Treatment for women with postpartum iron deficiency anaemia (Protocol)

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Treatment for women with postpartum iron deficiency anaemia

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the efficacy and safety of the available treatment modalities for women with PP-IDA. These include oral and parenteral iron supplementation, folate, erythropoietin, and blood transfusion.

BACKGROUND

Description of the condition

Women who give birth may develop postpartum anaemia (PPA), either because of excessive bleeding or pre-existing conditions in pregnancy. Severe PPA may be a serious problem being linked to possibly 40% of maternal deaths worldwide (WHO 2001). Anaemia also contributes to maternal death from other causes such as infections, malnutrition and bleeding (WHO 2012b). For some women, particularly in resource-poor countries, anaemia is a major cause of poor health (Bergmann 2010; Gupta 2010; Khan 2006; WHO 2012a).

Anaemia, including PPA, is defined by a lower than normal haemoglobin (Hb) value. Haemoglobin is the molecule contained within red blood cells that is responsible for transporting oxygen around the body. During pregnancy, most women have a reduction in their Hb concentration (WHO 2001). Postpartum anaemia may be caused by low dietary iron intake, blood loss, or infections, and the physiological changes during pregnancy and bleeding associated with childbirth can aggravate the condition (WHO 1999). Postpartum anaemia is associated with many symptoms, including breathlessness, palpitations (a sensation of increased heart rate), tiredness, as well as increased risk of infections. All of these symptoms may impact on a woman's ability to care for her baby (Bergmann 2010; Milman 2011).

In pregnancy, the circulating blood volume increases and prepares the woman for blood loss at delivery. Furthermore, bleeding and/or resorption of excess fluid in body tissues vary in extent between individuals (Milman 2011), and these changes have a major impact on maternal Hb concentrations. It is generally accepted that a low Hb concentration - usually less than 120 g/L - is indicative of anaemia in postpartum women, although there is considerable variation in the precise concentration that defines anaemia, and

also the time after birth at which this should be measured (Barroso 2011; Bergmann 2010; Bodnar 2005; Breymann 2010; Milman 2011; Richter 1995). Thus, PPA is poorly defined and the Hb level in the postpartum period (six weeks after delivery) depends strongly on how long after delivery it is measured (WHO 2012a). It should be emphasised that even though associations between a low Hb and clinical symptoms have been proven in population studies, the normal range of Hb is a statistical value derived from the population average, and an individual woman's Hb level does not necessarily reflect the clinical symptoms she may experience (WHO 2001). Since the correlation between the different clinical symptoms and the level of Hb in PPA is not well described, the clinical significance of a change in Hb level as a result of any given treatment remains uncertain. In clinical practice however, a low Hb level is the most commonly used laboratory test to support the clinical diagnosis of anaemia and it is generally understood that a major drop in the Hb level within a short time frame is likely to correlate with a large blood loss at delivery, which may lead to acute symptoms of anaemia.

During pregnancy, anaemia is also defined by low Hb levels and stratified into mild, moderate and severe anaemia (WHO 2002). Anaemia in pregnancy (e.g. due to insufficient dietary intake) as well as haemorrhage during or after birth are strong predictors for postpartum iron deficiency anaemia (PP-IDA) (Bodnar 2005; Milman 2011; Reveiz 2011). Iron deficiency anaemia is a condition where the low Hb is caused by an insufficient amount of iron in the body. To our knowledge, only one study has estimated the incidence of PP-IDA, at 4.2% among women in the United States examined within the first six months postpartum (Bodnar 2002). The condition PPA does not have a specific code in the International Classification of Diseases (ICD-10), but is included in the more general code 099.0 'Anaemia complicating pregnancy, childbirth and the puerperium' (WHO ICD 2010). At this point all definitions of PPA rely on Hb values alone, not symptoms. The classification of different stages of severity is also based only on Hb values (Milman 2012). In the postpartum period as well as in pregnancy, it remains unanswered whether treatment of anaemia outweighs the disadvantages of treatment (Reveiz 2011).

Based on the uncertainty regarding the clinical significance of the changes in Hb levels in the postpartum period, and the lack of agreement on a common definition of PPA based on laboratory values of Hb or other criteria, we designed this Cochrane review to evaluate the effect of any treatment of PPA by its effect on the presence and severity of clinical symptoms alone.

Description of the intervention

There are a number of treatment options for women with PPA, and the optimal modality, dose, benefits and harms may vary depending on the severity of anaemia, symptoms, possible side effects, available resources and factors such as geographic location, socioeconomic status and education. The treatment modalities include iron supplementation administered either orally or directly into a vein or muscle (parenterally), erythropoietin which stimulates red blood cell production, and substitution of red blood cells by blood transfusion.

How the intervention might work

Oral iron therapy

Oral iron supplemental therapy has been used for many years as a treatment for iron deficiency anaemia in general (Dudrick 1986), as well as in pregnancy (Pena-Rosas 2012). Oral iron supplementation is often the recommended treatment for mild to moderate iron deficiency anaemia (Bodnar 2005) because of its low cost and ease of use. The body has a limited capacity to absorb iron from the gut, and prolonged treatment over a period of several months is often required to improve the Hb concentration and relieve symptoms of anaemia (Auerbach 2008; Milman 2012; Van Wyck 2007; Westad 2008). Gastrointestinal adverse effects, such as constipation and nausea are common in oral iron supplementary therapy (al-Momen 1996; Bhandal 2006). This may affect the women's compliance with treatment and consequently prevent correction of anaemia.

Folate

Folate, also called folic acid and vitamin B_9, is a substance found in food and is naturally available in especially high concentrations in green vegetables. Folate is involved in the synthesis of DNA, cell division and growth in human cells. Folate deficiency can cause megaloblastic anaemia, not iron deficiency anaemia. However, folate is often added as an adjunct to iron supplementation because malnutrition often results in a lack of both iron and folate in the body. The long-term effect of folate supplementation and continuously high levels of folate in the blood have been associated to an increased risk of certain cancers (Almeida 2010). In this review, we will not consider folate supplementation as an independent treatment of anaemia.

Parenteral iron therapy

Parenteral administration of iron has been shown to produce a more rapid increase in the Hb concentration in iron deficiency anaemia during pregnancy (Milman 2012). Administered parenterally, iron supplementation has been associated with pain and redness (erythema) at the injection site and rarely, anaphylactic reactions, characterised by itching, redness and in severe cases angioedema (swelling), vascular collapse, bronchospasm (constriction of the airways) and shock (Barish 2012; Breymann 2008; Kochhar 2013; Seid 2008; Wysowski 2010). The use of new low-molecular iron (such as iron sucrose and ferric carboxymaltose)

may lower the risk of anaphylactic reactions but these products are expensive compared with oral iron supplemental therapy, which does not have these serious harms (Khalafallah 2012; Kochhar 2013).

Erythropoietin

Erythropoietin (EPO) is a hormone produced in the kidneys when blood oxygen levels are low. It acts to stimulate erythropoiesis (blood formation) in the bone marrow (Oster 2012). Initially, EPO was used for anaemia associated with renal (kidney) disease. Later, EPO was used to treat other forms of anaemia and has been used as an alternative to blood transfusion for the treatment of iron deficiency anaemia, including PP-IDA (Bergmann 2010; Oster 2012). 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, thromboembolic complications and seizures and, more recently, pure red-cell aplasia (Dodd 2004; Kliger 2012). Recent research has shown an association with certain haematological cancers, which led to a Food and Drug Agency (FDA) black box warning (label on the product warning against serious or life threatening risks). The use of EPO is now restricted to specific patient groups and is rarely used in postpartum anaemic patients (Bunn 2009; Oster 2012).

Blood transfusion

Transfusion of allogeneic blood can be used in the treatment of PPA and may be life-saving in the case of acute or major bleeding at the time of giving birth. Transfusion of one unit of red blood cells usually increases the Hb by 10 g/L (Wiesen 1994), but the clinical benefit of blood transfusions is not proven when given to mixed-patient populations with mild to moderate anaemia (Carson 2012). Also, there are associated risks, including donor-transmitted infections (particularly hepatitis and Human Immunodeficiency Virus (HIV)), transfusion-associated circulatory overload (TACO), and a variety of immunologic reactions such as fever, urticaria (skin rash and/or hives), anaphylaxis, transfusion-related lung injury (TRALI) or antibody formation which may interfere with future pregnancies (Fuller 2010; Hendrickson 2009; SHOT report 2011; Villanueva 2013). Blood transfusion may rarely cause acute haemolysis (breakdown of red blood cells) if incompatible blood is administered by mistake (Fuller 2010). Blood transfusions are expensive, as costs include screening for infection, cross-matching, storage and sterile and safe administration of blood products (Shander 2010). In low-income countries or during disasters, blood for transfusion may not be readily available.

Why it is important to do this review

Postpartum anaemia caused by insufficient iron intake and/or bleeding, i.e. PP-IDA is a common condition affecting women after childbirth and may be associated with symptoms that can influence survival, health and the ability to care for their baby. The treatment modalities available for PP-IDA have potential harms, some of which are serious. Since all women bleed at delivery, it is a common practice to administer treatment for PP-IDA. Some populations may benefit more than others, and in some populations treatment may be ineffective or even harmful. Women and care givers need information about the benefits and harms of the available treatments for PPA.

This is a protocol for a new review team to prepare a review on, 'Treatment for women with postpartum iron deficiency anaemia'. The review will update an earlier review by Dodd 2004 on this topic.

OBJECTIVES

To assess the efficacy and safety of the available treatment modalities for women with PP-IDA. These include oral and parenteral iron supplementation, folate, erythropoietin, and blood transfusion.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all published, unpublished and ongoing randomised controlled trials that compare a treatment for PP-IDA with placebo, no treatment, or another treatment for PP-IDA anaemia, including trials described in abstracts only and cluster-randomised trials. If we assess the overall quality of the trial to be sufficient, we will include both open-label trials and blinded trials, regardless of who was blinded. Quasi-randomised trials and trials using a cross-over design will be excluded.

Types of participants

Women with a postpartum Hb value of 120 g/L (7.4 millimoles per litre) or less, with treatment initiated up to six weeks after giving birth. We will distinguish between socioeconomic population groups, as this may affect the response to treatment.

Types of interventions

Iron supplementation administered orally or parenterally, either alone or in combination with folate, erythropoietin or blood transfusion started within the first six weeks after giving birth and compared with placebo, another treatment, or no treatment.

Types of outcome measures

Primary outcomes

1. Maternal mortality.
2. Fatigue (as reported by the women - verbalisation of fatigue or lack of energy and inability to maintain usual routines; measured by a scale or questionnaire; or as defined by the trial authors).

Secondary outcomes

1. Persistent anaemia symptoms during treatment. Any of the following symptoms: dyspnoea, tachypnoea, tachycardia, palpitations, orthostatic dizziness, syncopation, paleness.
2. Psychological well being (including cognitive performance); measured by the 'Blues Questionnaire' (Kennerley 1989), 'Self-report symptom inventory 90 [SCL-90-R]' (Schmitz 1999), 'SF36 [Medical Outcomes Study Short Form]' (Ware 2000) or similar questionnaire; or as defined by the trial authors).
3. Urinary tract infection, endometritis, or other infections (as defined by the trial authors).
4. Compliance to treatment (as defined by the trial authors).
5. Breastfeeding (at hospital discharge; six weeks postpartum; six months postpartum).
6. Length of hospital stay.
7. Any adverse events during treatment (each type of harm analysed individually, when possible).
8. Number of red blood cell transfusions (number of transfused women and number of red blood cell units per woman).

We will not apply any restrictions regarding follow-up periods, to avoid excluding data on any long-term benefits or harms.

Studies of included interventions that do not report any of the above mentioned outcomes will be described in the 'Characteristics of included studies' section, but will not be included in any meta-analyses.

We plan to include the following outcomes in the 'Summary of findings' table of the review, using the Grade Profiler programme (GRADEpro).

- Maternal mortality
- Fatigue
- Constipation (when treatment was oral iron substitution)
- Allergic reactions (when treatment was intravenous iron)

Search methods for identification of studies

Electronic searches

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 to the searching carried out by the Trials Search Co-ordinator, we plan to search the following trial registers for planned, ongoing or unpublished trials:

1. WHO ICTRP (http://apps.who.int/trialsearch/)
2. LILACS (www.bireme.br)

We will describe the search strategies for these two sources in full in the review.

Searching other resources

We will search the citation lists of relevant publications, review articles and included studies and contact manufacturers of parenteral iron pharmaceuticals for knowledge of any ongoing trials. We will not apply language restrictions.

Data collection and analysis

Selection of studies

Two review authors (Veronika Markova and Astrid Nørgaard) will independently assess for inclusion all the potential studies identified. Any disagreement will be resolved through discussion.

Data extraction and management

We will design a form to extract data. The form will contain information on bias assessment, inclusion and exclusion criteria, number of participants and discontinuations, demographic data, treatment regimens, and available information on the outcome measures.

For eligible studies, the same two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult Karsten Juhl Jørgensen at the Nordic Cochrane Centre. We will enter data into Review Manager software (RevMan 2012) and check for accuracy. When information regarding any of the above information items is unclear, we will attempt to contact authors of the original reports to provide further details.

If we identify trials with more than two study arms, we will include relevant arms in a meta-analysis. The remaining arm(s) will be described compared with the trials control arm. If comparisons in the trial cannot be included in a meta-analysis, but fulfil our inclusion criteria, we will describe the results in separate comparisons.

Assessment of risk of bias in included studies

Two review authors (Veronika Markova and Astrid Nørgaard) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* using a 'Risk of bias' table (Higgins 2011). Any disagreement will be resolved by discussion, or by involving a third assessor (Karsten Juhl Jørgensen or Jens Langhoff-Roos).

(1) Random sequence generation

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups, if possible.

We will assess the method as:

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

(2) Allocation concealment

If possible, we will describe for each included study the method used to conceal allocation to interventions prior to assignment of intervention arm and will assess whether intervention allocation could have been foreseen in advance of or during recruitment, or could be changed after assignment.

We will assess the methods as:

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

(3.1) Blinding of participants and personnel

We will describe for each included study the methods used, if any, to blind study participants and/or personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if participants and personnel were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment

We will describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), whether reasons for attrition or exclusion were reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses we undertake.

We will assess methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We will assess the methods as:

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

(6) Other bias

We will describe for each included study any important concerns we have about other possible sources of bias.

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

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

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Cochrane Handbook* (Higgins 2011). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact the findings. We will explore the impact of bias through sensitivity analyses - see Sensitivity analysis.

We will use Grade Profiler (GRADEpro) to produce a 'Summary of findings' table. Through this process we will asses the risk of bias for each of our primary outcomes, as well as for constipation with oral iron substitution and allergic reactions with intravenous iron supplementation.

Measures of treatment effect

Dichotomous data

For dichotomous data, we will present results as a summary risk ratio with 95% confidence intervals from a meta-analysis, if possible.

Continuous outcome data

For continuous outcome data, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trial results that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually-randomised trials. We will adjust the standard error of the cluster-randomised trials using the methods described in the *Cochrane Handbook* section 16.3.6. We will use an estimate of the intra cluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information from both types of studies if there is little heterogeneity between the results from trials using the two types of study design, and if the interaction between the effect of the intervention and the choice of randomisation unit is considered to be unlikely.

We will also perform a subgroup analysis to investigate the effects of the randomisation unit (cluster or individual).

Dealing with missing data

For the included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect through sensitivity analysis.

For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus the number of participants whose outcome data are known to be missing.

Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis using the T^2, I^2 and Chi^2 statistics. We will regard heterogeneity as substantial if an I^2 is greater than 30% and either a T^2 is greater than zero, or if there is a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

If there are 10 or more studies in a meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses.

Data synthesis

Statistical analysis will be performed with Review Manager software (RevMan 2012). We will use fixed-effect meta-analysis for data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If heterogeneity is sufficient to expect that the underlying treatment effects differ between trials, we will use random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.

If we use random-effects meta-analyses, the results will be presented as the average treatment effect with 95% confidence intervals, and the estimates of T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects meta-analysis to produce it.

We plan to carry out the following subgroup analyses, if necessary.

1. Study setting: low- versus high-income populations; high- versus low-education status.
2. Type of intravenous iron therapy: iron sucrose versus iron caboxymaltose.
3. Dose administered: high versus low dose.
4. Duration of treatment: four weeks versus longer.
5. Presence of an adjunct to iron supplementation: folate versus no folate.
6. Source of funding: public versus corporate.

Our primary outcomes may be used in the subgroup analyses.

1. Maternal mortality.
2. Fatigue (as reported by the women - verbalisation of fatigue or lack of energy and inability to maintain usual routines; measured by scale or questionnaire; or as defined by the trial authors).

We will assess subgroup differences by interaction tests available within RevMan (RevMan 2012). We will report the results of subgroup analyses quoting the χ^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We plan to carry out a sensitivity analysis based on trial design involving trials with a low risk of bias in all bias domains of the 'Risk of bias' tool, thus removing trials with a high or unclear risk of bias in any domain.

We will also carry out sensitivity analyses to explore the effects of random-effects analyses for outcomes with statistical heterogeneity and the effects of any assumptions made such as the value of the ICC used for cluster-randomised trials.

We will use our primary outcomes only (maternal mortality and fatigue) in the sensitivity analyses.

ACKNOWLEDGEMENTS

We acknowledge the important work of the previous review team (Dodd 2004).

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

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* *Indicates the major publication for the study*

CONTRIBUTIONS OF AUTHORS

Veronika Markova developed the protocol, searched the references for the background section and adjusted the methodology section, determining the outcomes and types of analyses of the future review.

Astrid Nørgaard helped developing the protocol and provided professional knowledge on current tendencies in anaemia treatment options and outcomes.

Karsten Juhl Jørgensen provided knowledge regarding the methods of Cochrane systematic reviews and protocols.

Jens Langhoff-Roos provided expert clinical knowledge on current treatment regiments for postpartum anaemia. He took part in initiating the project of this Cochrane review.

DECLARATIONS OF INTEREST

None known.