Effect of Prenatal Maternal Iron Deficiency Anaemia on Birth Weight: A Systematic Review

Protocol of Dissertation

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Master of Public Health, University of Nottingham
Submitted By: AHANKARI ANAND
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[Research Protocol]

Effect of Prenatal Maternal Iron Deficiency Anaemia on Birth Weight: A Systematic Review

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ABSTRACT

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

To assess the effect of prenatal maternal iron deficiency anaemia on birth weight
**BACKGROUND**

**Description of the condition**

Anaemia is a major public health issue in developing as well as developed countries. Recent findings suggest that there is a decline in the prevalence of iron deficiency anaemia among industrialized regions, but the global prevalence is still higher in the developing world compared to the expected decline rate (Mumbare et al., 2012). WHO estimate that worldwide 41% of women and 27% of children are anaemic (Stoltzfus, 2011). Among these, iron deficiency is the most common condition; it seldom exists individually and is often observed clinically in combinations with other diseases such as malaria, malnutrition, infectious diseases and hemoglobinopathies. This is one of the challenges in diagnosing anaemia and establishing the treatment strategies (Msolla and Kinabo, 1997). In 2002, WHO considered iron deficiency anaemia as a major contributing factor to be global burden of diseases.

Worldwide more than half of pregnant women are anaemic, and 80% of them are in the developing countries (Mumbare et al., 2012). Pregnant women and young children are most susceptible to iron deficiency anaemia (El Guindi et al., 2004). It is influenced by food intake, social status, healthcare services and knowledge of women, and therefore it is a multidimensional health issue, which need to be addressed to improve maternal and child health outcomes (Msolla and Kinabo, 1997).

The optimal level of nutrition during pregnancy is the key to positive health. Prenatal maternal iron deficiency is identified as a major maternal health issue due to its adverse effects on developing foetus (Muthayya, 2009). Research has proved that, chronic malnutrition during pregnancy influences the birth weight of new-born (Udipi et al., 2000). The Centre for Disease Control showed that maternal iron deficiency affects the health of both mother and child (Looker et al., 2002). Previous epidemiological research claimed that iron deficiency among pregnant woman is responsible for intrauterine growth reduction, cognitive impairments, nutritional deficiencies and in turn the birth weight of foetus (Walker, 1998).

The recent research evidence suggests that maternal iron deficiency in pregnancy increases the neonatal mortality and morbidity (Stoltzfus, 2011). If the haemoglobin level is less than 8 grams/dl, then the risk of a death during delivery increases 2-3 folds. Further, if the haemoglobin drops below 5grams/dl, then the risk of death increases 8-10 folds (Kalaivani, 2009). A literature review by Ramussen (2001) outlined that the low maternal haemoglobin concentration is more likely to result in preterm delivery and thus foetal birth weight. Since 2000, several epidemiological findings have shown the serious impact of maternal
iron deficiency anaemia on foetal health. The latest case control study by Banhidy et al. (2011) in Hungary identified significant association between anaemia and birth weight. Additionally, studies by El Guindi et al. (2004) in France, Willows et al. (2000) in Canada, Mumbare et al. (2012) in Thailand, Kidanto et al. (2009) in Tanzania and Martinez et al. (1995) in Mexico have shown the significant association between the prenatal iron deficiency anaemia and neonatal birth weight. Ramussen (2001) mentions in his literature review that the results from several epidemiological studies are significant across the world, which explains the global burden of anaemia among pregnant women. However, there have been no formal systematic reviews conducted to provide estimates of the magnitude of the effect of iron deficiency anaemia on birth weight.

**Why it is important to do this review**

Based on the present literature findings, it appears that iron deficiency anaemia is more likely to have adverse effects on foetal health outcomes. It has increased the substantial risk of maternal and child mortality. It is important to conduct this systematic review because the iron deficiency anaemia is most common condition in the pregnancy, and affects development of foetus as outlined in the introduction. There are several research studies organized throughout the world as stated above. However, a systematic review and meta-analysis is not yet conducted about the effect of iron deficiency anaemia on neonatal birth weight.

The review can bring major evidences from articles, and collaboratively analyse the relation between prenatal iron deficiency anaemia and birth weight. The review findings may be useful to determine iron supplementations during pregnancy, and could provide evidence for public health professionals to design nutrition policies and programs at national and international level. Further the review aims to obtain published and unpublished articles available among all languages, regions and countries across the world, which will improve the generalizability of the results. Therefore, there is a clear rationale that a systematic review is required to answer these questions to establish the impact of iron deficiency anaemia on birth weight.

**OBJECTIVES**

To assess the effect of prenatal maternal iron deficiency anaemia on birth weight

**METHODS**

Criteria for considering studies for this review
Type of Studies
This systematic review aims to include all published and unpublished articles, which have assessed the effect of prenatal maternal iron deficiency anaemia on birth weight. For the review, we will consider cross sectional surveys, case control studies, cohort designs and review articles. Randomised control trials (RCT) cannot be the desirable option to conduct research in iron deficiency anaemia, as it would not ethical to subject half of the samples to be anaemic, when the serious impact of anaemia is known. It is less likely that RCT have been conducted, therefore RCTs will be excluded. The review aims to include studies among all countries and languages. For non-English language studies, translations will be sought where possible.

Type of Participants
All participants in the reviewed studies will be pregnant women or women who have recently given birth (< 1 year).

Type of Exposure
The issue of standardised cut off of anaemia will be handled cautiously. The WHO norm for women haemoglobin at 12.0 grams/dl will be considered in this review as a standard cut off. If there is any issue with this cut off level, then the respective author will be contacted (if contact is available). Iron deficiency might occur with other clinical conditions, and haemoglobin level may be influenced by confounders such as coffee intake, alcohol, smoking, malnutrition, altitudes (Martinez at al., 1995). Therefore, a separate subgroup analysis will be carried out to deal with these differences, as explained in the methodology section.

Type of outcome measure
As birth weight will be the primary measured outcome, the weight immediately after birth will be considered. Other foetal outcomes such as nutritional status, blood indices or physical status will not be evaluated, as the main aim of this study is to analyse the effect of prenatal maternal iron deficiency anaemia on birth weight of neonates.

Search methods for identification of studies
Electronic search
An electronic search will be made through University of Nottingham database services using OVID or EBSCO platforms. The following four databases will be searched to obtain articles for this review.
- CINAHL plus using EBSCO platform (1968 to present)
- EMBASE using OVID platform (1980 to present)
- MEDLINE using OVID platform (1948 to present)
- Web of Science (1899 to present)

The search strategy is mentioned in the appendix section.

**Searching other resources**

**Handsearching of reference lists**

The references of all included studies will be scanned to check for further relevant articles based on their titles and abstract reading. The handsearching will be limited to first generation, as it is more likely to obtain relevant articles through reference list of eligible studies (De-Vet et al., 2008).

**Journals**

The online search will be conducted using the most recent issues of the following journals to identify further articles. These journals have been previously used in developing systematic reviews in anaemia and child health (Higgins and Green, 2009).

- Archives of Pediatrics & Adolescent Medicine
- Blood Reviews
- Clinical Pediatrics
- Child and maternal health observatory
- Current Problems in Pediatric and Adolescent Health Care
- European Journal of Haematology
- Hematology and Oncology Clinics of North America
- The Journal of Nutrition
- The Journal of Pediatrics
- The Pediatric Clinics of North America
- Pediatrics
- The Lancet

**Grey articles**

The grey literature such as conference proceedings, reports, individual research and on-going studies will be thoroughly checked using the eligibility criteria. Informally published material is not sourced by
the aforementioned databases. Generally, these are the documents published by the government, academia, business, industries or individual researchers. Therefore, we will make an effort to obtain grey literature from the following agencies:

- Conferences announcements will be obtained through ISI proceedings and conference paper index services.
- A search through e-Theses and e-Dissertations will be carried to identify grey literature.

**Personal contacts**

We aim to contact authors of relevant studies, experts in the maternal iron deficiency anaemia and maternal and child health services. We will contact major institutes who conduct research in iron deficiency especially during pregnancy across the world to find further eligible on-going or completed studies.

**Data Collection and analysis**

**Selection of studies**

Both authors will follow the search strategy on four databases selected specifically for this review. Initially as a first step, both authors will independently screen all search hits for relevance against eligibility criteria (titles and abstracts), and discard all those that are clearly irrelevant. We will retrieve full text papers for those articles or references for which a decision of eligibility cannot be made from title and abstract alone. If essential, we will seek further information from authors of respective articles, where the published information is insufficient to make a decision. The differences between opinions will be resolved through discussion and consensus. Both authors will analyse full text, and any disagreements will be resolved through discussion. We will note down details of full text studies which do not meet our eligibility criteria in the ‘Characteristics of excluded studies table’.

**Data extraction and management**

Both authors will independently extract data onto previously piloted standardized forms. During the procedure, any disagreement will be resolved by consensus and mutual understanding.

1. **General information**

Date of data extraction, study ID, name of authors, first author, author’s contact (if available), citation of paper, and objective of the study
2. Study details

Study design, location, settings, inclusion and exclusion criteria, sample size and power calculations, method of identification of anaemia, assessment of neonatal birth weight, units used, comparability between samples/groups based on age, ethnicity and weight.

3. Characteristics of participants

Total number of participants, medical and family history, level of haemoglobin, status of anaemia, previous abortions/operatives/obstetrics history, birth weight of previous babies (if available) and measurement of socioeconomic status.

4. Analysis

Identification of the type of analysis carried out to assess the effect of prenatal maternal iron deficiency anaemia on neonatal birth weight, confounders, confounder adjustments, significant findings, biases, limitations, statistical analysis and results.

5. Confounding

The confounders affecting prenatal maternal iron level and neonatal birth weight will be considered while analysing the measure of effect.

6. Outcomes

Neonatal birth weight will be assessed as a major outcome.

Assessment of risk of bias in included studies

Both authors will independently assess all included studies for possible risk of bias as mentioned in the Cochrane handbook (Higgins and Altman, 2009). We will evaluate study design, conduct and analysis of each study using Newcastle-Ottawa scale. Based on this scale, included studies will be analysed under three domains, which are selection, comparability and exposures. A study can be awarded maximum of one star for each numbered item in the selection and exposure category, while in case of comparability, each numbered item can be awarded with maximum of two stars (Higgins and Green, 2009).

Measurement of effect

The outcome will be presented as risk ratios (RR) with 95% confidence interval (CI). In case of continuous outcome, mean differences with standard errors and 95% CI will be reported. The birth
weights will be calculated in grams. The standardised mean difference (SMD) will be used to evaluate difference between birth weight of neonates of anaemic and non-anaemic women (if obtained in the included studies) to allow for potential differences of outcome among these two groups.

**Unit of analysis issue**

It is more likely that this issue relates with the multiple pregnancies or births, therefore we will exclude these observations from studies (Higgins and Altman, 2009).

**Dealing with missing data**

If any issue of missing data, for example missing standard errors is observed, then we will contact the author (if available) accordingly, and solve queries about the data presented in the paper. If contact cannot be established, then we will assess the effect of imputing parameters on the robustness of the findings.

**Data Synthesis**

A meta-analysis will be carried out using Review Manager Software [RevMan, 2011] based on the data from included studies (Deeks and Higgins, 2010). We will aim to use a fixed term effect at first instance, but if the issue of moderate heterogeneity ($I^2 > 30\%$) arises then we will use a random effect method (Macaskill et al., 2010). The conclusion will be made based on the quantitative synthesis presented through tabular format, as well as summary measures. If there are any discrepancies among study designs, then those will be presented through separate tables. The GRADE profiler will be applied to create a summary of findings as suggested in the Handbook (Schuneman et al., 2008). The summary finding will include birth weight as a primary outcome.

**Assessment of heterogeneity**

The heterogeneity among included studies will be calculated by the $I^2$ statistic to quantify amount of heterogeneity using the following guidelines: $I^2 > 30\%$ as moderate heterogeneity; $I^2 > 75\%$ as considerable heterogeneity. If considerable heterogeneity is detected between the studies, formal pooling will not be used. We will carry out subgroup analysis (Macaskill et al., 2010), if the data is available. We will use assessment criteria of risk of bias in each study to explore heterogeneity among included studies before performing the subgroup analysis (Reitsma et al., 2009).
Assessment of reporting bias

The publication bias will be assessed through the funnel plot method, if more than 10 studies are included in the meta-analysis (Macaskill et al., 2010).

Sensitive analysis

The heterogeneity will be evaluated through sensitivity analysis. We will place emphasis on the study design, biases, settings, outcome measurement and analysis among included studies (Reitsma et al., 2009). We will analyse study population and their presented haemoglobin status in relation to the neonatal outcome: in terms of birth weight. The meta-analysis will be carried out cautiously to deal with any issues of heterogeneity. In the paper, possible explanation of heterogeneity among included studies will be discussed.

The quality of our findings will be assessed by restricting our analyses to studies with a low risk of bias on each of the domains of the Newcastle-Ottawa scale through sensitivity analysis, as outlined previously.

ACKNOWLEDGEMENTS

None

REFERENCES


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APPENDICES

- All languages (55 languages: No limitations based on the language in any of the following search)
- No limitations on the type of the document (search will be made among 20 different types of documents as listed on the databases such as: Article, Meeting, Letter, Patent, Reference material, Art and literature, Abstract, Review, Book, Editorial, News, Thesis, Report, Case reports, Correction, Retraction, Other, Unspecified, Biography and Bibliography).
- No other limitation will be implemented for any of the search.

In order to obtain every article, the search will be conducted with broad terms such as Iron, Anaemia/Anaemia, and subsequently will be combined with term such as birth weight. The following four appendices explain search terms with each database.
Appendix 1. CINAHL (NHS Evidence) search strategy (1968 to 2012)

The search will be carried out in sets, as the CINAHL database needs to be searched through combinations. The primary search will include all applicable subheadings and the search will not be limited to any options on database such as language, year or location of study. To obtain maximum articles, search area will include all relevant subheadings in primary and secondary search.

Set 1) Search keyword: Anemia, Anaemia and Weight

A) Search with keyword as anemia (Include relevant subheadings of anaemia if illustrated as iron deficiency, macrocytic, microcytic, haemolytic, neonatal, maternal anemia).

B) Search with keyword as anaemia (Include relevant subheadings of anaemia if illustrated as iron deficiency, macrocytic, microcytic, haemolytic, neonatal, maternal anaemia).

C) Secondary search with keyword as weigh* (include relevant subheadings if illustrated such as neonatal weight, foetal weight, birth weight, neonatal outcomes, birth measurements and weight, infant outcomes).

D) Combination of A, B, C will be evaluated for relevant articles.

Set 2) Search keyword: Iron and Weight

A) Search with keyword as Iron, and relevant subheadings (such as iron deficiency, macrocytic, microcytic, haemolytic, neonatal, maternal iron deficiency) under this tree search will be included to obtain maximum articles.

B) Secondary search with keyword as Weigh* (include relevant subheadings such as neonatal weight, foetal weight, birth weight, neonatal outcomes, birth measurements and weight, infant outcomes).

C) Combination of A and B will be evaluated for relevant articles.

Appendix 2. EMBASE (Ovid) search strategy

The search will be made with following similar terms and will be combined with the secondary search.

1) Haemoglobin
2) Haemoglob*
3) H$emoglobin
4) Anemia explode all trees (MeSH)
5) An$emia,
6) Iron deficiency
Effect of Prenatal Maternal Iron Deficiency Anaemia on Birth Weight: A Systematic Review

7) AnSemi*
8) ferrous
9) ferritin

A) 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 =>

10) Maternal health
11) Iron depletion
12) Nutritional deficiency
13) Maternal mortality
14) Neonatal mortality
15) Iron storage
16) Iron shortage
17) Iron intake
18) Developmental disease
19) FSetus
20) Infant
21) Infants
22) Infan*
23) Newborn
24) Neonate
25) Pregnancy, (subheadings if illustrated such as Gestation, Gestational age, child bearing, parturient, labor, labour)

B) 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 =>
26) Birth weight
27) Weight
28) Weigh*

C) 26 or 27 or 28
D) Combination between
   1) A and C
   2) B and C
Appendix 3. MEDLINE (Ovid) search strategy
(Incl ude all relevant subheadings during search terms)

1) Anemia
2) Anaemia
3) An$emia
4) Iron
5) Haemoglobin
6) Iron
7) Ferritins
8) Ferrous
9) Ferritin
10) Ferr*
11) Iron deficiency
12) Haemoglob*
13) Ane*
14) H$emoglobin
15) An$emi*

A) 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 =>

16) Birth weight
17) Weight
18) Weigh*

B) 16 or 17 or 18 =>

Combination between A and B

19) Maternal mortality
20) Neonatal mortality
21) Mortality

C) 19 or 20 or 21 =>

Combination between

1) B and C
2) A and C
Appendix 4. Web of Science: Database inclusion (all years available from the 1899 to 2012)

For each set combinations will be made between A and B or A, B and C.

Set 1)
A) Anemia OR Iron OR Ferr* (Ferr* = Ferrous, Ferritin)  
   And  
B) Weigh* OR weight OR birth weight

Set 2)
A) Maternal health OR child health  
   And  
B) Weigh* OR weight OR birth weight  
   And  
C) Anemia

Set 3)
A) Neonat* (Neonates, neonate) OR Infan* (Infant, Infants, Infancy)  
   And  
B) Weigh* OR weight OR birth weight  
   And  
C) Anemia

STUDY ANALYSIS

Table 1: Basic Information about study

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Title of the study</th>
<th>First author</th>
<th>Journal and year</th>
<th>References</th>
<th>Study design and period</th>
<th>Location</th>
<th>Number of participants</th>
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Table 2: Statistical data presented in the study

<table>
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<th>First author</th>
<th>Ratios (Risk Ratio or Odds Ratio)</th>
<th>Confidence Interval (95%)</th>
<th>P value</th>
<th>Confounders</th>
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Table 3: Table per outcome

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<th>Outcome 2</th>
<th>Outcome 3</th>
<th>Outcome 4</th>
<th>Outcome 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>First author = (----------)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
Table 4: Studies need to be discussed with other author

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Title of the study</th>
<th>First author</th>
<th>Journal and year</th>
<th>Study design and period</th>
<th>Reason for discussions</th>
</tr>
</thead>
</table>

Table 5: Excluded Studies (Characteristics of excluded study tables)

<table>
<thead>
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<th>Sr. No.</th>
<th>Title of the study</th>
<th>First author</th>
<th>Journal and year</th>
<th>Study design and period</th>
<th>Reason for an exclusion</th>
</tr>
</thead>
</table>

**DEFINITION**

1) **Prenatal**: Existing or occurring before birth
2) **MeSH**: Medical Subject headings

**HISTORY**

Protocol first Published: Issue1, 2012

**CONTRIBUTION OF AUTHORS**

Both authors contributed in writing the protocol.

**DECLARATION OF INTEREST**

None known

**SOURCES OF SUPPORT**

**Internal Sources**

University of Nottingham, Nottingham, United Kingdom, NG7 2RD

**External Sources**

No sources of support supplied

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