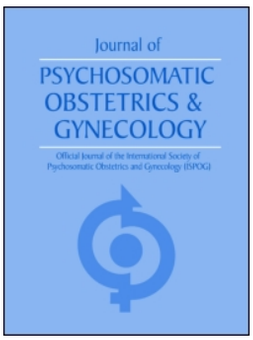

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REVIEW

Anaemia and depletion of iron stores as risk factors for postpartum depression: a literature review

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ABSTRACT

Purpose: Iron-deficiency and anaemia are common in pregnant and postpartum women because of increasing iron demand and blood loss. Many women also enter pregnancy with pre-depleted iron stores. We reviewed the evidence linking anaemia and/or iron-deficiency to postpartum depression (PPD).

Methods: We identified seventeen studies in four databases including randomized-controlled trials (RCTs) and observational studies assessing the impact of anaemia, iron-deficiency and iron supplementation on the risk of PPD. We extracted data on sample size, geographical region, obstetrical complications, measures of depression, haemoglobin, iron levels and intake of iron supplementation and critically appraised the results from the studies.

Results: Eight out of ten studies found higher risk for PPD (r −0.19 to −0.43 and ORs 1.70–4.64) in anaemic women. Low ferritin in the postpartum period but not during pregnancy was associated with increased risk of PPD. Iron supplementation in the postpartum period decreased risk of PPD in four out of five studies, whereas it did not protect from PPD if given during pregnancy. Limitations include study heterogeneity, discrepancy of prevalence of PPD and usage of a screening tool for evaluation of PPD.

Conclusion: Anaemia and/or iron-deficiency may contribute to PPD in at-risk women. Further studies should elucidate the association between these entities.

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Anaemia; ferritin; haemoglobin; iron; postpartum depression

Introduction

Postpartum depression (PPD) affects 9% of women [1]. It is linked to interference with breastfeeding and mother–infant interactions and reduced quality of childcare [2,3]. In addition to risk of suicide or recurrence of mental health illness in affected women [4,5], PPD can negatively impact developmental domains in offspring including emotional and cognitive functioning [2].

As pregnancy is associated with changes in physiological and nutritional needs, biological risk factors for PPD are a growing area of research interest. Iron demands are increased during pregnancy for foetal and placental development and increasing red blood cell mass [6]. In addition, many women enter pregnancy with insufficient iron stores, making iron deficiency one of the main nutritional deficiencies in expectant mothers [7]. Haemoglobin levels typically decrease during pregnancy with the expansion of the total blood volume. Many women will be affected by anaemia during gestation, the most common cause being iron-deficiency anaemia [6]. Iron stores and haemoglobin levels may be further reduced by blood loss at delivery.

A 2015 systematic review for the U.S. Preventive Task Force [6] led to inconclusive evidence for routine iron prenatal supplementation or screening for iron-deficiency anaemia in pregnancy on maternal or infant clinical outcomes apart from maternal haematological indices, though no study specifically measured depression as an outcome. However, the Center for Disease Control [8,9] recommends that women receive iron supplements as part of their prenatal care. In our article, we aim to review the evidence for the association between these conditions and for the benefit of repletion of iron stores for prevention or treatment of PPD.

Methods

Search strategy and article selection

In collaboration with a medical librarian, we conducted a literature review concerning anaemia and/or

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iron-deficiency and their association to PPD. We searched for articles indexed up to March 2017. The following databases were used: EBM Reviews, MEDLINE, EMBASE and CINAHL Complete. We included observational studies and randomized-controlled trials (RCTs).

The inclusion criteria were as follows: (1) studies had to be in English or French; (2) subjects had to be postpartum or pregnant because many cases of depression with peripartum onset start during pregnancy; (3) studies had to address iron stores or supplementation and/or haemoglobin; and (4) PPD had to be a primary or secondary outcome, measured by a validated scale such as the Edinburgh Postnatal Depression Scale (EPDS), the Center for Epidemiologic Studies-Depression-28 (CES-D-28), the Self-Report Symptom Inventory 90 Items-Revised (SCL-90-R) or a diagnostic interview.

Exclusion criteria were as follows: (1) studies that did not measure depression but only proxy outcomes such as quality of life and fatigue. This was done to decrease biases that could occur by confusing depression with less debilitating conditions; and (2) articles with a sample size smaller than 30.

Articles were selected based on inclusion and exclusion criteria and their references were searched for additional eligible articles.

Data extraction and appraisal

Two reviewers (AW and QDN) independently extracted the following data: sample size, country of origin, study design, haemoglobin and iron store measures when available, exposition to iron supplementation, measures and timing of PPD, impact of anaemia, iron stores or iron supplementation on PPD outcomes and information on postpartum haemorrhage. Results were independently appraised and compared looking at the associations between anaemia and PPD, iron stores and PPD, iron supplementation during pregnancy or after delivery and PPD. Because there was high heterogeneity in study design, we did not conduct a meta-analysis.

Results

We identified 379 articles across the databases. Duplicates were removed and titles and abstracts were reviewed, eliminating 353 studies. In the final analysis, 17 articles were included.

Of the 17 articles, 6 were randomized-controlled trials and 11 were observational studies, with 2 case-controls and 9 cohort studies. The sample size of the studies varied from 37 to 729 women. Publications originated from different countries including the US (2), Europe (8), Asia (2), Africa (1) and the Middle East (4). Fifteen studies assessed postpartum women while two included pregnant subjects during the third trimester. In one cohort study [10], postpartum depression occurred in only one woman restricting possible analyses. A summary of all results is shown in Table 1.

PPD instruments

Fifteen studies used the EPDS and two further validated results with a diagnostic interview. One study used the CES-D-28 for measurement of depressive symptoms and one used the SCL-90-R.

Haemoglobin levels and PPD

Ten studies examined the association between anaemia and PPD with seven finding a positive association, two finding none and one reporting results that were difficult to interpret because of possible errors in data. Most studies defined anaemia as a haemoglobin level less than 110 g/L, though there were variations in chosen thresholds from <100 g/L to <120 g/L.

Two studies conducted Pearson's correlations between postpartum haemoglobin levels and EPDS scores, with r scores of -0.35 [11] and -0.43 [12]. Corwin et al. [12] found that low haemoglobin levels at day 7 postpartum (but not at days 14 or 28) were associated to depression measured by the CES-D at 28 days postpartum. Overall haemoglobin levels in the first month postpartum were associated with a higher risk of depression ($r = -0.38$). Yilmaz et al. [13] found significant correlations between haemoglobin levels during the third trimester of pregnancy and EPDS scores ($r = -0.19$).

Three studies reported odd ratios for PPD in anaemic women and found that anaemia early after delivery conferred a higher risk of developing PPD, with significant odds ratio of 1.70 [14], 2.29 [15] and 4.64 [16]. However, the results in the study by Goshtasebi et al. [16] were inconsistent. Anaemia was defined as a haemoglobin level less than 110 g/L, but mean levels in the anaemic group were 115 g/L, making it difficult to understand how the authors arrived to their conclusion. Alharbi and Abdulghani [14] additionally concluded that gestational anaemia was associated with higher odds ratio of PPD though the reported confidence interval did not show significance (95% CI 1.44 (0.89–2.34). Eckerdal et al. [15] found that while anaemia at discharge was associated to an increased likelihood of PPD, there was no difference in

Table 1. Summary of results of the included studies on the association between anaemia, low iron stores and postpartum depression.

Authors (Reference)	Country	Number of subjects (*n*)	Study design and intervention	Postpartum depression measurement – tool and timing (Depressive symptoms measured as dichotomous or on a continuum)	Haematologic and iron status measurements	Main findings	Values
Albacar et al. [21]	Spain	729	Cohort	EPDS and confirmatory DIGS interview for scores <9 at 48 h PP, 8 weeks PP and 32 weeks PP (dichotomous)	Postnatal ferritin, transferrin, iron, sTfR	Strong association found between ferritin and PPD after control for confounding factors	OR =2.30, 95% CI (1.29–4.10) for ferritin <12 μg/L $p = .001$ OR =3.73, 95% CI (1.84–7.56) for ferritin <7.26 μg/L $p = .001$
						38.5% of women with PPD had depletion of iron stores versus 23.3% of women without PPD	$p = .007$
Alharbi et al. [14]	Saudi Arabia	352	Case-control	EPDS at 8–12 weeks PP (dichotomous)	Haemoglobin (Hb) during pregnancy and in postnatal period	Significant correlation between low Hb level in PP and PPD	$p = .015$
						Significantly more women with anaemia in PP had scores on the EPDS indicating PPD	OR =1.70 95% CI (1.05–2.74) $p = .03$
						Non-significant trend towards increased risk of PPD in women not taking iron supplements during pregnancy	OR =1.88 95% CI (0.66–5.34)
Armony-Sivan et al. [20]	China	137 (pilot sample) 567 (confirmatory sample)	Cohort	EPDS at 6 weeks PP EPDS at 24–48 h PP and 6 weeks PP (depression symptoms on a continuum and as dichotomous)	Haemoglobin, MCV, STfr, ferritin, Iron stores at mid and late pregnancy and at 3 days PP for a small sample	Pilot: No difference between EPDS score at 6 weeks PP in anaemic and non-anaemic women at mid-pregnancy nor end of pregnancy	$p = .69$ (mid-pregnancy)
						Confirmatory: No difference between EPDS score at 24–28 h PP or 6 weeks PP in anaemic and non-anaemic women at mid-pregnancy, late pregnancy or 3 days PP	$p = .51$ (late pregnancy)
						No significant correlation between hematological parameters except STfR in mid or late pregnancy or 3 days PP and EPDS scores at 24–48 h or 6 weeks PP	For Hb, MCV, ZPP, Ferritin and sTfR index, all $p > .05$ (r values <0.10)

(*continued*)

Table 1. Continued

Authors (Reference)	Country	Number of subjects (*n*)	Study design and intervention	Postpartum depression measurement – tool and timing (Depressive symptoms measured as dichotomous or on a continuum)	Haematologic and iron status measurements	Main findings	Values
Beard et al. [11]	South Africa	81	Randomized-controlled trial (anaemic women received vitamin C + folic acid or iron- + vitamin C + folic acid. There was also a control group of non-anaemic women receiving no supplements)	EPDS at 10 weeks and 9 months PP (depressive symptoms on a continuum)	Haemoglobin, MCV, transferrin saturation, ferritin at 6 weeks and 9 months PP	EPDS score significantly correlated to Hb levels	$r = -0.35$ $p < .005$
						Women receiving iron had lower EPDS scores at 9 months PP compared to women receiving placebo or non-anaemic subjects	$p < .05$
Corwin et al. [12]	United States	37	Cohort	CES-D at 28 days PP (depression symptoms on a continuum)	Haemoglobin at days 7, 14 and 28 PP	Significant correlation between Hb levels at day 7 and self-reported depressive symptoms at 28 days PP	$r = -4.26$ $p = .009$
						Significant negative correlation between overall mean Hb levels and CES-D score	$r = -0.381$ $p = .02$
Eckerdal et al. [15]	Sweden	446	Cohort	EPDS at 6 weeks PP(dichotomous)	Hb at discharge and at 6–8 weeks PP (measured or estimated by an algorithm)	Anaemia at discharge was significantly associated to PPD symptoms after controlling for confounders	OR =2.29 95% CI (1.15 − 4.58)
						No more anaemia at 6–8 weeks PP in women with or without PPD	$p = .99$
Ezzeddin et al. [25]	Iran	300	Case-control	EPDS had to be positive between 3 and 8 months PP for recruitment in the case group	Iron supplementation during pregnancy and in postpartum	No significant difference in iron supplementation during pregnancy between cases and controls	$p = .058$
						Not receiving iron supplementation in PP significantly augmented risk of developing PPD	OR =2.705 95% CI (1.628–4.496) $p < .001$
Holm et al. [23]	Denmark	196	Randomized-controlled trial (IV iron single dose or oral iron therapy)	EPDS at 3 days PP and 1, 3, 8 and 12 weeks PP (depressive symptoms on a continuum)	Haemoglobin, ferritin, iron, transferrin, transferrin saturation, reticulocyte count after delivery and at 3 days and 1, 3, 8 and 12 weeks PP	Significantly higher increase in mean Hb from baseline in the IV iron vs oral iron group	$p < .05$

(*continued*)

Table 1. Continued

Authors (Reference)	Country	Number of subjects (*n*)	Study design and intervention	Postpartum depression measurement – tool and timing (Depressive symptoms measured as dichotomous or on a continuum)	Haematologic and iron status measurements	Main findings	Values
						Significantly higher increase in in ferritin in IV iron vs oral iron group	$p < .05$
						Mean EPDS score significantly diminished more in the IV iron vs oral iron group	$p < .05$
Goshtasebi et al. [16]	Iran	264	Cohort	EPDS at 4–6 weeks PP (dichotomous)	Haemoglobin and ferritin at delivery	Anaemic mothers at delivery had significantly higher risk of developing PPD. However, anaemia was defined as Hb <110 g/L, but mean Hb in anaemic group was 115 g/L	OR =4.64 95% CI (1.33–16.08)
						No difference in ferritin level between the anaemic and non-anaemic group	
Meyer et al. [17]	Germany	71 anaemic women (and control group of 270 women)	Randomized-controlled trial (rhEPO vs placebo)	SCL-90-R at five days PP	Hematological parameters not given	Anaemic women as a group scored significantly higher on the depressive subscale than non-anaemic women	$p < .05$
Miller et al. [10]	United States	60	Cohort	EPDS at 1 day PP (dichotomous)	Haemoglobin and ferritin at admission and at day 1 PP	Only one women had positive EPDS score and no analysis made according to mean EPDS score	
Paoletti et al. [26]	Italy	552	Randomized-controlled trial (mineral and vitamin combination including iron vs calcium + vitamin D3)	EPDS at day 3, 15 and 30 PP (dichotomous)	Haemoglobin, serum iron, ferritin at day 3, 15 and 30 PP	Mean EPDS score was decreased in the intervention vs control group, even more so in the women with initial EPDS score suggestive of PPD	$p < .05$
						No significant differences between groups in hematological parameters after intervention	*p*: NS
Paterson et al. [19]	Ireland	528	Cohort	EPDS at 10 days PP, 4 and 6 weeks PP (dichotomous)	Haemoglobin at entry in study during pregnancy, at 34 weeks of gestation, after delivery and at 6 weeks PP	No association between Hb levels and EPDS scores at day 10 PP or 4 and 6 weeks PP	

(*continued*)

Table 1. Continued

Authors (Reference)	Country	Number of subjects (*n*)	Study design and intervention	Postpartum depression measurement – tool and timing (Depressive symptoms measured as dichotomous or on a continuum)	Haematologic and iron status measurements	Main findings	Values
						Non-anaemic primiparous women were the most at risk for high EPDS scores	
						No difference in postnatal Hb in women having taking iron supplementation or not during pregnancy	
Perello et al. [24]	Spain	72	Randomized-controlled trial (ferrous sucrose 200 mg IV/24h x 2 + oral iron vs IV placebo + oral iron)	EPDS at 48 hours, 1, 2 and 6 weeks PP	Haemoglobin, MCV, reticulocyte count ferritin, iron-binding capacity, iron levels at delivery and at 1, 2 and 6 weeks PP	IV iron + standard oral iron therapy did not significantly improve hematological parameters or EPDS scores in comparison to standard oral iron therapy + placebo	
Sheikh et al. [22]	Iran	70	Randomized-controlled trial (iron 50 mg PO vs placebo)	EPDS at day 7 PP. If positive, women were evaluated by a psychiatrist. If they were then considered to have postpartum depression, they were eligible for entry	Haemoglobin, MCV, haematocrit, MCH, serum iron, ferritin (women were excluded if Hb <105) at day 7 PP and at 7 weeks PP	EPDS scores significantly decreased in the iron-treated group vs. the placebo group	$p < .001$ vs $p = .13$
						The EPDS score was lower in the iron-treated group after intervention.	Median 9 vs. 12 $p = .01$
						The improvement rate for PPD was significantly higher in the iron-treated group	42.8 vs. 20% $p = .03$
						PPD cases after intervention had lower ferritin than the improved mothers	41.8 vs. 67 mg/dl $p = .03$
Tran et al. [18]	Vietnam	378	Cohort	EPDS at 12–20 weeks of pregnancy and during the last trimester (dichotomous)	Haemoglobin and ferritin at 12–20 weeks of pregnancy and during the last trimester	Significant pathway from common mental disorders and iron-deficiency anaemia via the length of time during which iron supplements were taken	OR =1.8 95% CI (1.1–2.6)
					Information on use of iron supplements	Direct effects of mental disorders on iron-deficiency anaemia in 3rd trimester were not significant	OR =1.09 95% CI (0.75–1.56)
Yilmaz et al. [13]	Turkey	450	Cohort	EPDS at 3rd trimester (depressive symptoms on a continuum)	Haemoglobin during routine 3rd trimester visit	EPDS scores significantly negatively correlated with Hb level	$r = -0.185$ $p = .000$

prevalence of anaemia at 6–8 weeks postpartum in women with or without PPD ($p = .99$). There was also no strong correlation between anaemia during pregnancy and EPDS scores at 6 weeks postpartum, the difference being only marginally significant ($p = .057$).

Meyer et al. [17] conducted a randomized-controlled trial where anaemic postpartum women were assigned to receive recombinant human erythropoietin (rhEPO) or placebo during the five days after delivery and were compared to a control group of non-anaemic women. Depressive symptoms were measured by the SCL-90-R at five days postpartum. When combined together as one group, anaemic women had worse scores on the depressive symptom dimension scale of the SCL-R-90 than non-anaemic women.

While the aforementioned studies hypothesised that anaemia led to development of depression, Tran et al. [18] interpreted their results otherwise, finding a significant indirect pathway from gestational depression to late pregnancy iron-deficiency anaemia via the length of time of iron intake. Direct pathways between depression and anaemia were not significant. Two studies found negative results. Paterson et al. [19] found that early postpartum anaemia was not associated to EPDS scores at ten days or 4 and 6 weeks postpartum. There was a non-significant trend for women whose haemoglobin had decreased from assessment during pregnancy to the early postpartum period to have higher scores on the EPDS at ten days postpartum. Armony-Sivan et al. [20] found no correlation between anaemia during pregnancy or after delivery and EPDS scores ($r < -0.10$). Timing of measures of haemoglobin and PPD were similar to other studies.

Iron stores and PPD

Five studies examined the association between iron stores and PPD, with three finding positive associations and two finding none.

Risk of PPD was reported as an odds ratio in two of the studies. Albacar et al. [21] found that low ferritin levels defined as $<12\,\mu g/L$ conferred 2.3 times greater odds of having PPD while ferritin levels $<7.26\,\mu g/L$ conferred an even higher likelihood of PPD (OR: 3.73), showing that as iron stores decreased, risk of developing PPD increased. More women with PPD were found to have depleted iron stores (38.5% versus 23.3%, $p = .007$).

In a well-designed RCT, Sheikh et al. [22] allocated postpartum non-anaemic women with PPD to receive oral iron supplementation versus placebo. Each group included subjects with and without iron-deficiency. After 6 weeks, the intervention group had higher median ferritin levels (78.2 vs 37 mg/dl). The mean EPDS score decreased in the intervention group ($p < .001$) but not in the placebo group ($p = .13$). More women in the iron-treated group no longer had PPD compared to controls (42.8 vs. 20%, $p = .03$) and women with continued depression had higher rates of iron deficiency than those no longer having PPD (27.1 vs. 4.5%, $p = .02$).

Holm et al. [23] found that women receiving IV iron after postpartum haemorrhage had better recovery of their ferritin levels and greater decrease in mean EPDS scores than those receiving oral iron.

Armony-Sivan et al. [20] found no correlation between iron stores and EPDS scores at 24–48 h or 6 weeks postpartum ($r < -0.10$). This was the only study that measured gestational but not postpartum iron stores. The association between iron stores and PPD may differ during these two periods. Because the former does not include the effect of ferritin decrease caused by blood loss at delivery, the association between ferritin and PPD may have been underpowered. Perello et al. [24] found that women receiving IV and oral iron improved their ferritin levels in comparison with women receiving only oral supplementation in the first two weeks after treatment, though the difference was no longer significant 6 weeks post-treatment. There were no differences in mean EPDS scores during this period.

Iron supplementation during pregnancy and risk of depression

Three studies compared PPD outcomes based on presence or absence of iron supplementation during pregnancy. In the study by Tran et al. [18] described earlier, depression indirectly increased risk of iron-deficiency anaemia in the third trimester by decreasing the length of time of intake of iron supplements. However, depression was defined as an EPDS score of 4 or more, a threshold much lower than was is typically used. Had the cut-off point been higher, the association between iron supplementation and anaemia may no longer have been significant. Alharbi and Abdulghani [14] found that women who had not received iron supplementation during their pregnancy had a non-significant trend towards increased likelihood of PPD (OR: 1.88 95% CI 0.66–5.34). Ezzeddin et al. [25] also found no difference in intake of iron supplementation during pregnancy between cases of PPD and controls, though the p values (.058) was near the significant threshold of 0.05.

Paterson et al. [19] and Alharbi and Abdulghani [14] found that iron supplementation during pregnancy did not influence postpartum haemoglobin levels,

suggesting that postpartum haematological parameters are influenced by other factors than pregnancy haematological indices (such as inflammation, blood loss, restoration of normal fluid volumes, etc.).

Eckerdal et al. [15] mentioned that iron supplementation was not associated to depression, though it was not specified if the authors were referring to iron supplementation during pregnancy or after delivery, impeding interpretation.

Iron supplementation after delivery and risk of PPD

Six studies assessed the relationship between iron supplementation after delivery and the risk of PPD. Five of these were randomized-controlled trials [11,22–24,26] and one was a case-control study [25].

Four RCTs found a positive association between iron supplementation and decrease in EPDS scores, though Paoletti et al. [26] concluded that iron had had a negligible role on the improvement of depression in the intervention group. Women were assigned to receive a combination of vitamin and minerals including iron or calcium and vitamin D3. After intervention, the mineral-vitamin group had a lower mean EPDS score than before and the effect was larger in women who had screened positive for PPD, independently of haematological parameters. Because post-intervention haematological indices including iron stores were similar in the two groups, the authors stated that iron was not responsible for this decrease. It is possible however that iron has beneficial effects on mood not mediated through haematological measures, though it is difficult to know which benefit can be ascribed to iron versus the other supplements. In addition, results may have been affected by the fact that all subjects were iron replete throughout the study.

Three out of the four studies finding a positive association did not report the magnitude of the effect of iron supplementation on EPDS scores; differences between intervention and control groups were only said to be significant ($p < .05$). In the study by Beard et al. [11], women in the iron group, the placebo-receiving group, and the control group comprised of non-anaemic women had similar mean EPDS scores at 10 weeks postpartum before intervention. However, the final EPDS scores were significantly lower in the iron group at 9 months postpartum. In the study by Sheikh et al. [22], iron supplementation in women with PPD was associated with an improvement in both mean EPDS score and number of women affected with PPD. Perello et al. [24] compared IV + oral iron versus placebo IV + oral iron in women with severe postpartum anaemia and found no benefit of IV iron added to oral supplementation in haemoglobin levels, long-term ferritin levels or EPDS scores. However, since there was no placebo group, no interpretation can be made comparing iron in a form or another versus placebo on PPD outcomes. In the case-control study by Ezzeddin et al. [25], not receiving iron after delivery was associated with an increased likelihood of PPD (OR 2.71 95% CI 1.63–4.50).

Discussion

The included studies were heterogeneous, with different populations and designs. Some compared haematological parameters in women with or without PPD, others compared PPD in women with or without anaemia, low iron stores, or both. These differences make comparisons between studies difficult. We only included studies measuring depression to avoid bias with similar conditions such as diminished quality of life and fatigue (a symptom of anaemia). All studies except two used the EPDS, a self-administered instrument designed for the assessment of peripartum depression. The EPDS is not a diagnostic tool and variation in the cut-offs the studies chose to assign women to 'PPD' vs. 'no-PPD' could have influenced the results.

Anaemia was associated with increased risk of PPD in 8 out of 10 studies comparing haemoglobin levels to depression scores though one seemed to have inaccurate data [16]. Paterson et al. [19] and Armony-Sivan et al. [20] found no association. In the former study, many women were lost to follow-up and it may be hypothesised that they were more likely to have been suffering from severe depression. This could have skewed the results if there was an underlying association between anaemia and PPD. Low ferritin was associated with a higher risk of PPD in three studies measuring ferritin during the postpartum period, but not in the study by Armony-Sivan et al. [20] where ferritin was measured during pregnancy. Gestational ferritin levels do not account for blood loss or postpartum haematological changes.

Iron supplementation in the postpartum period was associated to a decrease in EPDS scores in one case-control study and four RCTs. Iron supplementation during pregnancy does not appear protective of PPD.

Anaemia can be linked to blood loss caused by postpartum haemorrhage (PPH) and caesarean deliveries [27]. Eckerdal et al. [15] compared women with PPH to women with normal blood loss. There was no association between haemorrhage and PPD at 6 weeks postpartum ($p = .27$), though there was a trend for

women with bleeding to report a negative experience of delivery. Women with anaemia were more likely to have haemorrhaged and to have PPD. The authors suggested that variables such as negative self-reported delivery experience or trauma could have meditating roles in PPD development in women with obstetrical complications.

Despite them mostly using the same instrument, there was a wide variation in prevalence of PPD (1.6% to 33.2%) in the studies. Depression is a multifactorial disease and populations may have differed in baseline risk factors such as comorbidity or socioeconomic characteristics. Studies with higher prevalence may have categorised women whom would not have been clinically diagnosed as depressed as having PPD based on their EPDS score. In validation studies of the EPDS, only 50% of women with high scores were found to be depressed after psychiatric assessment [28]. We did not find a trend between the association of haemoglobin or iron stores with PPD and the reported prevalences.

Studies differed in construct of PPD as dichotomous (having or not PPD based on a EPDS threshold) or as a continuum of depressive symptoms (correlation with mean EPDS scores). Dichotomous categorisation decreases the power for finding associations because the threshold for PPD is higher. The two studies finding no association between haemoglobin levels and PPD used a dichotomous construct. As is the case when diagnosing all psychiatric illnesses using set criteria, it is difficult to balance the risk of overdiagnosis against the risk of overlooking clinically important symptoms that do not meet diagnostic criteria. Using a scale also carries the risk of finding statistically significant score changes with no real clinical impact. For example, in the study by Beard et al. [11], the mean EPDS score in the intervention group decreased from 2.5 to 2.1, a finding that was statistically significant though the initial mean score was already quite below the threshold for PPD.

There is no gold standard for assessing haemoglobin and iron status after birth. Because of blood loss, inflammatory response, and hemodynamic changes, haemoglobin and ferritin should not be measured before 48 h postpartum and become more reliable after one week [29]. Yet, many studies measured these parameters in the first days post-partum.

The association between anaemia, iron-deficiency and PPD is not demonstrated to be causal and may be bidirectional. Women with PPD may be less adherent to iron supplementation or present other predisposing factors to anaemia or iron-deficiency. On the other hand, because anaemia and iron-deficiency can lead to fatigue, these women may secondarily have impaired coping abilities, and at risk-subjects may spiral down into depression. Iron has a role in the synthesis of neurotransmitters associated with development of depression such as dopamine, serotonin and norepinephrine [28] and iron-deficiency has affective impacts outside of the postpartum period [30]. Anaemia has also been linked to depression in healthy, non pregnant or non postpartum adults [31]. This study found that anaemia was associated to a higher risk of depression in healthy adults (exempt of other medical comorbidity that could have explained the link between anaemia and depression).

Strengths of our review include the inclusion and analysis of studies measuring both haemoglobin and/or iron stores because these conditions are related. We also addressed a subject that is often overlooked though it may have serious clinical impacts that are easy to modify. However, the wide variation of methodologies and measures complicated data synthesis and did not allow conduct of a meta-analysis, a major limitation of our study.

Conclusion

The studies included in this review found differing results concerning the association between iron-deficiency and/or anaemia and PPD, but many suggested a significant association between low haemoglobin and/or iron deficiency and development of PPD as well as an improvement in mood with repletion of iron stores in the postpartum period, including randomized-controlled trials using robust designs.

Because PPD is a complex disease with many adverse impacts, identification of risk factors remains an important research objective. Our review emphasises significant areas of uncertainty in current data and could help guide further research to better understand the association between iron deficiency, anaemia, and PPD. Postpartum depression should be seen as a potential and serious outcome of low haemoglobin and iron stores.

Disclosure statement

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