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Effect of Postpartum Anaemia on Maternal Health-Related Quality of Life: A Systematic Review

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Abstract

Background: Postpartum anaemia remains a persistent and severe public health issue in many parts of the world. Studies have reported mixed findings on the effects of anaemia during the postpartum period on maternal health-related quality of life (HRQoL). We conducted this systematic review to summarise available evidence to inform public health practitioners on whether 1) anaemia negatively impact maternal health-related quality of life and 2) whether iron supplementation in anaemic women can improve maternal HRQoL during the postpartum period.

Methods: This review's protocol was registered online with PROSPERO (CRD42020206618). We extensively searched Embase, PubMed, Cochrane and Scopus through the HINARI website to identify studies that reported either association or effect of postpartum anaemia on fatigue, depression and mother-child interaction. We restricted our search to studies of human females published in English from databases inception until August 2020. We followed a guideline for reporting systematic reviews without meta-analysis to synthesise data.

Results: Ten out of 15 studies where the direction of effect could be determined reported a significant association between lower Hb levels and physical fatigue symptoms. Fourteen out of 19 studies also reported a significant association between Hb levels and postpartum depression. There was evidence in six of the seven and seven of the eight randomised controlled trials that iron replenishment significantly decreased physical fatigue and postpartum depression respectively. Two of the four included studies showed that anaemic mothers were less responsive and had negative feelings towards their children than non-anaemic mother.

Conclusion: Evidence from this review suggests that postpartum anaemia negatively affects health-related quality of life and that iron replenishment improved both symptoms of fatigue and depression. Nevertheless, it remains unclear whether postpartum anaemia affects mother-child interaction.

Keywords: postpartum anaemia, fatigue, postpartum depression, mother-child interaction, iron deficiency anaemia, systematic review

Background

Postpartum anaemia remains a persistent and severe public health issue in many parts of the world.^[1] The World Health Organisation defines postpartum anaemia as a haemoglobin concentration of <11g/dl at one-week post-delivery and <12g/dl in the first postpartum year.^[2] Although maternal iron stores are expected to replenish after delivery, the prevalence of anaemia in women after childbirth remains unacceptably high in developed (22-50%) and developing (50-80%) countries.^[3] Postpartum anaemia is mainly caused by untreated antenatal iron deficiency or anaemia and excessive blood loss during or after childbirth.^[3] In many women, postpartum anaemia is classified as anaemia due to iron deficiency.^[1,4] Iron deficiency anaemia (IDA) is the state in which there is insufficient body iron to maintain the tissue's normal physiological function, i.e. blood, brain and muscles.^[5] A reduction of serum ferritin below 30µg/l in settings where inflammatory conditions are uncommon is suggestive of ID.^[5]

Untreated postpartum anaemia affects the wellbeing of both the mother and child. Maternal ID or anaemia related complications may impair physical capacity and performance and negatively impact health-related quality of life.^[6] Health-Related Quality of Life (HRQoL) is the patient's self-report on how her wellbeing and functioning level are affected by individual health or medical treatment received.^[7] Symptoms such as fatigue, psychological distress (anxiety and depression), and altered mother-child relationship are common indicators of HRQoL.

Since health care is becoming more patient-centred, patient-reported outcomes such as quality of life are increasingly becoming important.^[8] Worldwide, studies have reported mixed results on the association between postpartum anaemia and maternal HRQoL. For example, Chandrasekaran et al.^[9] reported no association between postpartum anaemia and HRQoL. Conversely, Khalafallah et al.^[10] found a strong association between maternal iron stores and improved HRQoL. Due to controversies surrounding the role of iron deficiency or anaemia on maternal HRQoL and the fact that improved maternal HRQoL after

childbirth guarantees improved wellbeing of the child, family and society^[11]; reaching a consensus can be influential in deciding whether postpartum iron supplementation improves maternal wellbeing. Therefore, we conducted a systematic review to determine the effect of postpartum anaemia on maternal HRQoL in the first postpartum year.

Method

Protocol registration

This review's protocol was registered online with PROSPERO (CRD42020206618) following the Preferred Reporting Items for Systematic Reviews and Meta-analysis.^[12]

Search Strategy

We searched Embase, PubMed, Cochrane and Scopus through the HINARI website. Appendix 1 shows a detailed description of search terms. We restricted our search to studies of human females published in English from databases inception until August 2020. After that, the results were directly exported into EndNote reference management software (Endnote 2017), and all duplicates were removed. We also searched references of included articles for additional relevant studies.

Study Selection

Studies that reported either the effect or association between anaemia or iron deficiency on any domains of HRQoL in the first postpartum year, as traditionally defined in most literature, ^[13] were eligible. We included randomised and non-randomised controlled trials, controlled before and after trials, prospective cohort studies, case-control studies and longitudinal studies. We excluded cross-sectional, case series, narrative reviews, commentaries and qualitative studies. Two independent reviewers (EM and NP), working in parallel, screened titles and abstracts of the identified articles. After that, full articles were retrieved for further evaluation. Discrepancies between the two reviewers were resolved through discussion. Disagreements between the two were resolved through discussion with MNM and KP.

Data extraction and management

A standardised, pre-piloted data extraction form was used to extract data from included studies. For studies with dichotomous outcomes, we extracted the number of events and the number of participants in each group. We extracted the effect measure, which included both crude and adjusted ratios with their respective 95% confidence intervals and p-values. We extracted means and standard deviation for continuous outcome with normally distributed data while medians, range and p-value of the non-parametric test were extracted for continuous skewed data. We also extracted correlation coefficients for correlation studies and median or mean change from baseline for longitudinal studies.

Risk of bias assessment

Two reviewers (EM and NP) independently assessed the risk of bias in the included studies, and disagreements were resolved through discussion. For randomised trials, we used a revised Cochrane risk-of-bias tool for randomised trials (RoB-2). Thereafter the risk of bias in the individual study was judged as either “*low risk*” or “*moderate risk*” or “*high-risk bias*”.^[12] The Newcastle-Ottawa Scale was used to assess the risk of bias for cohort studies and case-control studies.^[14] We considered studies rated with ≥ 7 stars as good (moderate risk).^[15] We adopted and modified a tool for evaluating the risk of bias in non-randomised studies of interventions (ROBINS-I) for longitudinal observational studies.^[16] We assessed bias due to confounding, selection of participants, missing data, measurement of outcome, and selecting the reported outcomes. We dropped two domains that assess bias due to intervention classification and deviations from the intended interventions as these were deemed not applicable.^[16]

Data synthesis

We analysed the available data and described the results from the studies with missing data. Data has been grouped and analysed separately depending on whether it has reported the effect of maternal anaemia on either fatigue, depression or mother-child interaction. Due to heterogeneity in the included

study, a meta-analysis was not possible. Therefore, we followed reporting guidelines for Synthesis without meta-analysis (SWiM) in systematic reviews.^[17]

Results

The searches in Embase, PubMed, Cochrane Central Trial, and Scopus databases through the Hinari website identified 7,547 citations, of which 82 (1.1%) full articles were extracted and assessed for their eligibility. Of the 82 articles, 29 (35.4%) met the eligibility criteria. We further included one article identified by searching the references of the included articles (Figure 1). We categorised and reported our findings based on the three domains of HRQoL, which includes fatigue (physical health), depression (mental health) and mother-child interaction (social wellbeing).

Postpartum anaemia and fatigue

Fifteen studies reported either effect or association between postpartum anaemia and fatigue (**Table 1**). Tam et al.^[18] recruited 150 anaemic women ($Hb \geq 8 \leq 9.9$ g/dl) on day two postpartum and randomly allocated them to either the iron supplementation or placebo groups. At six weeks postpartum, the iron supplementation group reported improved general wellbeing compared to those in the placebo group (p -value < 0.05). The risk of bias in this study was judged to be low.^[18] Similarly, Holm et al. ^[19-21], in all their three randomised studies, found that rapid improvement of body iron levels reduced maternal fatigue. They reported a -0.97 (95%CI, -1.65; -0.23, $p=0.006$)^[20] and -2.3 (95%CI, -3.3; -1.3, $p=0.0001$)^[21] change in aggregate physical fatigue in favour of rapid iron replenishment through intravenous iron isomaltoside from baseline to week 12 postpartum.

Westad et al.^[22] enrolled 128 anaemic women ($Hb \geq 6.5 \leq 8.5$ g/dl) and randomly allocated them to either intravenous plus oral iron ($n=58$) or oral iron only group ($n=70$). They found a marked improvement in physical fatigue scores corresponding with rapid iron stores replenishment in women in the intervention group than the control group at 4, 8 and 12 weeks postpartum ($p=0.02$, $p=0.02$ and $p=0.03$ respectively).

160 Additionally, Prick et al.[23] recruited 521 anaemic women and randomly allocated them to either the RBC
161 transfusion group (n=259) or treatment according to the local protocol group (n=262). Their findings
162 showed that mean physical fatigues scores were 0.8 (95%CI, 0.1; -1.5, p=0.02) and 1.06 (95%CI, 0.3; -1.8,
163 p=0.01) lower in RBC transfusion arm than those in local protocol at day 3 and 1 week postpartum
164 respectively. Similar findings were also reported in a matched intervention trial conducted in Greece,
165 where women who received recombinant human erythropoietin reported fewer clinical symptoms of
166 fatigue (p=0.0012) compared to oral iron.[24] Three observational studies also reported a significant
167 association between lower haemoglobin levels and maternal reports of feeling low energy (p<0.05) [25],
168 general fatigue at baseline (p=0.002), which disappeared after a week [26] and a significant correlation
169 between low Hb levels and fatigue (r = -.44, p = .01, n=30).[27]

170 Conversely, Hamm et al. (2020) recruited 66 anaemic women and randomly allocated them to either
171 multiple units of packed RBC (n=33) or a single unit of packed RBC (n=33). Despite women in single unit
172 arm having significant lower Hb levels (7.8g/dl versus 8.7g/dl, p<0.001), there was no significant difference
173 in fatigue scores (p-value=0.13) between the two groups.[28] Additionally, similar findings were reported
174 in four observational studies. Chandrasekaran et al.[9] enrolled 248 women who had an elective caesarean
175 section. Only 103 women were followed up until six weeks postpartum. They found no significant
176 association between anaemia and maternal functional status (OR: -1.03, 95%CI: -0.34; 2.94). Güven et
177 al.[29] enrolled 198 healthy women with singleton delivery and reported that after adjusting for bleeding,
178 baseline Hb was not associated with fatigue at any study time point.[29] Furthermore, Van Der Woude et
179 al.[8] reported no significant difference in physical functioning between anaemic and non-anaemic women
180 after adjusting for the mode of delivery. Miller et al. [30] also reported no significant association between
181 percentage change in Hb or ferritin levels with any SF-36 and MFI sub-scales.

182 ***Postpartum anaemia and depression***

Table 2 presents results on the effect or association between postpartum anaemia and maternal depression. Evidence from 14 of the 19 included studies suggested that postpartum anaemia increases the risk of postpartum depression. Sheikh et al.[31] conducted a randomised, double-blind, placebo-controlled trial which enrolled 70 depressed mothers on day seven postpartum and randomised them in either oral iron group (n=35) or placebo group (n=35). At six weeks postpartum, mothers in the iron supplementation group reported a significant decrease in EPDS scores ($p<0.001$) with a 42.8% improvement rate, while the change in EPDS score was non-significant in the placebo group ($p=0.13$). Another well designed randomised, double-blind study also found a significant association between postpartum anaemia and increased clinical symptoms of postpartum blues ($p<0.05$).[32] Interestingly, Perello et al.[33] reported no significant difference in depression scores which corresponded with no difference in haematological parameters between women who received ferrous sucrose plus oral iron and oral iron only group. Beard et al.[34] reported a significant decrease in EPDS scores associated with higher levels of Hb and MCV (-0.35 ; $p<0.005$, and -0.34 ; $p<0.005$), respectively and the symptoms of depression reduced after iron therapy. The risk of bias (RoB-2) in all of the above studies was low.

Holms et al. [23,24] found that favourable changes of haematological parameters in women who received intravenous iron were associated with favourable changes in EPDS scores at all study time points ($p<0.05$). These findings were not different from those of Paoletti et al.[35], who also reported a significant association between haematological measures and psychological scores ($p<0.05$) at 15th and 30th day postpartum. Seven observational studies also reported postpartum anaemia as a significant risk factor for depression. In Japan, Maeda et al.[36] followed up 1128 mothers and reported that anaemia during the postpartum period significantly increased maternal depression at four weeks postpartum even after adjusting for other risk factors (AOR: 1.63, 95%CI; 1.17-2.26). Similarly, Eckerdal et al.[37], in their nested-cohort study, recruited 446 women in Sweden and found that maternal anaemia at discharge predicted the development of depression symptoms (AOR: 2.29, 95% CI; 1.15-4.58) at six weeks postpartum.

207 However, the authors did not indicate whether symptoms of depression were not present at the start of
208 the study. A case-controlled study by Alharbi et al.[38] recruited 352 women (117 cases and 235 controls)
209 in Saudi Arabia and found that low haemoglobin levels were a significant risk factor for maternal
210 depression (AOR: 1.70, 95%CI; 1.05-2.74, p=0.03) at 8-12 weeks postpartum.

211 Goshtasebi et al.[39] recruited 254 women at delivery in Iran and showed that Hb of <11g/dl at delivery
212 increased the risk for maternal depression (AOR; 4.64, 95% CI: 1.33-16.08) at 4-6 weeks postpartum.
213 Furthermore, Albacar et al.[40] recruited 729 women at 48 hours post-delivery in Spain and reported that
214 ferritin persisted as a single iron marker associated with depression (OR: 2.30, 95%CI; 1.29-4.10 and OR:
215 3.75, 95%CI: 1.84-7.56 when a ferritin cut off <12µg/l and <7.26µg/l was used respectively) at 8 and 32
216 weeks postpartum. Additionally, Güven et al.[29] in Denmark recruited 196 women at day three post-
217 delivery and reported that an increase of 1 in baseline Hb corresponded to a decrease of 1.13 (p<0.0001)
218 and 0.7 (p=0.02) of depression scores at one and three weeks postpartum respectively. Despite Corwin et
219 al.[41] recruiting only 37 women on day seven post-delivery in the USA, they found a significant negative
220 correlation between overall mean Hb levels and CES-D score (r=-0.38, p=0.02) at day 28 postpartum.

221 Conversely, Hamm et al.[28] found no significant difference in depression scores between women who
222 received multiple packed RBCs and single packed RBCs despite a significant difference in Hb level (8.7g/dl
223 versus 7.8g/dl, p<0.001). Four observational studies also reported similar findings. Chandrasekaran et al.[9]
224 reported no difference in either Hb or iron stores in women who had signs of postpartum depression
225 compared to those without (OR; -0.69, 95%CI: -0.15;2.49) at six weeks postpartum. Similarly, Armony-
226 Sivan et al.[42] found no association between maternal iron stores (measured by Hb, MCV, ZPP, ferritin
227 and sTfR) and postpartum depression in a Chinese population at various study time points (r=0.10).
228 Additionally, Miller et al.[30] recruited 63 women who were admitted to labour and delivery room in the
229 USA and reported no significant association between anaemia (Hb<12g/dl) and depression scores. These

findings were not different from those reported by Paterson et al.^[25] in Britain. They enrolled 1,010 postnatal women and found no relationship between EPDS scores and Hb levels at 4 or 6 weeks postpartum. However, women with low Hb levels had high EPDS scores, but again the difference was not statistically significant ($p>0.05$).

Postpartum anaemia and mother-child interaction

Mixed findings were reported on the effect of postpartum anaemia on mother-child interaction (Table 3). Murray-Kolb et al.^[43], enrolled 95 women at Khayelitsha, South Africa and randomised them into either IDA-placebo ($n=30$) or IDA-ferrous ($n=34$) and non-anaemic control mothers ($n=31$). Mother-child interaction was assessed using a 20 minutes' video recording and independently transcribed by two blinded research assistants. At nine months postpartum, the control and IDA-ferrous group scored significantly better on maternal sensitivity, non-hostility, and structuring scales and child responsiveness scale than did the IDA-placebo group ($p\text{-value} = 0.007$), whose iron stores remained low. Similarly, earlier in the same setting, Perez et al. ^[44] enrolled 81 mothers (anaemic= 51 and non-anaemic= 30). The anaemic mothers were randomised to either IDA-placebo ($n=21$) or IDA-ferrous ($n=30$). The mothers were matched according to age, parity and educational background. The study reported that anaemic mothers in the IDA-placebo group had negative statements towards their infants, less goal setting and responsiveness than mothers in non-anaemic and IDA-ferrous groups ($p < 0.05$) at nine months postpartum.

Unlike the above findings, Hamm et al. ^[28] reported that significant improvement in Hb levels in women who received multiple units of RBCs (8.7g/dl versus 7.8g/dl) did not lead to significant improvement in maternal attachment scores. Dearman et al.^[45] in their pilot case-control study enrolled 115 women ($\text{Hb}<10.5\text{g/dl}=57$ and non-anaemic=58) and reported no statistical difference in maternal perception of mother-infant bonding between the anaemic and non-anaemic group.

Discussion of Results

Two important findings on the effect of postpartum anaemia on maternal fatigue were noted. Firstly, evidence suggests that anaemia as indicated by low Hb or depleted iron stores, is associated with maternal postpartum fatigue, which can be treated by iron replenishment. Our findings are similar to a previous review that investigated the impact of intravenous iron treatment on HRQoL in patients with IDA.^[46] A small sample size not powered to evaluate the effect of iron replenishment on fatigue might explain inconsistent findings reported by Hamm et al.^[28] Secondly, little attention has been paid to the same condition in developing countries, and it remains unclear whether the above findings are applicable in the African context. A meta-analysis by Badr et al.^[47] aimed at identifying predicting factors for maternal postpartum fatigue recommended further studies to determine whether race/geographical region can predict postpartum fatigue.

We found mixed findings on the effect or association between anaemia or iron deficiency on postpartum depression. Our review couldn't determine the source of heterogeneity in the study findings. However, Azami et al. (2020) found that study quality, design, time of measuring both depression and anaemia did not influence their meta-analysis findings reporting postpartum anaemia as a significant risk factor for postpartum depression.^[48] Similarly, our findings suggest that either postpartum anaemia or iron deficiency is an independent risk factor of postpartum depression and iron replenishment in anaemic women lowered symptoms of postpartum depression. We recommend future studies to investigate why studies conducted in different setting produce varying results. Importantly, more studies should be done in Africa, considering that the prevalence of anaemia is very high in this region.

The association between anaemia and mother-child interaction/bonding remains unclear. Globally, researchers have paid little attention to this area. We only identified four studies that showed mixed findings. Two well-conducted studies reported that maternal anaemia negatively impacted mother-child interaction. Other studies that reported no association also had some shortfalls. For example, the sample

size in Hamm et al.[28] was not powered to evaluate the effects of anaemia on secondary outcomes such as mother-child attachment. Dearman et al.[45] also acknowledged that lack of association in their study might be due to the small sample size lacking power.

Study Limitation

Our study has two major limitations. Firstly, we limited our search to human studies published in English only because none of the authors is conversant with other languages. Secondly, these studies' results were not pooled together due to heterogeneity in study designs and reported measure of effects. However, we followed acceptable methods of data synthesis as recommended by Campbell et al.[17].

Conclusion

To our knowledge, this is the first systematic review that has determined the effect of postpartum anaemia on maternal health-related quality of life in a holistic approach by incorporating all domains of HRQoL. While it is clear from our findings that postpartum anaemia negatively affects health-related quality of life domains of physical and mental health and that iron replenishment tremendously improved symptoms of fatigue and depression, it remains unclear on its impact on mother-child interaction. There is a paucity of data from developing countries on the effect of postpartum anaemia on HRQoL. We, therefore, call for well-designed studies in Africa to provide contextual evidence. Nonetheless, we agree and call upon clinicians in developing countries to adhere to the World Health Organisation recommendation of routine iron supplementation to women until six weeks postpartum to improve maternal HRQoL during the postpartum period.

Abbreviations

CES-D; Center for Epidemiological Studies Depression Scale, EPDS; Edinburgh Postpartum Depression Scale, HRQoL; Health-Related Quality of Life, IDA; Iron Deficiency Anaemia, MFI; Multidimensional Fatigue Inventory scale, RBCs: Red Blood Cells, SF-36; 36-Item Short Form Survey

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304 **Availability of data and materials**

305 We used data from previously published articles that have been cited.

306 **Author's contributions**

307 Author EM envisioned the systematic review and drafted the manuscript. NP was involved in data search
308 and assessing articles for eligibility and the risk of bias. MNM and KP provided technical review and
309 resolved disagreements between EM and NP. All authors read and approved the final version of the
310 manuscript.

311 **Ethics approval and consent to participants**

312 Not applicable

313 **Consent for publication**

314 Not applicable

315 **Competing interest**

316 All authors declare no competing interest

317 **Reference**

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Figures

Figure 1

The searches in Embase, PubMed, Cochrane Central Trial, and Scopus databases through the Hinari website identified 7,547 citations, of which 82 (1.1%) full articles were extracted and assessed for their eligibility. Of the 82 articles, 29 (35.4%) met the eligibility criteria. We further included one article identified by searching the references of the included articles

Supplementary Files

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