (B) participant and outcome assessor blinded. Provider blinding unclear. Loss to follow up: (A) adequate. Ranged from 10-15%.
Participants	325 pregnant women with Hb (AA) and 232 pregnant women with Hb (AE) attending midwife centers in 80 villages from the Varin Chamrab district of Ubon Province. Chronic illness, complicated pregnancy, severe anemia (Hb < 80 g/L), hemoglobinopathies Hb (EE) and (EF), and unwillingness to cooperate were reason for exclusion. Individuals with Hb (AA) have normal hemoglobin 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	Women were divided into two groups according to Hb (AA) and Hb (AE) and studied separately. Women from each group were randomly assigned to one of the following interventions: group 1: placebo, supervised; group 2, 120 mg of elemental iron and 5 mg folic acid daily supervised; group 3, 240 mg of elemental iron daily supervised; group 4: 240 mg of elemental iron daily supervised; group 5: 120 mg elemental iron and 5 mg of folic acid, motivated but unsupervised; and group 6: 240 mg of elemental iron and 5 mg of folic acid daily, motivated but unsupervised. For the Hb (AE) group, women were randomly assigned to one of the following groups: group 7: placebo, supervised; group 8: 240 mg elemental iron and 5 mg of folic acid daily, supervised; group 9: 240 mg of elemental iron daily, supervised; group 10: 120 mg of elemental iron and 5 mg of folic acid daily, motivated but unsupervised, and group 11: 240 mg of elemental iron and 5 mg of folic acid daily, motivated but unsupervised. Elemental iron was given as ferrous sulphate. Starting and ending time of supplementation not stated.
Outcomes	Maternal: haemoglobin, 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.
Allocation concealment	B – Unclear

Study	**Chew 1996a**
Methods	Randomisation: (A) by computerized random numbers. Allocation concealment: (A) adequate by sealed envelopes. Blinding: (A) participant, care provider and outcome assessor blinded. Loss to follow up: (C) more than 20% lost to follow up.
Participants	256 clinically healthy pregnant women from low socio economic status attending one antenatal care clinic in Guatemala city 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.
Interventions	Women were randomly assigned to one of two groups: group 1: daily supervised intake of 60 mg elemental iron and 500 ug folic acid; group 2: weekly supervised intake of 180 mg of elemental iron and 3.5 mg of folic acid in one intake once a week. Iron given as ferrous sulphate. Supplementation started at different gestational age for each participant. Average gestational age at start was 20.5 weeks until 38th week.
Outcomes	Maternal: haemoglobin concentration at baseline and at term (38th week of gestation); side-effects and total iron intake. Infant: birthweight.
Notes	Supervised.
Allocation concealment	A – Adequate

Characteristics of included studies (*Continued*)

Study	**Chew 1996b**
Methods	Randomisation: (A) by computerized random numbers. Allocation concealment: (A) adequate by sealed envelopes. Blinding: (C) Inadequate. Participant and provider not blinded. Outcome assessor for laboratory blinded to groups. Loss to follow up: (C) inadequate
Participants	120 clinically healthy pregnant women attending one antenatal care clinic in Guatemala city and Hb > 80 g/L were recruited. Women are from low SES. City of Guatemala is at 1500 m above sea level, so values were adjusted by altitude subtracting 5 g/L in Hb.
Interventions	Women from low SES were randomly assigned to one of two groups: group 3: daily unsupervised intake of 60 mg elemental iron as ferrous sulphate and 500 ug 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 one intake once a week. Supplementation started at an average of 20.5 weeks of gestation until 38th week.
Outcomes	Maternal: haemoglobin concentration at baseline and at term (38th week of gestation); side-effects and total iron intake. Infant: birthweight.
Notes	Unsupervised.
Allocation concealment	A – Adequate

Study	**Chisholm 1966**
Methods	Randomisation: (B) method unclear. Allocation concealment: (A) adequate. Bottles containing the tablets had been numbered by random selection at source and the code was unknown during trial. Blinding (A) adequate. participant and provider blinded. Loss to follow up: (A) adequate. No losses to follow up.
Participants	360 non-anaemic women attending antenatal clinic 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 ug/L.
Interventions	Women were randomly assigned to one 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 ug folic acid daily; group 3: 900 mg elemental iron and 5 mg folic acid daily; group 4: placebo; group 5: 500 ug folic acid daily; group 6: 5 mg of folic acid daily. Iron and folic acid placebos were used. Supplementation started at 28th week until 40th week.
Outcomes	Maternal: haemoglobin, haematocrit, serum iron, serum folic acid activity, serum vitamin B12 estimation at 28 weeks of gestation and predelivery.
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.
Allocation concealment	A – Adequate

Study	**Cogswell 2003**
Methods	Randomisation: (A) by computerized random numbers. Allocation concealment: (A) adequate. Blinding: (A) participant and care provider blinded. Outcome assessor unclear. Loss to follow up: (C) more than 20% lost to follow up.
Participants	275 legally competent, non-imprisoned, non-anaemic, low-income pregnant women at < 20 weeks of gestation with ferritin levels above 20 ug/L enrolled at the Cuyahoga County, MetroHealth Center, Supplemental Nutrition Program for Women, Infants and Children in Cleveland, Ohio.
Interventions	Women were randomly assigned to one of two 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 (mean cell volume, haemoglobin 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.
Notes	Unsupervised. Women were re-evaluated at 28 weeks of gestation, and according to haemoglobin 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.
Allocation concealment	A – Adequate

Study	**De Benaze 1989**
Methods	Randomisation: (B) randomised but method used unclear. Allocation concealment: (A) adequate. Blinding: (A) adequate. Participant and provider blinded. Loss to follow up: (A) less than 20%.
Participants	191 non-anaemic pregnant women with 12-18 weeks of gestation attending antenatal care clinic at the Maternity at Poissy Hospital. 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	Women were randomly allocated to one 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.
Outcomes	Maternal: haemoglobin, 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 standard deviation of ln 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.
Allocation concealment	A – Adequate

Study	**Ekstrom 2002**
Methods	Randomisation: (A) adequate by cluster. Allocation concealment: (D) not used. Blinding: (C) neither participant nor provider blinded. Outcome assessor unclear. Loss to follow up: (C) more than 20% loss to follow up.
Participants	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 haemoglobin concentrations < 80 g/L.
Interventions	Each clinic was randomly assigned to one of two interventions: 60 mg of elemental iron as ferrous sulphate and 250 ug folic acid given in one tablet daily, or 120 mg of elemental iron as ferrous sulphate and 500 ug folic acid once a week (given in two tablets one day of the week). Supplementation continued until 6 weeks postpartum. Supplementation started at baseline for 12 weeks.
Outcomes	Maternal: haemoglobin concentration at baseline and after 12 weeks of supplementation. Compliance, side-effects, serum ferritin and serum transferrin receptors at 6 weeks postpartum.
Notes	Unsupervised. Cluster randomisation used among 52 antenatal clinics: n = 25 to daily supplementation and n = 25 to weekly supplementation. Two antenatal care units ceased operation during the trial period.

	Compliance was 104% and 68% for weekly and daily groups respectively. The compliance above 100% for the weekly means that more tablets that were indicated to be taken were ingested in the period of time.
Allocation concealment	D – Not used

Study	**Eskeland 1997**
Methods	Randomisation: (A) computer generated. Allocation concealment: (A) central allocation at trials office, sequentially numbered. Blinding: (A) participant and care provider blinded. Loss to follow up: (C) inadequate. 23% and 21% in groups included.
Participants	90 healthy non-anaemic pregnant women with singleton pregnancy of less than 13 weeks, attending an inner city maternity center in Bergen and willing to participate. Exclusion criteria: uncertain gestational age according to menstrual history, haemoglobin 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	Women were randomly allocated to one of the following: group 1: three tablets containing 1.2 mg heme iron from porcine blood and 9 mg of elemental iron as ferrous fumarate (Hemofer®) and one placebo tablet (total 27 mg elemental iron a day); group 2: one tablet containing 27 mg elemental iron as iron fumarate with 100 mg vitamin C (Collet®) and three placebo tablets; or group 3: four placebo tablets. Supplementation started at 20th week until 38-40th week.
Outcomes	Maternal: haemoglobin, erythrocytes count, haematocrit, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, reticulocytes, serum iron, total iron binding capacity, serum transferrin, erythrocyte protoporfirine at baseline and at 20, 28, 38 weeks, 8 wk postpartum, and 6 months postpartum; pregnancy complications: hypertension, pre-eclampsia, forceps, postpartum haemorrhage, maternal wellbeing 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.
Allocation concealment	A – Adequate

Study	**Hankin 1963**
Methods	Randomisation: (C) alternate by day of the week. Allocation concealment: (C) inadequate. Blinding: (C) inadequate. Open. Loss to follow up: (A) adequate. Less than 5% excluded.
Participants	174 primigravidae or secundigravidae at their first visit at the antenatal Clinic of Queen Elizabeth Hospital in Woodville, with ability to write and speak English.
Interventions	Women 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 unsupplemented. Supplementation started during 2nd trimester and ending time is unclear.
Outcomes	Maternal: haemoglobin and haematocrit at 20-30 wk, 30-40 wk, at 5 days, at 6 wk and at 3 months postpartum. Infant: haemoglobin from umbilical cord, at 6 wk, at 3 months and at 6 months of age (not reported).
Notes	Unsupervised. Compliance not reported.
Allocation concealment	C – Inadequate

Study	**Holly 1955**
Methods	Randomisation: (B) unclear. Allocation concealment: (B) unclear. Blinding: (C) neither participants nor provider blinded. Outcome assessor unclear. Loss to follow up: (B) unclear.

Characteristics of included studies (*Continued*)

Participants	207 pregnant women with less than 26 weeks of gestation and Hb > 100 g/L attending antenatal care clinic.
Interventions	Women were randomly assigned to one 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 subjects until delivery.
Outcomes	Maternal: haemoglobin, haematocrit, serum iron, erythrocyte protoporphyrin at 3-6 months and pre-delivery.
Notes	Unsupervised. Three iron salts were used: ferrous gluconate (n = 40), ferrous sulphate (n = 32) and Mol-Iron (n = 22). Groups were merged together by the author as iron treated group since the results were comparable. Compliance not reported.
Allocation concealment	B – Unclear

Study	**Hood 1960**
Methods	Randomisation: (B) unclear. Allocation concealment: (B) unclear. Blinding: (C) neither participant nor provider blinded. Outcome assessor unclear. Loss to follow up: (A) adequate. Less than 20%.
Participants	75 consecutive apparently healthy pregnant women with 32-34 weeks of gestation attending the maternity clinic at St Anthony's Hospital.
Interventions	Women were randomly divided in three 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.
Outcomes	Maternal: haemoglobin, haematocrit, incidence and severity of side-effects on a weekly basis until delivery.
Notes	Unsupervised. Group 2 is recorded as higher daily dose and group 3 as low daily dose. For any iron versus no treatment comparison groups were merged. Compliance not reported.
Allocation concealment	B – Unclear

Study	**Kerr 1958**
Methods	Randomisation: (A) adequate by cards shuffle. Allocation concealment: (B) unclear. Blinding: (C) participant blinded. Provider blinded to treatments but not to controls. Outcome assessor unclear. Loss to follow up: (C) inadequate. 23% of participants were lost to follow up.
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.
Interventions	Women were randomly allocated to one of 4 groups: group 1 received 35 mg of elemental iron as ferrous sulphate three times a day; group 2 received 35 mg of elemental iron as ferrous gluconate three times a day; group 3 received 35 mg of elemental iron as ferrous gluconate with 25 mg of ascorbic acid, three times a day; group 4 received placebo. Supplementation started at 24-25th week of gestation until term.
Outcomes	Maternal: haemoglobin, red cell count, haematocrit 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.
Allocation concealment	B – Unclear

Study	**Liu 1996**
Methods	Randomisation: (B) method unclear. Non-supplemented group was self-selected.

Characteristics of included studies (*Continued*)

	Allocation concealment: (A) adequate by sealed closed envelopes. Blinding: (C) participant nor provider blinded. Outcome assessor blinded. Follow up: (A) less than 20% lost to follow up.
Participants	395 healthy, anaemic and non anaemic, pregnant women attending prenatal care at 2 outpatient clinics at Changji Hospital and Shihezi Maternal and Child Health Station in Xianjiang. Women with Hb < 80 g/L were excluded. Maternal age was 25.15 ± 2.28 years.
Interventions	Women were randomly assigned to one of 3 groups: group 1: 60 mg elemental iron as ferrous sulphate and 0.25 mg of folic acid daily; group 2: 120 mg of elemental iron as ferrous sulphate and 0.5 mg of folic acid daily; group 3: 120 mg elemental iron as ferrous sulphate and 0.5 mg of folic acid once weekly. 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.
Outcomes	Maternal: haemoglobin concentration at 3, 5, 8 months and at term; serum ferritin concentrations at 3 months and at term in a subgroup; side-effects. Weight at entry and at term (not used in the review).
Notes	Unsupervised. Iron supplementation is not mandatory for women in China, if they have a Hb concentration > 80 g/L. Compliance for group 1 (daily 60 mg Fe), group 2 (daily 120 mg Fe) and group 3 (weekly 20 mg Fe) were 77%, 75% and 86% respectively.
Allocation concealment	A – Adequate

Study	**Makrides 2003**
Methods	Randomisation: (A) adequate by means of computer generated with balanced blocks and stratified for parity. Allocation concealment: (A) opaque bottles marked with sequential numerical code prepared by the Pharmacy Department of Women's & Children's Hospital. Blinding: (A) participant and care provider blinded. Loss to follow up: (A) adequate. Less than 20% lost to follow up.
Participants	430 non-anaemic pregnant women attending antenatal clinics at Women's and Children's Hospital in Adelaide with singleton or twin pregnancies and informed consent. Exclusion criteria: diagnosis of thalassemia, history of drug or alcohol abuse and history of vitamin and mineral preparations containing iron prior to enrolment in study.
Interventions	Women were randomly assigned to receive one tablet containing 20 mg of elemental iron daily between meals from week 20 until delivery or a placebo tablet.
Outcomes	Maternal: haemoglobin concentration at 28 wk, at delivery, and at 6 months postpartum; ferritin concentration at delivery and at 6 months postpartum; maternal gastrointestinal side-effects at 24 and 36 wk of gestation; serum zinc at delivery and at 6 month postpartum; maternal wellbeing at 36 wk of gestation, at 6 wk and at 6 months postpartum; pregnancy outcomes: type of birth, blood loss at delivery, gestational age. Infant: birthweight, birth length, birth head circumference, Apgar scores, and level of nursery care.
Notes	Unsupervised but monthly phone calls to encourage compliance. If anaemia was detected in the routine 28 wk 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.
Allocation concealment	A – Adequate

Study	**Menendez 1994**
Methods	Randomisation: (B) randomised but method unclear. Allocation concealment: (C) inadequate. Blinding: (C) inadequate. Participant and provider not blinded. Outcome assessor blinded. Loss to follow up: (C) inadequate. More than 20% lost to follow up.

Characteristics of included studies (*Continued*)

Participants	550 multigravidae 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, where malaria is endemic with high transmission during 4-5 months a year.
Interventions	Women 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 5 mg of folic acid but no antimalarial chemoprophylaxis. Supplementation started at 23-24 weeks until delivery.
Outcomes	Maternal: haemoglobin concentrations at baseline, 4-6 weeks before delivery and one 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 profilaxis is provided to primigravidae in The Gambia. Thirty 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. Compliance: estimated tablet consumption was 81.1 and 81.7 tablets in the iron and placebo groups respectively.
Allocation concealment	C – Inadequate

Study	**Milman 1991**
Methods	Randomisation: (B) method unclear. Allocation concealment: (B) unclear. Blinding: (A) adequate. Participant and provider blinded. Outcome assessor unclear. Loss to follow up: (A) adequate. Less than 20% lost to follow up.
Participants	248 healthy Caucasian Danish women attending Birth Clinic within 9-18 weeks of gestation and normal pregnancy. Exclusion criteria: complicated delivery, excessive smoking (> 9 cigarettes/day).
Interventions	Women 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.
Outcomes	Maternal: haemoglobin, haematocrit, 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 placentae, 7; preeclampsia, 3; partus praematurus, 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.
Allocation concealment	B – Unclear

Study	**Ortega-Soler 1998**
Methods	Randomisation: (B) not stated. Allocation concealment: (D) not used. Blinding: (B) unclear. Loss to follow up: (B) unclear.
Participants	41 healthy pregnant women, attending prenatal care clinics at Hospital Diego Paroissien in La Matanza, Province of Buenos Aires with serum ferritin below 50 mg/mL.
Interventions	Women were assigned to one of two 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.
Outcomes	Maternal: haemoglobin, erythrocyte protoporphyrine, serum ferritin at baseline and term, dietary intake.
Notes	Unsupervised. Compliance not reported.
Allocation concealment	D – Not used

Study	**Paintin 1966**
Methods	Randomisation: (B) method unclear. Allocation concealment: (A) sequentially numbered. Blinding: (A) participant and provider blind. Loss to follow up: (A) less than 5%.
Participants	180 primigravidae women with less than 20 wk gestation and Hb > 100 g/L attending antenatal clinic in Aberdeen Maternity Hospital.
Interventions	Women were randomly assigned to one of three 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.
Outcomes	Maternal: haemoglobin, haematocrit at baseline, and at weeks 20, 30, 36 of gestation and 7-13 days post-partum; 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.
Allocation concealment	A – Adequate

Study	**Pita Martin 1999**
Methods	Randomisation: (C) quasi randomised. Allocation concealment: (D) not used. Blinding: (C) neither participant nor provider blinded. Outcome assessor blinded. Loss to follow up: (C) inadequate. More than 20% lost to follow up.
Participants	203 healthy pregnant women with normal blood pressure at first visit, attending antenatal care clinic at Diego Paroissien Hospital in the Province of Buenos Aires.
Interventions	Women were assigned to one of three groups: group 1 received 60 mg of elemental iron as ferrous fumarate daily; group 2 received 60 mg elemental iron every three 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 34-37wk gestation, premature delivery. Infant: birthweight.
Notes	Unsupervised. 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. This study is used only for comparison between intermittent and daily iron supplementation (group 2 vs group 1). Compliance not reported.
Allocation concealment	D – Not used

Study	**Preziosi 1997**
Methods	Randomisation: (A) by random numbers. Allocation concealment: (A) packages of tablets numbered by manufacturer. Blinding: (A) participant and provider blinded. Outcome assessor blind. Loss to follow up: (B) unclear.

Characteristics of included studies (*Continued*)

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.
Interventions	Women were randomly assigned to one of two 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.
Outcomes	Maternal: haemoglobin concentration, mean corpuscular volume, haematocrit, 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, haemoglobin concentration, mean corpuscular volume, 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.
Allocation concealment	A – Adequate

Study	**Pritchard 1958**
Methods	Randomisation: (B) unclear. Allocation concealment: (B) unclear. Blinding: (C) inadequate. Neither participant no provider blinded. Outcome assessor not blinded. Loss to follow up: (B) unclear.
Participants	172 pregnant women believed to be in the second trimester of pregnancy by date of last menstrual period attending antenatal care clinic.
Interventions	Women were randomly assigned to one of three 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.
Outcomes	Maternal: haemoglobin concentration at baseline and at delivery.
Notes	Unsupervised. Only groups 2 (oral iron) and 3 (placebo) were included in this review. Compliance not reported.
Allocation concealment	B – Unclear

Study	**Puolakka 1980**
Methods	Randomisation: (B) method unclear. Allocation concealment: (B) unclear. Blinding: (C) open. Loss to follow up: (A) less than 20% lost to follow up.
Participants	32 healthy non-anaemic pregnant women attending antenatal care at maternity centers of Oulu University Central Hospital, with uncomplicated pregnancy of less than 16 weeks, and no earlier haematological problems.
Interventions	Women were randomly assigned to one of two 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 one month postpartum.
Outcomes	Maternal: haemoglobin, haematocrit, red cell count, leucocyte count, reticulocytes, mean corpuscular volume, mean corpuscular haemoglobin concentration, mean corpuscular haemoglobin, 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 month postpartum. Infant: birthweight, Apgar scores at 5 minutes.
Notes	Unsupervised. Compliance not reported.

Allocation concealment	B – Unclear

Study	**Ridwan 1996**
Methods	Randomisation: (A) block randomised by randomised numbers table. Allocation concealment: (D) not used. Blinding: (C) participant and care provider not blinded. Outcome assessor blind. Loss to follow up: (C) inadequate. More than 20% lost to follow up.
Participants	176 pregnant women with 8-24 weeks of gestation attending antenatal care at six health centers in West Java.
Interventions	Health centers were randomised to one of two interventions: weekly regimen, where women received 120 mg of elemental iron as ferrous sulphate with 0.50 mg of folic acid; or daily regimen where women received 60 mg of elemental iron as ferrous sulphate with 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.
Outcomes	Maternal: haemoglobin concentration, serum ferritin, weight at baseline and at 28-32 weeks of gestation; compliance to treatment and prevalence of parasitic infections.
Notes	Unsupervised but frequent contact with participants. Randomisation was made by health centers. Compliance measured by stool tests was 54.3% in the daily group and 62.2% in the weekly group. Adjustment by intraclass correlation coefficient to show effective sample size taking into account cluster randomisation and unit of analysis.
Allocation concealment	D – Not used

Study	**Robinson 1998**
Methods	Randomisation: (C) by alternating numbers. Allocation concealment: (B) unclear. Blinding: (C) participant and provider not blinded. Outcome assesor blinded. Loss to follow up: (C) more than 20% lost to follow up.
Participants	680 pregnant women served by 11 health centers from five subdistricts on or near the western end of the island of Seram in the Province of Maluku.
Interventions	Women were assigned to one of two interventions: group 1 received 60 mg of elemental iron as ferrous sulphate with 0.25 mg of folic acid daily by a traditional birth attendant; group 2 received 120 mg of elemental iron as ferrous sulphate with 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 centers, as a self administered without incentive.
Outcomes	Maternal: haemoglobin concentration at baseline and after 12 and 20 weeks of supplementation; serum ferritin at baseline and after 12 weeks of supplementation; compliance.
Notes	Daily group and control unsupervised. Weekly group supervised. Each group was further assigned alternatively by registration number to receive 500 mg of mebendazole or a placebo at the second trimester of pregnancy. Only groups 1 and 2 are used in this analysis. Compliance was 69.6%, 96.2% and 46.9% for groups 1, 2 and control respectively. The study area is endemic to Malaria.
Allocation concealment	B – Unclear

Study	**Romslo 1983**
Methods	Randomization: (B) method unclear. Allocation concealment: (B) unclear. Blinding: (C) participant blinded. Provider and outcome assesor unclear. Loss to follow up: (A) less than 20%.
Participants	52 healthy pregnant women attending outpatient Women's clinic at Haukeland Hospital, Bergen within first 10 weeks of a normal singleton pregnancy with uncomplicated delivery at 37-42 weeks.
Interventions	Women were randomly assigned to one of two groups: group 1 received 200 mg of elemental iron as ferrous sulphate daily; group 2 received placebo.

Characteristics of included studies (*Continued*)

	Supplementation started at 10 weeks of gestation.
Outcomes	Maternal: haemoglobin, haematocrit, plasma cell volume, erythrocyte count, leucocyte count, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, serum iron, 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.
Allocation concealment	B – Unclear

Study	**Svanberg 1975**
Methods	Randomisation: (B) unclear. Allocation concealment: (B) unclear. Blinding: (A) adequate. Participants blind, care provider blind and outcome assesor blind. Loss to follow up: (A) less than 20% lost to follow up.
Participants	60 healthy primiparous women attending antenatal care clinic 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	Women 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 postdelivery.
Outcomes	Maternal: iron absorption measurements; haemoglobin concentration, haematocrit, bone marrow haemosiderin, mean corpuscular haemoglobin concentration, 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%.
Allocation concealment	B – Unclear

Study	**Taylor 1982**
Methods	Randomisation: (B) randomised but method unclear. Allocation concealment: (B) unclear. Blinding: (C) open. Loss to follow up: (A) less than 20% lost to follow up.
Participants	48 healthy pregnant women with no adverse medical or obstetric history attending antenatal care clinic before 12 weeks of gestation.
Interventions	Women were randomly allocated to receive 325 mg of ferrous sulphate (about 65 mg elemental iron) and 350 ug of folic acid daily from 12 weeks until delivery.
Outcomes	Maternal: haemoglobin concentration, serum ferritin, mean cell volume 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.
Allocation concealment	B – Unclear

Study	**Tura 1989**
Methods	Randomisation: (A) adequate by random number lists. Allocation concealment: (A) adequate. Blinding: (C) open. Loss to follow up: (A) less than 20%.
Participants	254 non anaemic non iron deficient healthy pregnant women. Exclusion criteria: acquired or congenital anaemia, haemoglobinopathies, thalassemia, 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.

Characteristics of included studies (*Continued*)

Interventions	Women were randomly assigned to receive 40 mg of elemental iron containing 250 g of ferritin in a microgranulated gastric resistant capsule daily or no treatment from 12-16 weeks of gestation until the end of puerperium.
Outcomes	Maternal: haemoglobin concentration, red cell count, mean corpuscular volume, serum iron, total transferrin, transferrin saturation, serum ferritin at 12-16 weeks, two 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 two forms of iron preparation. This sample is not used in this review. Compliance reported as higher than 98.5%.
Allocation concealment	A – Adequate

Study	**Van Eijk 1978**
Methods	Randomisation: (B) not stated. Allocation concealment: (D) not used. Blinding: (C) open. Loss to follow up: (A) less than 20%.
Participants	30 pregnant women with uncomplicated pregnancies and deliveries attending antenatal care clinic at the University Hospital Obstetric Unit in Rotterdam.
Interventions	Women 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.
Outcomes	Maternal: haemoglobin concentration, serum iron, serum ferritin, transferrin concentration at baseline and every 3-4 weeks until delivery, and three months after delivery. Infant: haemoglobin concentration, transferrin, serum iron, serum ferritin in cord blood at term.
Notes	Unsupervised. Compliance not reported.
Allocation concealment	D – Not used

Study	**Wallenburg 1983**
Methods	Randomisation: (A) by random table numbers. Allocation concealment: (A) adequate by means of sealed envelopes. Blinding: (C) inadequate. Participant nor provider blinded. No placebo used. Loss to follow-up: (A) less than 20%.
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	Women were randomly assigned to one of two 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.
Outcomes	Maternal: haemoglobin, serum iron, serum transferrin and serum ferritin concentrations at 16, 28, 36 weeks, delivery, 6 and 12 weeks postpartum.
Notes	Unsupervised. Compliance not reported.
Allocation concealment	A – Adequate

Study	**Willoughby 1967**
Methods	Randomisation: (B) unclear. Allocation concealment: (B) unclear. Blinding: (B) unclear. Loss to follow up: (A) less than 20%.

Characteristics of included studies (*Continued*)

Participants	3599 pregnant women with Hb above 100 g/L at their antenatal care clinic visit at Queen's Mother's Hospital in Glasgow. Women who reported not taken the tablets regularly ere excluded as well as those diagnosed with anaemia during the study.
Interventions	Women were randomly allocated to one of five 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 ug of folic acid; group 4 received 105 mg of elemental iron daily with 300 ug of folic acid; and group 5 received 105 mg elemental iron daily with 450 ug of folic acid. Starting and ending time of supplementation variable.
Outcomes	Maternal: haemoglobin 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.
Allocation concealment	B – Unclear

Study	**Wills 1947**
Methods	Randomisation: (C) alternate. Allocation concealment: (D) not used. Blinding: (A) participant and care provider blinded. Outcome assesor blinded. Loss to follow up: (C) inadequate. More than 20% lost to follow up.
Participants	500 pregnant women attending antenatal care clinic at the Royal Free Hospital in London during wartime, with ages between 18-43 years. Women with severe anaemic or rheumatoid arthritis were excluded.
Interventions	Women 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.
Outcomes	Maternal: haemoglobin 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.
Allocation concealment	D – Not used

Study	**Winichagoon 2003**
Methods	Randomisation: (B) Cluster randomisation but method unclear. Allocation concealment: (D) not used. Blinding: (C) open. Loss to follow up: (C) more than 20% lost to follow up.
Participants	484 apparently healthy pregnant women with 13-17 weeks of gestation who had not received iron supplements before enrolling in the study, and who had a haemoglobin concentration > 80 g/L attending antenatal care clinics at the district hospital and 7 health centers from 54 villages in the Province of Khon-Kaen in northeast Thailand.
Interventions	The villages were grouped according to size and then randomised in 4 clusters to one of three interventions: group 1 received a daily regimen providing 60 mg of elemental iron as ferrous sulphate with 0.25 mg of folic acid daily; group 2 received 120 mg of elemental iron with 3.5 mg of folic acid once a week; and group 3 received 180 mg of elemental iron as ferrous sulphate with 3.5 mg of folic acid once a week. Supplementation started at 15 +/- 2 weeks until delivery.

Characteristics of included studies (*Continued*)

Outcomes	Maternal: haemoglobin concentration, serum ferritin, free erythrocite protoporphirin at baseline and at 35 +/- 2 weeks of gestation, and 4-6 months postpartum; haematocrit prior to delivery; weight at baseline and at 35 weeks of gestation; compliance, haemoglobin type, and hookworm prevalence. Infant: birthweight, haemoglobin concentration and serum ferritin at 4-6 months.
Notes	Unsupervised. Compliance not reported. Values adjusted to reflect effective sample size for cluster randomisation.
Allocation concealment	D – Not used

Study	**Young 2000**
Methods	Randomisation: (A) adequate by computer-generated random number table. Allocation concealment: (B) unclear. Blinding: (C) neither participant nor provider blinded. Outcome assessor unclear. Loss to follow up: (C) inadequate. More than 47% lost to follow up.
Participants	413 healthy non-severely anaemic pregnant women attending antenatal care at Ekwendeni Hospital or its mobile clinics in norther Malawi with less than 30 weeks of gestation at their first visit, stratified by initial haemoglobin concentration before randomisation. Supplementation starting time variable (22.2 +/- 4.8 weeks) and ending time variable (32.2 +/- 4.4 weeks of gestation).
Interventions	Women were randomly assigned within each anaemia grade category to one of two interventions: group 1 received 120 mg of elemental iron as ferrous sulphate with 0.5 mg of folic acid once a week; group 2 received 60 mg of elemental iron as ferrous sulphate with 0.25 mg of folic acid daily.
Outcomes	Maternal: haemoglobin concentration at baseline and after 8 weeks of supplementation; compliance, presence of side-effects, and prevalence of anaemia.
Notes	Unsupervised. Average gestational age at start was 22.2 +/- 4.8 wk and 32.2 +/- 4.4 wk at the end of study. Compliance estimated by self reporting was 76% and 60% in the weekly and daily groups respectively.
Allocation concealment	B – Unclear

Study	**Yu 1998**
Methods	Randomisation: (C) quasi randomised. Allocation concealment: (C) inadequate. Blinding: (C) inadequate. Participant and care provider not blinded. Outcome assesor blinded. Loss to follow up: (C) inadequate. More than 54% lost to follow up.
Participants	51 healthy pregnant women with 18-22 weeks of gestation who had not taken supplements or medication in the previous six months attending public health center in Ulsan, Korea
Interventions	Women were randomly assigned to one of two treatments: group 1 received 160 mg of elemental iron in one intake once a week; group 2 received 80 mg of elemental iron daily. Elemental iron was given in the form of ferrous sulphate. 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.
Outcomes	Maternal: haemoglobin concentration, serum ferritin, red blood cell count, haematocrit, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, serum iron, total iron binding capacity, transferrin saturation at baseline and after treatment; zinc status before and after treatment, weight gain, nutrient intake before and after treatment. Infant: birthweight.
Notes	Unsupervised. No compliance reported for all the groups. Analysis reported on high compliers only.
Allocation concealment	C – Inadequate

Fe: iron
Hb: haemoglobin

ITT: intention to treat
MCV: mean corpuscular volume
PCV: plasma cell volume
SES: socioeconomic status
vs: versus
wk: week

Characteristics of excluded studies

Study	Reason for exclusion
Aaseth 2001	67 non-anaemic pregnant women attending prenatal care clinics in Kingsvinger Hospital, in Kongsvinger, 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 anemia in the different trimesters of pregnancy. The same pregnant women were not followed.
Afifi 1978	260 pregnant women from Cairo, United Arab Republic were randomly allocated to two forms of iron: a slow release ferrous sulphate preparation and ferrous sulphate in addition to folic acid. Both groups received iron supplementation in different preparations. No comparisons allowed within the scope of this review.
Babior 1985	Fifteen healthy pregnant women 22-32 years old, in the first trimester of pregnancy from Boston, Massachusetts, USA were randomly assigned to three different multiple micronutrient preparations to assess absorption of iron.
Bergsjo 1987	Planned study registered at the Oxford Database of Perinatal Trials. Author contacted and informed the project was not completed.
Blot 1980	203 pregnant women attending prenatal care clinics during their 6th month visit were randomly allocated to either 105 mg of elemental iron with 500 mg of ascorbic acid or a placebo. Both groups received iron.
Brown 1972	109 pregnant women attending prenatal care clinics in Manchester, England were randomly allocated to one of three groups: group A: one tablet daily given in 'reminder packs', group B: one tablet daily given in loose forms, or group C two tablets daily given in loose form. Tablets contained 50 mg of elemental iron as slow release ferrous sulphate and 400 ug of folic acid. All groups received iron. No comparisons allowed within the scope of this review.
Burslem 1968	472 pregnant women attending the booking clinic were alternatively allocated to two forms of iron: a slow release ferrous sulphate preparation and folic acid or combined conventional ferrous sulphate/folic acid. Both groups received iron supplementation in different preparations. No comparisons allowed within the scope of this review.
Cantlie 1971	27 pregnant women 17-35 years of age from 4 participating obstetricians private practice clinics were randomly assigned to two groups: one with iron and one without iron. Both groups received a multivitamin supplement.
Carrasco 1962	Two liquid preparations were used in this study: one with D-sorbitol and the other without. Both preparations contained vitamin B12, vitamin B6, ferric pyrophosphate and folic acid.
Casanueva 2003a	120 singleton pregnant women were assigned to one of two groups, group 1: 60 mg of elemental iron given daily, and group 2: 120 mg of elemental iron once weekly. Each tablet contained in addition to iron and folic acid, 1 ug of vitamin B12. No comparisons allowed within the scope of this review.
Chanarin 1965	190 pregnant women attending antenatal clinic in St Mary's Hospital in London were randomly assigned to one of three groups: ferrous fumarate, ferrous fumarate and folic acid, or placebo. The outcomes measured include full blood count at 20th, 30th, 35th and 39th week of gestation and 6th day after delivery. The paper does not report standard deviations in the variables measured and cannot be included.
Chawla 1995	81 pregnant women with 20 +/- weeks of gestation from Ludhiana City, India were divided to one of three groups: group 1, 60 mg of elemental iron ad 500 ug of folic acid daily; group 2, 60 mg of elemental iron 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 haemoglobin, 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. None of the outcomes pre-specified in our protocol were recorded due to the varied time of final measurements.
Christian 2003	426 communities were randomised to one of five regimens in which pregnant women received daily supplements of 400 ug folic acid and vitamin A; 60 mg elemental iron as ferrous fumarate, 400 ug folic acid and vitamin A; 60 mg elemental as ferrous fumarate, 30 mg zinc sulphate, 400 ug folic acid and vitamin A; multiple micronutrients including vitamin A or 1000 ug vitamin A alone (control). 4926 pregnant women were followed and 4130 live born infants. No comparisons allowed within the scope of this review.
Dawson 1987	42 healthy women with less than 16 weeks of pregnancy were randomly assigned to receive either a multiple micronutrient supplement containing 65 mg of elemental iron or one multiple micronutrient supplement with no iron. Both groups received a multivitamin/multimineral supplement. No comparisons allowed within the scope of this review.
Dommisse 1983	146 pregnant women with less than 20 weeks of gestation 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. Both groups received a multivitamin supplement. No comparisons allowed 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 four supplementation groups according to the stage of pregnancy: 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. Data are presented without standard deviation.
Ekstrom 1996	176 pregnant women attending Ilula Lutheran Health Center's antenatal service with 21-26 weeks of gestational age and haemoglobin > 80 g/L were randomly assigned to receive 120 mg elemental iron as ferrous sulphate in conventional form or 50 mg elemental iron as gastric delivery system (GDS). Both groups received iron supplementation in different preparations. No comparisons allowed within the scope of this review.
Fenton 1977	154 pregnant women with less than 14 weeks of gestation, and who had not received or were receiving treatment for a blood disorder were divided into 2 groups according to the day in which they attended the clinic in Cardiff: group 1 received 60 mg of ferrous sulphate and group 2 received placebo. Haemoglobin concentration, mean corpuscular volume (MCV), serum ferritin, serum iron and total iron binding capacity were measured at 10-14 wk and at term. The data in the paper are presented with no standard deviation values.
Fleming 1974	146 consecutive pregnant women attending a public antenatal clinic in Western Australia before 20th week of gestation who had not received iron supplements and were willing to participate were assigned in sequences of 50 to one of the 5 interventions groups: group 1 received placebo; group 2 received 60 mg of elemental iron as ferrous sulphate; group 3 received 0.5 mg of folic acid; group 4 received 60 mg of elemental iron as ferrous sulphate and 0.5 mg of folic acid; and group 5 received 60 mg of elemental iron as ferrous sulphate and 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 week 20th. More than 20% of the women were lost to follow up and the allocation of the treatment in sequences was not randomised.
Fleming 1986	200 primigravidae women were randomly assigned to one of five 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, 1 mg of folic acid daily, and group 5: in addition to chloroquine and proguanil received 60 mg of elemental iron and 1 mg of folic acid daily. No comparisons allowed within the scope of this review.
Fletcher 1971	643 pregnant women attending antenatal clinic in London were randomly assigned to one of two groups: group 1 received 200 mg of ferrous sulphate; group 2 received 200 mg of ferrous sulphate with 5 mg of folic acid. Both groups received iron. No comparisons allowed within the scope of this review.
Foulkes 1982	568 apparently healthy pregnant women with less than 20 weeks of pregnancy and no prior iron supplementation were allocated alternatively to receive 100 mg of elemental iron and 350 ug of folic acid or no treatment. Ferritin and haemoglobin concentrations were measured at baseline and at 28 and 36 weeks of gestation and 2 days postpartum. Mean corpuscular volume and mean corpuscular haemoglobin were measured at 2 days postpartum.

	Only means and median are presented. No standard deviation is shown and for ferritin concentrations no ln-transformed data are presented. No data was possible to extract from the paper and subsequent communication with author.
Freire 1989	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 Quito's public obstetric hospital were randomly assigned to receive two tablets containing 78 mg of elemental iron as ferrous sulphate daily or placebo during a period of 2 months. Overall loss to follow up rate was 41.7%. Haemoglobin, PCV, red cell indices, serum ferritin, total iron binding capacity, serum folate, serum vitamin B12 at baseline and after 2 months. Prevalence of iron deficiency was estimated by response to therapy. No prespecified outcomes from this review are presented in the paper. No further data were available.
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 socio economic status were randomly assigned to receive one tablet containing 100 mg of elemental iron as ferrous sulphate with 500 ug of folic acid daily or once a week. Weekly intake was supervised. Duration of supplementation was 100 days. Haemoglobin 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. No prespecified outcomes in this review are reported. Serum ferritin values is reported as log transformed values but no standard deviations are presented.
Goonewardene 2001	92 pregnant women from 14-24 weeks of gestation attending the university antenatal clinic, in Galle, Sri Lanka were randomly assigned to one of three 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 three times a week; and group 3 (n = 31) received the same supplement in a daily fashion. All groups were receiving multiple micronutrients. No comparisons allowed within the scope of this review.
Gringras 1982	40 pregnant women attending antenatal care clinic were given a tablet containing 47 mg of elemental iron, as ferrous sulphate and 0.5 mg of folic acid or a tablet containing 100 mg of elemental iron as ferrous glycine sulphate. Both groups received iron. No comparisons allowed within the scope of this review.
Groner 1986	40 pregnant women attending antenatal care at the Adolescent Pregnancy Clinic and Obstetrics Clinics at the John Hopkins and Sinai Hospital in Baltimore, at or before 16 weeks of pregnancy with haematocrit equal or above 31% were randomly assigned to one of two groups: group 1 (n = 16) received 60 mg of elemental ion as ferrous fumarate and prenatal vitamins; or group 2 (n = 9) received only the prenatal vitamins. Two women objected the randomisation and 13 dropped out of the study. Both groups received multiple micronutrients. No comparisons allowed within the scope of this review.
Guldholt 1991	192 pregnant women were consecutively randomised to receive one of two treatments: group 1: received a vitamin-mineral tablet containing 15 mg of elemental iron or group 2: received a 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 were assessed during pregnancy for haemoglobin 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.
Hawkins 1987	No report available of the study results.
Hemminki 1989	2944 pregnant women were randomised to receive either routine or selective iron prophylaxis in 27 community maternity centers in Tampere and 5 other neighbouring communities, Finland. Women in the iron supplemented group were asked to take 100 mg of elemental iron no later than 17th week of gestation. If the haematocrit was lower than 0.30 on two consecutive visits, women in the selective group were given 100 mg of elemental iron daily as slow release form for two months or until the haematocrit increased to 0.32. 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.
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 two antenatal care clinics in London, England were assigned to one of three interventions: group 1 received 200 mg ferrous sulphate with 5 mg of folic acid three times a day; group 2 received 350 mg of ferrous aminoate with 50 ug of folic acid three times a day; and group 3 received 200 mg of ferrous sulphate with 500 ug of folic acid once a day. Intervention period was 3 weeks. All groups received iron and folic acid. 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 one of four 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 ug of folic acid in a single tablet; and group 4 received in addition to iron and folic acid, 2 ug of vitamin B12 in a single tablet. Loss to follow up was 65%. None of the pre-specified outcomes in the protocol was reported and no data were extractable from the paper.
Kann 1988	36 healthy non-anaemic pregnant women in second or third trimesters of gestation were randomly assigned to one of four prenatal commercial multivitamin/multimineral preparations: Stuartnatal 1+1; Stuart Prenatal; Materna; and Natalins Rx. All participants received multiple micronutrients. No comparisons allowed within 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 one of three groups: group 1 received 60 mg of elemental iron + 0.5 mg of folic acid once daily; group 2 received 120 mg of elemental iron + 0.5 mg of folic acid once daily; group 3 received 120 mg of elemental iron twice daily + 0.5 mg of folic acid. Duration of supplementation was 12-14 weeks. All participants received iron. No comparisons are 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 haemoglobin > 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 two 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.
Menon 1962	273 healthy pregnant women with 16-24 weeks of gestation and haemoglobin concentrations at or above 105 g/L attending antenatal care clinics were divided in order in which they were registered in three groups: group 1 was given 5 g of ferrous sulphate daily; group 2 received 5 mg of folic acid daily; and group 3 received 5 g of ferrous sulphate and 5 mg of folic acid daily. All participants were given 3 multivitamin tablets daily containing vitamin A, vitamin B, C and D. No comparisons allowed within the scope of this review.
Morgan 1961	356 pregnant women attending two 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. Not 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 one of four 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 ug of 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 ug of folic acid. All groups received iron. No comparisons allowed within the scope of this review.
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 were randomly assigned to one of two interventions: group 1 received 200 mg of ferrous sulphate (40 mg elemental iron) with 1 mg of folic acid once daily; and group 2 received 200 mg of ferrous sulphate with 1 mg of folic acid on two days of the week and placebo the rest of the days. Subjects and care providers were blind to the treatments. Outcomes measured include haemoglobin concentration and serum ferritin at baseline and during the three following consecutive visits as well as compliance and weight. Change in haemoglobin Z-score after supplementation was the main outcome

	variable, in women from different gestational ages and duration of intervention, thus not allowing outcomes prespecified in this review.
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 five groups: group 1 received 120 mg elemental iron as ferrous sulphate and 250 ug of folic acid; group 2 received 80 mg elemental iron as ferrous sulphate and 250 ug folic acid; group 3 received 120 mg of elemental iron, with 5 mg of zinc sulphate and 250 ug of folic acid; and group 4 received 80 mg of elemental iron as ferrous sulphate, with 5 mg of zinc sulphate and 250 ug of folic acid. All groups received iron and two groups received zinc in addition to iron and folic acid. No comparisons allowed within the scope of this review.
Pena-Rosas 2003	116 pregnant women of 10-30 wk of gestational age attended antenatal care clinics in Trujillo, Venezuela were randomly allocated to receive a 120 mg oral dose of iron as ferrous sulfate and 0.5 mg of folic acid weekly (n = 52) or 60 mg iron and 0.25 mg folic acid and a placebo twice weekly (n = 44). Haemoglobin, hematocrit, serum ferritin and transferrin saturation were estimated at baseline and at 36-39 wk of gestation. All groups received iron and folic acid in two intermittent regimens with no control group. No comparisons allowed within the scope of this review.
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. Haemoglobin concentration, prevalence of anaemia and nutrient consumption at baseline and after 10 weeks of supplementation were measured. None of the prespecified outcomes of this review were available. Gestational ages were variable among the participants.
Ramakrishnan 2003	873 pregnant women with less than 13 weeks of gestation who did not use micronutrient supplements were randomly assigned to receive a multiple micronutrient supplement or iron-only group. 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 one of two 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. 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 one of three groups: group 1 received 60 mg elemental iron and 0.5 mg of folic acid daily; group 2 received 120 mg elemental iron with 0.5 mg of folic acid daily; and group 3 received 240 mg elemental iron and 0.5 mg of folic acid daily. Elemental iron was given as ferrous sulphate. All groups received iron. No comparisons allowed within the scope of this review.
Roztocil 1994	84 non-anaemic pregnant women at Mazarik University Brno in Chech Republic were treated from week 20-24th with one capsule of Actiferrin Compositum, and from week 36th 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, 0.5 mg of folic acid, and 0.3 mg of cyanocobalamin. No comparisons allowed within the scope of this review.
Rybo 1971	117 pregnant women between 20-29 weeks of gestation were alternatively assigned during three consecutive two weeks periods to receive 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 weeks 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/
Sandstad 2003	233 pregnant women attending their second antenatal care visit at the University Health Services of Oslo, Norway with serum ferritin concentration < 60 ug/L were randomised to two different iron preparations, group 1 received one tablet containing 60 mg of elemental iron as ferrous sulphate daily; group 2 received three 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 center 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.
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 one of 11 different formulations and does 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 adde 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.
Siega-Riz 2004	966 pregnant women with less than 20 weeks of gestation were recruited and randomised into four treatment groups. Women with serum ferritin below 40 ug/L and haemoglobin concentration above 90 g/L were randomised to receive a multiple micronutrient supplement containing either 30 or 60 mg of elemental iron daily. Women with serum ferritin above 40 ug/L and no anaemia were randomised to receive a prenatal multiple micronutrient supplement containing 30 mg of elemental iron daily or no iron. Women were treated from baseline to 24–29 weeks' gestation. Compliance was measured by pill count, a questionnaire and pharmacy data. Outcome measured was anaemia, haemoglobin and serum ferritin concentrations at 24-29 weeks and at delivery. Intervention included multiple micronutrients. No comparisons allowed within the scope of this review.
Simmons 1993	376 pregnant women with ages between 16-35 y, with mild anaemia (Hb concentrations between 80-110 g/L) attending eight maternal and child health centers in Kingston, St. Andrews and Spanish Town, Jamaica, with gestational age between 14-22 weeks were randomly assigned to one of three groups: group 1 received one placebo tablet daily; group 2 received 100 mg of elemental iron as ferrous sulphate daily; group 3 received gastric delivery system capsule containing 50 mg of elemental iron daily. All women received 400 mg of folic acid. Outcomes measure included haemoglobin, haematocrit, 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. No prespecified outcomes are presented at the paper as gestational ages differed in the participants.
Sjostedt 1977	300 pregnant women attending the Maternity Welfare Center, in Oulu, Finland before the 5th month of pregnancy were randomly assigned to one of three interventions: group 1 received 100 mg of elemental iron daily as sustained-release tablets daily; group 2 received 200 mg of elemental iron daily as sustained-released 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 one of three 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 one of five 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 ug intramuscular once per 14 d; group 4 received 100 mg of elemental iron intramuscular + pteroylmonoglutamic acid + cyanocobalamin 100 ug intramuscular; and group 5 received iron dextran complex intramuscular in a single total dose infusion + 5 mg/d pteroylmonoglutamic acid + 100 ug intramuscular cyanocobalamin once per 14 days. All groups received iron at different doses and routes. No comparisons allowed within 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 a slow-release dose of 105 mg of elemental iron as ferrous sulphate and 350 ug of folic acid daily or 80 mg of elemental iron as ferrous fumarate and 400 ug 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.
Suharno 1993	251 pregnant women aged 17-35 years, parity 0-4 and haemoglobin concentrations between 80 and 109 g/L were randomly allocated to one of four groups: group 1 received 2.4 mg of retinol and one 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; and group 4 received two placebos for 8 weeks. Outcomes measured include: haemoglobin, haematocrit, serum ferritin, serum iron, total iron binding capacity, serum retinol, transferrin saturation, at baseline and after 8 weeks of supplementation. None of the pre specified outcomes in this review can be extracted from this paper.
Tampakoudis 1996	82 pregnant women with haemoglobin 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 haemoglobin, 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 haemoglobin concentration above 100 g/L attending antenatal clinic at the University Hospital at Kuala Lumpur, Malaysia were assigned to receive iron supplements or no treatment. Abstract only available. No additional information was available, including doses, regimens and other characteristics of the trial.
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.
Tholin 1995	83 healthy nulliparous non vegetarian, non-anaemic pregnant women with serum ferritin concentrations above 10 ug/L were randomly assigned to one of three groups: group 1 received 100 mg of elemental iron as ferrous sulphate daily; group 2 received placebo, and group 3 received dietary advice only. Blood haemoglobin, 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. No outcomes were extractable from this report for 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 or 100 mg of elemental iron from week 16th until delivery. All women received 0.3 mg of folic acid daily. All women received iron in different dose. No comparisons allowed 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 two groups by alternate allocation by clinic: group 1 received 140 mg of elemental iron daily as ferrous gluconate in four 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.
Willoughby 1966	350 consecutive pregnant women attending antenatal care clinic were allocated to one of five 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 ug of folic acid; group 4 received 105 mg of elemental iron daily with 300 ug of folic acid; and group 5 received 105 mg of elemental iron daily th 450 ug of folic acid. All women received a multivitamin preparation (Vivatel) free of folic acid.
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 ug of folic acid daily.
Wu 1998	369 pregnant women attending antenatal care at Beijing Hospital, China were divided into two groups according to their initial haemoglobin concentrations. Women with Hb 110 g/L or above were randomly assigned to one of two groups: group 1 (n = 96) received one 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 one of three groups: group 1 received 1 tablet of maternal supplement daily; group 2 received 0.9 g of ferrous sulphate daily; and group 3 received one tablet of Ferroids, a sustained released preparation daily. In the preventive group, women entered the study from 20-24 gestational weeks and. In the treatment groups, women less than 36 gestational weeks were accepted. No comparisons allowed due to the addition of other micronutrients in the treatment.

Characteristics of excluded studies (*Continued*)

Zittoun 1983	203 pregnant women attending antenatal clinic in Paris, France, with 28 +/- 2 weeks of gestation were studied. Women with Hb below 110 g/L (n = 48) were provided 105 mg of elemental iron and 500 mg of ascorbic acid. Women with Hb concentration above 110 g/L (were randomly assigned to receive 105 mg of elemental iron and 500 mg of ascorbic acid daily until delivery or placebo. Iron was provided in conjunction with vitamin C. No comparisons allowed within the scope of this review.

IU: international units

Characteristics of ongoing studies

Study	**Harvey 2004**
Trial name or title	Evaluation of the safety and efficacy of iron supplementation in pregnant women.
Participants	14 healthy pregnant women aged 18-40 years were recruited onto the study at less than 14 weeks of pregnancy. Volunteers were recruited through the Maternity Department of the Norfolk and Norwich University Hospital and local GP practices. Women were excluded if they were anaemic (Hb < 108 g/L), had low iron stores (Ferritin < 23 µg/L) or had donated blood during the previous 6 months. Other exclusion criteria included chronic illness, the taking of medication or nutritional supplements and smoking.
Interventions	Women were randomised to one of three groups: group 1 (n = 7) receiving placebo; group 2 (n = 1) receiving 20 mg of elemental iron daily; and group 3 (n = 6) receiving 100 mg of elemental iron daily. Iron provided as ferrous gluconate.
Outcomes	Iron status indicators in mother and neonates (serum ferritin, haemoglobin, transferrin saturation, transferrin receptors). Maternal zinc and copper absorption using stable isotope methodology. Maternal copper status (serum copper, caeruloplasmin). Maternal zinc status (exchangeable zinc pool, plasma zinc). Immune function (C3, C4, IgM, IgG, IgA, IL-2, IL-4). Antioxidant status (Ferric reducing ability of plasma (FRAP), superoxide dismutase, COMET assay).
Starting date	Recruiting finished January 2004.
Contact information	Linda J Harvey BSc., PhD Nutrition Division Institute of Food Research Norwich Research Park Colney Norwich NR4 7UA Tel: +44 (0) 1603 255000 FAX: +44 (0) 1603 507723 e-mail: linda.harvey@bbsrc.ac.uk
Notes	

ADDITIONAL TABLES

Table 01. Methodological quality assessment of included trials

Trial	Randomisation	Allocation	Blinding	Completeness of data	Quality rating
Barton 1994	A. Adequate	A. Adequate	A. Participant and care provider blinded	A. Adequate. Less than 5% lost to	HIGH

Table 01. Methodological quality assessment of included trials (*Continued*)

Trial	Randomisation	Allocation	Blinding	Completeness of data	Quality rating
				follow up	
Batu 1976	B. Unclear method	B. Unclear	B. Participant blinded. Care provider and outcome assessor not clear	B. Unclear	
Butler 1968	A. Adequate	A. Adequate	C. Open	C. Inadequate. More than 20% lost to follow up	
Buytaert 1983	A. Adequate	A. Adequate	C. Open	A. Adequate. Less than 20% lost to follow up	HIGH
Chanarin 1971	C. Quasi randomised by sequence assignment	C. Inadequate	A. Participant and care provider blinded	A. Adequate. Less than 20% lost to follow up	
Charoenlarp 1988	A. Adequate	B. Unclear	B. Participant and outcome assessor blinded. Care provider unclear		
Chew 1996a	A. Adequate	A. Adequate by sealed envelopes	A. Participant, care provider and outcome assessor blinded	A. Adequate. Less than 20% lost to follow up	HIGH
Chew 1996b	A. Adequate	A. Adequate by sealed envelopes	C. Participant and care provider not blinded. Outcome assessor blinded	C. Inadequate. More than 20% lost to follow up	
Chisholm 1966	B. Unclear method	A. Adequate	A. Participant and care provider blinded	A. Adequate. Less than 20% lost to follow up	
Cogswell 2003	A. Adequate	A. Adequate	A. Participant,care provider and outcome assessor blinded	C. Inadequate. More than 20% lost to follow up	HIGH
De Benaze 1989	B. Unclear method	A. Adequate	A. Participant and care provider blinded	A. Adequate. Less than 20% lost to follow up	
Ekstrom 2002	A. Adequate by cluster	D. Not used	C. Participant and care provider not blinded. Outcome assessor unclear	C. Inadequate. More than 20% lost to follow up	
Eskeland 1997	A. Adequate	A. Adequate	A. Participant, care provider and	C. Inadequate. More than 20% lost to	HIGH

Table 01. Methodological quality assessment of included trials (*Continued*)

Trial	Randomisation	Allocation	Blinding	Completeness of data	Quality rating
			outcome assessor blinded	follow up	
Hankin 1963	C. Quasi randomised by alternate assignment by day of the week	C. Inadequate	C. Open	A. Less than 5% excluded	
Holly 1955	B. Unclear method	B. Unclear	C. Participant and care provider not blinded. Outcome assessor unclear	B. Unclear	
Hood 1960	B. Unclear method	B. Unclear	C. Participant and care provider not blinded. Outcome assessor unclear	A. Adequate. Less than 20% lost to follow up	
Kerr 1958	A. Adequate	B. Unclear	C. Participant blinded. Care provider not blinded. Outcome assessor unclear	C. Inadequate. More than 20% lost to follow up	
Liu 1996	B. Unclear method	A. Adequate by sealed envelopes	C. Participant and care provider not blinded. Outcome assessor blinded	A. Adequate. Less than 5% lost to follow up	
Makrides 2003	A. Adequate	A. Adequate	A. Participant and care provider blinded	A. Adequate. Less than 5% loss to follow up	HIGH
Menendez 1994	B. Unclear method	C. Inadequate	C. Participant and care provider not blinded. Outcome assessor blinded	C. Inadequate. More than 20% lost to follow up	
Milman 1991	B. Unclear method	B. Unclear	A. Participant and care provider blinded. Outcome assessor unclear	A. Adequate. Less than 5% lost to follow up	
Ortega-Soler 1998	B. Not stated	D. Not used	B. Unclear	B. Unclear	
Paintin 1966	B. Unclear method	A. Adequate by sequential numbers	A. Participant and care provider blinded	A. Adequate. Less than 5% lost to follow up	
Pita 1999	C. Quasi randomised	D. Not used	C. Open	C. Inadequate. More than 20% lost to follow up	
Preziosi 1997	A. Adequate	A. Adequate	A. Participant	B. Unclear	HIGH

Table 01. Methodological quality assessment of included trials (*Continued*)

Trial	Randomisation	Allocation	Blinding	Completeness of data	Quality rating
			and care provider blinded. Outcome assessor blinded		
Pritchard 1958	B. Unclear method	B. Unclear	C. Open	B. Unclear	
Puolakka 1980	B. Unclear method	B. Unclear	C. Open	A. Adequate. Less than 20% lost to follow up	
Ridwan 1996	A. Adequate	D. Not used	C. Participant and care provider not blinded. Outcome assessor blinded	C. Inadequate. More than 20% lost to follow up	
Robinson 1998	C. Quasi randomised by alternate numbers	B. Unclear	C. Participant and care provider not blinded	C. More than 20% lost to follow up	
Romslo 1983	B. Unclear method	B. Unclear	C. Participant blinded. Care provider and outcome assessor not blinded	A. Adequate. Less than 20% lost to follow up	
Svanberg 1975	B. Unclear method	B. Unclear	A. Participant, care provider, and outcome assessor blinded	A. Adequate. Less than 20% lost to follow up	
Taylor 1982	B. Unclear method	B. Unclear	C. Open	A. Adequate. less than 20% lost to follow up	
Tura 1989	A. Adequate	A. Adequate	C. Open	A. Adequate. Less than 20% lost to follow up	HIGH
Van Eijk 1978	B. Not stated	D. Not used	C. Open	A. Adequate. Less than 20% loss to follow up	
Wallenburg 1983	A. Adequate	A. Adequate	C. Open	A. Adequate. Less than 20% lost to follow up	HIGH
Willoughby 1967	B. Unclear method	B. Unclear	B. Unclear	A. Adequate. Less than 20% lost to follow up	
Wills 1947	C. Quasi randomised by alternate allocation	D. Not used	A. Participant and care provider blinded. Outcome assessor blinded	C. Inadequate. More than 20% lost to follow up	

Table 01. Methodological quality assessment of included trials (*Continued*)

Trial	Randomisation	Allocation	Blinding	Completeness of data	Quality rating
Winichagoon 2003	B. Unclear method of cluster randomisation	D. Not used	C. Open	C. Inadequate. more than 20% lost to follow up	
Young 2000	A. Adequate	B. Unclear	C. Participant and care provider not blinded. Outcome assessor unclear	C. Inadequate. More than 20% lost to follow up	
Yu 1998	C. Quasi randomised	C. Inadequate	C. Open	C. More than 20% lost to follow up	

ANALYSES

Comparison 01. Daily iron alone versus no intervention/placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Low birthweight (less than 2500 g) (ALL)	4	1147	Relative Risk (Random) 95% CI	0.59 [0.23, 1.49]
02 Low birthweight (less than 2500 g) (BY SUBGROUPS)			Relative Risk (Random) 95% CI	Subtotals only
03 Birthweight (g) (ALL)	5	925	Weighted Mean Difference (Random) 95% CI	22.49 [-99.35, 144.34]
04 Birthweight (g) (BY SUBGROUPS)			Weighted Mean Difference (Random) 95% CI	Subtotals only
05 Premature delivery (less than 37 weeks of gestation) (ALL)	3	690	Relative Risk (Random) 95% CI	0.76 [0.47, 1.24]
06 Premature delivery (less 37 weeks of gestation) (BY SUBGROUPS)			Relative Risk (Random) 95% CI	Subtotals only
07 Maternal Hb concentration at term (g/L) (ALL)	15	1516	Weighted Mean Difference (Random) 95% CI	7.53 [4.40, 10.66]
08 Maternal Hb concentration at term (g/L) (BY SUBGROUPS)			Weighted Mean Difference (Random) 95% CI	Subtotals only
09 Anaemia at term (Hb less than 110 g/L) (not pre-specified)	13	1696	Relative Risk (Random) 95% CI	0.26 [0.16, 0.43]
10 Haemoconcentration at term (Hb more than 130 g/L) (ALL)	8	1222	Relative Risk (Random) 95% CI	3.01 [1.46, 6.19]
11 Haemoconcentration at term (Hb more than 130 g/L) (BY SUBGROUPS)			Relative Risk (Random) 95% CI	Subtotals only
12 Haemoconcentration during second or third trimester (ALL)	6	1133	Relative Risk (Random) 95% CI	1.90 [1.07, 3.35]
13 Haemoconcentration during second or third trimester (BY SUBGROUPS)			Relative Risk (Random) 95% CI	Subtotals only

14 Iron deficiency at term (as defined by two or more indicators) (ALL)	6	1108	Relative Risk (Random) 95% CI	0.44 [0.27, 0.70]
15 Iron deficiency at term (as defined by two or more indicators) (BY SUBGROUPS)			Relative Risk (Random) 95% CI	Subtotals only
16 Iron deficiency anaemia at term (ALL)	5	940	Relative Risk (Random) 95% CI	0.33 [0.16, 0.69]
17 Iron deficiency anaemia at term (BY SUBGROUPS)			Relative Risk (Random) 95% CI	Subtotals only
18 Side-effects (Any) (ALL)	6	1099	Relative Risk (Random) 95% CI	1.90 [1.09, 3.33]
19 Side-effects (Any) (BY SUBGROUPS)			Relative Risk (Random) 95% CI	Subtotals only
20 Very low birthweight (less than 1500 g) (ALL)	3	697	Relative Risk (Random) 95% CI	0.55 [0.03, 9.07]
24 Infant Hb concentration at 3 months (g/L) (ALL)	1	197	Weighted Mean Difference (Random) 95% CI	0.00 [-3.21, 3.21]
25 Infant serum ferritin concentration at 3 months (ug/L) (ALL)	1	197	Weighted Mean Difference (Random) 95% CI	19.00 [2.75, 35.25]
26 Infant Hb concentration at 6 months (g/L) (ALL)	1	197	Weighted Mean Difference (Random) 95% CI	-5.00 [-9.11, -0.89]
27 Infant serum ferritin concentration at 6 months (ug/L) (ALL)	1	197	Weighted Mean Difference (Random) 95% CI	11.00 [4.37, 17.63]
30 Very premature delivery (less than 34 weeks' gestation) (ALL)	3	690	Relative Risk (Random) 95% CI	0.32 [0.10, 1.09]
31 Severe anaemia at term (Hb less than 70 g/L) (ALL)	7	1024	Relative Risk (Random) 95% CI	4.83 [0.23, 99.88]
32 Moderate anaemia at term (Hb more than 70 g/L and less than 90 g/L) (ALL)	8	1141	Relative Risk (Random) 95% CI	0.94 [0.55, 1.62]
33 Severe anaemia at any time during second and third trimester (ALL)	6	1075	Relative Risk (Random) 95% CI	4.98 [0.24, 103.01]
34 Moderate anaemia at any time during second or third trimester (ALL)	7	1252	Relative Risk (Random) 95% CI	0.59 [0.35, 1.01]
36 Puerperal infection (ALL)	1	1442	Relative Risk (Random) 95% CI	0.58 [0.14, 2.40]
37 Antepartum haemorraghe (ALL)	1	430	Relative Risk (Random) 95% CI	2.97 [0.12, 72.56]
38 Postpartum haemorraghe (ALL)	3	583	Relative Risk (Random) 95% CI	0.77 [0.47, 1.27]
39 Transfusion provided (ALL)	1	32	Relative Risk (Random) 95% CI	0.33 [0.01, 7.62]
40 Haemoglobin concentration within one month postpartum (ALL)	4	833	Weighted Mean Difference (Random) 95% CI	6.10 [3.70, 8.49]
41 Severe anaemia at postpartum (Hb less than 80 g/L) (ALL)	6	778	Relative Risk (Random) 95% CI	Not estimable

42 Moderate anaemia at postpartum (Hb more than 80 g/L and less than 100 g/L) (ALL)	3	478	Relative Risk (Random) 95% CI	2.81 [0.12, 68.54]
43 Diarrhoea (ALL)	1	173	Relative Risk (Random) 95% CI	0.98 [0.09, 10.61]
44 Constipation (ALL)	2	580	Relative Risk (Random) 95% CI	0.88 [0.18, 4.40]
45 Nausea (ALL)	3	650	Relative Risk (Random) 95% CI	2.38 [0.49, 11.52]
46 Heartburn (ALL)	1	408	Relative Risk (Random) 95% CI	1.00 [0.82, 1.22]
47 Vomiting (ALL)	2	477	Relative Risk (Random) 95% CI	0.88 [0.38, 2.07]
48 Maternal death (death while pregnant or within 42 days of termination of pregnancy) (ALL)	1	47	Relative Risk (Random) 95% CI	Not estimable
49 Maternal wellbeing/satisfaction (ALL)	1	49	Relative Risk (Random) 95% CI	0.91 [0.77, 1.08]
50 Placental abruption (ALL)	1	1442	Relative Risk (Random) 95% CI	2.88 [0.12, 70.53]
52 Pre-eclampsia (ALL)	1	47	Relative Risk (Random) 95% CI	0.96 [0.06, 14.43]
93 Cesarean delivery (not prespecified)	3	508	Relative Risk (Random) 95% CI	1.06 [0.75, 1.50]
94 Birth length in cm (not prespecified)	4	877	Weighted Mean Difference (Random) 95% CI	0.24 [-0.17, 0.65]
95 Forceps or vacuum delivery (not prespecified)	2	477	Odds Ratio (Random) 95% CI	1.59 [0.93, 2.74]
96 Breastfeeding at least 4 months (not prespecified)	1	48	Relative Risk (Random) 95% CI	1.00 [0.89, 1.13]
97 Haemoglobin concentration at 4-8 weeks' postpartum (g/L) (not prespecified)	7	586	Weighted Mean Difference (Random) 95% CI	2.28 [0.40, 4.16]
98 Apgar score < 7 at 5 minutes (not prespecified)	2	475	Relative Risk (Random) 95% CI	0.74 [0.17, 3.28]
99 Apgar Score at 5 min (not prespecified)	2	228	Weighted Mean Difference (Random) 95% CI	0.27 [-0.07, 0.62]

Comparison 02. Intermittent iron alone versus daily iron alone

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
03 Birthweight (ALL)	1	41	Weighted Mean Difference (Random) 95% CI	-68.00 [-398.33, 262.33]
05 Premature delivery (less than 37 weeks of gestation) (ALL)	1	41	Relative Risk (Random) 95% CI	0.46 [0.02, 8.96]
12 Haemoconcentration during second or third trimester (Hb more than 130 g/L) (ALL)	2	64	Relative Risk (Random) 95% CI	0.54 [0.18, 1.58]
33 Severe anaemia at any time during second and third trimester (Hb less than 70 g/L) (ALL)	2	64	Relative Risk (Random) 95% CI	Not estimable
34 Moderate anaemia at any time during second or third trimester (ALL)	2	64	Relative Risk (Random) 95% CI	2.42 [0.16, 35.56]

Comparison 03. Daily iron-folic acid versus no intervention/placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Low birthweight (less than 2500 g) (ALL)	1	48	Relative Risk (Random) 95% CI	5.00 [0.25, 98.96]
03 Birthweight (ALL)	1	45	Weighted Mean Difference (Random) 95% CI	-32.00 [-213.62, 149.62]
05 Premature delivery (less than 37 weeks of gestation) (ALL)	1	48	Relative Risk (Random) 95% CI	7.00 [0.38, 128.61]
07 Haemoglobin concentration at term (ALL)	4	179	Weighted Mean Difference (Random) 95% CI	12.00 [2.93, 21.07]
08 Haemoglobin concentration at term (BY SUBGROUPS)			Weighted Mean Difference (Random) 95% CI	Subtotals only
09 Anaemia at term (Hb less than 110 g/L) (not pre-specified)	3	346	Relative Risk (Random) 95% CI	0.27 [0.12, 0.56]
10 Haemoconcentration at term (Hb more than 130 g/L) (ALL)	2	222	Relative Risk (Random) 95% CI	1.28 [0.24, 6.78]
11 Haemoconcentration at term (Hb more than 130 g/L) (BY SUBGROUPS)			Relative Risk (Random) 95% CI	Subtotals only
18 Side-effects (Any) (ALL)	1	456	Relative Risk (Random) 95% CI	44.32 [2.77, 709.09]
20 Very low birthweight (less than 1500 g) (ALL)	1	48	Relative Risk (Random) 95% CI	5.00 [0.25, 98.96]
21 Perinatal death (ALL)	2	145	Relative Risk (Random) 95% CI	2.50 [0.10, 59.88]
29 Admission to special care unit (ALL)	1	48	Relative Risk (Random) 95% CI	Not estimable
30 Very premature delivery (less than 34 weeks' gestation) (ALL)	1	48	Relative Risk (Random) 95% CI	5.00 [0.25, 98.96]
31 Severe anaemia at term (Hb less than 70 g/L) (ALL)	2	136	Relative Risk (Random) 95% CI	Not estimable
32 Moderate anaemia at term (Hb more than 70g/L and less than 90 g/L) (ALL)	2	136	Relative Risk (Random) 95% CI	Not estimable
33 Severe anaemia at any time during second and third trimester (Hb less than 70 g/L) (ALL)	2	164	Relative Risk (Random) 95% CI	Not estimable
34 Moderate anaemia at any time during second or third trimester (ALL)	2	164	Relative Risk (Random) 95% CI	Not estimable
35 Infection during pregnancy (including urinary tract infections) (ALL)	1	48	Relative Risk (Random) 95% CI	1.00 [0.15, 6.53]
36 Puerperal infection (ALL)	1	2863	Relative Risk (Random) 95% CI	0.55 [0.13, 2.28]
37 Antepartum haemorraghe (ALL)	2	145	Relative Risk (Random) 95% CI	1.25 [0.22, 7.12]
38 Postpartum haemorraghe (ALL)	1	68	Relative Risk (Random) 95% CI	0.12 [0.00, 2.71]

40 Haemoglobin concentration within one month postpartum (ALL)	1	45	Weighted Mean Difference (Random) 95% CI	10.40 [4.03, 16.77]
41 Severe anaemia at postpartum (Hb less than 80 g/L) (ALL)	1	67	Relative Risk (Random) 95% CI	Not estimable
42 Moderate anaemia at postpartum (Hb more than 80 g/L and less than 100 g/L) (ALL)	1	67	Relative Risk (Random) 95% CI	Not estimable
50 Placental abruption (ALL)	1	2863	Relative Risk (Random) 95% CI	8.19 [0.49, 138.16]
52 Pre-eclampsia (ALL)	1	48	Relative Risk (Random) 95% CI	3.00 [0.13, 70.16]
92 Oedema during pregnancy (not prespecified)	1	67	Relative Risk (Random) 95% CI	2.82 [0.99, 8.09]
93 Cesarean delivery (not prespecified)	1	97	Relative Risk (Random) 95% CI	0.83 [0.22, 3.13]
97 Haemoglobin concentration at 4-8 weeks postpartum (not prespecified)	2	112	Weighted Mean Difference (Random) 95% CI	2.01 [-0.68, 4.70]

Comparison 04. Intermittent iron-folic acid versus daily iron-folic acid

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Low birthweight (less than 2500 g) (ALL)	3	650	Relative Risk (Random) 95% CI	0.99 [0.50, 1.97]
02 Low birthweight (less than 2500 g) (BY SUBGROUPS)			Relative Risk (Random) 95% CI	Subtotals only
03 Birthweight (ALL)	3	650	Weighted Mean Difference (Random) 95% CI	-8.36 [-73.56, 56.85]
04 Birthweight (BY SUBGROUPS)			Weighted Mean Difference (Random) 95% CI	Subtotals only
07 Haemoglobin concentration at term (ALL)	3	475	Weighted Mean Difference (Random) 95% CI	-0.83 [-4.74, 3.08]
08 Haemoglobin concentration at term (BY SUBGROUPS)			Weighted Mean Difference (Random) 95% CI	Subtotals only
09 Anaemia at term (Hb < 110 g/L) (not prespecified)	3	475	Relative Risk (Random) 95% CI	1.20 [0.78, 1.83]
10 Haemoconcentration at term (Hb more than 130 g/L) (ALL)	3	475	Relative Risk (Random) 95% CI	0.93 [0.47, 1.82]
11 Haemoconcentration at term (Hb more than 130 g/L) (BY SUBGROUPS)			Relative Risk (Random) 95% CI	Subtotals only
12 Haemoconcentration during second or third trimester (Hb more than 130 g/L) (ALL)	5	1031	Relative Risk (Random) 95% CI	0.41 [0.21, 0.80]
13 Haemoconcentration during second or third trimester (Hb more than 130 g/L) (BY SUBGROUPS)			Relative Risk (Random) 95% CI	Subtotals only
16 Iron deficiency anaemia at term (based on two or more indicators) (ALL)	1	156	Relative Risk (Random) 95% CI	0.71 [0.08, 6.63]

18 Side-effects (any) (ALL)	6	1227	Relative Risk (Random) 95% CI	0.80 [0.54, 1.17]
19 Side-effects (any) (BY SUBGROUPS)			Relative Risk (Random) 95% CI	Subtotals only
20 Very low birthweight (less than 1500 g) (ALL)			Relative Risk (Random) 95% CI	Subtotals only
27 Infant ferritin concentration at 6 months (ug/L) (ALL)	1	88	Weighted Mean Difference (Random) 95% CI	0.09 [0.05, 0.13]
31 Severe anaemia at term (Hb less than 70 g/L) (ALL)	3	475	Relative Risk (Random) 95% CI	Not estimable
32 Moderate anaemia at term (Hb more than 70g/L and less than 90 g/L) (ALL)	3	475	Relative Risk (Random) 95% CI	1.03 [0.07, 16.23]
33 Severe anaemia at any time during second and third trimester (Hb less than 70 g/L) (ALL)	5	1160	Relative Risk (Random) 95% CI	Not estimable
34 Moderate anaemia at any time during second or third trimester (ALL)	5	1031	Relative Risk (Random) 95% CI	2.80 [0.39, 19.88]
41 Severe anaemia at postpartum (Hb less than 80 g/L) (ALL)	1	169	Relative Risk (Random) 95% CI	0.43 [0.04, 4.64]
42 Moderate anaemia at postpartum (Hb more than 80 g/L and less than 100 g/L) (ALL)	1	169	Relative Risk (Random) 95% CI	1.14 [0.26, 4.95]
43 Diarrhea (ALL)	3	473	Relative Risk (Random) 95% CI	1.26 [0.56, 2.81]
44 Constipation (ALL)	3	473	Relative Risk (Random) 95% CI	1.08 [0.51, 2.29]
45 Nausea (ALL)	4	774	Relative Risk (Random) 95% CI	0.71 [0.36, 1.40]
46 Heartburn (ALL)	3	473	Relative Risk (Random) 95% CI	0.78 [0.29, 2.06]
47 Vomiting (ALL)	4	774	Relative Risk (Random) 95% CI	1.69 [1.15, 2.47]
68 Ln (serum ferritin concentration) 4-8 wk postpartum (not prespecified)	1	160	Weighted Mean Difference (Random) 95% CI	-0.13 [-0.42, 0.16]
70 Low serum ferritin concentration at post partum (4-8 wk) (not prespecified)	1	146	Relative Risk (Random) 95% CI	1.19 [0.40, 3.57]
71 High serum transferrin receptors at 6 weeks postpartum (not prespecified)	1	146	Relative Risk (Random) 95% CI	0.69 [0.36, 1.33]
97 Haemoglobin concentration at 4-8 weeks postpartum (not prespecified)	1	146	Weighted Mean Difference (Random) 95% CI	2.00 [-3.86, 7.86]

INDEX TERMS

Medical Subject Headings (MeSH)

Anemia, Iron-Deficiency [prevention & control]; *Dietary Supplements; Folic Acid [*administration & dosage]; Iron [*administration & dosage]; Pregnancy Complications, Hematologic [prevention & control]; Pregnancy Outcome; Prenatal Care [methods]; Randomized Controlled Trials

MeSH check words

Female; Humans; Pregnancy

COVER SHEET

Title	Effects of routine oral iron supplementation with or without folic acid for women during pregnancy
Authors	Pena-Rosas JP, Viteri FE
Contribution of author(s)	Juan Pablo Pena-Rosas and Fernando Viteri co-wrote the protocol and the review. Juan Pablo Pena-Rosas abstracted the trial data and carried out the analysis with the technical support and guidance of Fernando Viteri. Both took primary responsibility in producing the final manuscript. Disclaimer: "The findings and conclusions in this review are those of the authors and do not necessarily represent the Centers for Disease Control and Prevention (CDC)".
Issue protocol first published	2004/2
Review first published	2006/3
Date of most recent amendment	17 May 2006
Date of most recent SUBSTANTIVE amendment	18 April 2006
What's New	This review updates two previously published Cochrane Reviews on iron and iron and folate supplementation during pregnancy (Mahomed 1998; Mahomed 2000). It aims to evaluate the effectiveness of supplementation with iron alone or in combination with folic acid on functional outcomes in the mother and the infant rather than just haematological indicators. It also evaluates the regimen schedules by comparing intermittent (less frequent than daily) supplement intake with the standard daily regimens and the effects of these interventions on side-effects and haemoconcentration. The comparisons in this review were reduced to four comparisons instead of eight as stated in the protocol. The subgroup analyses were considered only for the primary outcomes.
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	23 June 2005
Date new studies found and included/excluded	01 April 2004
Date authors' conclusions section amended	Information not supplied by author
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GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 01 Low birthweight (less than 2500 g) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 01 Low birthweight (less than 2500 g) (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Cogswell 2003	5/117	16/96		32.0	0.26 [0.10, 0.67]
× Eskeland 1997	0/28	0/26		0.0	Not estimable
Makrides 2003	12/216	9/214		34.8	1.32 [0.57, 3.07]
Menendez 1994	7/231	12/219		33.2	0.55 [0.22, 1.38]
Total (95% CI)	592	555		100.0	0.59 [0.23, 1.49]

Total events: 24 (Treatment (daily)), 37 (Control (no iron))

Test for heterogeneity chi-square=6.37 df=2 p=0.04 I^2 =68.6%

Test for overall effect z=1.12 p=0.3

Analysis 01.02. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 02 Low birthweight (less than 2500 g) (BY SUBGROUPS)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 02 Low birthweight (less than 2500 g) (BY SUBGROUPS)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Early gestational age (less than 20 weeks of gestation or pre-pregnancy) at start of supplementation					
Cogswell 2003	5/117	16/96		48.9	0.26 [0.10, 0.67]
Makrides 2003	12/216	9/214		51.1	1.32 [0.57, 3.07]
Subtotal (95% CI)	333	310		100.0	0.59 [0.12, 2.96]
Total events: 17 (Treatment (daily)), 25 (Control (no iron))					
Test for heterogeneity chi-square=6.29 df=1 p=0.01 I² =84.1%					
Test for overall effect z=0.64 p=0.5					
02 Late gestational age (20 weeks or more of gestation) at start of supplementation					
× Eskeland 1997	0/28	0/26		0.0	Not estimable
Menendez 1994	7/231	12/219		100.0	0.55 [0.22, 1.38]
Subtotal (95% CI)	259	245		100.0	0.55 [0.22, 1.38]
Total events: 7 (Treatment (daily)), 12 (Control (no iron))					
Test for heterogeneity: not applicable					
Test for overall effect z=1.27 p=0.2					
04 Non-anaemic at start of supplementation					
Cogswell 2003	5/117	16/96		48.9	0.26 [0.10, 0.67]
× Eskeland 1997	0/28	0/26		0.0	Not estimable
Makrides 2003	12/216	9/214		51.1	1.32 [0.57, 3.07]
Subtotal (95% CI)	361	336		100.0	0.59 [0.12, 2.96]
Total events: 17 (Treatment (daily)), 25 (Control (no iron))					
Test for heterogeneity chi-square=6.29 df=1 p=0.01 I² =84.1%					
Test for overall effect z=0.64 p=0.5					
06 Unspecified/mixed anaemic status at start of supplementation					
Menendez 1994	7/231	12/219		100.0	0.55 [0.22, 1.38]
Subtotal (95% CI)	231	219		100.0	0.55 [0.22, 1.38]
Total events: 7 (Treatment (daily)), 12 (Control (no iron))					
Test for heterogeneity: not applicable					
Test for overall effect z=1.27 p=0.2					
08 Daily lower dose (60 mg elemental iron or less)					
Cogswell 2003	5/117	16/96		32.0	0.26 [0.10, 0.67]
× Eskeland 1997	0/28	0/26		0.0	Not estimable

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Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Makrides 2003	12/216	9/214		34.8	1.32 [0.57, 3.07]
Menendez 1994	7/231	12/219		33.2	0.55 [0.22, 1.38]
Subtotal (95% CI)	592	555		100.0	0.59 [0.23, 1.49]
Total events: 24 (Treatment (daily)), 37 (Control (no iron))					
Test for heterogeneity chi-square=6.37 df=2 p=0.04 I^2 =68.6%					
Test for overall effect z=1.12 p=0.3					

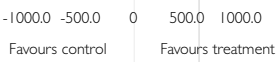
Analysis 01.03. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 03 Birthweight (g) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 03 Birthweight (g) (ALL)

Study	Treatment (daily) N	Mean(SD)	Control (no iron) N	Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Cogswell 2003	117	3277.00 (500.70)	96	3072.00 (635.59)		22.1	205.00 [48.81, 361.19]
Eskeland 1997	28	3689.60 (388.36)	26	3610.70 (502.87)		14.7	78.90 [-162.05, 319.85]
Makrides 2003	216	3406.00 (597.00)	214	3449.00 (580.00)		26.9	-43.00 [-154.25, 68.25]
Preziosi 1997	99	3046.00 (408.00)	98	3016.00 (450.00)		26.0	30.00 [-89.99, 149.99]
Puolakka 1980	16	3400.00 (400.00)	15	3700.00 (500.00)		10.2	-300.00 [-620.06, 20.06]
Total (95% CI)	476		449			100.0	22.49 [-99.35, 144.34]
Test for heterogeneity chi-square=10.70 df=4 p=0.03 I^2 =62.6%							
Test for overall effect z=0.36 p=0.7							



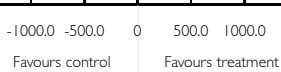
Analysis 01.04. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 04 Birthweight (g) (BY SUBGROUPS)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 04 Birthweight (g) (BY SUBGROUPS)

Study	Treatment (daily) N	Mean(SD)	Control (no iron) N	Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
01 Early gestational age (less than 20 weeks of gestation or pre-pregnancy) at start of supplementation							
Cogswell 2003	117	3277.00 (500.70)	96	3072.00 (635.59)		26.6	205.00 [48.81, 361.19]
Makrides 2003	216	3406.00 (597.00)	214	3449.00 (580.00)		30.9	-43.00 [-154.25, 68.25]
Paintin 1966	60	3302.00 (385.00)	57	3325.00 (371.00)		28.5	-23.00 [-159.99, 113.99]
Puolakka 1980	16	3400.00 (400.00)	15	3700.00 (500.00)		13.9	-300.00 [-620.06, 20.06]
Subtotal (95% CI)	409		382			100.0	-7.14 [-158.36, 144.09]
Test for heterogeneity chi-square=10.66 df=3 p=0.01 I^2 =71.9%							
Test for overall effect z=0.09 p=0.9							
02 Late gestational age (20 weeks or more of gestation) at start of supplementation							
Eskeland 1997	28	3689.60 (388.36)	26	3610.70 (502.87)		19.9	78.90 [-162.05, 319.85]
Preziosi 1997	99	3046.00 (408.00)	98	3016.00 (450.00)		80.1	30.00 [-89.99, 149.99]
Subtotal (95% CI)	127		124			100.0	39.72 [-67.69, 147.12]
Test for heterogeneity chi-square=0.13 df=1 p=0.72 I^2 =0.0%							
Test for overall effect z=0.72 p=0.5							
04 Non-anaemic at start of supplementation							
Cogswell 2003	117	3277.00 (500.70)	96	3072.00 (635.59)		28.8	205.00 [48.81, 361.19]
Eskeland 1997	28	3689.60 (388.36)	26	3610.70 (502.87)		22.0	78.90 [-162.05, 319.85]
Makrides 2003	216	3406.00 (597.00)	214	3449.00 (580.00)		32.4	-43.00 [-154.25, 68.25]
Puolakka 1980	16	3400.00 (400.00)	15	3700.00 (500.00)		16.8	-300.00 [-620.06, 20.06]
Subtotal (95% CI)	377		351			100.0	12.15 [-164.99, 189.29]
Test for heterogeneity chi-square=10.69 df=3 p=0.01 I^2 =71.9%							
Test for overall effect z=0.13 p=0.9							
06 Unspecified/mixed anaemic status at start of supplementation							
Paintin 1966	60	3302.00 (385.00)	57	3325.00 (371.00)		43.4	-23.00 [-159.99, 113.99]
Preziosi 1997	99	3046.00 (408.00)	98	3016.00 (450.00)		56.6	30.00 [-89.99, 149.99]
Subtotal (95% CI)	159		155			100.0	6.99 [-83.27, 97.25]
Test for heterogeneity chi-square=0.33 df=1 p=0.57 I^2 =0.0%							
Test for overall effect z=0.15 p=0.9							
07 Daily low dose (60 mg elemental iron or less)							
Cogswell 2003	117	3277.00 (500.70)	96	3072.00 (635.59)		24.9	205.00 [48.81, 361.19]



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Study	Treatment (daily) N	Mean(SD)	Control (no iron) N	Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Eskeland 1997	28	3689.60 (388.36)	26	3610.70 (502.87)		15.6	78.90 [-162.05, 319.85]
Makrides 2003	216	3406.00 (597.00)	214	3449.00 (580.00)		31.8	-43.00 [-154.25, 68.25]
Paintin 1966	60	3302.00 (385.00)	57	3325.00 (371.00)		27.7	-23.00 [-159.99, 113.99]
Subtotal (95% CI)	421		393			100.0	43.36 [-74.70, 161.43]
Test for heterogeneity chi-square=7.20 df=3 p=0.07 I² =58.3%							
Test for overall effect z=0.72 p=0.5							
08 Daily higher dose (more than 60 mg elemental iron)							
Paintin 1966	56	3284.00 (530.00)	57	3325.00 (371.00)		36.1	-41.00 [-209.95, 127.95]
Preziosi 1997	99	3046.00 (408.00)	98	3016.00 (450.00)		48.3	30.00 [-89.99, 149.99]
Puolakka 1980	16	3400.00 (400.00)	15	3700.00 (500.00)		15.6	-300.00 [-620.06, 20.06]
Subtotal (95% CI)	171		170			100.0	-47.09 [-189.44, 95.27]
Test for heterogeneity chi-square=3.67 df=2 p=0.16 I² =45.5%							
Test for overall effect z=0.65 p=0.5							

Analysis 01.05. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 05 Premature delivery (less than 37 weeks of gestation) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 05 Premature delivery (less than 37 weeks of gestation) (ALL)

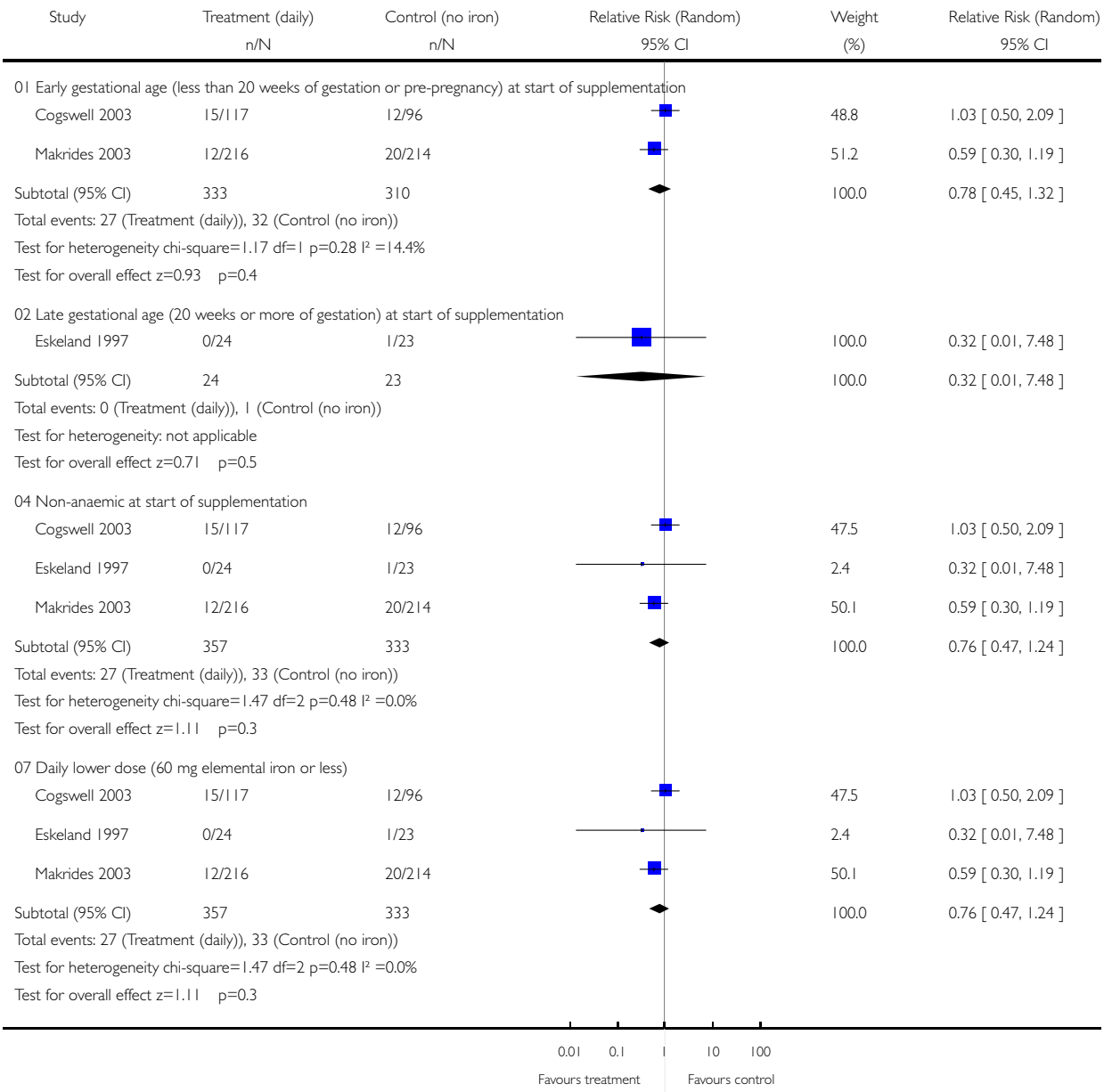
Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Cogswell 2003	15/117	12/96		47.5	1.03 [0.50, 2.09]
Eskeland 1997	0/24	1/23		2.4	0.32 [0.01, 7.48]
Makrides 2003	12/216	20/214		50.1	0.59 [0.30, 1.19]
Total (95% CI)	357	333		100.0	0.76 [0.47, 1.24]
Total events: 27 (Treatment (daily)), 33 (Control (no iron))					
Test for heterogeneity chi-square=1.47 df=2 p=0.48 I² =0.0%					
Test for overall effect z=1.11 p=0.3					

Analysis 01.06. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 06 Premature delivery (less 37 weeks of gestation) (BY SUBGROUPS)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 06 Premature delivery (less 37 weeks of gestation) (BY SUBGROUPS)



Analysis 01.07. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 07 Maternal Hb concentration at term (g/L) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

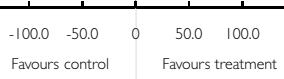
Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 07 Maternal Hb concentration at term (g/L) (ALL)

Study	Treatment (daily)		Control (no iron)		Weighted Mean Difference (Random)	Weight	Weighted Mean Difference (Random)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Batu 1976	30	113.00 (10.00)	22	97.00 (11.00)		6.5	16.00 [10.17, 21.83]
Butler 1968	27	136.00 (9.87)	6	135.00 (7.10)		6.0	1.00 [-5.79, 7.79]
Buytaert 1983	24	127.29 (12.80)	21	124.07 (8.05)		6.3	3.22 [-2.95, 9.39]
Chanarin 1971	49	124.00 (9.80)	46	114.00 (9.50)		7.4	10.00 [6.12, 13.88]
Cogswell 2003	90	121.40 (10.39)	62	121.70 (10.48)		7.6	-0.30 [-3.68, 3.08]
De Benaze 1989	44	130.00 (10.00)	25	122.00 (10.00)		6.9	8.00 [3.09, 12.91]
Eskeland 1997	24	125.70 (7.80)	21	112.80 (6.50)		7.3	12.90 [8.72, 17.08]
Makrides 2003	200	127.00 (13.00)	193	120.00 (12.00)		7.9	7.00 [4.53, 9.47]
Milman 1991	99	128.90 (8.00)	107	118.90 (10.00)		7.9	10.00 [7.54, 12.46]
Ortega-Soler 1998	18	104.00 (11.00)	23	115.00 (14.00)		5.6	-11.00 [-18.65, -3.35]
Puolakka 1980	16	132.00 (12.00)	15	111.00 (9.00)		5.7	21.00 [13.56, 28.44]
Romslo 1983	22	126.00 (8.00)	23	113.00 (10.00)		6.7	13.00 [7.72, 18.28]
Tura 1989	129	121.00 (8.00)	112	119.00 (10.00)		8.0	2.00 [-0.31, 4.31]
Van Eijk 1978	15	132.13 (11.27)	15	112.79 (16.11)		4.5	19.34 [9.39, 29.29]
Wallenburg 1983	18	128.90 (11.30)	20	125.60 (11.30)		5.8	3.30 [-3.90, 10.50]
Total (95% CI)	805		711			100.0	7.53 [4.40, 10.66]

Test for heterogeneity chi-square=111.84 df=14 p=<0.0001 I^2 =87.5%

Test for overall effect z=4.71 p<0.00001



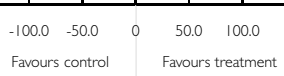
Analysis 01.08. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 08 Maternal Hb concentration at term (g/L) (BY SUBGROUPS)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 08 Maternal Hb concentration at term (g/L) (BY SUBGROUPS)

Study	Treatment (daily) N	Mean(SD)	Control (no iron) N	Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
01 Early gestational age (less than 20 weeks of gestation or pre-pregnancy) at start of supplementation							
Buytaert 1983	24	127.29 (12.80)	21	124.07 (8.05)		8.2	3.22 [-2.95, 9.39]
Chanarin 1971	49	124.00 (9.80)	46	114.00 (9.50)		10.0	10.00 [6.12, 13.88]
Cogswell 2003	90	121.40 (10.39)	62	121.70 (10.48)		10.4	-0.30 [-3.68, 3.08]
De Benaze 1989	44	130.00 (10.00)	25	122.00 (10.00)		9.2	8.00 [3.09, 12.91]
Makrides 2003	200	127.00 (13.00)	193	120.00 (12.00)		11.0	7.00 [4.53, 9.47]
Milman 1991	99	128.90 (8.00)	107	118.90 (10.00)		11.0	10.00 [7.54, 12.46]
Puolakka 1980	16	132.00 (12.00)	15	111.00 (9.00)		7.2	21.00 [13.56, 28.44]
Romslo 1983	22	126.00 (8.00)	23	113.00 (10.00)		8.9	13.00 [7.72, 18.28]
Tura 1989	129	121.00 (8.00)	112	119.00 (10.00)		11.1	2.00 [-0.31, 4.31]
Van Eijk 1978	15	132.13 (11.27)	15	112.79 (16.11)		5.5	19.34 [9.39, 29.29]
Wallenburg 1983	18	128.90 (11.30)	20	125.60 (11.30)		7.4	3.30 [-3.90, 10.50]
Subtotal (95% CI)	706		639			100.0	8.05 [4.85, 11.25]
Test for heterogeneity chi-square=70.20 df=10 p=<0.0001 I^2 =85.8%							
Test for overall effect z=4.93 p<0.00001							
02 Late gestational age (20 weeks or more of gestation) at start of supplementation							
Batu 1976	30	113.00 (10.00)	22	97.00 (11.00)		32.9	16.00 [10.17, 21.83]
Butler 1968	27	136.00 (9.87)	6	135.00 (7.10)		30.9	1.00 [-5.79, 7.79]
Eskeland 1997	24	125.70 (7.80)	21	112.80 (6.50)		36.2	12.90 [8.72, 17.08]
Subtotal (95% CI)	81		49			100.0	10.24 [2.45, 18.04]
Test for heterogeneity chi-square=11.90 df=2 p=0.003 I^2 =83.2%							
Test for overall effect z=2.58 p=0.01							
03 Unspecified/mixed gestational age at start of supplementation							
Ortega-Soler 1998	18	104.00 (11.00)	23	115.00 (14.00)		100.0	-11.00 [-18.65, -3.35]
Subtotal (95% CI)	18		23			100.0	-11.00 [-18.65, -3.35]
Test for heterogeneity: not applicable							
Test for overall effect z=2.82 p=0.005							
04 Non-anaemic at start of supplementation							
Buytaert 1983	24	127.29 (12.80)	21	124.07 (8.05)		11.1	3.22 [-2.95, 9.39]



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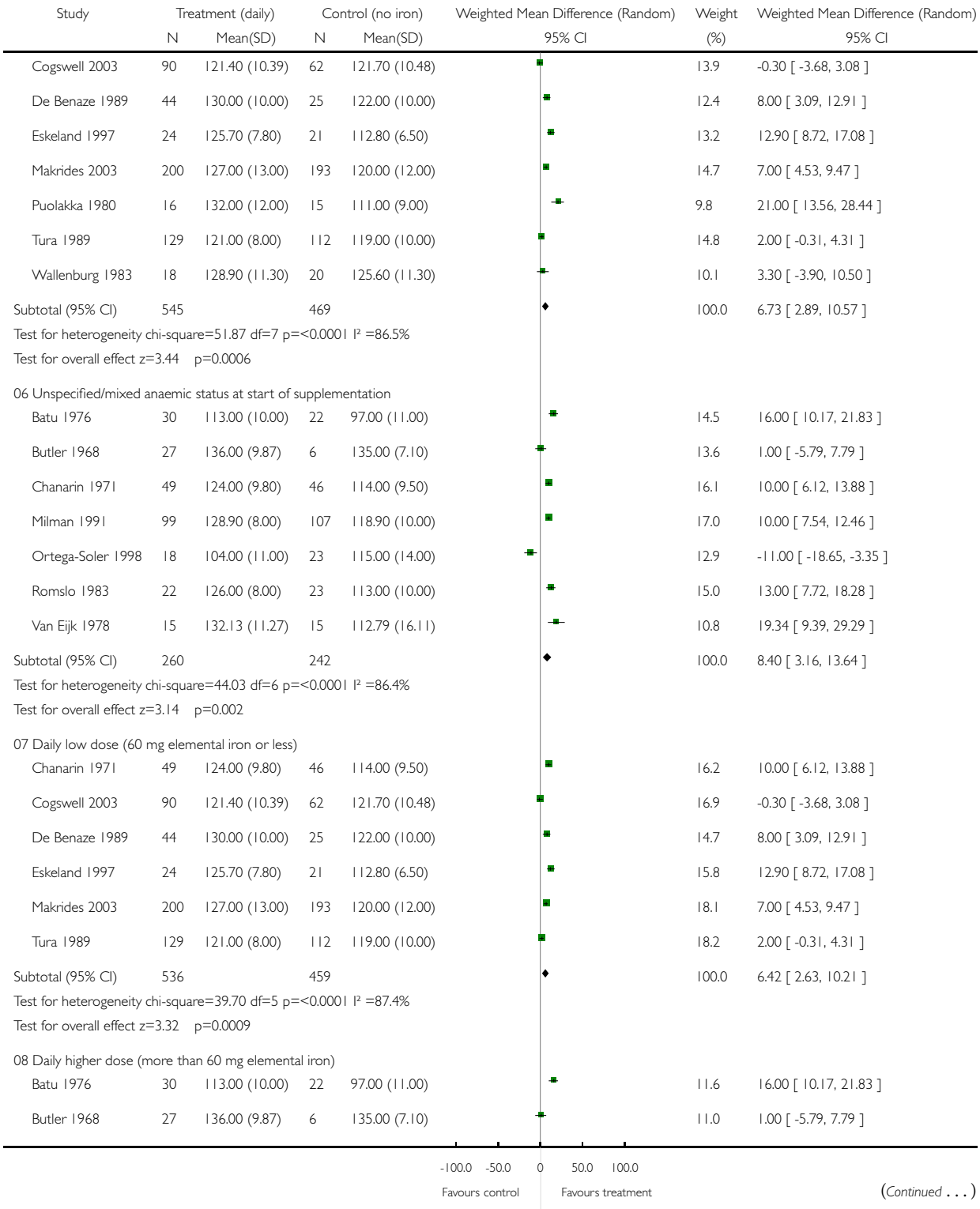

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Study	Treatment (daily) N	Mean(SD)	Control (no iron) N	Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Buytaert 1983	24	127.29 (12.80)	21	124.07 (8.05)		11.4	3.22 [-2.95, 9.39]
Milman 1991	99	128.90 (8.00)	107	118.90 (10.00)		13.1	10.00 [7.54, 12.46]
Ortega-Soler 1998	18	104.00 (11.00)	23	115.00 (14.00)		10.5	-11.00 [-18.65, -3.35]
Puolakka 1980	16	132.00 (12.00)	15	111.00 (9.00)		10.6	21.00 [13.56, 28.44]
Romslo 1983	22	126.00 (8.00)	23	113.00 (10.00)		11.9	13.00 [7.72, 18.28]
Van Eijk 1978	15	132.13 (11.27)	15	112.79 (16.11)		9.1	19.34 [9.39, 29.29]
Wallenburg 1983	18	128.90 (11.30)	20	125.60 (11.30)		10.8	3.30 [-3.90, 10.50]
Subtotal (95% CI)	269		252			100.0	8.38 [3.10, 13.66]
Test for heterogeneity chi-square=59.84 df=8 p=<0.0001 I² =86.6%							
Test for overall effect z=3.11 p=0.002							

Analysis 01.09. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 09 Anaemia at term (Hb less than 110 g/L) (not pre-specified)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 09 Anaemia at term (Hb less than 110 g/L) (not pre-specified)

Study	Treatment (any iron) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Batu 1976	17/36	29/34		14.0	0.55 [0.38, 0.80]
Chanarin 1971	1/49	9/46		4.3	0.10 [0.01, 0.79]
Chisholm 1966	3/60	20/60		8.3	0.15 [0.05, 0.48]
Cogswell 2003	12/90	11/62		11.3	0.75 [0.35, 1.59]
De Benaze 1989	3/44	8/25		7.8	0.21 [0.06, 0.73]
Eskeland 1997	0/24	7/21		2.6	0.06 [0.00, 0.97]
Holly 1955	1/94	23/55		4.5	0.03 [0.00, 0.18]
Makrides 2003	14/200	30/193		12.4	0.45 [0.25, 0.82]
Milman 1991	0/100	15/107		2.6	0.03 [0.00, 0.57]
Preziosi 1997	41/99	69/98		14.6	0.59 [0.45, 0.77]
Pritchard 1958	6/74	23/49		10.7	0.17 [0.08, 0.39]

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Study	Treatment (any iron) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Puolakka 1980	0/16	6/15		2.6	0.07 [0.00, 1.18]
Romslo 1983	1/22	7/23		4.3	0.15 [0.02, 1.12]
Total (95% CI)	908	788		100.0	0.26 [0.16, 0.43]
Total events: 99 (Treatment (any iron)), 257 (Control (no iron))					
Test for heterogeneity chi-square=45.72 df=12 p=<0.0001 I^2 =73.8%					
Test for overall effect z=5.26 p<0.00001					

Analysis 01.10. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 10 Haemoconcentration at term (Hb more than 130 g/L) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 10 Haemoconcentration at term (Hb more than 130 g/L) (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Butler 1968	20/27	4/6		18.6	1.11 [0.60, 2.04]
Chisholm 1966	3/60	0/60		4.7	7.00 [0.37, 132.66]
Cogswell 2003	0/90	12/62		5.0	0.03 [0.00, 0.46]
Eskeland 1997	8/24	0/21		5.1	14.96 [0.92, 244.55]
Holly 1955	46/94	6/55		17.1	4.49 [2.05, 9.81]
Makrides 2003	82/200	29/193		20.3	2.73 [1.88, 3.97]
Milman 1991	30/100	3/107		13.8	10.70 [3.37, 33.96]
Pritchard 1958	30/74	4/49		15.4	4.97 [1.87, 13.22]
Total (95% CI)	669	553		100.0	3.01 [1.46, 6.19]
Total events: 219 (Treatment (daily)), 58 (Control (no iron))					
Test for heterogeneity chi-square=28.92 df=7 p=0.0001 I^2 =75.8%					
Test for overall effect z=3.00 p=0.003					

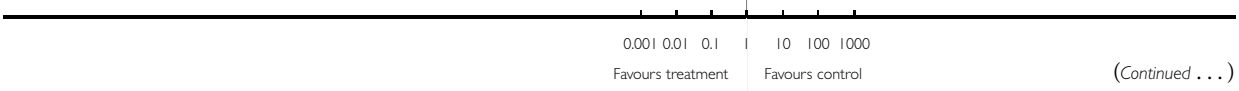
Analysis 01.11. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 11 Haemoconcentration at term (Hb more than 130 g/L) (BY SUBGROUPS)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 11 Haemoconcentration at term (Hb more than 130 g/L) (BY SUBGROUPS)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Early gestational age (less than 20 weeks of gestation or pre-pregnancy) at start of supplementation					
Cogswell 2003	0/90	12/62		22.5	0.03 [0.00, 0.46]
Makrides 2003	82/200	29/193		41.0	2.73 [1.88, 3.97]
Milman 1991	30/100	3/107		36.4	10.70 [3.37, 33.96]
Subtotal (95% CI)	390	362		100.0	1.60 [0.22, 11.41]
Total events: 112 (Treatment (daily)), 44 (Control (no iron))					
Test for heterogeneity chi-square=16.71 df=2 p=0.0002 I^2 =88.0%					
Test for overall effect z=0.47 p=0.6					
02 Late gestational age (20 weeks or more of gestation) at start of supplementation					
Butler 1968	20/27	4/6		43.2	1.11 [0.60, 2.04]
Chisholm 1966	3/60	0/60		27.9	7.00 [0.37, 132.66]
Eskeland 1997	8/24	0/21		28.9	14.96 [0.92, 244.55]
Subtotal (95% CI)	111	87		100.0	3.94 [0.31, 50.47]
Total events: 31 (Treatment (daily)), 4 (Control (no iron))					
Test for heterogeneity chi-square=8.72 df=2 p=0.01 I^2 =77.1%					
Test for overall effect z=1.05 p=0.3					
03 Unspecified/mixed gestational age at start of supplementation					
Holly 1955	46/94	6/55		61.0	4.49 [2.05, 9.81]
Pritchard 1958	30/74	4/49		39.0	4.97 [1.87, 13.22]
Subtotal (95% CI)	168	104		100.0	4.67 [2.53, 8.60]
Total events: 76 (Treatment (daily)), 10 (Control (no iron))					
Test for heterogeneity chi-square=0.03 df=1 p=0.87 I^2 =0.0%					
Test for overall effect z=4.94 p<0.00001					
04 Non-anaemic at start of supplementation					
Cogswell 2003	0/90	12/62		30.0	0.03 [0.00, 0.46]
Eskeland 1997	8/24	0/21		30.1	14.96 [0.92, 244.55]
Makrides 2003	82/200	29/193		39.9	2.73 [1.88, 3.97]
Subtotal (95% CI)	314	276		100.0	1.15 [0.05, 24.75]
Total events: 90 (Treatment (daily)), 41 (Control (no iron))					
Test for heterogeneity chi-square=13.68 df=2 p=0.001 I^2 =85.4%					
Test for overall effect z=0.09 p=0.9					



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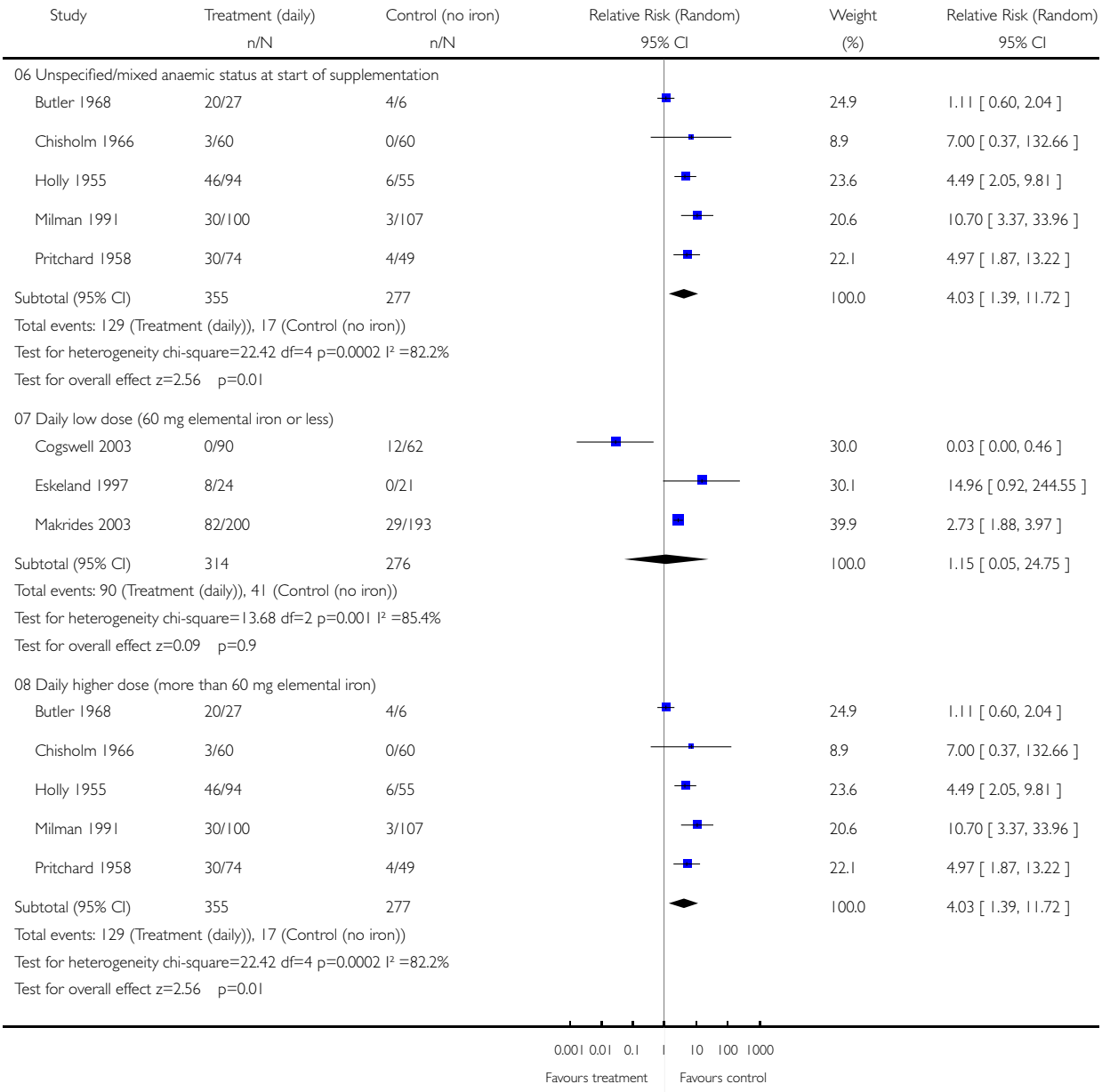

Analysis 01.12. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 12 Haemoconcentration during second or third trimester (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 12 Haemoconcentration during second or third trimester (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Cogswell 2003	23/110	18/86		18.4	1.00 [0.58, 1.73]
Eskeland 1997	12/24	8/23		16.8	1.44 [0.72, 2.86]
Holly 1955	21/94	15/55		18.2	0.82 [0.46, 1.45]
Makrides 2003	83/206	32/205		20.5	2.58 [1.80, 3.70]
Milman 1991	19/100	4/107		12.7	5.08 [1.79, 14.43]
Pritchard 1958	30/74	4/49		13.4	4.97 [1.87, 13.22]
Total (95% CI)	608	525		100.0	1.90 [1.07, 3.35]

Total events: 188 (Treatment (daily)), 81 (Control (no iron))

Test for heterogeneity chi-square=24.50 df=5 p=0.0002 I^2 =79.6%

Test for overall effect z=2.21 p=0.03

Analysis 01.13. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 13 Haemoconcentration during second or third trimester (BY SUBGROUPS)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 13 Haemoconcentration during second or third trimester (BY SUBGROUPS)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Early gestational age (less than 20 weeks of gestation or pre-pregnancy) at start of supplementation					
Cogswell 2003	23/110	18/86		35.7	1.00 [0.58, 1.73]
Makrides 2003	83/206	32/205		39.4	2.58 [1.80, 3.70]
Milman 1991	19/100	4/107		24.9	5.08 [1.79, 14.43]
Subtotal (95% CI)	416	398		100.0	2.18 [0.97, 4.89]

Total events: 125 (Treatment (daily)), 54 (Control (no iron))

Test for heterogeneity chi-square=11.16 df=2 p=0.004 I^2 =82.1%

Test for overall effect z=1.89 p=0.06

02 Late gestational age (20 weeks or more of gestation) at start of supplementation					
Eskeland 1997	12/24	8/23		100.0	1.44 [0.72, 2.86]

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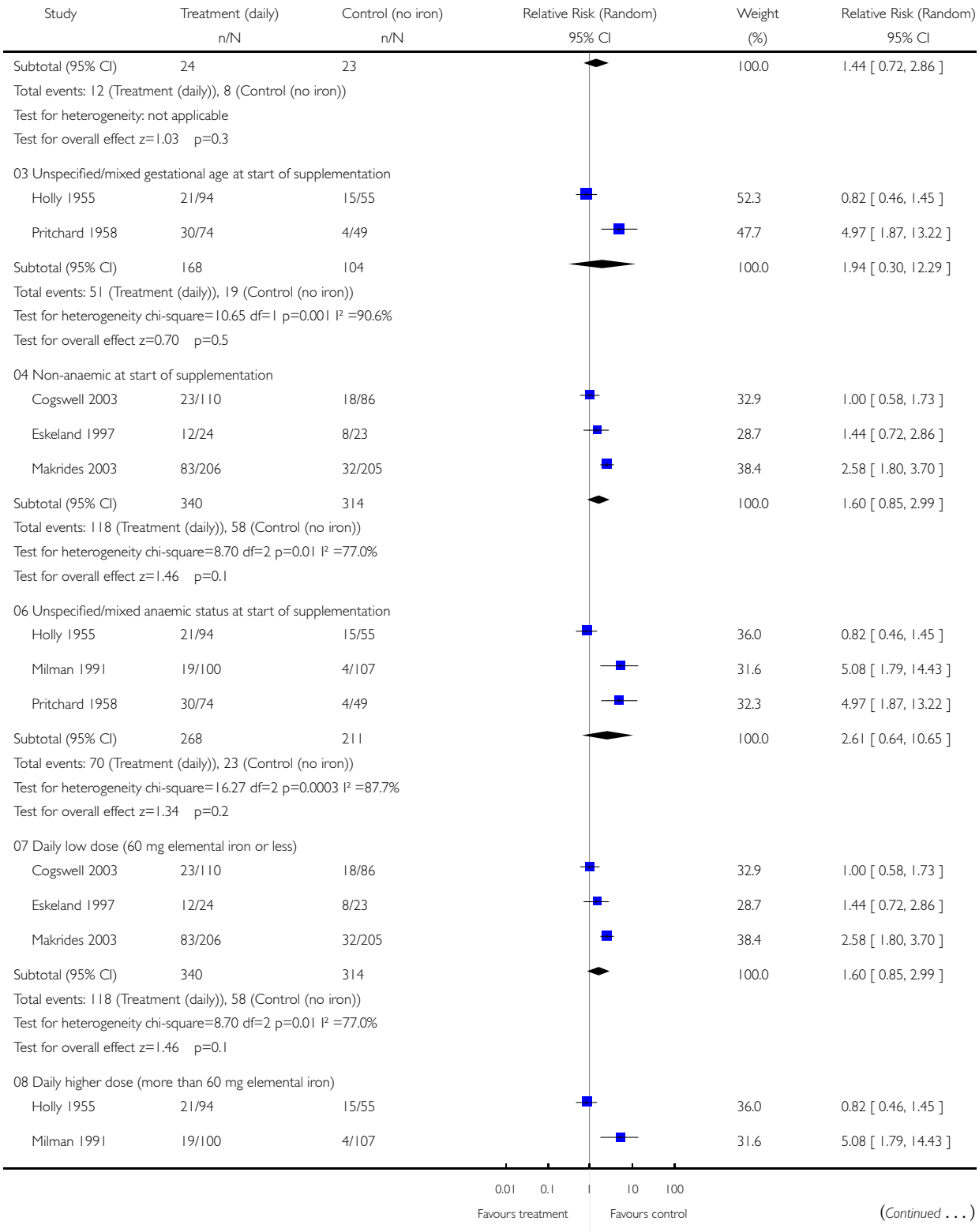

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Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Pritchard 1958	30/74	4/49		32.3	4.97 [1.87, 13.22]
Subtotal (95% CI)	268	211		100.0	2.61 [0.64, 10.65]
Total events: 70 (Treatment (daily)), 23 (Control (no iron))					
Test for heterogeneity chi-square=16.27 df=2 p=0.0003 I^2 =87.7%					
Test for overall effect z=1.34 p=0.2					

Analysis 01.14. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 14 Iron deficiency at term (as defined by two or more indicators) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 14 Iron deficiency at term (as defined by two or more indicators) (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Cogswell 2003	26/85	27/59		18.8	0.67 [0.44, 1.02]
Eskeland 1997	15/99	49/98		17.7	0.30 [0.18, 0.50]
Makrides 2003	65/186	102/176		21.0	0.60 [0.48, 0.76]
Milman 1991	4/63	31/57		11.4	0.12 [0.04, 0.31]
Preziosi 1997	3/24	14/20		10.1	0.18 [0.06, 0.53]
Tura 1989	67/129	63/112		21.0	0.92 [0.73, 1.17]
Total (95% CI)	586	522		100.0	0.44 [0.27, 0.70]
Total events: 180 (Treatment (daily)), 286 (Control (no iron))					
Test for heterogeneity chi-square=38.60 df=5 p=<0.0001 I^2 =87.0%					
Test for overall effect z=3.43 p=0.0006					

Analysis 01.15. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 15 Iron deficiency at term (as defined by two or more indicators) (BY SUBGROUPS)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 15 Iron deficiency at term (as defined by two or more indicators) (BY SUBGROUPS)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Early gestational age (less than 20 weeks of gestation or pre-pregnancy) at start of supplementation					
Cogswell 2003	26/85	27/59		25.9	0.67 [0.44, 1.02]
Makrides 2003	65/186	102/176		30.2	0.60 [0.48, 0.76]
Milman 1991	4/63	31/57		13.6	0.12 [0.04, 0.31]
Tura 1989	67/129	63/112		30.2	0.92 [0.73, 1.17]
Subtotal (95% CI)	463	404		100.0	0.56 [0.35, 0.90]
Total events: 162 (Treatment (daily)), 223 (Control (no iron))					
Test for heterogeneity chi-square=21.64 df=3 p=<0.0001 I^2 =86.1%					
Test for overall effect z=2.38 p=0.02					
02 Late gestational age (20 weeks or more of gestation) at start of supplementation					
Eskeland 1997	15/99	49/98		82.4	0.30 [0.18, 0.50]
Preziosi 1997	3/24	14/20		17.6	0.18 [0.06, 0.53]
Subtotal (95% CI)	123	118		100.0	0.28 [0.17, 0.44]
Total events: 18 (Treatment (daily)), 63 (Control (no iron))					
Test for heterogeneity chi-square=0.74 df=1 p=0.39 I^2 =0.0%					
Test for overall effect z=5.49 p<0.00001					
04 Non-anaemic at start of supplementation					
Cogswell 2003	26/85	27/59		23.0	0.67 [0.44, 1.02]
Eskeland 1997	15/99	49/98		20.6	0.30 [0.18, 0.50]
Makrides 2003	65/186	102/176		28.2	0.60 [0.48, 0.76]
Tura 1989	67/129	63/112		28.2	0.92 [0.73, 1.17]
Subtotal (95% CI)	499	445		100.0	0.60 [0.41, 0.90]
Total events: 173 (Treatment (daily)), 241 (Control (no iron))					
Test for heterogeneity chi-square=18.25 df=3 p=0.0004 I^2 =83.6%					
Test for overall effect z=2.50 p=0.01					
06 Unspecified/mixed anaemic status at start of supplementation					
Milman 1991	4/63	31/57		55.7	0.12 [0.04, 0.31]
Preziosi 1997	3/24	14/20		44.3	0.18 [0.06, 0.53]
Subtotal (95% CI)	87	77		100.0	0.14 [0.07, 0.29]
Total events: 7 (Treatment (daily)), 45 (Control (no iron))					
Test for heterogeneity chi-square=0.33 df=1 p=0.57 I^2 =0.0%					

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Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Test for overall effect z=5.26 p<0.00001					
07 Daily low dose (60 mg elemental iron or less)					
Cogswell 2003	26/85	27/59		23.0	0.67 [0.44, 1.02]
Eskeland 1997	15/99	49/98		20.6	0.30 [0.18, 0.50]
Makrides 2003	65/186	102/176		28.2	0.60 [0.48, 0.76]
Tura 1989	67/129	63/112		28.2	0.92 [0.73, 1.17]
Subtotal (95% CI)	499	445		100.0	0.60 [0.41, 0.90]
Total events: 173 (Treatment (daily)), 241 (Control (no iron))					
Test for heterogeneity chi-square=18.25 df=3 p=0.0004 I^2 =83.6%					
Test for overall effect z=2.50 p=0.01					
08 Daily higher dose (more than 60 mg elemental iron)					
Milman 1991	4/63	31/57		55.7	0.12 [0.04, 0.31]
Preziosi 1997	3/24	14/20		44.3	0.18 [0.06, 0.53]
Subtotal (95% CI)	87	77		100.0	0.14 [0.07, 0.29]
Total events: 7 (Treatment (daily)), 45 (Control (no iron))					
Test for heterogeneity chi-square=0.33 df=1 p=0.57 I^2 =0.0%					
Test for overall effect z=5.26 p<0.00001					

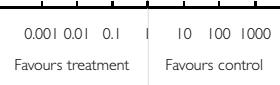
Analysis 01.16. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 16 Iron deficiency anaemia at term (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 16 Iron deficiency anaemia at term (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Cogswell 2003	10/88	9/63		28.8	0.80 [0.34, 1.84]
Eskeland 1997	0/24	6/21		5.8	0.07 [0.00, 1.13]
Makrides 2003	6/198	20/185		27.6	0.28 [0.12, 0.68]
Milman 1991	0/63	10/57		5.9	0.04 [0.00, 0.72]
Tura 1989	9/129	23/112		31.9	0.34 [0.16, 0.70]
Total (95% CI)	502	438		100.0	0.33 [0.16, 0.69]
Total events: 25 (Treatment (daily)), 68 (Control (no iron))					
Test for heterogeneity chi-square=7.77 df=4 p=0.10 I^2 =48.5%					
Test for overall effect z=2.97 p=0.003					



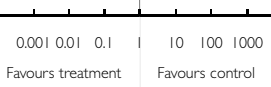
Analysis 01.17. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 17 Iron deficiency anaemia at term (BY SUBGROUPS)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 17 Iron deficiency anaemia at term (BY SUBGROUPS)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Early gestational age (less than 20 weeks of gestation or pre-pregnancy) at start of supplementation					
Cogswell 2003	10/88	9/63		30.7	0.80 [0.34, 1.84]
Makrides 2003	6/198	20/185		29.2	0.28 [0.12, 0.68]
Milman 1991	0/63	10/57		5.8	0.04 [0.00, 0.72]
Tura 1989	9/129	23/112		34.3	0.34 [0.16, 0.70]
Subtotal (95% CI)	478	417		100.0	0.37 [0.18, 0.76]
Total events: 25 (Treatment (daily)), 62 (Control (no iron))					
Test for heterogeneity chi-square=6.12 df=3 p=0.11 I^2 =50.9%					
Test for overall effect z=2.71 p=0.007					
02 Late gestational age (20 weeks or more of gestation) at start of supplementation					
Eskeland 1997	0/24	6/21		100.0	0.07 [0.00, 1.13]
Subtotal (95% CI)	24	21		100.0	0.07 [0.00, 1.13]
Total events: 0 (Treatment (daily)), 6 (Control (no iron))					
Test for heterogeneity: not applicable					
Test for overall effect z=1.87 p=0.06					
04 Non-anaemic at start of supplementation					
Cogswell 2003	10/88	9/63		30.8	0.80 [0.34, 1.84]
Eskeland 1997	0/24	6/21		4.8	0.07 [0.00, 1.13]
Makrides 2003	6/198	20/185		28.9	0.28 [0.12, 0.68]
Tura 1989	9/129	23/112		35.4	0.34 [0.16, 0.70]
Subtotal (95% CI)	439	381		100.0	0.39 [0.20, 0.74]
Total events: 25 (Treatment (daily)), 58 (Control (no iron))					
Test for heterogeneity chi-square=5.04 df=3 p=0.17 I^2 =40.4%					
Test for overall effect z=2.89 p=0.004					
06 Unspecified/mixed anaemic status at start of supplementation					
Milman 1991	0/63	10/57		100.0	0.04 [0.00, 0.72]
Subtotal (95% CI)	63	57		100.0	0.04 [0.00, 0.72]
Total events: 0 (Treatment (daily)), 10 (Control (no iron))					
Test for heterogeneity: not applicable					
Test for overall effect z=2.19 p=0.03					



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Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
07 Daily low dose (60 mg elemental iron or less)					
Cogswell 2003	10/88	9/63		30.8	0.80 [0.34, 1.84]
Eskeland 1997	0/24	6/21		4.8	0.07 [0.00, 1.13]
Makrides 2003	6/198	20/185		28.9	0.28 [0.12, 0.68]
Tura 1989	9/129	23/112		35.4	0.34 [0.16, 0.70]
Subtotal (95% CI)	439	381		100.0	0.39 [0.20, 0.74]
Total events: 25 (Treatment (daily)), 58 (Control (no iron))					
Test for heterogeneity chi-square=5.04 df=3 p=0.17 I^2 =40.4%					
Test for overall effect z=2.89 p=0.004					
08 Daily higher dose (more than 60 mg elemental iron)					
Milman 1991	0/63	10/57		100.0	0.04 [0.00, 0.72]
Subtotal (95% CI)	63	57		100.0	0.04 [0.00, 0.72]
Total events: 0 (Treatment (daily)), 10 (Control (no iron))					
Test for heterogeneity: not applicable					
Test for overall effect z=2.19 p=0.03					

Analysis 01.18. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 18 Side-effects (Any) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 18 Side-effects (Any) (ALL)

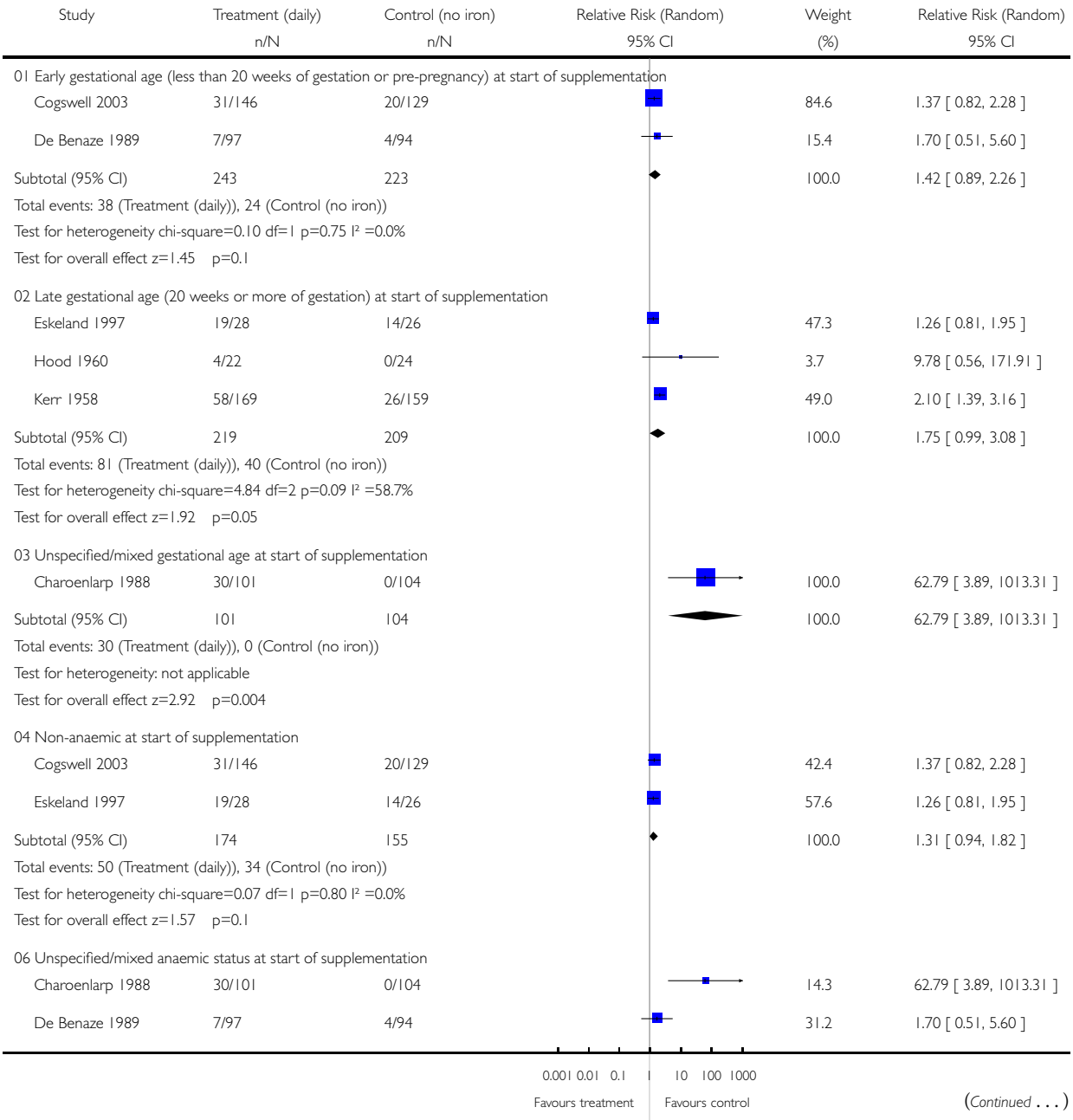
Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Charoenlarp 1988	30/101	0/104		3.6	62.79 [3.89, 1013.31]
Cogswell 2003	31/146	20/129		25.5	1.37 [0.82, 2.28]
De Benaze 1989	7/97	4/94		13.1	1.70 [0.51, 5.60]
Eskeland 1997	19/28	14/26		26.9	1.26 [0.81, 1.95]
Hood 1960	4/22	0/24		3.4	9.78 [0.56, 171.91]
Kerr 1958	58/169	26/159		27.5	2.10 [1.39, 3.16]
Total (95% CI)	563	536		100.0	1.90 [1.09, 3.33]
Total events: 149 (Treatment (daily)), 64 (Control (no iron))					
Test for heterogeneity chi-square=15.81 df=5 p=0.007 I^2 =68.4%					
Test for overall effect z=2.25 p=0.02					

Analysis 01.19. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 19 Side-effects (Any) (BY SUBGROUPS)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 19 Side-effects (Any) (BY SUBGROUPS)



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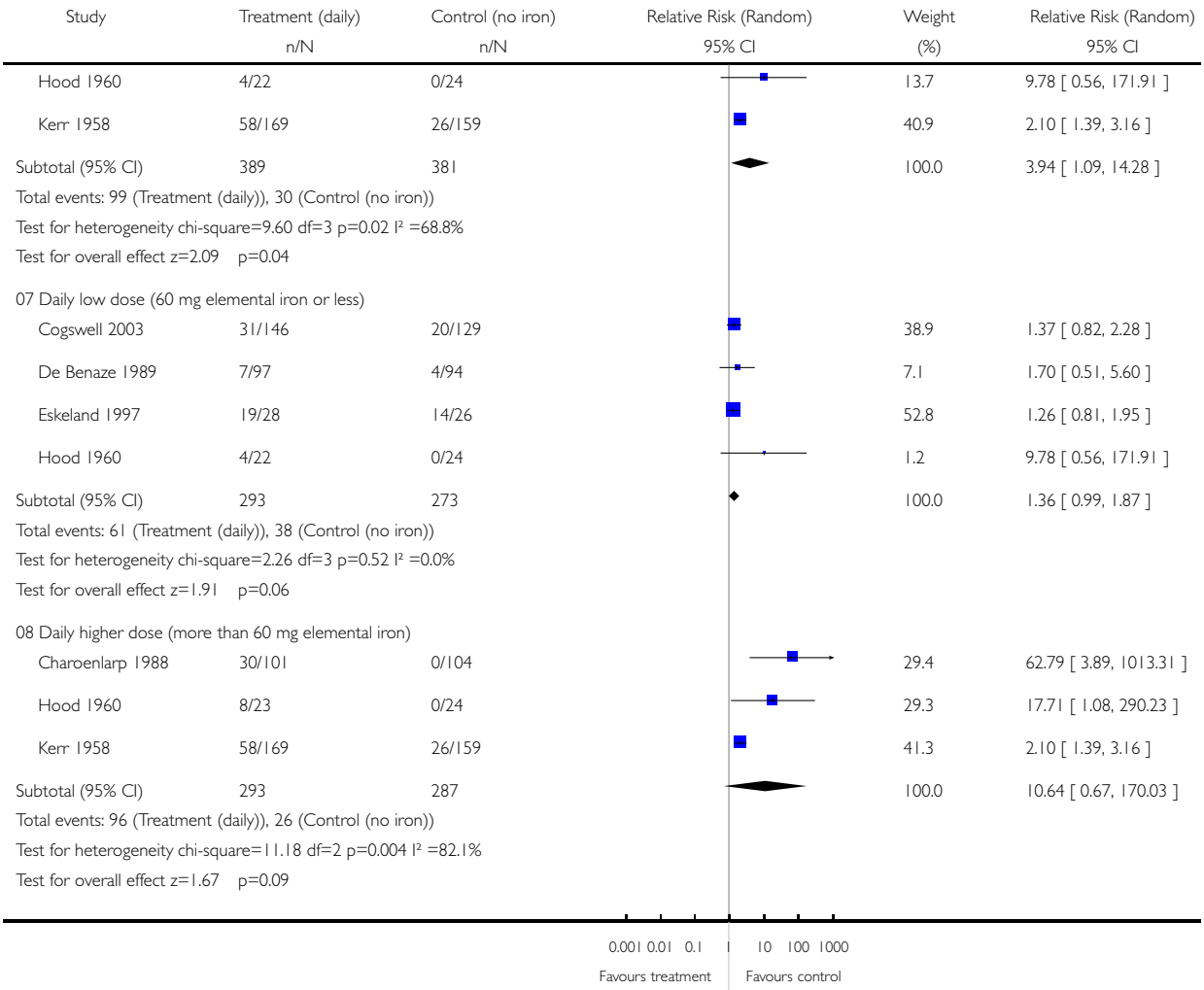


Analysis 01.20. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 20 Very low birthweight (less than 1500 g) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 20 Very low birthweight (less than 1500 g) (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Cogswell 2003	0/117	3/96		45.3	0.12 [0.01, 2.25]
× Eskeland 1997	0/28	0/26		0.0	Not estimable
Makrides 2003	2/216	1/214		54.7	1.98 [0.18, 21.69]
Total (95% CI)	361	336		100.0	0.55 [0.03, 9.07]

Total events: 2 (Treatment (daily)), 4 (Control (no iron))

Test for heterogeneity chi-square=2.19 df=1 p=0.14 I^2 =54.4%

Test for overall effect z=0.42 p=0.7

Analysis 01.24. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 24 Infant Hb concentration at 3 months (g/L) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 24 Infant Hb concentration at 3 months (g/L) (ALL)

Study	Treatment (daily) N	Mean(SD)	Control (No iron) N	Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Preziosi 1997	99	105.00 (12.00)	98	105.00 (11.00)		100.0	0.00 [-3.21, 3.21]
Total (95% CI)	99		98			100.0	0.00 [-3.21, 3.21]

Test for heterogeneity: not applicable

Test for overall effect z=0.00 p=1

Analysis 01.25. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 25 Infant serum ferritin concentration at 3 months (ug/L) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 25 Infant serum ferritin concentration at 3 months (ug/L) (ALL)

Study	Treatment (daily) N	Mean(SD)	Control (No iron) N	Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Preziosi 1997	99	99.00 (63.00)	98	80.00 (53.00)		100.0	19.00 [2.75, 35.25]
Total (95% CI)	99		98			100.0	19.00 [2.75, 35.25]
Test for heterogeneity: not applicable							
Test for overall effect z=2.29 p=0.02							

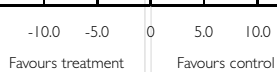
Analysis 01.26. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 26 Infant Hb concentration at 6 months (g/L) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 26 Infant Hb concentration at 6 months (g/L) (ALL)

Study	Treatment (daily) N	Mean(SD)	Control (No iron) N	Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Preziosi 1997	99	105.00 (12.00)	98	110.00 (17.00)		100.0	-5.00 [-9.11, -0.89]
Total (95% CI)	99		98			100.0	-5.00 [-9.11, -0.89]
Test for heterogeneity: not applicable							
Test for overall effect z=2.38 p=0.02							



Analysis 01.27. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 27 Infant serum ferritin concentration at 6 months (ug/L) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 27 Infant serum ferritin concentration at 6 months (ug/L) (ALL)

Study	Treatment (daily) N	Mean(SD)	Control (No iron) N	Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Preziosi 1997	99	26.00 (27.00)	98	15.00 (20.00)		100.0	11.00 [4.37, 17.63]
Total (95% CI)	99		98			100.0	11.00 [4.37, 17.63]
Test for heterogeneity: not applicable							
Test for overall effect z=3.25 p=0.001							

Analysis 01.30. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 30 Very premature delivery (less than 34 weeks' gestation) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 30 Very premature delivery (less than 34 weeks' gestation) (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Cogswell 2003	1/117	5/96		32.8	0.16 [0.02, 1.38]
Eskeland 1997	0/24	1/23		15.0	0.32 [0.01, 7.48]
Makrides 2003	2/216	4/214		52.3	0.50 [0.09, 2.68]
Total (95% CI)	357	333		100.0	0.32 [0.10, 1.09]

Total events: 3 (Treatment (daily)), 10 (Control (no iron))

Test for heterogeneity chi-square=0.64 df=2 p=0.73 I^2 =0.0%

Test for overall effect z=1.82 p=0.07

Analysis 01.31. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 31 Severe anaemia at term (Hb less than 70 g/L) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 31 Severe anaemia at term (Hb less than 70 g/L) (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× Butler 1968	0/27	0/6		0.0	Not estimable
× Cogswell 2003	0/90	0/62		0.0	Not estimable
× Eskeland 1997	0/24	0/21		0.0	Not estimable
× Holly 1955	0/94	0/55		0.0	Not estimable
Makrides 2003	2/200	0/193		100.0	4.83 [0.23, 99.88]
× Milman 1991	0/100	0/107		0.0	Not estimable
× Romslo 1983	0/22	0/23		0.0	Not estimable
Total (95% CI)	557	467		100.0	4.83 [0.23, 99.88]

Total events: 2 (Treatment (daily)), 0 (Control (no iron))

Test for heterogeneity: not applicable

Test for overall effect z=1.02 p=0.3

Analysis 01.32. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 32 Moderate anaemia at term (Hb more than 70 g/L and less than 90 g/L) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 32 Moderate anaemia at term (Hb more than 70 g/L and less than 90 g/L) (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× Butler 1968	0/27	0/6		0.0	Not estimable
× Cogswell 2003	0/90	0/62		0.0	Not estimable
× Eskeland 1997	0/24	0/21		0.0	Not estimable
× Holly 1955	0/94	0/55		0.0	Not estimable
Makrides 2003	1/200	3/193		5.7	0.32 [0.03, 3.07]
× Milman 1991	0/100	0/107		0.0	Not estimable
Paintin 1966	18/60	17/57		94.3	1.01 [0.58, 1.75]
× Romslo 1983	0/22	0/23		0.0	Not estimable
Total (95% CI)	617	524		100.0	0.94 [0.55, 1.62]

Total events: 19 (Treatment (daily)), 20 (Control (no iron))

Test for heterogeneity chi-square=0.95 df=1 p=0.33 I^2 =0.0%

Test for overall effect z=0.22 p=0.8

Analysis 01.33. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 33 Severe anaemia at any time during second and third trimester (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

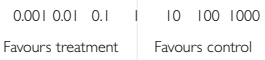
Outcome: 33 Severe anaemia at any time during second and third trimester (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× Butler 1968	0/49	0/16		0.0	Not estimable
× Cogswell 2003	0/110	0/86		0.0	Not estimable
× Eskeland 1997	0/24	0/23		0.0	Not estimable
× Holly 1955	0/94	0/55		0.0	Not estimable
Makrides 2003	2/206	0/205		100.0	4.98 [0.24, 103.01]
× Milman 1991	0/100	0/107		0.0	Not estimable
Total (95% CI)	583	492		100.0	4.98 [0.24, 103.01]

Total events: 2 (Treatment (daily)), 0 (Control (no iron))

Test for heterogeneity: not applicable

Test for overall effect z=1.04 p=0.3



Analysis 01.34. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 34 Moderate anaemia at any time during second or third trimester (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 34 Moderate anaemia at any time during second or third trimester (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× Butler 1968	0/49	0/16		0.0	Not estimable
× Cogswell 2003	0/110	0/86		0.0	Not estimable
× Eskeland 1997	0/24	0/23		0.0	Not estimable
× Holly 1955	0/94	0/55		0.0	Not estimable
Makrides 2003	1/206	3/205		5.6	0.33 [0.03, 3.16]
× Milman 1991	0/100	0/107		0.0	Not estimable
Paintin 1966	22/120	17/57		94.4	0.61 [0.36, 1.06]
Total (95% CI)	703	549		100.0	0.59 [0.35, 1.01]

Total events: 23 (Treatment (daily)), 20 (Control (no iron))

Test for heterogeneity chi-square=0.28 df=1 p=0.60 I^2 =0.0%

Test for overall effect z=1.92 p=0.06

Analysis 01.36. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 36 Puerperal infection (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 36 Puerperal infection (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Willoughby 1967	3/736	5/706		100.0	0.58 [0.14, 2.40]
Total (95% CI)	736	706		100.0	0.58 [0.14, 2.40]
Total events: 3 (Treatment (daily)), 5 (Control (no iron))					
Test for heterogeneity: not applicable					
Test for overall effect z=0.76 p=0.4					

Analysis 01.37. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 37 Antepartum haemorraghe (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 37 Antepartum haemorraghe (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Makrides 2003	1/216	0/214		100.0	2.97 [0.12, 72.56]
Total (95% CI)	216	214		100.0	2.97 [0.12, 72.56]
Total events: 1 (Treatment (daily)), 0 (Control (no iron))					
Test for heterogeneity: not applicable					
Test for overall effect z=0.67 p=0.5					

Analysis 01.38. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 38 Postpartum haemorraghe (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 38 Postpartum haemorraghe (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Butler 1968	0/49	1/17		2.5	0.12 [0.01, 2.81]
Eskeland 1997	1/24	1/23		3.4	0.96 [0.06, 14.43]
Wills 1947	26/260	26/210		94.2	0.81 [0.48, 1.35]
Total (95% CI)	333	250		100.0	0.77 [0.47, 1.27]

Total events: 27 (Treatment (daily)), 28 (Control (no iron))

Test for heterogeneity chi-square=1.39 df=2 p=0.50 I^2 =0.0%

Test for overall effect z=1.01 p=0.3

Analysis 01.39. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 39 Transfusion provided (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 39 Transfusion provided (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Puolakka 1980	0/16	1/16		100.0	0.33 [0.01, 7.62]
Total (95% CI)	16	16		100.0	0.33 [0.01, 7.62]

Total events: 0 (Treatment (daily)), 1 (Control (no iron))

Test for heterogeneity: not applicable

Test for overall effect z=0.69 p=0.5

Analysis 01.40. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 40 Haemoglobin concentration within one month postpartum (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

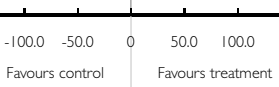
Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 40 Haemoglobin concentration within one month postpartum (ALL)

Study	Treatment (daily) N	Mean(SD)	Control (no iron) N	Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Hankin 1963	115	142.00 (13.90)	49	138.00 (13.30)		19.1	4.00 [-0.51, 8.51]
Menendez 1994	207	104.00 (19.90)	203	99.00 (17.70)		24.9	5.00 [1.36, 8.64]
Milman 1991	62	134.20 (7.00)	59	128.90 (10.00)		29.7	5.30 [2.21, 8.39]
Wills 1947	88	133.80 (10.41)	50	124.25 (9.75)		26.3	9.55 [6.08, 13.02]
Total (95% CI)	472		361			100.0	6.10 [3.70, 8.49]

Test for heterogeneity chi-square=5.24 df=3 p=0.16 I^2 =42.7%

Test for overall effect z=4.99 p<0.00001



Analysis 01.41. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 41 Severe anaemia at postpartum (Hb less than 80 g/L) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 41 Severe anaemia at postpartum (Hb less than 80 g/L) (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× Butler 1968	0/49	0/16		0.0	Not estimable
× Eskeland 1997	0/24	0/23		0.0	Not estimable
× Holly 1955	0/94	0/55		0.0	Not estimable
× Makrides 2003	0/189	0/177		0.0	Not estimable
× Milman 1991	0/63	0/57		0.0	Not estimable
× Puolakka 1980	0/16	0/15		0.0	Not estimable
Total (95% CI)	435	343		0.0	Not estimable

Total events: 0 (Treatment (daily)), 0 (Control (no iron))

Test for heterogeneity: not applicable

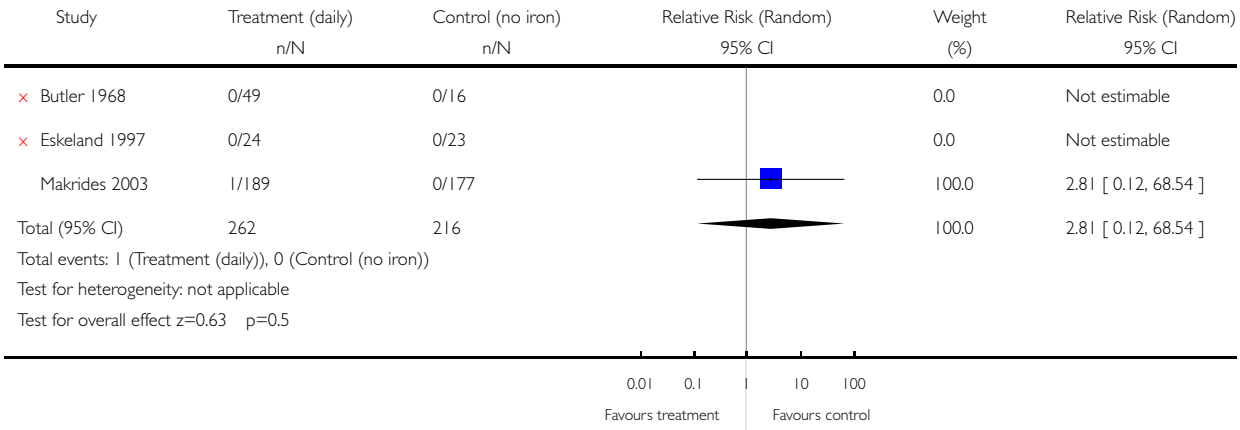
Test for overall effect: not applicable

Analysis 01.42. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 42 Moderate anaemia at postpartum (Hb more than 80 g/L and less than 100 g/L) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 42 Moderate anaemia at postpartum (Hb more than 80 g/L and less than 100 g/L) (ALL)

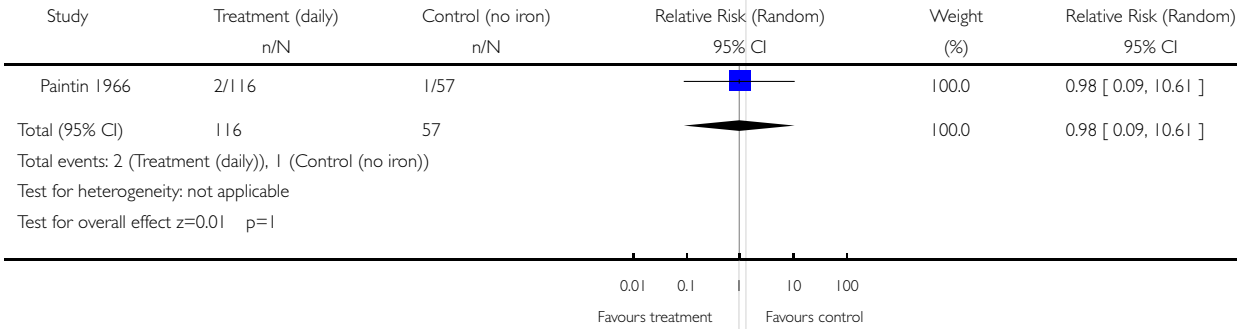


Analysis 01.43. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 43 Diarrhoea (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 43 Diarrhoea (ALL)



Analysis 01.44. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 44 Constipation (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 44 Constipation (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Makrides 2003	18/204	12/203		70.6	1.49 [0.74, 3.02]
Paintin 1966	1/116	2/57		29.4	0.25 [0.02, 2.65]
Total (95% CI)	320	260		100.0	0.88 [0.18, 4.40]

Total events: 19 (Treatment (daily)), 14 (Control (no iron))

Test for heterogeneity chi-square=2.03 df=1 p=0.15 I^2 =50.8%

Test for overall effect z=0.16 p=0.9

Analysis 01.45. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 45 Nausea (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 45 Nausea (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Hood 1960	12/45	0/24		21.1	13.59 [0.84, 219.98]
Makrides 2003	51/204	45/204		59.4	1.13 [0.80, 1.61]
Paintin 1966	3/116	0/57		19.5	3.47 [0.18, 66.06]
Total (95% CI)	365	285		100.0	2.38 [0.49, 11.52]

Total events: 66 (Treatment (daily)), 45 (Control (no iron))

Test for heterogeneity chi-square=3.94 df=2 p=0.14 I^2 =49.3%

Test for overall effect z=1.08 p=0.3

Analysis 01.46. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 46 Heartburn (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 46 Heartburn (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Makrides 2003	100/204	100/204		100.0	1.00 [0.82, 1.22]
Total (95% CI)	204	204		100.0	1.00 [0.82, 1.22]
Total events: 100 (Treatment (daily)), 100 (Control (no iron))					
Test for heterogeneity: not applicable					
Test for overall effect z=0.00 p=1					

Analysis 01.47. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 47 Vomiting (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 47 Vomiting (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Hood 1960	3/45	0/24		8.0	3.80 [0.20, 70.74]
Makrides 2003	21/204	27/204		92.0	0.78 [0.45, 1.33]
Total (95% CI)	249	228		100.0	0.88 [0.38, 2.07]
Total events: 24 (Treatment (daily)), 27 (Control (no iron))					
Test for heterogeneity chi-square=1.11 df=1 p=0.29 I^2 =10.2%					
Test for overall effect z=0.28 p=0.8					

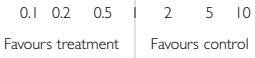
Analysis 01.48. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 48 Maternal death (death while pregnant or within 42 days of termination of pregnancy) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 48 Maternal death (death while pregnant or within 42 days of termination of pregnancy) (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× Eskeland 1997	0/24	0/23		0.0	Not estimable
Total (95% CI)	24	23		0.0	Not estimable
Total events: 0 (Treatment (daily)), 0 (Control (no iron))					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



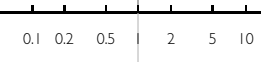
Analysis 01.49. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 49 Maternal wellbeing/satisfaction (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 49 Maternal wellbeing/satisfaction (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Eskeland 1997	21/24	24/25		100.0	0.91 [0.77, 1.08]
Total (95% CI)	24	25		100.0	0.91 [0.77, 1.08]
Total events: 21 (Treatment (daily)), 24 (Control (no iron))					
Test for heterogeneity: not applicable					
Test for overall effect z=1.06 p=0.3					

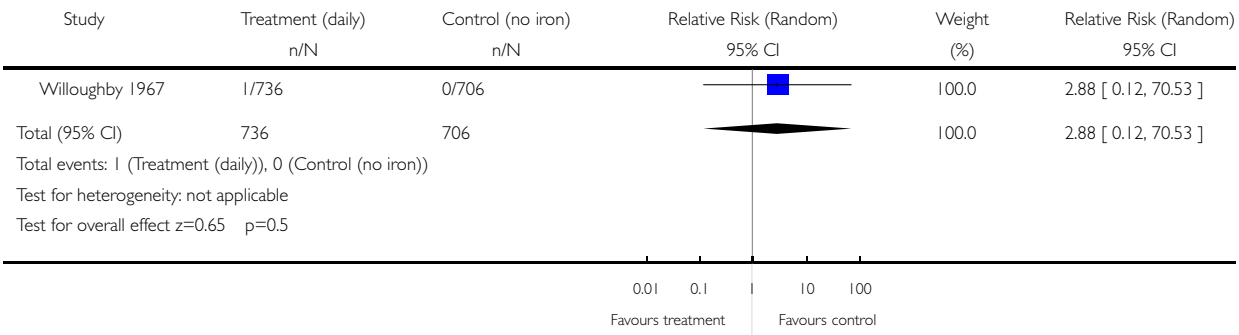


Analysis 01.50. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 50 Placental abruption (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 50 Placental abruption (ALL)

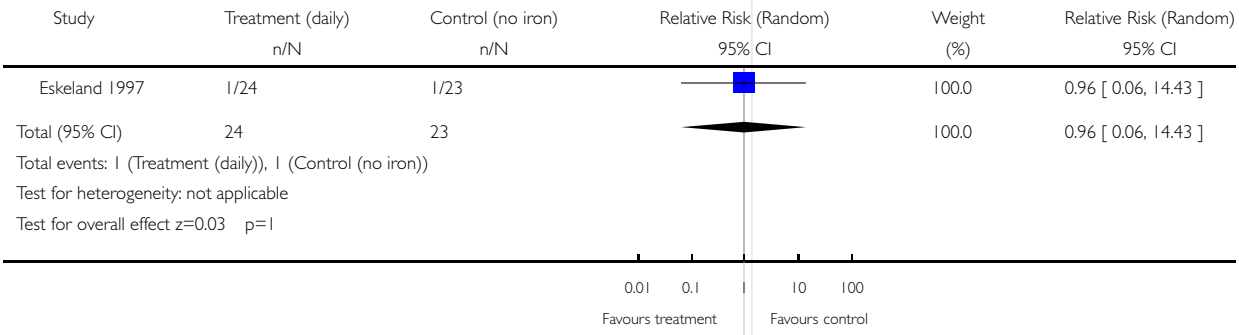


Analysis 01.52. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 52 Pre-eclampsia (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 52 Pre-eclampsia (ALL)



Analysis 01.93. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 93 Cesarean delivery (not prespecified)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 93 Cesarean delivery (not prespecified)

Study	Treatment (any iron) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Eskeland 1997	0/24	1/23		1.2	0.32 [0.01, 7.48]
Makrides 2003	51/216	47/214		98.8	1.08 [0.76, 1.52]
× Puolakka 1980	0/16	0/15		0.0	Not estimable
Total (95% CI)	256	252		100.0	1.06 [0.75, 1.50]
Total events: 51 (Treatment (any iron)), 48 (Control (no iron))					
Test for heterogeneity chi-square=0.56 df=1 p=0.45 I² =0.0%					
Test for overall effect z=0.33 p=0.7					

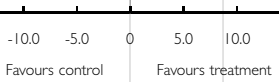
Analysis 01.94. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 94 Birth length in cm (not prespecified)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 94 Birth length in cm (not prespecified)

Study	Treatment (any iron) N	Mean(SD)	Control (no iron) N	Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Cogswell 2003	106	49.66 (2.90)	90	49.31 (3.66)		17.0	0.35 [-0.59, 1.29]
Eskeland 1997	28	50.50 (1.71)	26	50.50 (2.37)		12.5	0.00 [-1.11, 1.11]
Makrides 2003	216	49.90 (3.20)	214	50.00 (2.80)		38.7	-0.10 [-0.67, 0.47]
Preziosi 1997	99	48.10 (2.10)	98	47.40 (2.50)		31.8	0.70 [0.05, 1.35]
Total (95% CI)	449		428			100.0	0.24 [-0.17, 0.65]
Test for heterogeneity chi-square=3.56 df=3 p=0.31 I² =15.8%							
Test for overall effect z=1.17 p=0.2							



Analysis 01.95. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 95 Forceps or vacuum delivery (not prespecified)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 95 Forceps or vacuum delivery (not prespecified)

Study	Treatment (any iron) n/N	Control (no iron) n/N	Odds Ratio (Random) 95% CI	Weight (%)	Odds Ratio (Random) 95% CI
Eskeland 1997	4/24	2/23		9.0	2.10 [0.35, 12.76]
Makrides 2003	34/216	23/214		91.0	1.55 [0.88, 2.73]
Total (95% CI)	240	237		100.0	1.59 [0.93, 2.74]

Total events: 38 (Treatment (any iron)), 25 (Control (no iron))

Test for heterogeneity chi-square=0.10 df=1 p=0.75 I^2 =0.0%

Test for overall effect z=1.69 p=0.09

Analysis 01.96. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 96 Breastfeeding at least 4 months (not prespecified)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

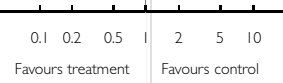
Outcome: 96 Breastfeeding at least 4 months (not prespecified)

Study	Treatment (any iron) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Eskeland 1997	24/25	22/23		100.0	1.00 [0.89, 1.13]
Total (95% CI)	25	23		100.0	1.00 [0.89, 1.13]

Total events: 24 (Treatment (any iron)), 22 (Control (no iron))

Test for heterogeneity: not applicable

Test for overall effect z=0.06 p=1



Analysis 01.97. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 97 Haemoglobin concentration at 4-8 weeks' postpartum (g/L) (not prespecified)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 97 Haemoglobin concentration at 4-8 weeks' postpartum (g/L) (not prespecified)

Study	Treatment (any iron) N	Mean(SD)	Control (no iron) N	Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Butler 1968	49	140.00 (8.40)	16	138.00 (6.00)		15.6	2.00 [-1.76, 5.76]
Buytaert 1983	24	138.57 (8.05)	21	141.79 (8.05)		11.5	-3.22 [-7.93, 1.49]
Eskeland 1997	25	128.70 (8.76)	23	124.70 (8.18)		11.3	4.00 [-0.79, 8.79]
Svanberg 1975	24	134.00 (8.18)	26	129.00 (7.64)		12.7	5.00 [0.60, 9.40]
Tura 1989	123	127.00 (9.00)	100	125.00 (10.00)		23.8	2.00 [-0.52, 4.52]
Wallenburg 1983	18	136.90 (9.66)	20	136.90 (9.66)		7.6	0.00 [-6.15, 6.15]
Wills 1947	60	131.82 (8.98)	57	127.38 (9.89)		17.5	4.44 [1.01, 7.87]
Total (95% CI)	323		263			100.0	2.28 [0.40, 4.16]

Test for heterogeneity chi-square=9.31 df=6 p=0.16 I^2 =35.5%

Test for overall effect z=2.37 p=0.02

Analysis 01.98. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 98 Apgar score < 7 at 5 minutes (not prespecified)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 98 Apgar score < 7 at 5 minutes (not prespecified)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Makrides 2003	3/216	4/214		100.0	0.74 [0.17, 3.28]
× Romslo 1983	0/22	0/23		0.0	Not estimable
Total (95% CI)	238	237		100.0	0.74 [0.17, 3.28]

Total events: 3 (Treatment (daily)), 4 (Control (no iron))

Test for heterogeneity: not applicable

Test for overall effect z=0.39 p=0.7

Analysis 01.99. Comparison 01 Daily iron alone versus no intervention/placebo, Outcome 99 Apgar Score at 5 min (not prespecified)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 01 Daily iron alone versus no intervention/placebo

Outcome: 99 Apgar Score at 5 min (not prespecified)

Study	Treatment (daily) N	Mean(SD)	Control (no iron) N	Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Preziosi 1997	99	9.60 (2.00)	98	9.20 (2.00)		37.3	0.40 [-0.16, 0.96]
Puolakka 1980	16	9.20 (0.50)	15	9.00 (0.70)		62.7	0.20 [-0.23, 0.63]
Total (95% CI)	115		113			100.0	0.27 [-0.07, 0.62]

Test for heterogeneity chi-square=0.31 df=1 p=0.58 I^2 =0.0%

Test for overall effect z=1.58 p=0.1

Analysis 02.03. Comparison 02 Intermittent iron alone versus daily iron alone, Outcome 03 Birthweight (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 02 Intermittent iron alone versus daily iron alone

Outcome: 03 Birthweight (ALL)

Study	Intermittent iron N	Mean(SD)	Control (daily) N	Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Pita Martin 1999	12	3157.00 (529.00)	29	3225.00 (384.00)		100.0	-68.00 [-398.33, 262.33]
Total (95% CI)	12		29			100.0	-68.00 [-398.33, 262.33]

Test for heterogeneity: not applicable

Test for overall effect z=0.40 p=0.7

Analysis 02.05. Comparison 02 Intermittent iron alone versus daily iron alone, Outcome 05 Premature delivery (less than 37 weeks of gestation) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 02 Intermittent iron alone versus daily iron alone

Outcome: 05 Premature delivery (less than 37 weeks of gestation) (ALL)

Study	Intermittent iron n/N	Control (daily) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Pita Martin 1999	0/12	2/29		100.0	0.46 [0.02, 8.96]
Total (95% CI)	12	29		100.0	0.46 [0.02, 8.96]
Total events: 0 (Intermittent iron), 2 (Control (daily))					
Test for heterogeneity: not applicable					
Test for overall effect z=0.51 p=0.6					

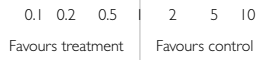
Analysis 02.12. Comparison 02 Intermittent iron alone versus daily iron alone, Outcome 12 Haemoconcentration during second or third trimester (Hb more than 130 g/L) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 02 Intermittent iron alone versus daily iron alone

Outcome: 12 Haemoconcentration during second or third trimester (Hb more than 130 g/L) (ALL)

Study	Intermittent iron n/N	Control (daily) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Pita Martin 1999	2/12	11/29		63.5	0.44 [0.11, 1.69]
Yu 1998	2/13	2/10		36.5	0.77 [0.13, 4.55]
Total (95% CI)	25	39		100.0	0.54 [0.18, 1.58]
Total events: 4 (Intermittent iron), 13 (Control (daily))					
Test for heterogeneity chi-square=0.24 df=1 p=0.62 I^2 =0.0%					
Test for overall effect z=1.13 p=0.3					



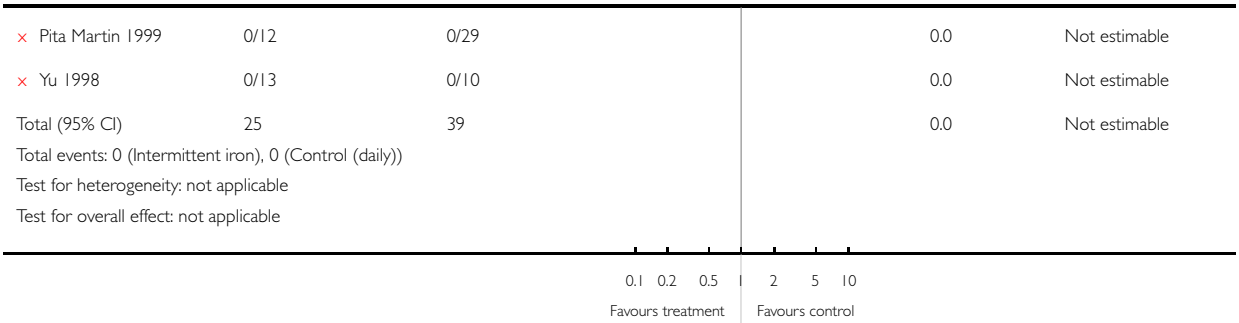
Analysis 02.33. Comparison 02 Intermittent iron alone versus daily iron alone, Outcome 33 Severe anaemia at any time during second and third trimester (Hb less than 70 g/L) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 02 Intermittent iron alone versus daily iron alone

Outcome: 33 Severe anaemia at any time during second and third trimester (Hb less than 70 g/L) (ALL)

Study	Intermittent iron n/N	Control (daily) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× Pita Martin 1999	0/12	0/29		0.0	Not estimable
× Yu 1998	0/13	0/10		0.0	Not estimable
Total (95% CI)	25	39		0.0	Not estimable
Total events: 0 (Intermittent iron), 0 (Control (daily))					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



Analysis 02.34. Comparison 02 Intermittent iron alone versus daily iron alone, Outcome 34 Moderate anaemia at any time during second or third trimester (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 02 Intermittent iron alone versus daily iron alone

Outcome: 34 Moderate anaemia at any time during second or third trimester (ALL)

Study	Intermittent iron n/N	Control (daily) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Pita Martin 1999	1/12	1/29		100.0	2.42 [0.16, 35.56]
× Yu 1998	0/13	0/10		0.0	Not estimable
Total (95% CI)	25	39		100.0	2.42 [0.16, 35.56]
Total events: 1 (Intermittent iron), 1 (Control (daily))					
Test for heterogeneity: not applicable					
Test for overall effect z=0.64 p=0.5					

Analysis 03.01. Comparison 03 Daily iron-folic acid versus no intervention/placebo, Outcome 01 Low birthweight (less than 2500 g) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 03 Daily iron-folic acid versus no intervention/placebo

Outcome: 01 Low birthweight (less than 2500 g) (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Taylor 1982	2/24	0/24		100.0	5.00 [0.25, 98.96]
Total (95% CI)	24	24		100.0	5.00 [0.25, 98.96]

Total events: 2 (Treatment (daily)), 0 (Control (no iron))

Test for heterogeneity: not applicable

Test for overall effect z=1.06 p=0.3

Analysis 03.03. Comparison 03 Daily iron-folic acid versus no intervention/placebo, Outcome 03 Birthweight (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 03 Daily iron-folic acid versus no intervention/placebo

Outcome: 03 Birthweight (ALL)

Study	Treatment (daily) N	Mean(SD)	Control (no iron) N	Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Taylor 1982	21	3470.00 (365.00)	24	3502.00 (232.00)		100.0	-32.00 [-213.62, 149.62]
Total (95% CI)	21		24			100.0	-32.00 [-213.62, 149.62]

Test for heterogeneity: not applicable

Test for overall effect z=0.35 p=0.7

Analysis 03.05. Comparison 03 Daily iron-folic acid versus no intervention/placebo, Outcome 05 Premature delivery (less than 37 weeks of gestation) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 03 Daily iron-folic acid versus no intervention/placebo

Outcome: 05 Premature delivery (less than 37 weeks of gestation) (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Taylor 1982	3/24	0/24		100.0	7.00 [0.38, 128.61]
Total (95% CI)	24	24		100.0	7.00 [0.38, 128.61]
Total events: 3 (Treatment (daily)), 0 (Control (no iron))					
Test for heterogeneity: not applicable					
Test for overall effect z=1.31 p=0.2					

Analysis 03.07. Comparison 03 Daily iron-folic acid versus no intervention/placebo, Outcome 07 Haemoglobin concentration at term (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 03 Daily iron-folic acid versus no intervention/placebo

Outcome: 07 Haemoglobin concentration at term (ALL)

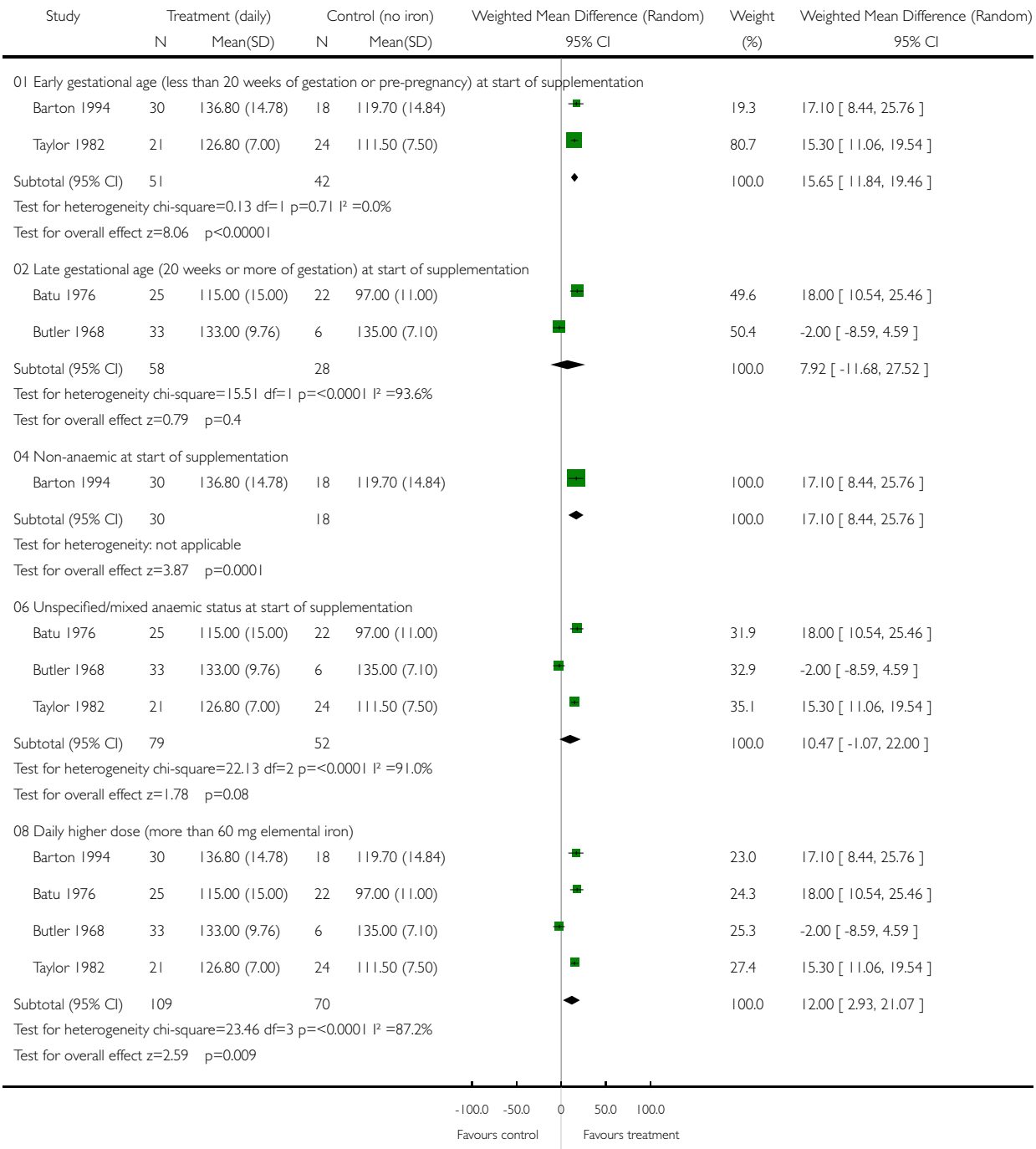
Study	Treatment (daily) N	Mean(SD)	Control (no iron) N	Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Barton 1994	30	136.80 (14.78)	18	119.70 (14.84)		23.0	17.10 [8.44, 25.76]
Batu 1976	25	115.00 (15.00)	22	97.00 (11.00)		24.3	18.00 [10.54, 25.46]
Butler 1968	33	133.00 (9.76)	6	135.00 (7.10)		25.3	-2.00 [-8.59, 4.59]
Taylor 1982	21	126.80 (7.00)	24	111.50 (7.50)		27.4	15.30 [11.06, 19.54]
Total (95% CI)	109		70			100.0	12.00 [2.93, 21.07]
Test for heterogeneity chi-square=23.46 df=3 p=<0.0001 I^2 =87.2%							
Test for overall effect z=2.59 p=0.009							

Analysis 03.08. Comparison 03 Daily iron-folic acid versus no intervention/placebo, Outcome 08 Haemoglobin concentration at term (BY SUBGROUPS)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 03 Daily iron-folic acid versus no intervention/placebo

Outcome: 08 Haemoglobin concentration at term (BY SUBGROUPS)



Analysis 03.09. Comparison 03 Daily iron-folic acid versus no intervention/placebo, Outcome 09 Anaemia at term (Hb less than 110 g/L) (not pre-specified)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 03 Daily iron-folic acid versus no intervention/placebo

Outcome: 09 Anaemia at term (Hb less than 110 g/L) (not pre-specified)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× Barton 1994	0/53	0/44		0.0	Not estimable
Batu 1976	10/32	29/34		57.8	0.37 [0.22, 0.62]
Chisholm 1966	7/123	20/60		42.2	0.17 [0.08, 0.38]
Total (95% CI)	208	138		100.0	0.27 [0.12, 0.56]

Total events: 17 (Treatment (daily)), 49 (Control (no iron))

Test for heterogeneity chi-square=2.50 df=1 p=0.11 I^2 =60.1%

Test for overall effect z=3.45 p=0.0006

Analysis 03.10. Comparison 03 Daily iron-folic acid versus no intervention/placebo, Outcome 10 Haemoconcentration at term (Hb more than 130 g/L) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 03 Daily iron-folic acid versus no intervention/placebo

Outcome: 10 Haemoconcentration at term (Hb more than 130 g/L) (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Butler 1968	19/33	4/6		76.2	0.86 [0.46, 1.63]
Chisholm 1966	4/123	0/60		23.8	4.43 [0.24, 80.92]
Total (95% CI)	156	66		100.0	1.28 [0.24, 6.78]

Total events: 23 (Treatment (daily)), 4 (Control (no iron))

Test for heterogeneity chi-square=1.74 df=1 p=0.19 I^2 =42.4%

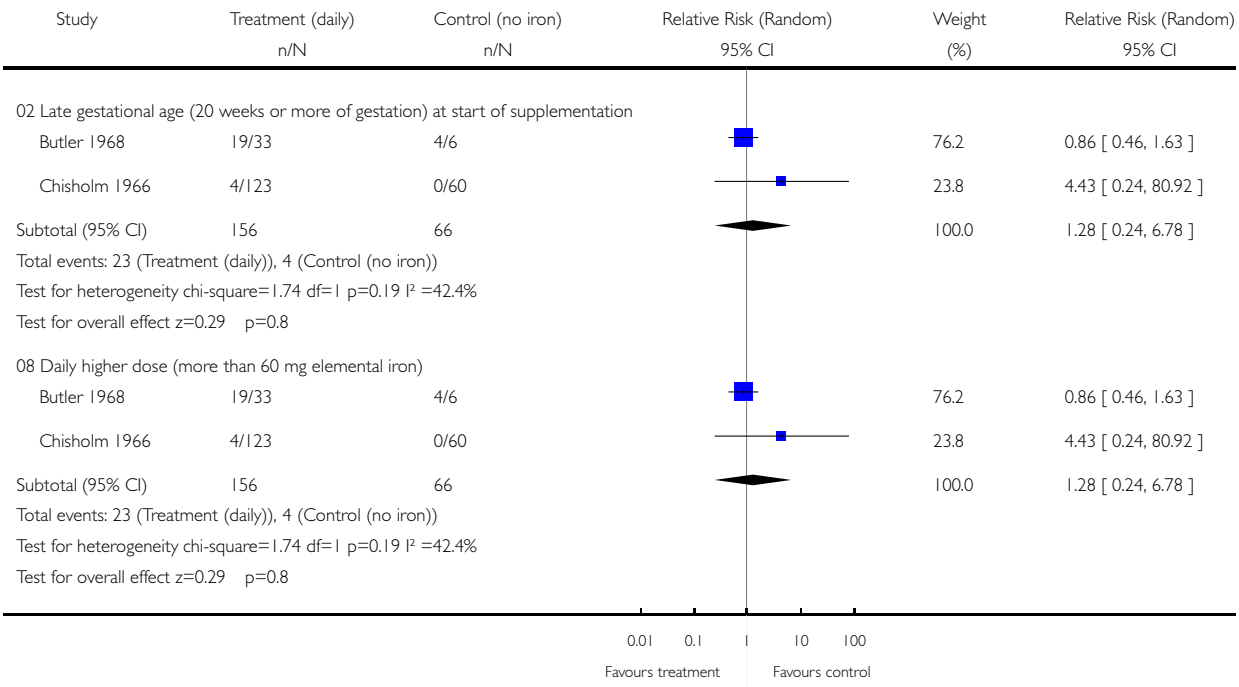
Test for overall effect z=0.29 p=0.8

Analysis 03.11. Comparison 03 Daily iron-folic acid versus no intervention/placebo, Outcome 11 Haemoconcentration at term (Hb more than 130 g/L) (BY SUBGROUPS)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 03 Daily iron-folic acid versus no intervention/placebo

Outcome: 11 Haemoconcentration at term (Hb more than 130 g/L) (BY SUBGROUPS)

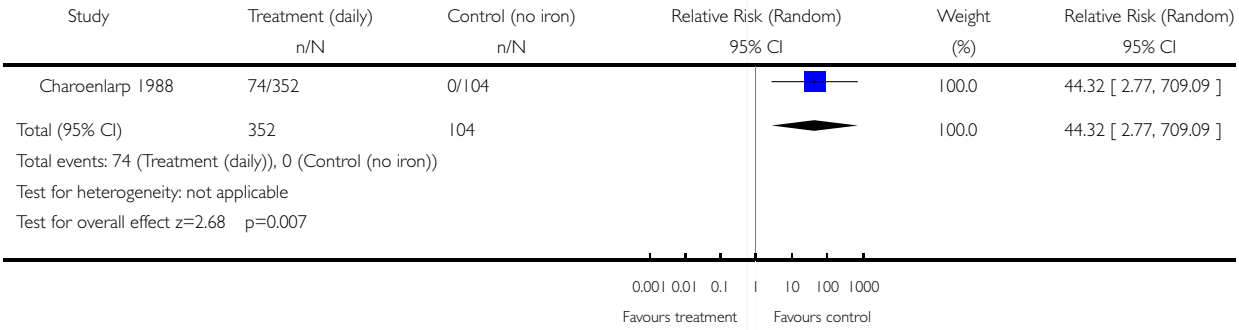


Analysis 03.18. Comparison 03 Daily iron-folic acid versus no intervention/placebo, Outcome 18 Side-effects (Any) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 03 Daily iron-folic acid versus no intervention/placebo

Outcome: 18 Side-effects (Any) (ALL)

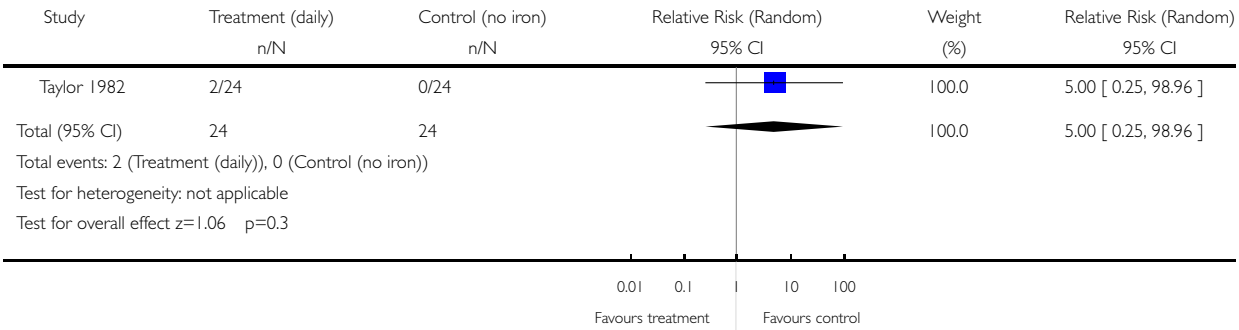


Analysis 03.20. Comparison 03 Daily iron-folic acid versus no intervention/placebo, Outcome 20 Very low birthweight (less than 1500 g) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 03 Daily iron-folic acid versus no intervention/placebo

Outcome: 20 Very low birthweight (less than 1500 g) (ALL)

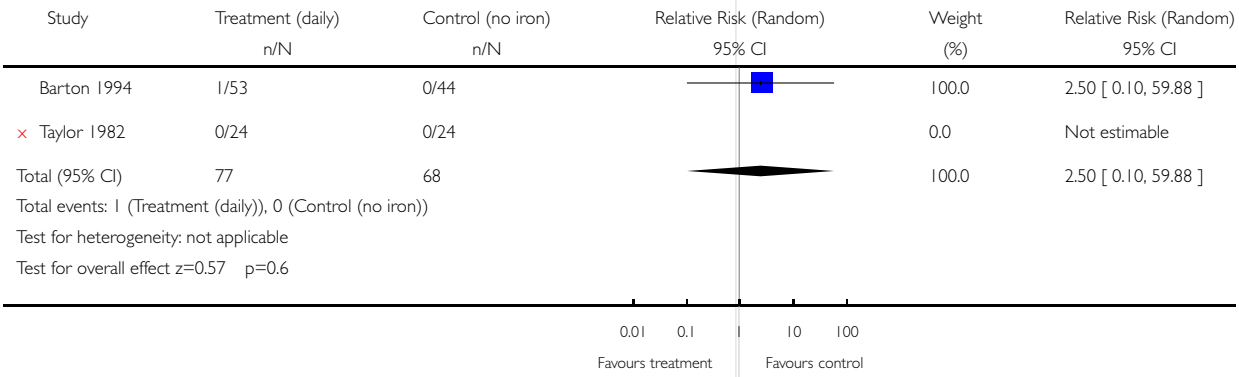


Analysis 03.21. Comparison 03 Daily iron-folic acid versus no intervention/placebo, Outcome 21 Perinatal death (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 03 Daily iron-folic acid versus no intervention/placebo

Outcome: 21 Perinatal death (ALL)



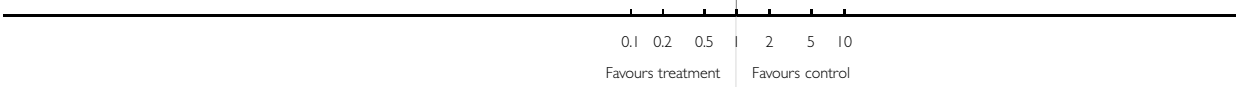
Analysis 03.29. Comparison 03 Daily iron-folic acid versus no intervention/placebo, Outcome 29 Admission to special care unit (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 03 Daily iron-folic acid versus no intervention/placebo

Outcome: 29 Admission to special care unit (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× Taylor 1982	0/24	0/24		0.0	Not estimable
Total (95% CI)	24	24		0.0	Not estimable
Total events: 0 (Treatment (daily)), 0 (Control (no iron))					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



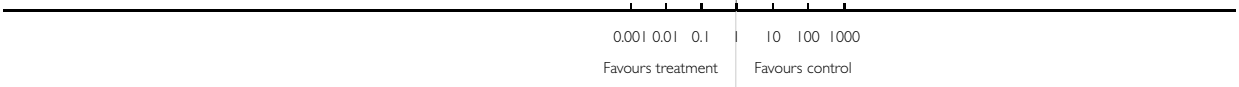
Analysis 03.30. Comparison 03 Daily iron-folic acid versus no intervention/placebo, Outcome 30 Very premature delivery (less than 34 weeks' gestation) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 03 Daily iron-folic acid versus no intervention/placebo

Outcome: 30 Very premature delivery (less than 34 weeks' gestation) (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Taylor 1982	2/24	0/24		100.0	5.00 [0.25, 98.96]
Total (95% CI)	24	24		100.0	5.00 [0.25, 98.96]
Total events: 2 (Treatment (daily)), 0 (Control (no iron))					
Test for heterogeneity: not applicable					
Test for overall effect z=1.06 p=0.3					



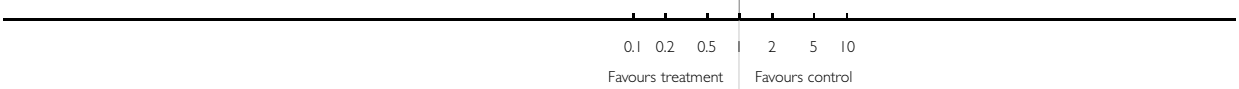
Analysis 03.31. Comparison 03 Daily iron-folic acid versus no intervention/placebo, Outcome 31 Severe anaemia at term (Hb less than 70 g/L) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 03 Daily iron-folic acid versus no intervention/placebo

Outcome: 31 Severe anaemia at term (Hb less than 70 g/L) (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× Barton 1994	0/53	0/44		0.0	Not estimable
× Butler 1968	0/33	0/6		0.0	Not estimable
Total (95% CI)	86	50		0.0	Not estimable
Total events: 0 (Treatment (daily)), 0 (Control (no iron))					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



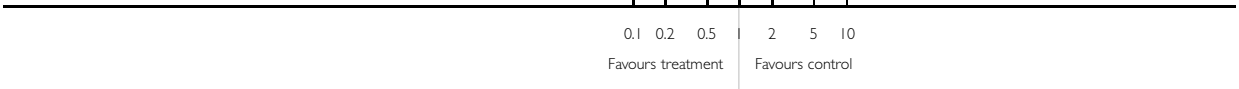
Analysis 03.32. Comparison 03 Daily iron-folic acid versus no intervention/placebo, Outcome 32 Moderate anaemia at term (Hb more than 70g/L and less than 90 g/L) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 03 Daily iron-folic acid versus no intervention/placebo

Outcome: 32 Moderate anaemia at term (Hb more than 70g/L and less than 90 g/L) (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× Barton 1994	0/53	0/44		0.0	Not estimable
× Butler 1968	0/33	0/6		0.0	Not estimable
Total (95% CI)	86	50		0.0	Not estimable
Total events: 0 (Treatment (daily)), 0 (Control (no iron))					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



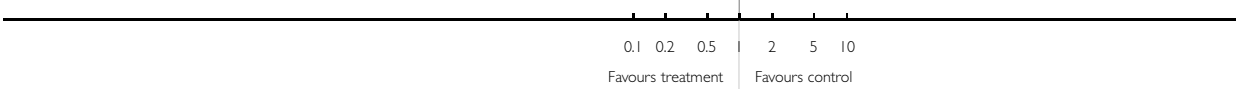
Analysis 03.33. Comparison 03 Daily iron-folic acid versus no intervention/placebo, Outcome 33 Severe anaemia at any time during second and third trimester (Hb less than 70 g/L) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 03 Daily iron-folic acid versus no intervention/placebo

Outcome: 33 Severe anaemia at any time during second and third trimester (Hb less than 70 g/L) (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× Barton 1994	0/53	0/44		0.0	Not estimable
× Butler 1968	0/51	0/16		0.0	Not estimable
Total (95% CI)	104	60		0.0	Not estimable
Total events: 0 (Treatment (daily)), 0 (Control (no iron))					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



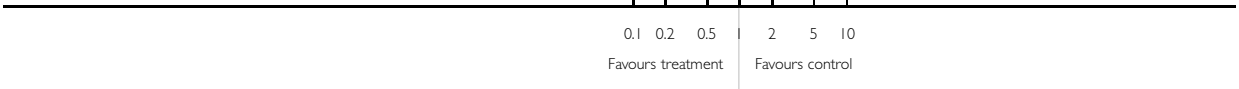
Analysis 03.34. Comparison 03 Daily iron-folic acid versus no intervention/placebo, Outcome 34 Moderate anaemia at any time during second or third trimester (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 03 Daily iron-folic acid versus no intervention/placebo

Outcome: 34 Moderate anaemia at any time during second or third trimester (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× Barton 1994	0/53	0/44		0.0	Not estimable
× Butler 1968	0/51	0/16		0.0	Not estimable
Total (95% CI)	104	60		0.0	Not estimable
Total events: 0 (Treatment (daily)), 0 (Control (no iron))					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



Analysis 03.35. Comparison 03 Daily iron-folic acid versus no intervention/placebo, Outcome 35 Infection during pregnancy (including urinary tract infections) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 03 Daily iron-folic acid versus no intervention/placebo

Outcome: 35 Infection during pregnancy (including urinary tract infections) (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Taylor 1982	2/24	2/24		100.0	1.00 [0.15, 6.53]
Total (95% CI)	24	24		100.0	1.00 [0.15, 6.53]
Total events: 2 (Treatment (daily)), 2 (Control (no iron))					
Test for heterogeneity: not applicable					
Test for overall effect z=0.00 p=1					

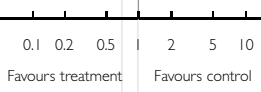
Analysis 03.36. Comparison 03 Daily iron-folic acid versus no intervention/placebo, Outcome 36 Puerperal infection (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 03 Daily iron-folic acid versus no intervention/placebo

Outcome: 36 Puerperal infection (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Willoughby 1967	5/2157	3/706		100.0	0.55 [0.13, 2.28]
Total (95% CI)	2157	706		100.0	0.55 [0.13, 2.28]
Total events: 5 (Treatment (daily)), 3 (Control (no iron))					
Test for heterogeneity: not applicable					
Test for overall effect z=0.83 p=0.4					



Analysis 03.37. Comparison 03 Daily iron-folic acid versus no intervention/placebo, Outcome 37 Antepartum haemorraghe (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 03 Daily iron-folic acid versus no intervention/placebo

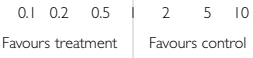
Outcome: 37 Antepartum haemorraghe (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Barton 1994	3/53	2/44		100.0	1.25 [0.22, 7.12]
× Taylor 1982	0/24	0/24		0.0	Not estimable
Total (95% CI)	77	68		100.0	1.25 [0.22, 7.12]

Total events: 3 (Treatment (daily)), 2 (Control (no iron))

Test for heterogeneity: not applicable

Test for overall effect z=0.25 p=0.8



Analysis 03.38. Comparison 03 Daily iron-folic acid versus no intervention/placebo, Outcome 38 Postpartum haemorraghe (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 03 Daily iron-folic acid versus no intervention/placebo

Outcome: 38 Postpartum haemorraghe (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Butler 1968	0/51	1/17		100.0	0.12 [0.00, 2.71]
Total (95% CI)	51	17		100.0	0.12 [0.00, 2.71]

Total events: 0 (Treatment (daily)), 1 (Control (no iron))

Test for heterogeneity: not applicable

Test for overall effect z=1.34 p=0.2

Analysis 03.40. Comparison 03 Daily iron-folic acid versus no intervention/placebo, Outcome 40 Haemoglobin concentration within one month postpartum (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 03 Daily iron-folic acid versus no intervention/placebo

Outcome: 40 Haemoglobin concentration within one month postpartum (ALL)

Study	Treatment (daily) N	Mean(SD)	Control (no iron) N	Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Taylor 1982	21	124.40 (11.20)	24	114.00 (10.50)		100.0	10.40 [4.03, 16.77]
Total (95% CI)	21		24			100.0	10.40 [4.03, 16.77]
Test for heterogeneity: not applicable							
Test for overall effect z=3.20 p=0.001							

Analysis 03.41. Comparison 03 Daily iron-folic acid versus no intervention/placebo, Outcome 41 Severe anaemia at postpartum (Hb less than 80 g/L) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 03 Daily iron-folic acid versus no intervention/placebo

Outcome: 41 Severe anaemia at postpartum (Hb less than 80 g/L) (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× Butler 1968	0/51	0/16		0.0	Not estimable
Total (95% CI)	51	16		0.0	Not estimable
Total events: 0 (Treatment (daily)), 0 (Control (no iron))					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 03.42. Comparison 03 Daily iron-folic acid versus no intervention/placebo, Outcome 42 Moderate anaemia at postpartum (Hb more than 80 g/L and less than 100 g/L) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 03 Daily iron-folic acid versus no intervention/placebo

Outcome: 42 Moderate anaemia at postpartum (Hb more than 80 g/L and less than 100 g/L) (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× Butler 1968	0/51	0/16		0.0	Not estimable
Total (95% CI)	51	16		0.0	Not estimable
Total events: 0 (Treatment (daily)), 0 (Control (no iron))					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 03.50. Comparison 03 Daily iron-folic acid versus no intervention/placebo, Outcome 50 Placental abruption (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 03 Daily iron-folic acid versus no intervention/placebo

Outcome: 50 Placental abruption (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Willoughby 1967	12/2157	0/706		100.0	8.19 [0.49, 138.16]
Total (95% CI)	2157	706		100.0	8.19 [0.49, 138.16]
Total events: 12 (Treatment (daily)), 0 (Control (no iron))					
Test for heterogeneity: not applicable					
Test for overall effect z=1.46 p=0.1					

Analysis 03.52. Comparison 03 Daily iron-folic acid versus no intervention/placebo, Outcome 52 Pre-eclampsia (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 03 Daily iron-folic acid versus no intervention/placebo

Outcome: 52 Pre-eclampsia (ALL)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Taylor 1982	1/24	0/24		100.0	3.00 [0.13, 70.16]
Total (95% CI)	24	24		100.0	3.00 [0.13, 70.16]
Total events: 1 (Treatment (daily)), 0 (Control (no iron))					
Test for heterogeneity: not applicable					
Test for overall effect z=0.68 p=0.5					

Analysis 03.92. Comparison 03 Daily iron-folic acid versus no intervention/placebo, Outcome 92 Oedema during pregnancy (not prespecified)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 03 Daily iron-folic acid versus no intervention/placebo

Outcome: 92 Oedema during pregnancy (not prespecified)

Study	Treatment (daily) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Butler 1968	27/51	3/16		100.0	2.82 [0.99, 8.09]
Total (95% CI)	51	16		100.0	2.82 [0.99, 8.09]
Total events: 27 (Treatment (daily)), 3 (Control (no iron))					
Test for heterogeneity: not applicable					
Test for overall effect z=1.93 p=0.05					

Analysis 03.93. Comparison 03 Daily iron-folic acid versus no intervention/placebo, Outcome 93 Cesarean delivery (not prespecified)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 03 Daily iron-folic acid versus no intervention/placebo

Outcome: 93 Cesarean delivery (not prespecified)

Study	Treatment (any iron) n/N	Control (no iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Barton 1994	4/53	4/44		100.0	0.83 [0.22, 3.13]
Total (95% CI)	53	44		100.0	0.83 [0.22, 3.13]
Total events: 4 (Treatment (any iron)), 4 (Control (no iron))					
Test for heterogeneity: not applicable					
Test for overall effect z=0.27 p=0.8					

Analysis 03.97. Comparison 03 Daily iron-folic acid versus no intervention/placebo, Outcome 97 Haemoglobin concentration at 4-8 weeks postpartum (not prespecified)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 03 Daily iron-folic acid versus no intervention/placebo

Outcome: 97 Haemoglobin concentration at 4-8 weeks postpartum (not prespecified)

Study	Treatment (daily) N	Mean(SD)	Control (no iron) N	Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Butler 1968	51	139.00 (7.14)	16	138.00 (6.00)		58.0	1.00 [-2.53, 4.53]
Taylor 1982	21	130.30 (4.50)	24	126.90 (9.20)		42.0	3.40 [-0.75, 7.55]
Total (95% CI)	72		40			100.0	2.01 [-0.68, 4.70]
Test for heterogeneity chi-square=0.74 df=1 p=0.39 I^2 =0.0%							
Test for overall effect z=1.46 p=0.1							

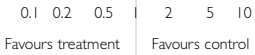
Analysis 04.01. Comparison 04 Intermittent iron-folic acid versus daily iron-folic acid, Outcome 01 Low birthweight (less than 2500 g) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 04 Intermittent iron-folic acid versus daily iron-folic acid

Outcome: 01 Low birthweight (less than 2500 g) (ALL)

Study	Intermittent iron n/N	Control (daily) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Chew 1996a	6/99	8/109		44.9	0.83 [0.30, 2.30]
Chew 1996b	3/35	3/32		20.1	0.91 [0.20, 4.21]
Winichagoon 2003	9/236	4/139		35.0	1.33 [0.42, 4.22]
Total (95% CI)	370	280		100.0	0.99 [0.50, 1.97]
Total events: 18 (Intermittent iron), 15 (Control (daily))					
Test for heterogeneity chi-square=0.37 df=2 p=0.83 I^2 =0.0%					
Test for overall effect z=0.02 p=1					



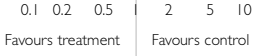
Analysis 04.02. Comparison 04 Intermittent iron-folic acid versus daily iron-folic acid, Outcome 02 Low birthweight (less than 2500 g) (BY SUBGROUPS)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 04 Intermittent iron-folic acid versus daily iron-folic acid

Outcome: 02 Low birthweight (less than 2500 g) (BY SUBGROUPS)

Study	Intermittent iron n/N	Control (daily) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Early gestational age (less than 20 weeks of gestation or pre-pregnancy) at start of supplementation					
Winichagoon 2003	9/236	4/139		100.0	1.33 [0.42, 4.22]
Subtotal (95% CI)	236	139		100.0	1.33 [0.42, 4.22]
Total events: 9 (Intermittent iron), 4 (Control (daily))					
Test for heterogeneity: not applicable					
Test for overall effect z=0.48 p=0.6					
03 Unspecified/mixed gestational age at start of supplementation					
Chew 1996a	6/99	8/109		69.0	0.83 [0.30, 2.30]
Chew 1996b	3/35	3/32		31.0	0.91 [0.20, 4.21]
Subtotal (95% CI)	134	141		100.0	0.85 [0.36, 1.99]
Total events: 9 (Intermittent iron), 11 (Control (daily))					
Test for heterogeneity chi-square=0.01 df=1 p=0.91 I^2 =0.0%					
Test for overall effect z=0.37 p=0.7					
07 Daily low dose (60 mg elemental iron or less)					
Chew 1996a	6/99	8/109		44.9	0.83 [0.30, 2.30]



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Study	Intermittent iron n/N	Control (daily) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Chew 1996b	3/35	3/32		20.1	0.91 [0.20, 4.21]
Winichagoon 2003	9/236	4/139		35.0	1.33 [0.42, 4.22]
Subtotal (95% CI)	370	280		100.0	0.99 [0.50, 1.97]
Total events: 18 (Intermittent iron), 15 (Control (daily))					
Test for heterogeneity chi-square=0.37 df=2 p=0.83 I^2 =0.0%					
Test for overall effect z=0.02 p=1					

Analysis 04.03. Comparison 04 Intermittent iron-folic acid versus daily iron-folic acid, Outcome 03 Birthweight (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 04 Intermittent iron-folic acid versus daily iron-folic acid

Outcome: 03 Birthweight (ALL)

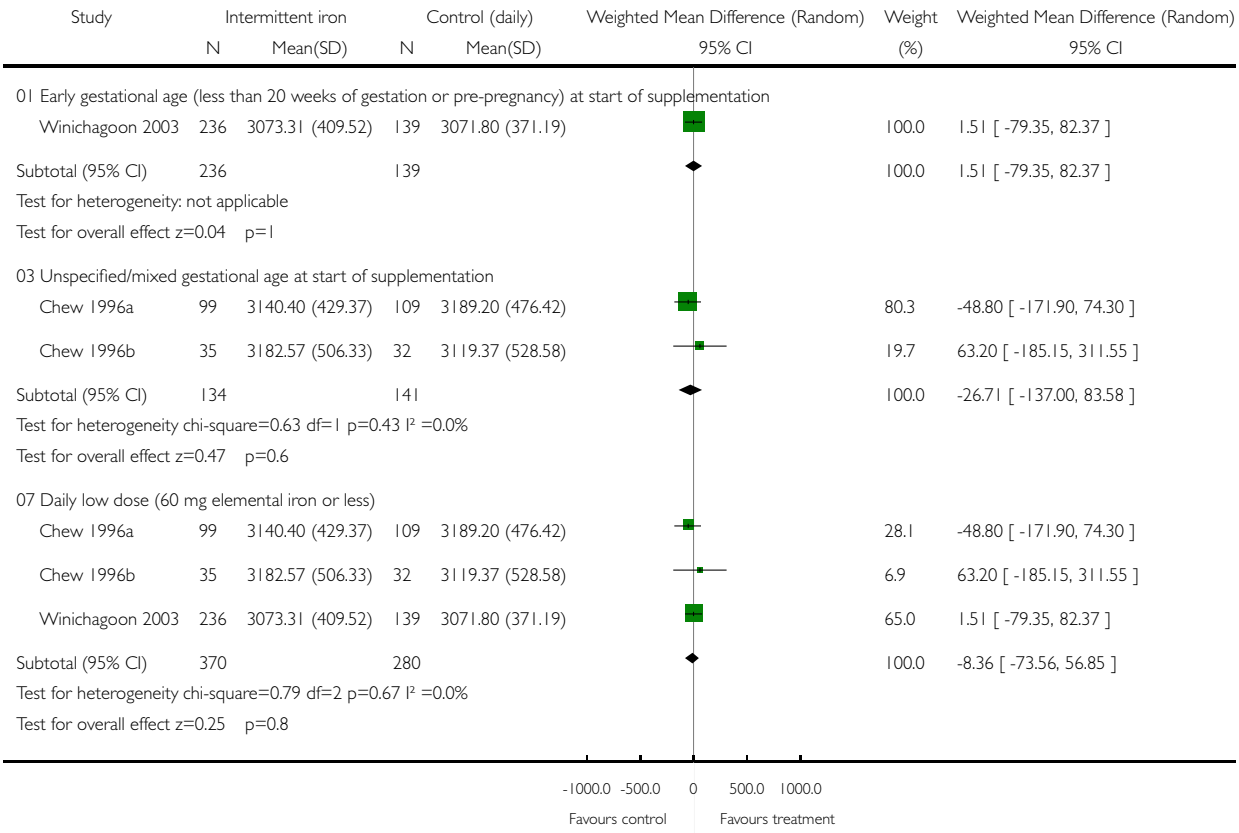
Study	Intermittent iron N	Mean(SD)	Control (daily) N	Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Chew 1996a	99	3140.40 (429.37)	109	3189.20 (476.42)		28.1	-48.80 [-171.90, 74.30]
Chew 1996b	35	3182.57 (506.33)	32	3119.37 (528.58)		6.9	63.20 [-185.15, 311.55]
Winichagoon 2003	236	3073.31 (409.52)	139	3071.80 (371.19)		65.0	1.51 [-79.35, 82.37]
Total (95% CI)	370		280			100.0	-8.36 [-73.56, 56.85]
Test for heterogeneity chi-square=0.79 df=2 p=0.67 I^2 =0.0%							
Test for overall effect z=0.25 p=0.8							

Analysis 04.04. Comparison 04 Intermittent iron-folic acid versus daily iron-folic acid, Outcome 04 Birthweight (BY SUBGROUPS)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 04 Intermittent iron-folic acid versus daily iron-folic acid

Outcome: 04 Birthweight (BY SUBGROUPS)

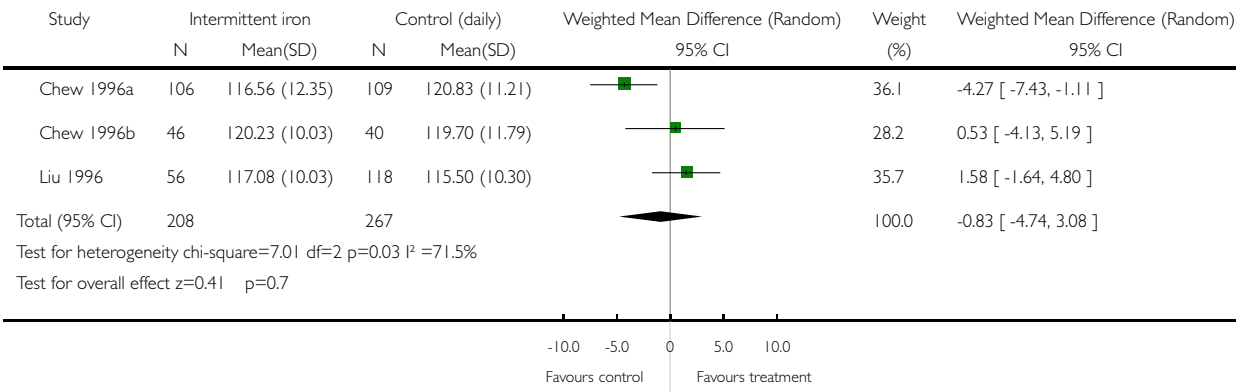


Analysis 04.07. Comparison 04 Intermittent iron-folic acid versus daily iron-folic acid, Outcome 07 Haemoglobin concentration at term (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 04 Intermittent iron-folic acid versus daily iron-folic acid

Outcome: 07 Haemoglobin concentration at term (ALL)

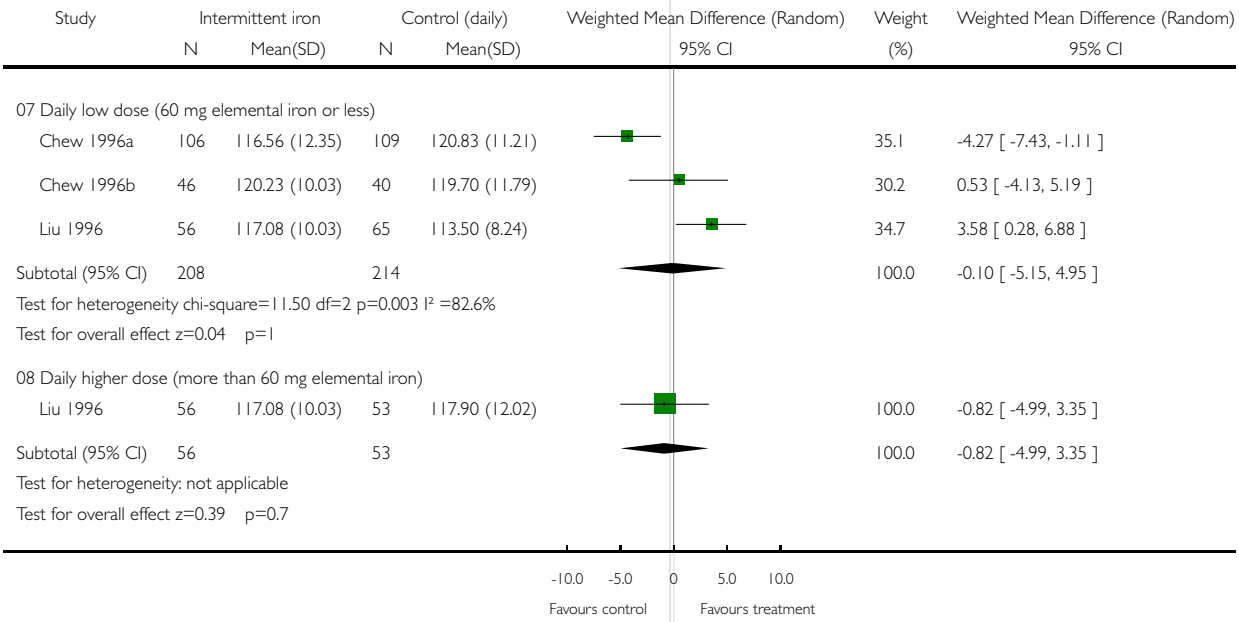


Analysis 04.08. Comparison 04 Intermittent iron-folic acid versus daily iron-folic acid, Outcome 08 Haemoglobin concentration at term (BY SUBGROUPS)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 04 Intermittent iron-folic acid versus daily iron-folic acid

Outcome: 08 Haemoglobin concentration at term (BY SUBGROUPS)



Analysis 04.09. Comparison 04 Intermittent iron-folic acid versus daily iron-folic acid, Outcome 09 Anaemia at term (Hb < 110 g/L) (not prespecified)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 04 Intermittent iron-folic acid versus daily iron-folic acid

Outcome: 09 Anaemia at term (Hb < 110 g/L) (not prespecified)

Study	Intermittent iron n/N	Control (daily) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Chew 1996a	30/106	19/109		44.3	1.62 [0.98, 2.70]
Chew 1996b	8/46	6/40		16.7	1.16 [0.44, 3.06]
Liu 1996	13/56	32/118		39.0	0.86 [0.49, 1.50]
Total (95% CI)	208	267		100.0	1.20 [0.78, 1.83]

Total events: 51 (Intermittent iron), 57 (Control (daily))

Test for heterogeneity chi-square=2.75 df=2 p=0.25 I^2 =27.4%

Test for overall effect z=0.82 p=0.4

Analysis 04.10. Comparison 04 Intermittent iron-folic acid versus daily iron-folic acid, Outcome 10 Haemoconcentration at term (Hb more than 130 g/L) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 04 Intermittent iron-folic acid versus daily iron-folic acid

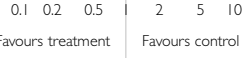
Outcome: 10 Haemoconcentration at term (Hb more than 130 g/L) (ALL)

Study	Intermittent iron n/N	Control (daily) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Chew 1996a	14/106	24/109		51.1	0.60 [0.33, 1.10]
Chew 1996b	8/46	4/40		25.4	1.74 [0.57, 5.35]
Liu 1996	4/56	7/118		23.5	1.20 [0.37, 3.94]
Total (95% CI)	208	267		100.0	0.93 [0.47, 1.82]

Total events: 26 (Intermittent iron), 35 (Control (daily))

Test for heterogeneity chi-square=3.16 df=2 p=0.21 I^2 =36.8%

Test for overall effect z=0.22 p=0.8

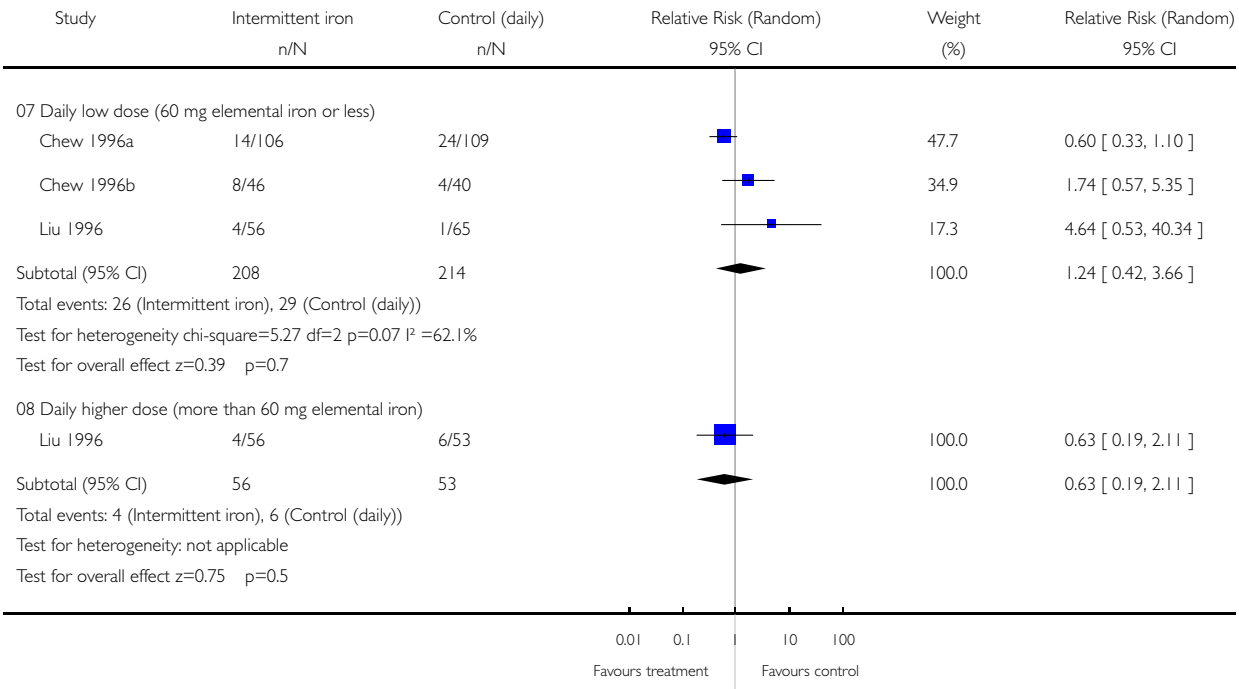


Analysis 04.11. Comparison 04 Intermittent iron-folic acid versus daily iron-folic acid, Outcome 11 Haemoconcentration at term (Hb more than 130 g/L) (BY SUBGROUPS)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 04 Intermittent iron-folic acid versus daily iron-folic acid

Outcome: 11 Haemoconcentration at term (Hb more than 130 g/L) (BY SUBGROUPS)



Analysis 04.12. Comparison 04 Intermittent iron-folic acid versus daily iron-folic acid, Outcome 12 Haemoconcentration during second or third trimester (Hb more than 130 g/L) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 04 Intermittent iron-folic acid versus daily iron-folic acid

Outcome: 12 Haemoconcentration during second or third trimester (Hb more than 130 g/L) (ALL)

Study	Intermittent iron n/N	Control (daily) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Ekstrom 2002	6/87	23/79		22.7	0.24 [0.10, 0.55]
Liu 1996	15/89	32/162		28.5	0.85 [0.49, 1.49]
× Ridwan 1996	0/33	0/32		0.0	Not estimable
Robinson 1998	8/187	35/192		24.8	0.23 [0.11, 0.49]
Winichagoon 2003	10/107	12/63		24.0	0.49 [0.23, 1.07]
Total (95% CI)	503	528		100.0	0.41 [0.21, 0.80]
Total events: 39 (Intermittent iron), 102 (Control (daily))					
Test for heterogeneity chi-square=10.51 df=3 p=0.01 I^2 =71.5%					
Test for overall effect z=2.62 p=0.009					

Analysis 04.13. Comparison 04 Intermittent iron-folic acid versus daily iron-folic acid, Outcome 13 Haemoconcentration during second or third trimester (Hb more than 130 g/L) (BY SUBGROUPS)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 04 Intermittent iron-folic acid versus daily iron-folic acid

Outcome: 13 Haemoconcentration during second or third trimester (Hb more than 130 g/L) (BY SUBGROUPS)

Study	Intermittent iron n/N	Control (daily) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Early gestational age (less than 20 weeks of gestation or pre-pregnancy) at start of supplementation					
Winichagoon 2003	10/107	12/63		100.0	0.49 [0.23, 1.07]
Subtotal (95% CI)	107	63		100.0	0.49 [0.23, 1.07]
Total events: 10 (Intermittent iron), 12 (Control (daily))					
Test for heterogeneity: not applicable					
Test for overall effect z=1.79 p=0.07					
02 Late gestational age (20 weeks or more of gestation) at start of supplementation					
Ekstrom 2002	6/87	23/79		100.0	0.24 [0.10, 0.55]
Subtotal (95% CI)	87	79		100.0	0.24 [0.10, 0.55]
Total events: 6 (Intermittent iron), 23 (Control (daily))					
Test for heterogeneity: not applicable					
Test for overall effect z=3.34 p=0.0008					

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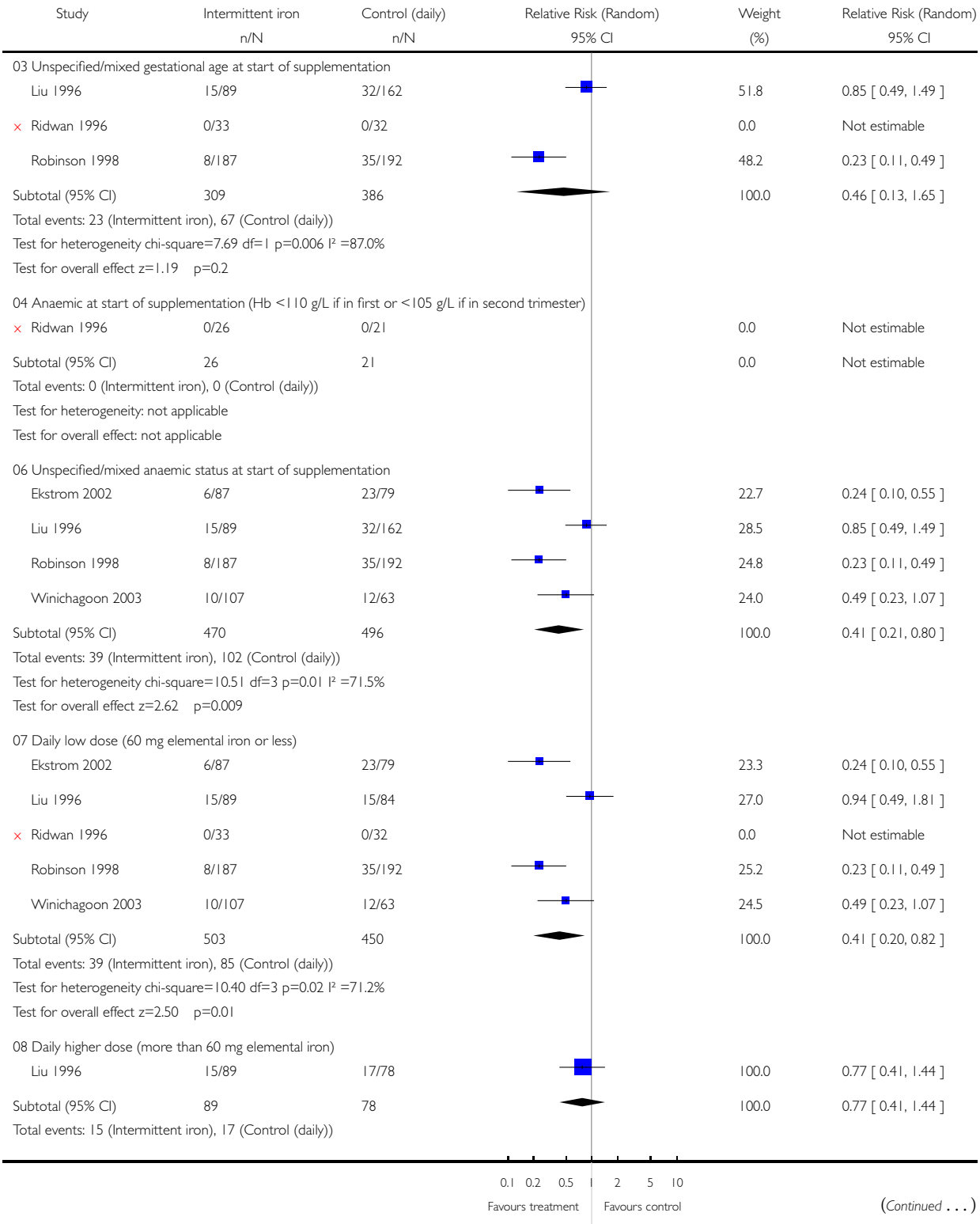

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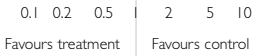
Study	Intermittent iron n/N	Control (daily) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Test for heterogeneity: not applicable					
Test for overall effect z=0.81 p=0.4					



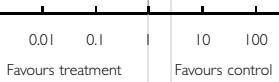
Analysis 04.16. Comparison 04 Intermittent iron-folic acid versus daily iron-folic acid, Outcome 16 Iron deficiency anaemia at term (based on two or more indicators) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 04 Intermittent iron-folic acid versus daily iron-folic acid

Outcome: 16 Iron deficiency anaemia at term (based on two or more indicators) (ALL)

Study	Intermittent iron n/N	Control (daily) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Liu 1996	1/50	3/106		100.0	0.71 [0.08, 6.63]
Total (95% CI)	50	106		100.0	0.71 [0.08, 6.63]
Total events: 1 (Intermittent iron), 3 (Control (daily))					
Test for heterogeneity: not applicable					
Test for overall effect z=0.30 p=0.8					



Analysis 04.18. Comparison 04 Intermittent iron-folic acid versus daily iron-folic acid, Outcome 18 Side-effects (any) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 04 Intermittent iron-folic acid versus daily iron-folic acid

Outcome: 18 Side-effects (any) (ALL)

Study	Intermittent iron n/N	Control (daily) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Chew 1996a	55/106	70/109		21.4	0.81 [0.64, 1.02]
Chew 1996b	42/46	31/40		22.0	1.18 [0.97, 1.42]
Ekstrom 2002	53/86	53/86		21.3	1.00 [0.79, 1.27]
Liu 1996	7/117	43/120		12.3	0.17 [0.08, 0.36]
Robinson 1998	19/156	14/145		13.9	1.26 [0.66, 2.42]
Young 2000	6/104	9/112		9.1	0.72 [0.26, 1.95]
Total (95% CI)	615	612		100.0	0.80 [0.54, 1.17]

Total events: 182 (Intermittent iron), 220 (Control (daily))

Test for heterogeneity chi-square=36.34 df=5 p=<0.0001 I^2 =86.2%

Test for overall effect z=1.15 p=0.2

Analysis 04.19. Comparison 04 Intermittent iron-folic acid versus daily iron-folic acid, Outcome 19 Side-effects (any) (BY SUBGROUPS)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 04 Intermittent iron-folic acid versus daily iron-folic acid

Outcome: 19 Side-effects (any) (BY SUBGROUPS)

Study	Intermittent iron n/N	Control (daily) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
02 Late gestational age (20 weeks or more of gestation) at start of supplementation					
Ekstrom 2002	53/86	53/86		100.0	1.00 [0.79, 1.27]
Subtotal (95% CI)	86	86		100.0	1.00 [0.79, 1.27]

Total events: 53 (Intermittent iron), 53 (Control (daily))

Test for heterogeneity: not applicable

Test for overall effect z=0.00 p=1

03 Unspecified/mixed gestational age at start of supplementation					
Chew 1996a	55/106	70/109		24.6	0.81 [0.64, 1.02]
Chew 1996b	42/46	31/40		25.0	1.18 [0.97, 1.42]
Liu 1996	7/117	43/120		17.4	0.17 [0.08, 0.36]

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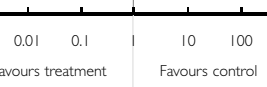
Study	Intermittent iron n/N	Control (daily) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Robinson 1998	19/156	14/145		19.0	1.26 [0.66, 2.42]
Young 2000	6/104	9/112		14.0	0.72 [0.26, 1.95]
Subtotal (95% CI)	529	526		100.0	0.72 [0.42, 1.26]
Total events: 129 (Intermittent iron), 167 (Control (daily))					
Test for heterogeneity chi-square=39.39 df=4 p=<0.0001 I^2 =89.8%					
Test for overall effect z=1.15 p=0.2					
07 Daily low dose (60 mg elemental iron or less)					
Chew 1996a	55/106	70/109		25.2	0.81 [0.64, 1.02]
Chew 1996b	42/46	31/40		27.0	1.18 [0.97, 1.42]
Ekstrom 2002	53/86	53/86		25.0	1.00 [0.79, 1.27]
Liu 1996	7/117	12/64		6.8	0.32 [0.13, 0.77]
Robinson 1998	19/156	14/145		10.5	1.26 [0.66, 2.42]
Young 2000	6/104	9/112		5.5	0.72 [0.26, 1.95]
Subtotal (95% CI)	615	556		100.0	0.92 [0.71, 1.19]
Total events: 182 (Intermittent iron), 189 (Control (daily))					
Test for heterogeneity chi-square=15.18 df=5 p=0.010 I^2 =67.1%					
Test for overall effect z=0.61 p=0.5					
08 Daily higher dose (more than 60 mg elemental iron)					
Liu 1996	7/117	31/56		100.0	0.11 [0.05, 0.23]
Subtotal (95% CI)	117	56		100.0	0.11 [0.05, 0.23]
Total events: 7 (Intermittent iron), 31 (Control (daily))					
Test for heterogeneity: not applicable					
Test for overall effect z=5.77 p<0.00001					



Analysis 04.20. Comparison 04 Intermittent iron-folic acid versus daily iron-folic acid, Outcome 20 Very low birthweight (less than 1500 g) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 04 Intermittent iron-folic acid versus daily iron-folic acid

Outcome: 20 Very low birthweight (less than 1500 g) (ALL)

Study	Intermittent iron n/N	Control (daily) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× Chew 1996a	0/106	0/109		0.0	Not estimable
× Chew 1996b	0/35	0/32		0.0	Not estimable
× Winichagoon 2003	0/236	0/139		0.0	Not estimable
Subtotal (95% CI)	377	280		0.0	Not estimable
Total events: 0 (Intermittent iron), 0 (Control (daily))					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 04.27. Comparison 04 Intermittent iron-folic acid versus daily iron-folic acid, Outcome 27 Infant ferritin concentration at 6 months (ug/L) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 04 Intermittent iron-folic acid versus daily iron-folic acid

Outcome: 27 Infant ferritin concentration at 6 months (ug/L) (ALL)

Study	Intermittent iron N	Mean(SD)	Control (daily) N	Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Winichagoon 2003	43	3.95 (0.09)	45	3.86 (0.08)		100.0	0.09 [0.05, 0.13]
Total (95% CI)	43		45			100.0	0.09 [0.05, 0.13]
Test for heterogeneity: not applicable							
Test for overall effect z=4.95 p<0.00001							

Analysis 04.31. Comparison 04 Intermittent iron-folic acid versus daily iron-folic acid, Outcome 31 Severe anaemia at term (Hb less than 70 g/L) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 04 Intermittent iron-folic acid versus daily iron-folic acid

Outcome: 31 Severe anaemia at term (Hb less than 70 g/L) (ALL)

Study	Intermittent iron n/N	Control (daily) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× Chew 1996a	0/106	0/109		0.0	Not estimable
× Chew 1996b	0/46	0/40		0.0	Not estimable
× Liu 1996	0/56	0/118		0.0	Not estimable
Total (95% CI)	208	267		0.0	Not estimable

Total events: 0 (Intermittent iron), 0 (Control (daily))

Test for heterogeneity: not applicable

Test for overall effect: not applicable

Analysis 04.32. Comparison 04 Intermittent iron-folic acid versus daily iron-folic acid, Outcome 32 Moderate anaemia at term (Hb more than 70g/L and less than 90 g/L) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 04 Intermittent iron-folic acid versus daily iron-folic acid

Outcome: 32 Moderate anaemia at term (Hb more than 70g/L and less than 90 g/L) (ALL)

Study	Intermittent iron n/N	Control (daily) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Chew 1996a	1/106	1/109		100.0	1.03 [0.07, 16.23]
× Chew 1996b	0/46	0/40		0.0	Not estimable
× Liu 1996	0/56	0/118		0.0	Not estimable
Total (95% CI)	208	267		100.0	1.03 [0.07, 16.23]

Total events: 1 (Intermittent iron), 1 (Control (daily))

Test for heterogeneity: not applicable

Test for overall effect z=0.02 p=1

Analysis 04.33. Comparison 04 Intermittent iron-folic acid versus daily iron-folic acid, Outcome 33 Severe anaemia at any time during second and third trimester (Hb less than 70 g/L) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 04 Intermittent iron-folic acid versus daily iron-folic acid

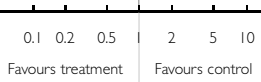
Outcome: 33 Severe anaemia at any time during second and third trimester (Hb less than 70 g/L) (ALL)

Study	Intermittent iron n/N	Control (daily) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× Ekstrom 2002	0/87	0/79		0.0	Not estimable
× Liu 1996	0/61	0/110		0.0	Not estimable
× Ridwan 1996	0/33	0/32		0.0	Not estimable
× Robinson 1998	0/187	0/192		0.0	Not estimable
× Winichagoon 2003	0/238	0/141		0.0	Not estimable
Total (95% CI)	606	554		0.0	Not estimable

Total events: 0 (Intermittent iron), 0 (Control (daily))

Test for heterogeneity: not applicable

Test for overall effect: not applicable



Analysis 04.34. Comparison 04 Intermittent iron-folic acid versus daily iron-folic acid, Outcome 34 Moderate anaemia at any time during second or third trimester (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 04 Intermittent iron-folic acid versus daily iron-folic acid

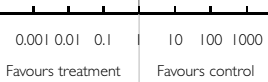
Outcome: 34 Moderate anaemia at any time during second or third trimester (ALL)

Study	Intermittent iron n/N	Control (daily) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Ekstrom 2002	9/87	1/79		37.9	8.17 [1.06, 63.07]
Liu 1996	1/89	4/162		35.9	0.46 [0.05, 4.01]
× Ridwan 1996	0/33	0/32		0.0	Not estimable
Robinson 1998	3/187	0/192		26.1	7.19 [0.37, 138.18]
× Winichagoon 2003	0/107	0/63		0.0	Not estimable
Total (95% CI)	503	528		100.0	2.80 [0.39, 19.88]

Total events: 13 (Intermittent iron), 5 (Control (daily))

Test for heterogeneity chi-square=4.15 df=2 p=0.13 I^2 =51.9%

Test for overall effect z=1.03 p=0.3



Analysis 04.41. Comparison 04 Intermittent iron-folic acid versus daily iron-folic acid, Outcome 41 Severe anaemia at postpartum (Hb less than 80 g/L) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 04 Intermittent iron-folic acid versus daily iron-folic acid

Outcome: 41 Severe anaemia at postpartum (Hb less than 80 g/L) (ALL)

Study	Intermittent iron n/N	Control (daily) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Ekstrom 2002	1/91	2/78		100.0	0.43 [0.04, 4.64]
Total (95% CI)	91	78		100.0	0.43 [0.04, 4.64]
Total events: 1 (Intermittent iron), 2 (Control (daily))					
Test for heterogeneity: not applicable					
Test for overall effect z=0.70 p=0.5					

Analysis 04.42. Comparison 04 Intermittent iron-folic acid versus daily iron-folic acid, Outcome 42 Moderate anaemia at postpartum (Hb more than 80 g/L and less than 100 g/L) (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 04 Intermittent iron-folic acid versus daily iron-folic acid

Outcome: 42 Moderate anaemia at postpartum (Hb more than 80 g/L and less than 100 g/L) (ALL)

Study	Intermittent iron n/N	Control (daily) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Ekstrom 2002	4/91	3/78		100.0	1.14 [0.26, 4.95]
Total (95% CI)	91	78		100.0	1.14 [0.26, 4.95]
Total events: 4 (Intermittent iron), 3 (Control (daily))					
Test for heterogeneity: not applicable					
Test for overall effect z=0.18 p=0.9					

Analysis 04.43. Comparison 04 Intermittent iron-folic acid versus daily iron-folic acid, Outcome 43 Diarrhea (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 04 Intermittent iron-folic acid versus daily iron-folic acid

Outcome: 43 Diarrhea (ALL)

Study	Intermittent iron n/N	Control (daily) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Chew 1996a	4/106	9/109		25.9	0.46 [0.15, 1.44]
Chew 1996b	20/46	8/40		38.6	2.17 [1.08, 4.39]
Ekstrom 2002	13/86	9/86		35.6	1.44 [0.65, 3.20]
Total (95% CI)	238	235		100.0	1.26 [0.56, 2.81]

Total events: 37 (Intermittent iron), 26 (Control (daily))

Test for heterogeneity chi-square=5.22 df=2 p=0.07 I^2 =61.7%

Test for overall effect z=0.56 p=0.6

Analysis 04.44. Comparison 04 Intermittent iron-folic acid versus daily iron-folic acid, Outcome 44 Constipation (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 04 Intermittent iron-folic acid versus daily iron-folic acid

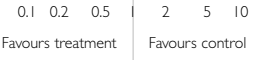
Outcome: 44 Constipation (ALL)

Study	Intermittent iron n/N	Control (daily) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Chew 1996a	5/106	13/109		24.5	0.40 [0.15, 1.07]
Chew 1996b	27/46	10/40		34.1	2.35 [1.30, 4.23]
Ekstrom 2002	53/86	51/86		41.3	1.04 [0.82, 1.32]
Total (95% CI)	238	235		100.0	1.08 [0.51, 2.29]

Total events: 85 (Intermittent iron), 74 (Control (daily))

Test for heterogeneity chi-square=10.63 df=2 p=0.005 I^2 =81.2%

Test for overall effect z=0.21 p=0.8



Analysis 04.45. Comparison 04 Intermittent iron-folic acid versus daily iron-folic acid, Outcome 45 Nausea (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 04 Intermittent iron-folic acid versus daily iron-folic acid

Outcome: 45 Nausea (ALL)

Study	Intermittent iron n/N	Control (daily) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Chew 1996a	4/106	6/109		21.9	0.69 [0.20, 2.36]
Chew 1996b	2/46	4/40		14.0	0.43 [0.08, 2.25]
Ekstrom 2002	15/86	12/86		43.5	1.25 [0.62, 2.51]
Robinson 1998	3/156	9/145		20.6	0.31 [0.09, 1.12]
Total (95% CI)	394	380		100.0	0.71 [0.36, 1.40]

Total events: 24 (Intermittent iron), 31 (Control (daily))

Test for heterogeneity chi-square=4.30 df=3 p=0.23 I^2 =30.3%

Test for overall effect z=1.00 p=0.3

Analysis 04.46. Comparison 04 Intermittent iron-folic acid versus daily iron-folic acid, Outcome 46 Heartburn (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 04 Intermittent iron-folic acid versus daily iron-folic acid

Outcome: 46 Heartburn (ALL)

Study	Intermittent iron n/N	Control (daily) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Chew 1996a	6/106	23/109		30.3	0.27 [0.11, 0.63]
Chew 1996b	35/46	24/40		38.2	1.27 [0.94, 1.71]
Ekstrom 2002	12/86	10/86		31.5	1.20 [0.55, 2.63]
Total (95% CI)	238	235		100.0	0.78 [0.29, 2.06]

Total events: 53 (Intermittent iron), 57 (Control (daily))

Test for heterogeneity chi-square=13.97 df=2 p=0.0009 I^2 =85.7%

Test for overall effect z=0.50 p=0.6

Analysis 04.47. Comparison 04 Intermittent iron-folic acid versus daily iron-folic acid, Outcome 47 Vomiting (ALL)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 04 Intermittent iron-folic acid versus daily iron-folic acid

Outcome: 47 Vomiting (ALL)

Study	Intermittent iron n/N	Control (daily) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Chew 1996a	15/106	12/109		28.5	1.29 [0.63, 2.62]
Chew 1996b	19/46	11/40		38.7	1.50 [0.82, 2.76]
Ekstrom 2002	18/86	8/86		23.8	2.25 [1.03, 4.90]
Robinson 1998	10/156	3/145		8.9	3.10 [0.87, 11.04]
Total (95% CI)	394	380		100.0	1.69 [1.15, 2.47]
Total events: 62 (Intermittent iron), 34 (Control (daily))					
Test for heterogeneity chi-square=2.14 df=3 p=0.54 I^2 =0.0%					
Test for overall effect z=2.70 p=0.007					

Analysis 04.68. Comparison 04 Intermittent iron-folic acid versus daily iron-folic acid, Outcome 68 Ln (serum ferritin concentration) 4-8 wk postpartum (not prespecified)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 04 Intermittent iron-folic acid versus daily iron-folic acid

Outcome: 68 Ln (serum ferritin concentration) 4-8 wk postpartum (not prespecified)

Study	Intermittent iron N	Mean(SD)	Control (daily) N	Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Ekstrom 2002	88	3.75 (1.01)	72	3.88 (0.85)		100.0	-0.13 [-0.42, 0.16]
Total (95% CI)	88		72			100.0	-0.13 [-0.42, 0.16]
Test for heterogeneity: not applicable							
Test for overall effect z=0.88 p=0.4							

Analysis 04.70. Comparison 04 Intermittent iron-folic acid versus daily iron-folic acid, Outcome 70 Low serum ferritin concentration at post partum (4-8 wk) (not prespecified)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 04 Intermittent iron-folic acid versus daily iron-folic acid

Outcome: 70 Low serum ferritin concentration at post partum (4-8 wk) (not prespecified)

Study	Intermittent iron n/N	Control (daily iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Ekstrom 2002	7/79	5/67		100.0	1.19 [0.40, 3.57]
Total (95% CI)	79	67		100.0	1.19 [0.40, 3.57]
Total events: 7 (Intermittent iron), 5 (Control (daily iron))					
Test for heterogeneity: not applicable					
Test for overall effect z=0.31 p=0.8					

Analysis 04.71. Comparison 04 Intermittent iron-folic acid versus daily iron-folic acid, Outcome 71 High serum transferrin receptors at 6 weeks postpartum (not prespecified)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 04 Intermittent iron-folic acid versus daily iron-folic acid

Outcome: 71 High serum transferrin receptors at 6 weeks postpartum (not prespecified)

Study	Intermittent iron n/N	Control (daily iron) n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Ekstrom 2002	13/79	16/67		100.0	0.69 [0.36, 1.33]
Total (95% CI)	79	67		100.0	0.69 [0.36, 1.33]
Total events: 13 (Intermittent iron), 16 (Control (daily iron))					
Test for heterogeneity: not applicable					
Test for overall effect z=1.11 p=0.3					

Analysis 04.97. Comparison 04 Intermittent iron-folic acid versus daily iron-folic acid, Outcome 97 Haemoglobin concentration at 4-8 weeks postpartum (not prespecified)

Review: Effects of routine oral iron supplementation with or without folic acid for women during pregnancy

Comparison: 04 Intermittent iron-folic acid versus daily iron-folic acid

Outcome: 97 Haemoglobin concentration at 4-8 weeks postpartum (not prespecified)

Study	Intermittent iron		Control (daily iron)		Weighted Mean Difference (Random)	Weight	Weighted Mean Difference (Random)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Ekstrom 2002	79	130.00 (18.00)	67	128.00 (18.00)		100.0	2.00 [-3.86, 7.86]
Total (95% CI)	79		67			100.0	2.00 [-3.86, 7.86]
Test for heterogeneity: not applicable							
Test for overall effect z=0.67 p=0.5