Author’s response to reviews

Title: Screening for Iron Deficiency and Iron Deficiency Anaemia in Pregnancy: A Structured Review and Gap Analysis Against UK National Screening Criteria

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Author’s response to reviews: see over
24 July 2015

Dear Dr Shazly

Re: Screening for iron deficiency anaemia and iron deficiency anaemia in pregnancy; a structured review and gap analysis against national UK national screening criteria.

Thank you very much for your letter dated the 6th of July. We are pleased that our manuscript is still being considered for publication in BMC Pregnancy and Childbirth. We appreciate the opportunity to resubmit our manuscript.

We would like to thank the reviewers for carefully considering our manuscript and for their constructive comments. We have responded to the areas they have highlighted as fully as possible. Appended to this letter is a point-by-point response to their comments.

As instructed, we have uploaded a revised version of the manuscript through the journal’s website. We look forward to your response.

With best wishes,

Dr Ruramayi Rukuni
(on behalf of co-authors Professor Marian Knight, Professor Mike Murphy, Professor David Roberts and Dr Simon Stanworth)
In response to the comments of the first reviewer:

Minor Essential Revisions:

Line 156: It is unclear how intrauterine contraceptive device use can increase risk of iron deficiency. Could a clause be added to clarify this?
We have modified this sentence to clarify that intrauterine contraceptive devices have been shown to contribute to the increased risk of iron deficiency by increasing menstrual blood loss by 30-50%.

Line 314: Please clarify what 'routine supplementation' refers to. Is this iron supplementation in a pill form or prenatal vitamins?
We have modified this sentence to clarify that routine supplementation used here refers to supplementation with iron tablets.

Line 323: Please provide a reference for the sentence that ends with 'standards'
We have included a specific example of the UK antenatal screening programme for sickle cell and thalassaemia, which has randomised control trial evidence of effectiveness, with quality assurance processes in place and published screening programme standards. The reference for these standards has been included.

Line 338: In addition, increasing the sensitivity of testing may be achieved simply by more widespread measurement of ferritin. This should be addressed briefly in the paragraph.
A sentence to explain that wider use of ferritin could contribute to increasing the sensitivity of testing has been included.

Line 559: In table 2, under 'acceptability and efficacy of treatments' a reference is needed for the statement that IV iron causes infections.
A reference to systematic review evidence showing infection as a consequence of IV iron has been included in the table.

Discretionary Revisions: The authors may consider shortening the manuscript in portions that would allow (for instance, the background and the importance of the problem), as the manuscript is currently somewhat lengthy.
After careful review of the manuscript, we feel that the information contained is important to give the full picture of the gaps and have not shortened further at this stage.

In response to the comments of the second reviewer

Minor comments:

Line 41:
What does it mean “the natural history.... “? It is well known how ID without anaemia develops in women, namely by an imbalance of iron losses and uptake which can be due to various reasons.
We have removed the term natural history to avoid misunderstanding. We have rewritten and simplified this point by stating that the clinical consequences of iron deficiency alone are not well understood.

Page 3, line 65:
That is exactly the question, whether ID is preventable, because in most countries and despite all efforts of health institutions it does not really work.
The reviewer is absolutely correct, and hence our first step to addressing this by conducting this analysis of the gaps in relevant research evidence concerning screening programmes.

Page 5, line 129: See:
Authors might include this study in their review since it shows data on in a high income country.
Thank you for highlighting this paper. We have added the reference to the section as suggested. We have also rewritten this section to emphasise that the particular gap in the literature relates to evidence regarding whether pregnant women with iron deficiency in the absence of anaemia require treatment and whether iron deficiency alone in this context has clinical consequences.

Page 6, line 156: IU device is correct only for the non gestagen containing devices. If they are coated by gestegens they actually improve ID!
We have amended this section to specifically explain that intrauterine devices without hormonal preparations increased iron deficiency by contributing to increased menstrual losses.

Page 7, line 184: Serum transferrin receptor is not available in many places and many obstetricians do not know how to interpret the results. I would doubt that it can be used in a screening program.
We have included a sentence to explain that serum transferrin receptor is currently not widely used in clinical practice. Table 4 also provides information relating to the complexity and availability of this test.

Page 8, line 194: See above, Hepcidin is expensive, a very sensible array, few experience in many labs. I think far too early to recommend.
We have acknowledged the novelty of this assay and the potential it offers to identify women who are iron deficient and may absorb iron and previously state the WHO/CDC recommendation that Hb with Ferritin or serum transferrin receptor currently represent the best tests for screening in populations. Table 4 also provides information relating to the complexity and availability of these tests.

Line 200:
Most used cut offs for pregnancy now are according to the CDC publications which define: 5th percentile of Hb in first and third trimester < 110 G/L and in second trimester < 105 G/L.
We have modified this sentence to clarify that the guidance adopted by NICE is the same as CDC published guidelines.

Page 10, line 239: Parenteral iron is not warranted in early pregnancy! due to safety regulations.
We have included a sentence within this section to explain that IV iron is only recommended for use from the second trimester.
Page 14, line 339: See above, might be available in a few labs/ countries but cannot be recommended in various countries. Authors should focus on ferritin for now. Please see our earlier response concerning hepcidin.

Page 16, Conclusion I think consequences of anaemia, especially severe anaemia are quite well documented. Problem remains consequence of ID alone. We have modified this sentence to clarify that it is specifically the consequences of mild to moderate anaemia and iron deficiency alone that remain poorly understood.

References Ref. 18: Cmaj, use capitals “CMAJ”
This reference has been corrected.

Table 3: Evidence very low See some literature attached such as the study from Sudan in anaemic women and the dramatic impact on maternal and fetal morbidity. More than low evidence here. Actually published in BMC: Severe anaemia is associated with a higher risk for preeclampsia and poor perinatal outcomes in Kassala hospital, eastern Sudan BMC Research Notes 2011, 4:311 doi:10.1186/1756-0500-4-311 The level of evidence as ‘low evidence’ here is based on the GRADE system. The assigned grade is reflective of the whole body of evidence identified for each mentioned outcome. The above mentioned study is a case control study and therefore based on the hierarchy of evidence employed within the GRADE scoring system it would be classified as providing low evidence.