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Treatment for women with postpartum iron deficiency anaemia (Review)

Dodd JM, Dare MR, Middleton P

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[Intervention Review]

Treatment for women with postpartum iron deficiency anaemia

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ABSTRACT

Background

Postpartum anaemia is associated with breathlessness, tiredness, palpitations and maternal infections. Blood transfusions or iron supplementation have been used in the treatment of iron deficiency anaemia. Recently other anaemia treatments, in particular erythropoietin therapy, have also been used.

Objectives

To assess the clinical effects of treatments for postpartum anaemia, including oral, intravenous or subcutaneous iron/folate supplementation and erythropoietin administration, and blood transfusion.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 May 2004), the Cochrane Central Register of Controlled Trials (*The Cochrane Library*, Issue 1, 2003), MEDLINE (1966 to March 2003), EMBASE (1980 to March 2003), Current Contents and ACP Journal Club (from inception to March 2003). We updated this search on 7 June 2012 and added the results to the awaiting classification section.

Selection criteria

Randomised controlled trials (RCTs) comparing therapy for postpartum iron deficiency anaemia (oral, intravenous or subcutaneous administration of iron, folate, erythropoietin or blood transfusion) with placebo, another treatment or no treatment.

Data collection and analysis

Two reviewers independently assessed trial quality and extracted data.

Main results

Six included RCTs involving 411 women described treatment with erythropoietin or iron as their primary interventions. No RCTs were identified that assessed treatment with blood transfusion. Few outcomes relating to clinical maternal and neonatal factors were reported: studies focused largely on surrogate outcomes such as haematological indices. Overall, the methodological quality of the included RCTs was reasonable; however, their usefulness in this review is restricted by the interventions and outcomes reported.

When compared with iron therapy only, erythropoietin increased the likelihood of lactation at discharge from hospital (1 RCT, n = 40; relative risk (RR) 1.90, 95% confidence interval (CI) 1.21 to 2.98). No apparent effect on need for blood transfusions was found, when erythropoietin plus iron was compared to treatment with iron only (2 RCTs, n = 100; RR 0.20, 95% CI 0.01 to 3.92), although the RCTs may have been of

insufficient size to rule out important clinical differences. Haematological indices (haemoglobin and haemocrit) showed some increases when erythropoietin was compared to iron only, iron and folate, but not when compared with placebo.

Authors' conclusions

There is some limited evidence of favourable outcomes for treatment of postpartum anaemia with erythropoietin. However, most of the available literature focuses on laboratory haematological indices, rather than clinical outcomes. Further high-quality trials assessing the treatment of postpartum anaemia with iron supplementation and blood transfusions are required. Future trials may also examine the significance of the severity of anaemia in relation to treatment, and an iron-rich diet as an intervention.

[Note: The 27 citations in the awaiting classification section of the review may alter the conclusions of the review once assessed.]

PLAIN LANGUAGE SUMMARY

Treatment for women with postpartum iron deficiency anaemia

Erythropoietin, a hormone, may help to treat women who develop anaemia after giving birth, but there may be rare adverse events.

Women with anaemia after childbirth may feel tired and breathless and are at risk of infection. Traditional treatments include iron supplementation and blood transfusion for severe anaemia. A hormone, erythropoietin, may help improve iron levels in the blood and the woman's ability to lactate. However, rare adverse events (damage to red blood cells) have been reported. No studies examined the effects of oral iron supplementation alone, the most common treatment for this type of anaemia, or blood transfusions as treatments for women with anaemia after childbirth. More research, particularly of simple interventions such as oral iron supplementation, is required.

BACKGROUND

Anaemia after the birth of a baby (postpartum anaemia) is a common problem throughout the world and for most women is self limiting, resolving within a week (Atkinson 1994). For some women however, particularly in resource-poor countries, it is a major cause of maternal morbidity (poor health) and mortality (Ekanem 1996; Harrison 1989; Kumar 1989; Rosenfield 1989). In this setting, anaemia may result from inadequate dietary intake, parasitic infection or malaria, and may be exacerbated by the physiological effects of pregnancy and blood loss at the time of birth (WHO 1999). Worldwide, anaemia contributed to approximately 20% of the 515,000 maternal deaths in 1995 (WHO 1999). Anaemia is often associated with other markers on blood testing of low iron stores in the body. During pregnancy most women show a fall in haemoglobin concentration as part of a normal response to pregnancy, where there is an increase in plasma and the circulating blood volume, which protects the woman from the blood loss associated with birth. The generally accepted threshold for anaemia in nonpregnant women is a haemoglobin concentration of less than 12 g/dL (WHO 2001). However, it should be noted that this is a value statistically derived from deviations from the population mean, and does not necessarily mean that the woman will have clinical symptoms associated with anaemia (WHO 2001).

Anaemia in the postpartum period may be associated with an increased prevalence of breathlessness, tiredness, palpitations and maternal infections, particularly of the urinary tract (Gibbs 1980; Vora 1998). Such symptoms may cause women to experience difficulty caring for their baby, and may influence the emotional bond the mother has with her baby (Gilbert 1987).

Blood transfusions have been used in the treatment of postpartum anaemia, but there are risks associated with its use. These include reactions secondary to contamination (most commonly with leukocytes or red blood cells), infections (particularly with hepatitis, Human Immunodeficiency Virus (HIV) and cytomegalovirus), fluid overload, allergic reactions, lung injury and air embolism (Klapholz 1990; Naef 1995a; Nolan 1991; Skolnick 1992; Waymack 1990). Immunological reactions may be 'minor' and include fever, chills, urticaria (skin rash and/or hives), or more severe, including acute haemolysis (breakdown of red blood cells) arising from administration of incompatible blood (Naef 1995b). Hepatitis C infection is estimated to occur in approximately 0.1% of all patients who receive blood. The cost of blood transfusions includes extensive costs of screening the blood for infection, storage and sterile administration of blood products, all of which may generate increased financial burden, particularly in under-resourced countries (Ekanem 1996).

Given the risks of blood transfusion and financial constraints, attention has been directed towards other forms of treatment of anaemia such as iron supplements and erythropoietin therapy, both oral (by mouth) and parenteral (by intravenous, intramuscular or subcutaneous injection). Erythropoietin is a hormone that is produced by the body and acts to stimulate red blood cell production.

Oral iron therapy has been used for centuries as a treatment of iron deficiency anaemia (Dudrick 1986), and has been used to treat iron deficiency anaemia during pregnancy (Mahomed 2003). The use of oral iron therapy is associated with some side-effects, including constipation, nausea and gastric irritation. When given by injection, iron has been associated with pain and redness (erythema) at the injection site, and rarely anaphylactic reaction, characterised by itching, redness and in severe cases angioedema (swelling), vascular collapse, bronchospasm (constriction of the airways) and shock. Erythropoietin (EPO) therapy is a relatively recently identified alternative to blood transfusions for the treatment of iron deficiency anaemia, and has been used extensively in the treatment of anaemia associated with renal (kidney) disease. There are a few case reports of EPO therapy in people who have refused blood transfusions on religious grounds, with positive outcomes (Davis 1990), thus highlighting the potential use of EPO in the treatment of other forms of iron deficiency anaemia. Adverse effects of EPO treatment include mild flu-like symptoms such as sore throat, cough, fever, muscle pains and weakness, headache and fatigue. Uncommon, but more serious adverse effects include hypertension (high blood pressure) and seizures and, more recently, pure red-cell aplasia (Casadevall 2002).

OBJECTIVES

To evaluate the effects of treatments for postpartum anaemia, including oral, intramuscular, intravenous or subcutaneous iron/folate supplementation and erythropoietin administration, and blood transfusion.

METHODS

Criteria for considering studies for this review

Types of studies

All published, unpublished and ongoing randomised controlled trials with reported data which compared outcomes for women who were administered therapy for postpartum iron deficiency anaemia with outcomes in women who were given a placebo, another treatment or no treatment.

Types of participants

Women with a haemoglobin value of less than 12 g/dl (WHO 2001) up to six weeks after birth.

Types of interventions

The administration of therapy (iron, folate, erythropoietin or blood transfusion) by oral, intravenous, intramuscular or subcutaneous routes for postpartum iron deficiency anaemia when compared with placebo, another treatment or no treatment, started in the first six weeks after birth.

Types of outcome measures

Maternal outcomes

(1) Use of blood transfusion(s) - when the treatment has been with iron, folate or erythropoietin.
(2) Fatigue (as reported by the women - verbalisation of fatigue or lack of energy and inability to maintain usual routines; and as defined by trial authors).
(3) Tolerance for physical load (as defined by the trial authors).
(4) Dyspnoea (as reported by the women - distressful sensation of uncomfortable breathing; and as defined by the trial authors).
(5) Tachypnoea (increase in respiratory rate as defined by trial authors).

(6) Tachycardia (heart rate greater than 100 beats per minute or as defined by trial authors).
(7) Palpitations (as reported by women - pounding or racing of the heart; and as defined by trial authors).
(8) Orthostatic dizziness (as reported by the women - a sensation on standing of faintness and whirling or inability to maintain balance in a standing or seated position; and as defined by trial authors).
(9) Syncope (transient loss of consciousness and postural tone caused by reduced cerebral blood flow, and often preceded by a sensation of light headedness, as defined by trial authors).
(10) Headache (as defined by trial authors).
(11) Not breastfeeding:
(a) at hospital discharge;
(b) six weeks postpartum;
(c) six months postpartum.
(12) Infection up to six weeks postpartum:
(a) urinary tract infection requiring treatment;
(b) endometritis requiring treatment.
(13) Psychological wellbeing (measured by the 'Blues Questionnaire', 'Self-report symptom inventory 90 [SCL-90-R]' or similar questionnaire).

Use of health resources

(1) Length of postnatal hospital stay.
(2) Readmission to hospital after primary hospital discharge.
(3) Costs of treatment:
(a) for the woman;
(b) for the health service.

Maternal satisfaction with care

1. Woman satisfied with care.

Adverse effects of treatment

(1) Thromboembolic complications:
(a) deep venous thrombosis (blood clots in the veins of the leg) requiring treatment;
(b) pulmonary embolism (blood clots in the lung).
(2) Anaphylactic reactions (characterised by itching, angioedema (swelling) and in severe cases, vascular collapse, bronchospasm (constriction of the airways) and shock).
(3) Gastrointestinal symptoms when the treatment is iron supplementation (diarrhoea, constipation, nausea, heartburn and upper abdominal discomfort).
(4) When the intervention has been treatment with erythropoietin: mild flu-like symptoms (sore throat, cough, fever, muscular pains and weakness, chills, respiratory symptoms, headache, and fatigue), hypertension (blood pressure persistently exceeding 140/90 mm Hg), hypertensive encephalopathy (headache, convulsions and coma), seizures (focal or generalised), hyperkalaemia (plasma concentration > 4.5 mmol/L or serum concentration > 4.9 mmol/L) and hyperphosphataemia (> 1.50 mmol/L).
(5) Viral infection - as shown by positive serology on blood testing.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (30 May 2004). We updated this search on 7 June 2012 and added the results to Studies awaiting classification.

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

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

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

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

In addition, we searched the Cochrane Controlled Trials Register (March 2003), MEDLINE (1966 to March 2003), EMBASE (1980 to March 2003), Current Contents and ACP journal club (1991 to March 2003) using the MeSH headings 'anemia', 'postpartum', 'puerperium', 'treatment', 'treatment - outcome', 'therapy', 'drug - therapy', 'transfusion'.

Searching other resources

We also searched the citation lists of relevant publications, review articles and included studies.

We did not apply any language restrictions.

Data collection and analysis

Two reviewers (Jodie Dodd and Marianna Dare) performed the search and selection of trials for inclusion in the review, with discrepancies resolved by discussion. Excluded studies are detailed in the 'Characteristics of excluded studies' table. Included studies were assessed for quality and methodological details without consideration of the results. Data were extracted separately by two of the three authors and double entered. Discrepancies were resolved by discussion. There was no blinding of authorship.

For all included randomised trials, we assigned quality scores for concealment of allocation to each trial, as described in section VI of the Cochrane Reviewers' Handbook (Clarke 2003):
A = adequate;
B = unclear;
C = inadequate;
D = not used.

Completeness of follow up was assessed for each included study as follows:
A = less than 3% of participants excluded;
B = 3% to 9.9% of participants excluded;
C = 10% to 19.9% of participants excluded;
D = 20% or more of the participants excluded;
E = unclear.

For blinding of assessment of outcome:
A = neither the investigator (outcome assessor) nor participant knew or were likely to guess the allocated allotment;
B = either the investigator (outcome assessor) or participant knew the allocation. Or neither knew, but the outcome means that it is likely a significant portion of the participant's allocation could be easily identified;
C = no blinding - investigator (outcome assessor) and participant knew (or were likely to guess) the allocated treatment;
D = unclear.

Descriptive data included the authors, year of publication, setting, country, time span of trial, pretrial calculation of sample size and the number of participants randomised and analysed.

For dichotomous data, results for each study were expressed as relative risks with 95% confidence intervals and combined for meta-analysis with the RevMan Manager software (RevMan 2004). For continuous data we expressed results for each study as weighted mean differences with 95% confidence intervals. We used a random effects model.

We investigated heterogeneity in the data using the I^2 statistic and cautiously explored it using sensitivity analyses (I^2 > 50% was regarded as statistically significant heterogeneity).

Planned subgroup analyses were:

1. dose administered;
2. frequency of administration;
3. duration of treatment;
4. study setting - resource-poor versus resource-rich countries;
5. severity of anaemia at trial entry;
6. concurrent disease at trial entry (including HIV, sickle cell disease, thalassaemia).

We were unable to perform most of the planned subgroup analyses due to the smallnumber of included trials. We explored results associated with route of treatment administration and duration of treatment for some outcomes when iron was compared with erythropoietin (*see* 'Graphs and tables'). Timing of outcome measurement varied across trials. To facilitate analyses, we grouped the results into two measurement periods, reflecting short- and longer-term effects: within the first two weeks after treatment, and between two weeks and six weeks after treatment.

RESULTS

Description of studies

Thirteen studies describing treatment of postpartum anaemia were identified, with seven not meeting the selection criteria. (Twenty-seven reports from an updated search in June 2012 have been added to Studies awaiting classification.) We excluded two trials because of inadequate randomisation (Danko 1990; Huch 1992), one because it did not report on interventions defined as appropriate for inclusion in the review (Osmond 1953), two reported results on women who were not anaemic (Mara 2001; Picha 1975), one combined pregnant and postpartum women with anaemia in the study population (Casparis 1996) and one summarised the results of trials that were reported in included studies (Zimmermann 1995).

The six included randomised controlled trials (RCTs) involved 411 women (Breymann 1996; Breymann 2000; Lebrecht 1995; Makrydimas 1998; Meyer 1995; Zimmermann 1994). Some of the RCTs reported on more than one intervention. Four RCTs compared treatment with erythropoietin and iron to treatment with iron only (Breymann 1996; Breymann 2000; Makrydimas 1998; Lebrecht 1995), one RCT compared treatment with erythropoietin to treatment with placebo (Meyer 1995), two RCTs compared different routes of erythropoietin administration (intravenous versus subcutaneous) (Breymann 1996; Zimmermann 1994), and one RCT compared erythropoietin given as one dose with that given as two doses (Zimmermann 1994). No RCTs were identified that described results of folate therapy or blood transfusion as an intervention.

In Breymann 1996, 300 units/kg of erythropoietin (EPO) were administered to women in the EPO group once, and in Breymann 2000, this dose was administered daily for four days. In Lebrecht 1995, 20,000 units of EPO were given to women as a single dose. In Makrydimas 1998, 200 units/kg of EPO were administered to women in the EPO group daily for 15 days. Meyer 1995 administered 10,000 units of EPO twice. In Zimmermann 1994, two doses of 150 units/kg were compared with a single dose of 300 units/kg of EPO.

All RCTs focused on haematological indices in their results, with limited information regarding clinical outcomes. Of the clinical outcomes described, use of blood transfusions was described by two RCTs (Breymann 2000; Makrydimas 1998), not lactating by one RCT (Makrydimas 1998), thromboembolic complications by two RCTs (Lebrecht 1995; Makrydimas 1998), serious reactions by two RCTs (Breymann 1996; Breymann 2000), and side-effects for erythropoietin by two RCTs (Lebrecht 1995; Zimmermann 1994).

Details of each RCT are given in the 'Characteristics of included studies' table.

Risk of bias in included studies

Three trials reported using sealed envelopes to allocate women to treatment groups (Breymann 1996; Breymann 2000; Zimmermann 1994). The remaining three studies, though stated to be randomised studies, were unclear in their method of concealment of allocation. All six trials were coded B for allocation concealment.

Blinding to intervention for either investigators or women did not appear to have occurred in any of the studies. Insufficient information was provided to determine whether blinding of outcome assessors had occurred in any of the studies.

No losses to follow up were reported, except for Meyer 1995 who described a drop-out rate of over 20% (with no differences in dropout rate between the intervention and control groups).

Effects of interventions

Included studies described treatment with erythropoietin or iron as their primary interventions. Women in both the intervention and control groups received iron supplementation in all studies except one (Meyer 1995). No studies were identified that described treatment with blood transfusion, and for each intervention there were only one or two studies that reported the same outcomes and thus had results that could be combined.

Few of the prespecified outcomes were reported by the studies regarding 'maternal outcomes', 'use of health resources', 'maternal satisfaction with care', and 'side-effects of treatment'.

The remainder of the results reported in the studies were blood indices. While these were not prespecified in the protocol as outcome measures that were of relevance to the population, we decided that to omit haematological outcomes altogether when reporting the results of the review would mean that much of the data reported by the studies would be lost. Thus we have presented the outcomes for the haematological studies as subsidiary outcomes reported by the reviewers in each section. The results are presented in dot point form to allow easier interpretation. The small number of women in the groups studied meant the confidence intervals were wide. Larger groups may have provided statistically significant results. Further details are provided in 'Graphs and tables'.

(1) Any treatment versus placebo

Intravenous (i.v.) erythropoietin (EPO) versus i.v. placebo

Maternal outcomes (see Other data tables)

- For the Blues Questionnaire (used to assess postpartum depression), statistically significant increases were seen for the items 'able to concentrate', ' elated', 'happy', 'confident' and 'calm' when EPO was compared with placebo (Meyer 1995).

Use of health resources

- No data were provided for these outcomes.

Maternal satisfaction with care

- No data were provided for these outcomes.

Adverse effects

- No data were provided for these outcomes.

Subsidiary outcomes - (as reported by the authors, not prespecified by reviewers)

- No significant difference was observed in haemoglobin (weighted mean difference (WMD) 0.40 g/dL 95% confidence interval (CI) -0.26 to 1.06) or haematocrit (WMD 1.60% 95% CI -0.42 to 3.62) within two weeks after treatment (Meyer 1995; 71 women).

(2) EPO versus any other treatment

EPO plus iron versus iron alone

Maternal outcomes

- The relative risk (RR) for needing blood transfusion for EPO plus iron compared with iron only was 0.20; 95% CI 0.01 to 3.92 (100 women in two trials (Breymann 2000; Makrydimas 1998)).
- Women treated with EPO plus iron were more likely to be lactating when discharged from hospital than women treated with iron only (RR 1.90; 95% CI 1.21 to 2.98). This was reported by one trial describing 40 women (Makrydimas 1998).

Use of health resources

- No data were provided for these outcomes.

Maternal satisfaction with care

- No data were provided for these outcomes.

Adverse effects

- No adverse effects of treatment were seen in either the EPO + iron or iron alone groups (no thromboembolic complications reported in two trials (Breymann 2000; Makrydimas 1998; 96 women) and no anaphylactic reactions reported in three trials (Breymann 1996; Breymann 2000; Lebrecht 1995; 186 women).

Subsidiary outcomes (as reported by the authors - not prespecified by reviewers)

Haemoglobin within two weeks after treatment

- No difference was seen in haemoglobin within two weeks after treatment when EPO i.v. + iron was compared with oral or i.v. iron only (WMD 0.45 g/dL 95% CI -0.16 to 1.06; Breymann 1996; 60 women) or with oral and i.v. iron only (WMD 0.40 g/dL 95% CI -0.22 to 1.02; Lebrecht 1995; 36 women); or with i.v. iron (WMD 0.20% increase 95% CI -0.27% to 0.67%; Breymann 2000; 40 women).
- When i.v. EPO + iron was compared with oral iron only, however, there was an increase in haemoglobin (WMD 0.70% increase 95% CI 0.23 to 1.17; Breymann 2000; 40 women).
- When subcutaneous (s.c.) EPO + iron was compared with oral or i.v. iron only, there was a decrease in haemoglobin (-0.55 g/dL 95% CI -0.99 to -0.11; Breymann 1996; 60 women).

Haemoglobin >2 weeks to 6 weeks after treatment

- No differences were seen for EPO + iron versus iron only regardless of route - i.v. EPO + iron compared with oral or i.v. iron only (WMD 0.40 g/dL 95% CI -0.09 to 0.89; Breymann 1996; 60 women); s.c. EPO + iron compared with oral or i.v. iron only (WMD 0.30 g/dL 95% CI -0.34 to 0.94; Breymann 1996; 60 women); or i.v. EPO + iron compared with oral and i.v. iron (WMD 0.40 g/dL 95% CI -0.20 to 1.00).

Haematocrit (%) within 2 weeks after treatment

- Haematocrit values were greater with EPO + iron compared with iron (either i.v. or oral) in Breymann 2000: WMD 2.30% 95% CI 1.89 to 2.71 compared with i.v. iron (40 women) and WMD 3.50% 95% CI 3.19 to 3.81 compared with oral iron (40 women).
- In contrast, no significant difference was seen when EPO + iron was compared with oral and i.v. iron (WMD 1.50% 95% CI -0.38 to 3.38; Lebrecht 1995; 36 women).

Haematocrit (%) between two and six weeks after treatment

- No significant difference was seen when EPO + iron was compared with oral and i.v. iron (WMD 0.10% 95% CI -3.06 to 3.26; Lebrecht 1995; 36 women)

(3) Comparing routes of EPO administration - subcutaneous versus intravenous

Maternal outcomes

- No data were available for these outcomes.

Use of health resources

- No data were available for these outcomes.

Maternal satisfaction

- No data were available for these outcomes.

Adverse effects

- No adverse effects were reported when comparing different routes of erythropoietin administration in Zimmermann 1994 (95 women).

Subsidiary outcomes (as reported by authors, not an outcome prespecified by reviewers)

Haemoglobin (g/dL) within two weeks after treatment:

- No differences were seen between i.v. and s.c. routes within two weeks after treatment (WMD -0.34 g/dL 95% CI -0.94 to 0.26; Breymann 1996; Zimmermann 1994; total of 145 women). However statistically significant heterogeneity was noted in the i.v. versus s.c. comparison when EPO was given as one dose (I^2 = 70.7%). This may have been due to all women in Breymann 1996 receiving iron i.v. whereas in Zimmermann 1994, women received only oral iron supplementation.

Haemoglobin (g/dL) between two weeks to six weeks after treatment:

- Similarly no differences were seen later (WMD 0.02 g/dL 95% CI -0.27 to 0.32; Breymann 1996; Zimmermann 1994; total of 145 women).

Haematocrit (%) within two weeks after treatment:

- No difference was seen in the haematocrit value (WMD -0.48% 95% CI -1.83 to 0.86; Zimmermann 1994; 95 women).

Haematocrit (%) between two weeks to six weeks after treatment:

- Similarly no differences were seen later (WMD -0.72% 95% CI -1.66 to 0.21; Zimmermann 1994; 95 women).

DISCUSSION

The methodological quality of the included studies is generally reasonable; however their usefulness in this review is restricted by the interventions and outcomes reported. There is very limited information relating to clinical outcomes in the included studies, despite extensive reporting of haematological indices.

Laboratory haemoglobin values may not directly reflect the woman's clinical state. It is unclear whether the women involved in the original studies were clinically symptomatic, and treatment of a woman's symptoms would seem more appropriate than treatment determined by an arbitrary level of haemoglobin or values from other haematological indices. A haemoglobin of less than 12 g/dL is a very conservative marker for iron deficiency anaemia, and many women may not experience symptoms (and therefore will not require treatment) at this level. Most studies in the review reported results for women with an haemoglobin of 10 g/dL or less, but did not categorise the severity of anaemia for analysis. Future studies would benefit from further assessment of the results of treatment according to the severity of anaemia.

The availability of blood transfusion and issues related to safety and sterility mean that it has a limited role in treatment for women in low- and middle-income countries. Similarly, erythropoietin is expensive and therefore not a realistic treatment option for those women at greatest risk of postpartum anaemia. Pure red cell aplasia has been reported as a rare adverse effect of erythropoietin, which is thought to be a consequence of antibody formation (Casadevall 2002). One of the companies marketing erythropoietin (as EPREX) has recommended that it should be given intravenously where possible, since this may reduce the risk of antibody formation (AADRB 2002).

As women in resource-poor countries are more likely to suffer morbidity and/or mortality secondary to postpartum anaemia, future trials should address the role of simple and cost-effective strategies to improve clinical outcomes for these women, in particular the role of oral iron therapy.

AUTHORS' CONCLUSIONS

Implications for practice

There is limited evidence for favourable outcomes for treatment of postpartum anaemia with erythropoietin, with small studies suggesting improved lactation, without an increase in side-effects. Haematological indices also appear to be favourably affected by treatment with erythropoietin, although how this relates to clinical practice is uncertain.

Information regarding the route of administration of erythropoietin is poor, as is information relating to outcomes following treatment with iron and blood transfusions. The possibility of rare adverse effects (such as red cell aplasia) needs to be monitored.

Implications for research

Further high quality trials are required that assess the treatment of postpartum anaemia with oral and parental iron and blood transfusions and focus on clinically relevant outcomes such as maternal outcomes, safety and use of health resources. The effectiveness of common interventions such as iron-rich diet should also be assessed.

[Note: The 27 citations in the awaiting classification section of the review may alter the conclusions of the review once assessed.]

ACKNOWLEDGEMENTS

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

Jacci Parsons (Department of Public Health, University of Adelaide) and Professor Crowther (Department of Obstetrics and Gynaecology, University of Adelaide) for their help designing and developing the protocol and the review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Breymann 1996

Methods	Randomised single centre study. Allocation concealment: sealed envelopes.
Participants	90 women. Inclusion criteria: postpartum haemoglobin < 10.0 g/ dL 48-72 h after delivery, normal cardiac and renal function, oral iron substitution during pregnancy. Exclusion criteria: pregnancy anaemia, peripartal infection, peripartal blood transfusion, haematological disease, previous myelosuppressive medications, history of thromboembolism, haemosiderosis, iron intolerance or rheumatoid polyarthritis.
Interventions	Group 1 (n = 30): saccharated iron 100mg, once i.v. Oral iron sulphate (160 mg elemental iron per day) and folic acid 0.7 mg per day for 6 weeks. Group 2 (n = 30): rhEPO 300 U/kg once s.c. Saccharated iron 100 mg once i.v. and oral iron sulphate (160 mg elemental iron per day) and folic acid 0.7 mg per day for 6 weeks. Group 3 (n = 30): rhEPO 300 U/kg once i.v., saccharated iron 100 mg once i.v., oral iron sulphate (160 mg elemental iron per day) and folic acid (0.7 mg/day) for 6 weeks. Treatment started 48-72 h after birth.
Outcomes	Blood samples taken on days 1, 4, 14 and 42 after the start of therapy. Vital signs recorded daily until discharge. Blood indices: haemoglobin, packed cell volume, reticulocyte count, serum iron and transferrin concentrations, serum ferritin concentration, C-reactive protein concentration.
Notes	Some results have been extracted from graphs presented in the paper.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Breymann 2000

Methods	Randomised, placebo-controlled single-centre study.

Breymann 2000 *(Continued)*

	Allocation concealment: sealed envelopes containing numbers allocated to one of three groups.
Participants	60 postpartum women (divided into 3 groups of 20). Inclusion criteria: haemoglobin < 10 g/ dL 24-72 h after delivery. Exclusion criteria: pregnancy anaemia or anaemia prior to delivery, peripartal blood transfusion, anaemia as a result of causes other than blood loss, history of thromboembolism, signs of infection with a rectal temperature > 38.5 degrees, history of seizures, alcohol and/or drug abuse, renal or hepatic dysfunction, previous myelosuppressive medication, haemosiderosis, history of iron intolerance, and rheumatoid polyarthritis.
Interventions	Placebo refers to rhEPO only, all women received iron therapy. Group 1 (n = 20): rhEPO 300 U/kg body weight daily i.v. on days 1-4 and iron sucrose 200 mg i.v. daily. Group 2 (n = 20): rhEPO placebo (saline i.v.) and iron sucrose as per group 1. Group 3 (n = 20); (control): oral elemental iron sulphate (80 mg) and folic acid one hour before meals on an empty stomach.
Outcomes	Blood indices (taken prior to treatment and on days 4, 7 and 14): absolute reticulocyte count, haematocrit and haemoglobin and red cell indices, iron status markers (serum ferritin, iron, transferrin), serum EPO, CRP, vitamin B12 and folic acid levels. Other: vital signs and the incidence and severity of serious or unusual adverse events.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Lebrecht 1995

Methods	Randomised, placebo-controlled single centre study. Allocation concealment: not stated.
Participants	36 women. Inclusion criteria: Hb < 9 g/dL on day two postpartum, after birth of a healthy child at least 38 weeks gestation. Exclusion criteria: anaemia from other causes, caesarean at delivery, cardiovascular illness, history of thromboembolic disease, infection, alcohol or drug dependence, blood transfusions, and renal or hepatic impairment.
Interventions	Group 1 (n = 24): given 20,000 IE rHuEPO i.v.. Group 2 (n = 12): placebo. For both groups, injections were administered on the second day postpartum. Both groups received iron i.v. on day 2, and oral iron for 4 weeks thereafter.
Outcomes	Blood samples taken immediately before therapy and on days 3, 4, 7, 14 and 28. Haemoglobin, haematocrit, erythrocyte count, reticulocytes, WCC, platelets, ferritin, transferrin saturation, and biochemical parameters were measured. On days 2, 7, 14 and 28 a survey regarding quality of life was filled out by participants. On days 2 and 28 the following clinical parameters were analysed: blood pressure, pulse, temperature.
Notes	It is unclear from the text of the article whether the results have been expressed as means and standard deviations, however, for the purpose of this review, we have interpreted the results as means and standard deviations.

Lebrecht 1995 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Makrydimas 1998

Methods	Randomised, single centre study. Allocation concealment: not stated.
Participants	40 women on the first day following birth. Inclusion criteria: Hb levels < 10 g/dl on day 1 postpartum, age 19-44 years, absence of serious illness including pre-eclampsia.
Interventions	Group 1 (n = 20): rHuEPO 200 IU/kg/day s.c. for 15 days, oral iron 200 mg/day for 40 days and folic acid 5 mg/day for 40 days. Group 2 (n = 20): Iron 200 mg/day and folic acid 5 mg/day for (both orally) for 40 days.
Outcomes	Blood samples were taken before birth and on days 1, 3, 5, 10, 15 and 40 postdelivery. Blood indices measured: haemoglobin, haematocrit, platelets, electrolytes, creatinine, serum iron, ferritin, total iron binding capacity, B12, folic acid, liver and renal function tests. Serum EPO levels. Clinical indices: temperature, blood pressure, subjective symptoms (side-effects - flu-like symptoms) and ECG (on days 1, 15 and 40). Ability to lactate and psychological wellbeing were noted.
Notes	Many of the results have been expressed as medians.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Meyer 1995

Methods	Randomized, double-blind, placebo-controlled multicentre study. Allocation concealment: not stated.
Participants	90 (71) women postpartum. Inclusion criteria: women with a haemoglobin of less than 10 g/dl.
Interventions	Intervention referred to rhEPO. Intervention group (n = 35): EPREX 10,000 IU i.v. at 24 hours. Control group (n = 36): placebo i.v. at 24 hours.
Outcomes	On day 5 postpartum the haemoglobin level was measured. Psychopathology was measured using two questionnaires; the "Blues Questionnaire" during the first five consecutive days postpartum and the "SCL-90-R", used on the 5th day postpartum, before discharge from the hospital and at the time of presumed peak of mood changes shortly after delivery.

Meyer 1995 *(Continued)*

Notes	There was a relatively high drop-out rate of more than 20% (number of women analysed was 71). Drop-outs were due to withdrawal of consent or transferral of the child to an intensive care unit. Some data were extracted from graphs.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Zimmermann 1994

Methods	Randomised study. Allocation concealment: sealed envelopes.
Participants	95 women postpartum. Inclusion criteria: Hb < 10 g/dl within 3 days after birth, stable cardiac function and normal renal function (urine output > 1 ml per hour). Exclusion criteria: high BP, pre-eclampsia or eclampsia, fever > 38.0 degrees, peripartum blood transfusions, oncologic or haematologic disease, myelosuppressive medications, history of thromboembolic events, treatment with other cytokines.
Interventions	Group 1 (n = 26): rHuEPO 150 U/kg body weight s.c. once daily for two consecutive days. Group 2 (n = 25): rHuEPO 150 U/kg body weight i.v. once daily for two consecutive days. Group 3 (n = 22): rHuEPO 300 U/kg body weight s.c. once only. Group 4 (n = 22): rHuEPO 300 U/kg body weight i.v. once only. All women received oral iron supplements (80 mg ferrous sulphate) and folic acid (0.35 mg) twice daily, regardless of iron supplementation during pregnancy. Therapy was begun 72 hours after birth at the latest.
Outcomes	Blood was taken at day 0, day 4, day 14 and day 42. Blood indices measured: haemoglobin, haematocrit, platelets, reticulocytes, CRP, ferritin. Clinical measurements: blood pressure, temperature, lactation during the first 5 days.
Notes	Reports results of different concentrations and routes of administration of erythropoietin rather than EPO versus other methods of treatment.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

BP: blood pressure
CRP: C-reactive protein
ECG: electrocardiogram
EPO: erythropoietin
h: hours
Hb: haemoglobin
IU (and IE): international units
i.v.: intravenous
rhEPO or rHuEPO: recombinant human erythropoietin
s.c.: subcutaneous

WCC: white cell count

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

Study	Reason for exclusion
Casparis 1996	Population combined women with anaemia during pregnancy and postpartum anaemia.
Danko 1990	Trial was quasi-randomised.
Huch 1992	Trial was quasi-randomised.
Mara 2001	Population reported in the study included women who were not anaemic.
Osmond 1953	The intervention focuses on crude liver extract, an intervention not prespecified for inclusion.
Picha 1975	The study assessed the usefulness of iron therapy in prevention, not treatment, of postpartum anaemia.
Zimmermann 1995	All three trials reported by the trials are reported in other included studies.

DATA AND ANALYSES

Comparison 1. EPO i.v. versus placebo i.v.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Self-Report Symptom Inventory 90 Items - Revised (SCL-90-R)			Other data	No numeric data
2 Items of the Blues Questionnaire showing statistically significant difference by day 5			Other data	No numeric data
3 Haemoglobin (g/dL) within 2 weeks after treatment	1	71	Mean Difference (IV, Random, 95% CI)	0.40 [-0.26, 1.06]
4 Haematocrit (%) within 2 weeks after treatment	1	71	Mean Difference (IV, Random, 95% CI)	1.60 [-0.42, 3.62]

Analysis 1.1. Comparison 1 EPO i.v. versus placebo i.v., Outcome 1 Self-Report Symptom Inventory 90 Items - Revised (SCL-90-R).

Self-Report Symptom Inventory 90 Items - Revised (SCL-90-R)			
Study	Item number	Erythropoietin	Placebo
Meyer 1995	20 - crying easily	Factor value - 1.4	Factor value - 1.47
Meyer 1995	24 - temper outbursts	Factor value - 0.65	Factor value - 0.61
Meyer 1995	30 - feeling blue	Factor value - 0.8	Factor value - 0.85
Meyer 1995	14 - low in energy	Factor value - 1.10	Factor value - 1.19
Meyer 1995	71 - feeling everything is an effort	Factor value - 0.72	Factor value - 0.80
Meyer 1995			

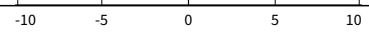
Self-Report Symptom Inventory 90 Items - Revised (SCL-90-R)			
Study	**Item number**	**Erythropoietin**	**Placebo**
Meyer 1995			
Meyer 1995			
Meyer 1995			
Meyer 1995			

Analysis 1.2. Comparison 1 EPO i.v. versus placebo i.v., Outcome 2 Items of the Blues Questionnaire showing statistically significant difference by day 5.

Items of the Blues Questionnaire showing statistically significant difference by day 5			
Study	**Item number**	**Erythropoietin**	**Placebo**
Meyer 1995	Item 3 - able to concentrate	% yes - 40	% yes - 31
Meyer 1995	Item 5 - elated	% yes - 20	% yes - 19
Meyer 1995	Item 8 - alert	% yes - 33	% yes - 35
Meyer 1995	Item 12 - relaxed	% yes - 20	% yes - 33
Meyer 1995	Item 18 - happy	% yes - 40	% yes - 27
Meyer 1995	Item 19 - confident	% yes - 29	% yes - 28
Meyer 1995	Item 24 - lively	% yes - 16	% yes - 16
Meyer 1995	Item 28 - calm	% yes - 29	% yes - 28
Meyer 1995			
Meyer 1995			

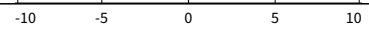
Analysis 1.3. Comparison 1 EPO i.v. versus placebo i.v., Outcome 3 Haemoglobin (g/dL) within 2 weeks after treatment.

Study or subgroup	Erythropoietin		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Meyer 1995	35	9.6 (1.5)	36	9.2 (1.4)		100%	0.4[-0.26,1.06]
Total ***	**35**		**36**			**100%**	**0.4[-0.26,1.06]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.18(P=0.24)							



Analysis 1.4. Comparison 1 EPO i.v. versus placebo i.v., Outcome 4 Haematocrit (%) within 2 weeks after treatment.

Study or subgroup	Erythropoietin		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Meyer 1995	35	28.8 (4.3)	36	27.2 (4.3)		100%	1.6[-0.42,3.62]
Total ***	**35**		**36**			**100%**	**1.6[-0.42,3.62]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.55(P=0.12)							

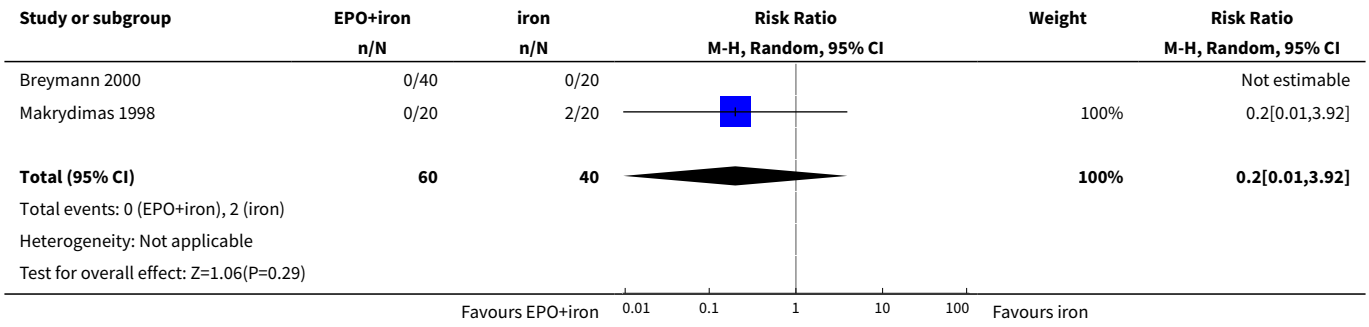


Comparison 2. EPO + iron versus iron

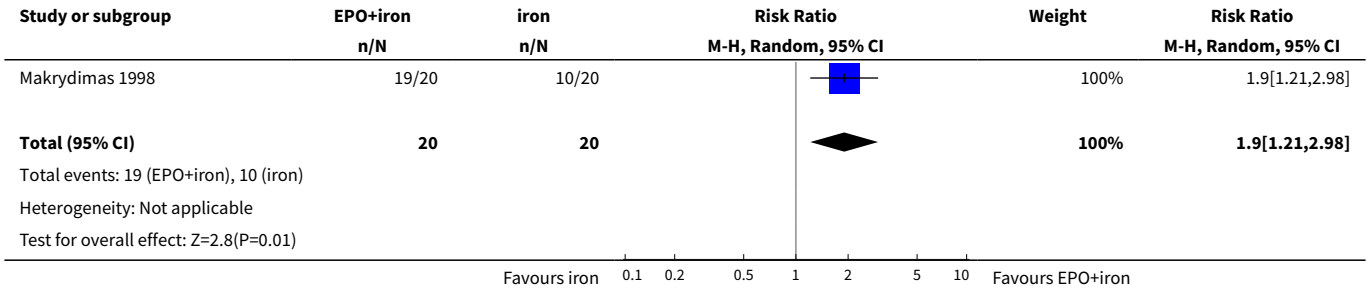
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Use of blood transfusions	2	100	Risk Ratio (M-H, Random, 95% CI)	0.2 [0.01, 3.92]
2 Lactating	1	40	Risk Ratio (M-H, Random, 95% CI)	1.9 [1.21, 2.98]
3 Thromboembolic complications	2	96	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Anaphylactic/serious reaction	3	186	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Length of postnatal hospital stay, median (days)			Other data	No numeric data
6 Haemoglobin (g/dL) within 2 weeks after treatment	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 EPO iv + iron versus iron (oral or iv)	1	60	Mean Difference (IV, Random, 95% CI)	0.45 [-0.16, 1.06]
6.2 EPO sc + iron versus iron (oral or iv)	1	60	Mean Difference (IV, Random, 95% CI)	-0.55 [-0.99, -0.11]
6.3 EPO iv + iron versus iron (oral + iv)	1	36	Mean Difference (IV, Random, 95% CI)	0.40 [-0.22, 1.02]
7 Haemoglobin increase (%) within 2 weeks after treatment	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 EPO iv + iron versus iron iv	1	40	Mean Difference (IV, Random, 95% CI)	0.20 [-0.27, 0.67]
7.2 EPO iv + iron versus oral iron	1	40	Mean Difference (IV, Random, 95% CI)	0.70 [0.23, 1.17]
8 Haemoglobin (g/dL) > 2 weeks to 6 weeks after treatment	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 EPO iv + iron versus iron (oral or iv)	1	60	Mean Difference (IV, Random, 95% CI)	0.40 [-0.09, 0.89]
8.2 EPO sc + iron versus iron (oral or iv)	1	60	Mean Difference (IV, Random, 95% CI)	0.30 [-0.34, 0.94]
8.3 EPO iv + iron versus iron (oral + iv)	1	36	Mean Difference (IV, Random, 95% CI)	0.40 [-0.20, 1.00]
9 Haemoglobin (g/dL) median			Other data	No numeric data
10 Haematocrit (%) within 2 weeks after treatment	2		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 EPO iv + iron versus iron iv	1	40	Mean Difference (IV, Random, 95% CI)	2.30 [1.89, 2.71]
10.2 EPO iv + iron versus oral iron	1	40	Mean Difference (IV, Random, 95% CI)	3.5 [3.19, 3.81]
10.3 EPO iv + iron versus iron (oral + iv)	1	36	Mean Difference (IV, Random, 95% CI)	1.5 [-0.38, 3.38]
11 Haematocrit > 35% 2 weeks after treatment	1	60	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.95, 2.23]
12 Haematocrit (%) > 2 weeks to 6 weeks after treatment	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
12.1 EPO iv + iron versus iron (oral + iv)	1	36	Mean Difference (IV, Random, 95% CI)	0.10 [-3.06, 3.26]
13 Haematocrit (median %)			Other data	No numeric data

Analysis 2.1. Comparison 2 EPO + iron versus iron, Outcome 1 Use of blood transfusions.



Analysis 2.2. Comparison 2 EPO + iron versus iron, Outcome 2 Lactating.

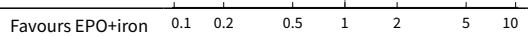


Analysis 2.3. Comparison 2 EPO + iron versus iron, Outcome 3 Thromboembolic complications.

Study or subgroup	EPO+iron n/N	iron n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Breymann 2000	0/40	0/20			Not estimable
Lebrecht 1995	0/24	0/12			Not estimable
Total (95% CI)	**64**	**32**			**Not estimable**
Total events: 0 (EPO+iron), 0 (iron)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Analysis 2.4. Comparison 2 EPO + iron versus iron, Outcome 4 Anaphylactic/serious reaction.

Study or subgroup	EPO+iron n/N	iron n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Breymann 1996	0/60	0/30			Not estimable
Breymann 2000	0/40	0/20			Not estimable
Lebrecht 1995	0/24	0/12			Not estimable
Total (95% CI)	**124**	**62**			**Not estimable**
Total events: 0 (EPO+iron), 0 (iron)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

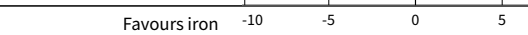


Analysis 2.5. Comparison 2 EPO + iron versus iron, Outcome 5 Length of postnatal hospital stay, median (days).

	Length of postnatal hospital stay, median (days)	
Study	EPO+iron+folate (n=2	iron+folate (n=20)
Makrydimas 1998	11 (range 10-16)	14 (range 11-19)

Analysis 2.6. Comparison 2 EPO + iron versus iron, Outcome 6 Haemoglobin (g/dL) within 2 weeks after treatment.

Study or subgroup	EPO+iron N	Mean(SD)	iron N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.6.1 EPO iv + iron versus iron (oral or iv)							
Breymann 1996	30	11.7 (1.6)	30	11.3 (0.6)		100%	0.45[-0.16,1.06]
Subtotal ***	**30**		**30**			**100%**	**0.45[-0.16,1.06]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.46(P=0.15)							
2.6.2 EPO sc + iron versus iron (oral or iv)							
Breymann 1996	30	10.7 (1.1)	30	11.3 (0.6)		100%	-0.55[-0.99,-0.11]
Subtotal ***	**30**		**30**			**100%**	**-0.55[-0.99,-0.11]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.45(P=0.01)							



Study or subgroup	EPO+iron N	EPO+iron Mean(SD)	iron N	iron Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.6.3 EPO iv + iron versus iron (oral + iv)							
Lebrecht 1995	24	10.6 (1.2)	12	10.2 (0.7)		100%	0.4[-0.22,1.02]
Subtotal ***	**24**		**12**			**100%**	**0.4[-0.22,1.02]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.26(P=0.21)							

Favours iron -10 -5 0 5 10 Favours EPO+iron

Analysis 2.7. Comparison 2 EPO + iron versus iron, Outcome 7 Haemoglobin increase (%) within 2 weeks after treatment.

Study or subgroup	EPO+iron N	EPO+iron Mean(SD)	iron N	iron Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.7.1 EPO iv + iron versus iron iv							
Breymann 2000	20	3.1 (0.7)	20	2.9 (0.8)		100%	0.2[-0.27,0.67]
Subtotal ***	**20**		**20**			**100%**	**0.2[-0.27,0.67]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.84(P=0.4)							
2.7.2 EPO iv + iron versus oral iron							
Breymann 2000	20	3.1 (0.7)	20	2.4 (0.8)		100%	0.7[0.23,1.17]
Subtotal ***	**20**		**20**			**100%**	**0.7[0.23,1.17]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.94(P=0)							

Favours iron -10 -5 0 5 10 Favours EPO+iron

Analysis 2.8. Comparison 2 EPO + iron versus iron, Outcome 8 Haemoglobin (g/dL) > 2 weeks to 6 weeks after treatment.

Study or subgroup	EPO+iron N	EPO+iron Mean(SD)	iron N	iron Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.8.1 EPO iv + iron versus iron (oral or iv)							
Breymann 1996	30	12.7 (1.1)	30	12.3 (0.8)		100%	0.4[-0.09,0.89]
Subtotal ***	**30**		**30**			**100%**	**0.4[-0.09,0.89]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.61(P=0.11)							
2.8.2 EPO sc + iron versus iron (oral or iv)							
Breymann 1996	30	12.6 (1.6)	30	12.3 (0.8)		100%	0.3[-0.34,0.94]
Subtotal ***	**30**		**30**			**100%**	**0.3[-0.34,0.94]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.92(P=0.36)							
2.8.3 EPO iv + iron versus iron (oral + iv)							
Lebrecht 1995	24	12 (0.8)	12	11.6 (0.9)		100%	0.4[-0.2,1]
Subtotal ***	**24**		**12**			**100%**	**0.4[-0.2,1]**
Heterogeneity: Not applicable							

Favours iron -10 -5 0 5 10 Favours EPO+iron

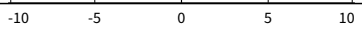
Study or subgroup	EPO+iron N	EPO+iron Mean(SD)	iron N	iron Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for overall effect: Z=1.3(P=0.19)							

Analysis 2.9. Comparison 2 EPO + iron versus iron, Outcome 9 Haemoglobin (g/dL) median.

Study	Days after	Haemoglobin (g/dL) median EPO+iron+folate	Iron+folate
Makrydimas 1998	2d	7.8	7.3
Makrydimas 1998	4d	8.4	7.6
Makrydimas 1998	14d	10.3	8.9
Makrydimas 1998	39d	12.2	11.6

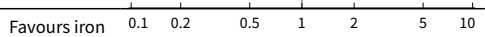
Analysis 2.10. Comparison 2 EPO + iron versus iron, Outcome 10 Haematocrit (%) within 2 weeks after treatment.

Study or subgroup	EPO+iron N	EPO+iron Mean(SD)	iron N	iron Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.10.1 EPO iv + iron versus iron iv							
Breymann 2000	20	38 (0.5)	20	35.7 (0.8)		100%	2.3[1.89,2.71]
Subtotal ***	**20**		**20**			**100%**	**2.3[1.89,2.71]**
Heterogeneity: Not applicable							
Test for overall effect: Z=10.9(P<0.0001)							
2.10.2 EPO iv + iron versus oral iron							
Breymann 2000	20	38 (0.5)	20	34.5 (0.5)		100%	3.5[3.19,3.81]
Subtotal ***	**20**		**20**			**100%**	**3.5[3.19,3.81]**
Heterogeneity: Not applicable							
Test for overall effect: Z=22.14(P<0.0001)							
2.10.3 EPO iv + iron versus iron (oral + iv)							
Lebrecht 1995	24	34.3 (3.4)	12	32.8 (2.3)		100%	1.5[-0.38,3.38]
Subtotal ***	**24**		**12**			**100%**	**1.5[-0.38,3.38]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.56(P=0.12)							



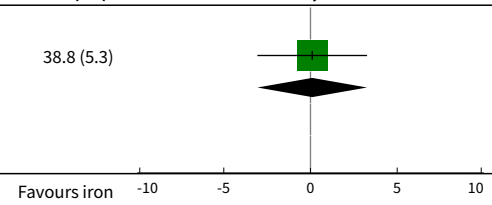
Analysis 2.11. Comparison 2 EPO + iron versus iron, Outcome 11 Haematocrit > 35% 2 weeks after treatment.

Study or subgroup	EPO+iron n/N	iron n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Breymann 2000	32/40	11/20		100%	1.45[0.95,2.23]
Total (95% CI)	**40**	**20**		**100%**	**1.45[0.95,2.23]**
Total events: 32 (EPO+iron), 11 (iron)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.73(P=0.08)					



Analysis 2.12. Comparison 2 EPO + iron versus iron, Outcome 12 Haematocrit (%) > 2 weeks to 6 weeks after treatment.

Study or subgroup	EPO+iron N	EPO+iron Mean(SD)	Iron N	Iron Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.12.1 EPO iv + iron versus iron (oral + iv)							
Lebrecht 1995	24	38.9 (2.5)	12	38.8 (5.3)		100%	0.1[-3.06,3.26]
Subtotal ***	**24**		**12**			**100%**	**0.1[-3.06,3.26]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.06(P=0.95)							



Analysis 2.13. Comparison 2 EPO + iron versus iron, Outcome 13 Haematocrit (median %).

Study	Days after	Haematocrit (median %) EPO+iron+folate	Iron+folate
Makrydimas 1998	2	25	22
Makrydimas 1998	4	27	24
Makrydimas 1998	14	32	27
Makrydimas 1998	39	37	35

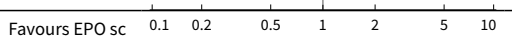
Comparison 3. EPO s.c. versus EPO i.v.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse effects reported for EPO	1	95	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Haemoglobin (g/dL) within 2 weeks after treatment	2	155	Mean Difference (IV, Random, 95% CI)	-0.34 [-0.94, 0.26]
2.1 EPO given as 2 doses over 2 days	1	51	Mean Difference (IV, Random, 95% CI)	0.0 [-0.55, 0.55]
2.2 EPO given as one dose	2	104	Mean Difference (IV, Random, 95% CI)	-0.54 [-1.42, 0.34]
3 Haemoglobin (g/dL) > 2 weeks to 6 weeks after treatment	2	155	Mean Difference (IV, Random, 95% CI)	0.02 [-0.27, 0.32]
3.1 EPO given as 2 doses over 2 days	1	51	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.51, 0.31]
3.2 EPO given as one dose	2	104	Mean Difference (IV, Random, 95% CI)	0.15 [-0.27, 0.58]
4 Haematocrit (%) within 2 weeks after treatment	1	95	Mean Difference (IV, Random, 95% CI)	-0.48 [-1.83, 0.86]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 EPO given as 2 doses over 2 days	1	51	Mean Difference (IV, Random, 95% CI)	-1.0 [-2.94, 0.94]
4.2 EPO as one dose	1	44	Mean Difference (IV, Random, 95% CI)	0.0 [-1.87, 1.87]
5 Haematocrit (%) > 2 weeks to 6 weeks after treatment	1	95	Mean Difference (IV, Random, 95% CI)	-0.72 [-1.66, 0.21]
5.1 EPO given as 2 doses over 2 days	1	51	Mean Difference (IV, Random, 95% CI)	-1.0 [-2.10, 0.10]
5.2 EPO as one dose	1	44	Mean Difference (IV, Random, 95% CI)	0.0 [-1.77, 1.77]

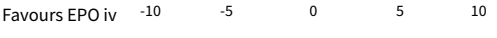
Analysis 3.1. Comparison 3 EPO s.c. versus EPO i.v., Outcome 1 Adverse effects reported for EPO.

Study or subgroup	EPO sc n/N	EPO iv n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Zimmermann 1994	0/48	0/47			Not estimable
Total (95% CI)	**48**	**47**			**Not estimable**
Total events: 0 (EPO sc), 0 (EPO iv)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



Analysis 3.2. Comparison 3 EPO s.c. versus EPO i.v., Outcome 2 Haemoglobin (g/dL) within 2 weeks after treatment.

Study or subgroup	EPO sc N	EPO sc Mean(SD)	EPO iv N	EPO iv Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.2.1 EPO given as 2 doses over 2 days							
Zimmermann 1994	26	11.3 (1.1)	25	11.3 (0.9)		36.6%	0[-0.55,0.55]
Subtotal ***	**26**		**25**			**36.6%**	**0[-0.55,0.55]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.2.2 EPO given as one dose							
Breymann 1996	30	10.7 (1.1)	30	11.7 (1.6)		30.93%	-1[-1.69,-0.31]
Zimmermann 1994	22	11.5 (1.4)	22	11.6 (0.7)		32.47%	-0.1[-0.75,0.55]
Subtotal ***	**52**		**52**			**63.4%**	**-0.54[-1.42,0.34]**
Heterogeneity: Tau^2=0.29; Chi^2=3.42, df=1(P=0.06); I^2=70.74%							
Test for overall effect: Z=1.2(P=0.23)							
Total ***	**78**		**77**			**100%**	**-0.34[-0.94,0.26]**
Heterogeneity: Tau^2=0.18; Chi^2=5.4, df=2(P=0.07); I^2=62.95%							
Test for overall effect: Z=1.12(P=0.26)							



Study or subgroup	EPO sc N	EPO sc Mean(SD)	EPO iv N	EPO iv Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for subgroup differences: Chi²=1.04, df=1 (P=0.31), I²=4.24%							

Favours EPO iv -10 -5 0 5 10 Favours EPO sc

Analysis 3.3. Comparison 3 EPO s.c. versus EPO i.v., Outcome 3 Haemoglobin (g/dL) > 2 weeks to 6 weeks after treatment.

Study or subgroup	EPO sc N	EPO sc Mean(SD)	EPO iv N	EPO iv Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.3.1 EPO given as 2 doses over 2 days							
Zimmermann 1994	26	12.6 (0.7)	25	12.7 (0.8)		51.28%	-0.1[-0.51,0.31]
Subtotal ***	**26**		**25**			**51.28%**	**-0.1[-0.51,0.31]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.47(P=0.64)							
3.3.2 EPO given as one dose							
Breymann 1996	30	12.6 (1.6)	30	12.7 (1.1)		18.14%	-0.1[-0.79,0.59]
Zimmermann 1994	22	12.8 (1)	22	12.5 (0.8)		30.58%	0.3[-0.24,0.84]
Subtotal ***	**52**		**52**			**48.72%**	**0.15[-0.27,0.58]**
Heterogeneity: Tau²=0; Chi²=0.8, df=1(P=0.37); I²=0%							
Test for overall effect: Z=0.7(P=0.48)							
Total ***	**78**		**77**			**100%**	**0.02[-0.27,0.32]**
Heterogeneity: Tau²=0; Chi²=1.49, df=2(P=0.47); I²=0%							
Test for overall effect: Z=0.15(P=0.88)							
Test for subgroup differences: Chi²=0.69, df=1 (P=0.41), I²=0%							

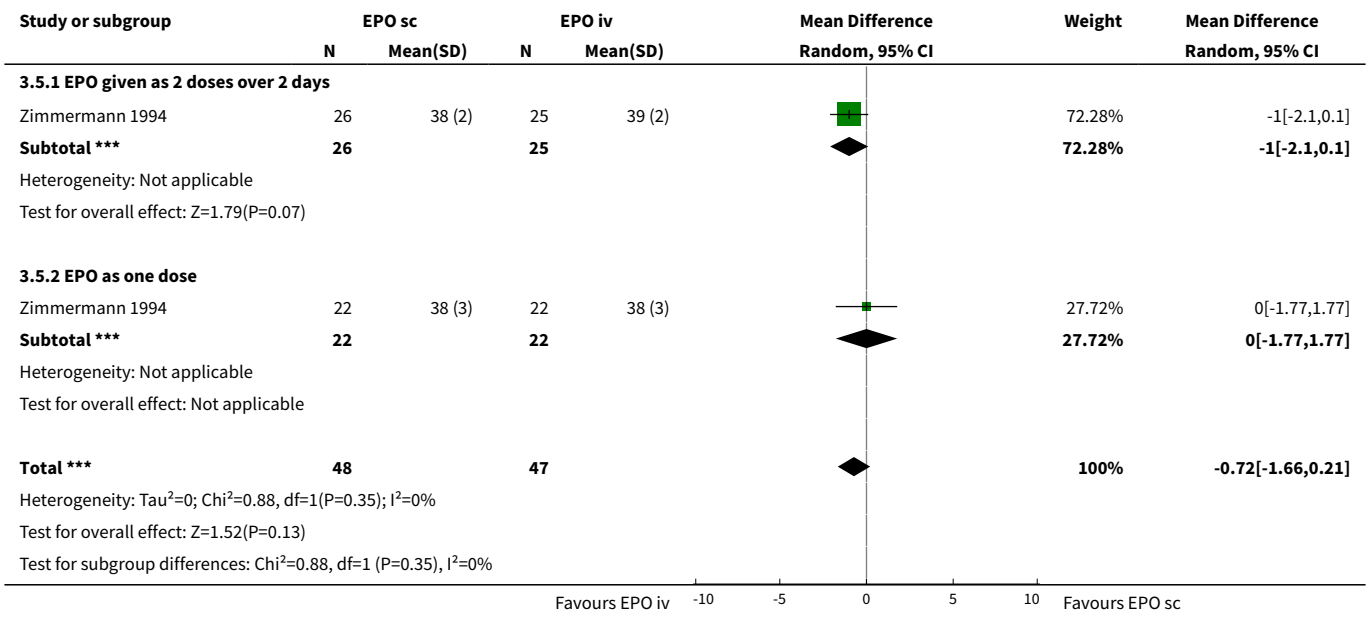
Favours EPO iv -10 -5 0 5 10 Favours EPO sc

Analysis 3.4. Comparison 3 EPO s.c. versus EPO i.v., Outcome 4 Haematocrit (%) within 2 weeks after treatment.

Study or subgroup	EPO sc N	EPO sc Mean(SD)	EPO iv N	EPO iv Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.4.1 EPO given as 2 doses over 2 days							
Zimmermann 1994	26	34 (4)	25	35 (3)		48.24%	-1[-2.94,0.94]
Subtotal ***	**26**		**25**			**48.24%**	**-1[-2.94,0.94]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.01(P=0.31)							
3.4.2 EPO as one dose							
Zimmermann 1994	22	35 (4)	22	35 (2)		51.76%	0[-1.87,1.87]
Subtotal ***	**22**		**22**			**51.76%**	**0[-1.87,1.87]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**48**		**47**			**100%**	**-0.48[-1.83,0.86]**
Heterogeneity: Tau²=0; Chi²=0.53, df=1(P=0.47); I²=0%							
Test for overall effect: Z=0.7(P=0.48)							
Test for subgroup differences: Chi²=0.53, df=1 (P=0.47), I²=0%							

Favours EPO iv -10 -5 0 5 10 Favours EPO sc

Analysis 3.5. Comparison 3 EPO s.c. versus EPO i.v., Outcome 5 Haematocrit (%) > 2 weeks to 6 weeks after treatment.



WHAT'S NEW

Date	Event	Description
9 September 2015	Amended	Text has been added to Published notes to explain that this review will not be updated and has been superseded by Markova 2015.

HISTORY

Protocol first published: Issue 2, 2003
Review first published: Issue 4, 2004

Date	Event	Description
7 June 2012	Amended	Search updated. Twenty-seven reports added to Studies awaiting classification (Backe 2009; Beard 2005; Bhandal 2004; Bhandal 2006; Breymann 2007; Breymann 2008; Daniilidis 2011; Dede 2005; Haidar 2005; Hashmi 2006; Jansen 2007; Krafft 2011; Murray-Kolb 2009; Palacio 2007; Perez 2005; Prick 2010; Prick 2012; Seid 2007; Seid 2008; Tam 2005; Van der Woude 2011; Van Rhenen 2005; Van Wyck 2007; Verma 2011; Wagstrom 2007; Westad 2008; Westad 2009). Information about the updating of this review has been added to Published notes.

Date	Event	Description
20 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Jodie Dodd (JD) and Marianna Dare (MD) formulated and wrote the protocol; retrieved the papers and applied the study selection criteria. JD, MD and Philippa Middleton (PM) extracted the data; MD compiled the review and, together, JD, MD and PM analysed the data and wrote the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Department of Obstetrics and Gynaecology, University of Adelaide, Australia.

External sources

- Department of Health and Ageing, Australia.

NOTES

This review will no longer be updated by the current review team and has been superseded by a new review on this topic, see Markova 2015.

INDEX TERMS

Medical Subject Headings (MeSH)

Anemia, Iron-Deficiency [blood] [*drug therapy]; Erythropoietin [*therapeutic use]; Iron [*therapeutic use]; Puerperal Disorders [blood] [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans