

MIDIRS ReView

Daily oral iron supplementation during pregnancy



Peña-Rosas JP, De-Regil LM, Dowswell T *et al* (2012).
Daily oral iron supplementation during pregnancy.
Cochrane Database of Systematic Reviews, Issue 12.

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Iron is widely known to be an essential mineral that plays a number of key and important roles in the human body. While general consumer information in the UK advises that most people can get adequate amounts of iron from their diet (NHS Choices 2012), there is a perception that pregnant women are more likely than non-pregnant people to be deficient in iron, and global concerns about iron deficiency and its consequences in pregnant women form the foundation of this review:

*'Iron deficiency is thought to be the most common nutrient deficiency among pregnant women (WHO 1992). Iron deficiency involves an insufficient supply of iron to the cells following depletion of the body's reserves. Its main causes are a diet poor in absorbable iron, an increased requirement for iron (e.g. during pregnancy) not covered through the diet, a loss of iron due to parasitic infections, particularly hookworm, and other blood losses (Crompton 2002; INACG 2002a). Chronic iron deficiency frequently turns into iron deficiency anaemia' (Peña-Rosas *et al* 2012:5).*

The global prevalence of anaemia in pregnant women is estimated by the World Health Organization (WHO) and US Centers for Disease Control and Prevention (CDC) (2008) to be 41.8% and the prescription of iron supplements is one of the most common interventions encountered by pregnant women. Many organisations recommend iron supplementation routinely during pregnancy (Peña-Rosas *et al* 2012), and few women query the need for supplementation, whether offered as routine prophylaxis or in response to a diagnosed deficiency, although some may seek more natural forms rather than those prescribed by their caregiver. Iron supplements can lead to constipation and other side effects, and some debate remains, as will be discussed below. This article discusses the content and considers the implications of the latest Cochrane review on daily oral iron supplementation during pregnancy, which is the most recent update in a series of reviews on the topic by the same group of reviewers. In contrast to the previous version (Peña-Rosas & Viteri 2009), this review specifically looks at the outcomes of daily (as opposed to intermittent) iron supplementation.

Acknowledging the complexity

The background section of the current review makes for interesting reading, and includes a number of debates which acknowledge the complexity of this area. Briefly, the notable issues include that:

- 'While iron deficiency is the most common cause of anaemia, other causes such as [...] infections [...] deficiencies [of other vitamins and minerals] and genetically inherited traits [...] may be causal factors' (Peña-Rosas *et al* 2012:5).
- 'Anaemia during pregnancy is diagnosed if a woman's haemoglobin (Hb) concentration is lower than 110 g/L at sea level, although it is recognized that during the second trimester Hb concentrations naturally decrease by approximately 5 g/L (WHO 2011)' (Peña-Rosas *et al* 2012:5).
- While iron deficiency can be measured quite precisely in non-pregnant people:
 - the relevant laboratory tests may not be available in some areas where pregnant women are cared for;
 - the accuracy of tests may also be limited where infections such as malaria are very prevalent;
 - the tests do not correlate well with each other because they reflect different aspects of iron metabolism;
 - we do not have clear consensus on what is normal, in part because haemodilution is known to be a normal occurrence in pregnancy.

Iron is often prescribed in conjunction with folic acid, and this review considers studies looking at both of these regimens. Previous studies have shown that iron supplementation can reduce the incidence of anaemia or lead to an increase in haemoglobin (Hb) but Peña-Rosas *et al* (2012) argue that this scope is too narrow and that the efficacy, effectiveness and safety of iron (and iron with folic acid) supplementation needs to be considered in relation to its possible impact upon maternal and child health. Another key issue which Peña-Rosas *et al* (2012) introduce from the outset is that of malaria, a parasite to which 40% of the world's population is exposed. They note that anaemia is the most common complication of malaria and is responsible for the highest number of malaria-related deaths.

*'Provision of iron in malaria-endemic areas has been a long standing controversy due to concerns that iron therapy may exacerbate infections, in particular malaria in childhood (Oppenheimer 2001). Although the mechanisms by which additional iron can benefit the parasite are far from clear, it is possible that lower dose supplementation might be an effective intervention to prevent anaemia and improve malaria treatment in malaria endemic areas since less iron is available for the parasite (NIH 2011). The potential interaction between malaria interventions and iron interventions in pregnancy has not been well studied. Malaria intermittent preventive treatment (IPT) is recommended for pregnant women in areas of high transmission who are particularly vulnerable to contracting malaria or suffering its consequences. A total of 35 of 45 sub-Saharan African countries had adopted IPT for pregnant women as national policy by the end of 2008 (WHO 2011c)' (Peña-Rosas *et al* 2012:5).*

Putting this review into context

*'The effectiveness of different iron treatments for anaemia among pregnant women in clinical practice (Revez 2011) and the effects of supplementation with iron and vitamin A during pregnancy (Van den Broek 2010) are covered in other Cochrane Reviews. A planned review will assess the effectiveness of oral folate supplementation alone during pregnancy on haematological and biochemical parameters during pregnancy and on pregnancy outcomes (Haider 2008). The effects and safety of periconceptional folate supplementation for preventing birth defects (De Regil 2010) and the effects of multiple vitamin and mineral supplements during pregnancy have also been reviewed elsewhere (Haider 2006). A separate review addresses the effectiveness of intermittent iron and folic acid supplementation regimens for women during pregnancy (Peña-Rosas 2012)' (Peña-Rosas *et al* 2012:7-8).*

Objectives, methods and bias

The objective of this review was: *'To assess the effects of daily oral use of iron supplements by pregnant women, either alone or in conjunction with folic acid or with other vitamins and minerals as a public health intervention'* (Peña-Rosas *et al* 2012:8).

The authors searched for studies that fit their criteria, focusing on *'...randomised and quasi-randomised trials comparing the effects of daily oral prenatal supplements of iron, or iron + folic acid or iron + other vitamins and minerals supplements among pregnant women'* (Peña-Rosas *et al* 2012:8). They excluded studies which looked at multiple combinations of other vitamins and minerals (unless all women received these and iron supplementation was additional) and focused on iron as a preventative measure rather than as treatment. Pregnant women in the included studies could be of any age and parity, and a number of comparisons were planned which took into account the different interventions that are used:

1. *Any supplements containing iron versus same supplements without iron or no treatment/placebo (no iron or placebo).*
2. *Any supplements containing iron and folic acid versus same supplements without iron or folic acid (no iron + folic acid or placebo).*
3. *Supplementation with iron alone versus no treatment/placebo.*
4. *Supplementation with iron + folic acid versus no treatment/placebo.*
5. *Supplementation with iron + folic acid versus folic acid alone (without iron) supplementation.*
6. *Supplementation with iron + other vitamins and minerals supplementation versus same other vitamins and minerals (without iron) supplementation.*
7. *Supplementation with iron + folic acid + other vitamins and minerals versus folic acid + same other vitamins and minerals (without iron) supplementation.*
8. *Supplementation with iron + folic acid + other vitamins and minerals versus same other vitamins and minerals (without iron + folic acid) supplementation'* (Peña-Rosas *et al* 2012:8).

The authors included a total of 60 trials in this review, of which 43 trials involving more than 27,402 women contributed data for the comparisons. The trials were carried out between 1936 and the present day in 27 countries across the globe, although most were conducted in the last 20 years. Around a third were carried out in countries where malaria is present and, although the review authors acknowledge a bias towards English language studies, the review includes studies conducted in a variety of nations and settings.

A significant number of clinical and laboratory outcome measures relating to maternal, perinatal, postpartum and infant factors were considered. Studies were assessed for inclusion and risk of bias as per standard Cochrane protocols, and all the usual checks and measures appear to be in place. Many of the included studies had a high risk of bias in at least one area, and in even more cases the risk of bias was unclear. Around half of the trials which contributed data did not adequately report their randomisation method, around half lacked evidence of appropriate methods of blinding allocation, and around a quarter of the included trials had a high loss to follow-up. The reviewers also discuss the problem of selective reporting of results, although they note that this is very difficult to assess.

Lumping and splitting

One of the ongoing issues with reviews such as this one is the fact that, although data from many research studies are included, the included studies have been carried out in different countries, using different interventions, looking at different outcomes measures and so on. The reviewers (and, indeed, anyone else interested in looking at the area) have to face the very difficult task of trying to decide whether to 'lump' or 'split' when determining the scope of a review.

If one is looking to gather as many studies – and participants – into the mix as possible, they might be said to be 'lumping'. Their data may have more power in one sense, because they have included more women overall, but some of those women might be very, very different from each other, which means that recommendations are very broad. The review might conclude that something is either recommended or not recommended for all women, but some people may see this as not very helpful, because the results are drawn from studies carried out with women who are so different from each other that they don't have as much meaning than if they related to populations that were a bit more homogenous.

The opposite end of this spectrum is where reviewers attempt to 'split' the studies and look more specifically, for instance by focusing on women having their first baby, who live in countries where malaria is endemic, who have normal Hb at the beginning of pregnancy and who are given a specific dosage of iron. It might seem that the results of such a review would be more helpful for a woman who falls into that category, than the results of a broad review, but the problems with the 'splitting' approach include that there might be so little data that the results are not significant, which is arguably even less helpful than a broad recommendation.

Results

The reviewers present the results in each of the eight categories of interventions listed above, although no studies met their criteria in the last two categories. They also included an overall summary of findings. It is notable that, in all but one of the areas where the results suggested a difference between the intervention and control groups, the quality of the evidence was less than ideal. The only difference which was supported by a high level of evidence was in relation to maternal anaemia at term, defined as Hb less than 110 g/L at 37 weeks' gestation or more.



In the results section of the Peña-Rosas *et al* abstract, which is likely to be more widely read than the (very long) full review, the authors suggest that: '*Prenatal supplementation with daily iron are [sic] effective to reduce the risk of low birthweight, and to prevent maternal anaemia and iron deficiency in pregnancy. Associated maternal side effects and particularly high Hb concentrations during pregnancy at currently used doses suggest the need to update recommendations on doses and regimens for routine iron supplementation*' (Peña-Rosas *et al* 2012:2).

Although the substantial differences that exist between the treatment groups and the risk of bias also need to be borne in mind when considering the following result, in the first and broadest category, '*...data from 11 trials involving 4418 women suggest that women who receive daily oral iron supplementation are more likely to report side effects of any kind than women taking placebo or not taking any iron as part of supplements (25.3% versus 9.91% reporting side effects; average RR 2.36; 95% CI 0.96 to 5.82)*' (Peña-Rosas *et al* 2012:26). This is a one in four chance of side effects (although, again, there is a risk of bias) and the reviewers stress the need to evaluate highly bioavailable iron compounds that may have fewer side effects.

Recommendations and discussion

The overarching recommendation of this review is that: '*supplementation with iron to pregnant women may be used as a preventive strategy to improve maternal and infant outcomes in all settings, including those where malaria is endemic*' (Peña-Rosas *et al* 2012:41). It is important to recall that the reviewers considered the use of iron as a preventative measure, and not as treatment where a woman has been found to have a low Hb following blood screening, which may be the more common approach in high-income countries.

Whether the Peña-Rosas *et al* review justifies any change in the information offered to pregnant women will be up to the individual practitioner, and related questions concerning the interpretation of such evidence in practice are considered elsewhere in this edition (Wickham 2013). The complexities and uncertainties that are intrinsic to this review, as well as the debates that exist around 'lumping' and 'splitting' and the philosophical issues raised by the notion of universal prophylaxis make this an interesting topic to ponder. It is likely that iron supplementation will continue to be one of the most common pregnancy-related interventions and that the question of whether global supplementation is justified will continue to be discussed and reviewed on many levels for the foreseeable future.

References

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