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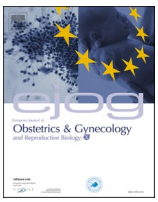

Incidence of postpartum depression after treatment of postpartum anaemia with intravenous ferric carboxymaltose, intravenous ferric derisomaltose or oral ferrous sulphate: A randomized clinical trial

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ABSTRACT

Objectives: This study aimed to explore whether the type of iron preparation used to treat postpartum anaemia affects the incidence of postpartum depression and whether the risk of postpartum depression is higher in postpartum patients with anaemia who were adequately treated compared to the general postpartum population.
Study design: Single-center, open-label, randomized trial. Women were allocated to receive intravenous ferric carboxymaltose, intravenous ferric derisomaltose or oral ferrous sulphate. Intravenous iron was given in one or two doses, while ferrous sulphate as two 80 mg tablets once daily. Primary outcome was postpartum depression measured by Edinburgh Postnatal Depression Scale (EPDS) six weeks postpartum. Haematological parameters were analyzed as secondary outcomes. Kruskal-Wallis test was used for group comparison ($p < 0.05$ significant). The chi-square test was applied to compare categorical variables as well as the group of all subjects treated for anaemia in the study with the historical data for the Slovenian postpartum population.
Results: Three-hundred women with postpartum anemia (hemoglobin < 100 g/L within 48-hours postpartum) were included between September 2020 and March 2022 in tertiary perinatal center. Most characteristics were similar across groups. EPDS score at six weeks postpartum did not differ between groups. The treatment modality of postpartum anaemia did not have a statistically significant effect on the EPDS score six weeks after treatment ($p = 0.10$), nor did it have a statistically significant effect on the difference in EPDS scores before and after treatment ($p = 0.68$). The proportions of participants who scored 10 or more points on the EPDS scores at six weeks postpartum were not statistically different between the groups ($p = 0.79$). The proportion of participants with an EPDS score of 10 or more at six weeks postpartum in the total study population did not differ significantly from previously reported proportion of postpartum women with EPDS score of 10 or more in the general population (12 % vs. 21 %; $p < 0.001$).
Conclusions: Maternal depression at 6 weeks postpartum did not differ in women treated for postpartum anemia with intravenous ferric carboxymaltose, intravenous ferric derisomaltose or oral ferrous sulphate. Participants with postpartum anaemia who are adequately treated with either oral or intravenous iron preparations are not at a higher risk of postpartum depression than the general population at six weeks postpartum.

1. Introduction

Postpartum iron deficiency anaemia is defined as a blood haemoglobin (Hb) level below 100 g/L. Although there are limited data on the prevalence of postpartum anaemia worldwide. Postpartum anaemia remains a persistent public health issue in many parts of the world [1] Studies conducted in high-income countries have reported that 10–30 % of postpartum women were anaemic [2]. The main cause is pre-existing anaemia in pregnancy combined with blood loss at childbirth. It is associated with postpartum depression, fatigue, and reduced cognitive abilities of the mother [1, 2, 3]. Postpartum depression is a depressive episode that develops in the puerperium at any time during the first year

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postpartum, most commonly within the first four weeks postpartum [4]. In Slovenia, 10–20 % of women in the first year postpartum suffer from severe depression and/or anxiety [5]. Postpartum depression is an important risk factor for suicide and is one of the most common causes of maternal mortality in the developed world [6]. Screening for postpartum depression is optimally performed two to six weeks after delivery using the Edinburgh Postnatal Depression Scale (EPDS). The psychosocial risk factors for depression are well understood, however, less is known about the physical factors. Nevertheless, association between postpartum anaemia and postpartum depression has been well described [7]. There are several options for the treatment of postpartum anaemia; oral iron medication, intravenous iron therapy, and blood transfusion. Oral iron is an effective, simple, safe and inexpensive source of iron replacement and is therefore the standard treatment for mild to moderate postpartum anaemia [2,8]. Parenteral therapy with novel iron compounds is chosen for severe anaemia and in cases where the patient does not respond to oral therapy [2,8]. Because of the potential for severe side effects, transfusions should only be administered to women with severe symptomatic anemia after birth [9]. Previous studies comparing oral and intravenous iron therapy for the treatment of anaemia have mainly focused on haematological indicators. There has been no study that has primarily investigated the incidence of postpartum depression and suicidal ideation in women with postpartum anaemia treated with oral vs. intravenous therapy. We aimed to explore whether the type of iron preparation used to treat postpartum anaemia affects the incidence of postpartum depression and whether, regardless of the iron preparation used, the risk of postpartum depression is higher in postpartum patients with anaemia who were adequately treated compared to the general postpartum population.

2. Material and methods

We invited women who delivered at the Ljubljana Maternity Hospital between September 2020 and March 2022 with anaemia (Hb $<$ 100 g/L) in the first 48 h after childbirth to participate. Exclusion criteria were history of anaemia due to known causes other than iron deficiency or blood loss after delivery, active infection, hypersensitivity to study medications, and renal or hepatic impairment. We did also not include women who did not speak Slovenian well enough to complete the EPDS questionnaire used to assess postpartum depression.

After receiving their informed consent, patients were firstly randomly assigned to one of three groups (1:1:1) using a computer-generated randomization process Secondly, they completed the Edinburgh Postnatal Depression Scale (EPDS) questionnaire upon inclusion in the study. Depending on the group to which the participant was assigned, iron supplement was administered according to the planned protocol. No subject received placebo alone. The dose of iron to be administered intravenously was calculated on the basis of the Ganzoni formula, which takes into account the patient's pre-pregnancy body weight and Hb values at the beginning of treatment. The iron preparations were diluted in 250 mL of 0.9 % sodium chloride and administered over 15–30 min. In accordance with the maximum single-dose limits, the subjects received ferric carboxymaltose (Iroprem®, Sandoz, Slovenia) (up to 1000 mg in a single dose) in the first group and ferric derisomaltose (Monofer®, Ewopharma, Denmark) (up to 1500 mg in a single dose) in the second group. If necessary, they received the remainder of the calculated dose after one week. The third group received ferrous sulphate (Tardyferon®, Pierre Fabre Médicament, France) with instructions to take regularly two tablets (2 ×80 mg) every 24 h up to six weeks postpartum.

The second phase of the study had participants undergo a follow-up exam and retake the EDPS questionnaire when they returned to the Ljubljana Maternity Hospital six weeks after childbirth.

The study was approved by National Medical Ethics Committee (approval date: 17 April 2019, approval number: 0120–117/2019/5) and registered at ClinicalTrials.gov (NCT03957057).

3. Statistical methods

A predetermined statistical analysis plan was applied for the analysis of all data. We analysed: the difference in median EPDS score between groups at 6 weeks postpartum; the difference in EPDS score between groups at inclusion and postpartum; the difference in the proportion of participants with EPDS scores $\geq$ 10 points between groups at 6 weeks postpartum; the difference in the proportion of participants with suicidal ideation between groups at six weeks postpartum; the difference in the proportion of participants with EPDS scores $\geq$ 10 points at six weeks postpartum in the total study population and in the general population of postpartum women in Slovenia from the previously published study by Koprivnik et al. [10].

Statistical analyses were performed using SPSS software (version 27.0; IBM Corporation, Armonk, New York). The Shapiro-Wilk test was used to assess the normality of the distribution of continuous variables. Due to non-normal distributions, comparisons across groups were made using the Kruskal-Wallis test. The chi-square test was applied to compare categorical variables as well as the group of all subjects treated for anaemia in the study with the historical data for the Slovenian postpartum population. A $p < 0.05$ value was considered to be statistically significant.

4. Results

Overall, 300 participants were included in the study. We excluded four women who received blood transfusion after iron supplementation and 18 women who did not attend a follow-up after six weeks and did not complete the EPDS questionnaire. Thus, 278 participants were included in the final analysis. There were no statistically significant differences between the groups in the baseline clinical characteristics (age, body mass index before conception and at delivery, proportion of multiple pregnancies, number of previous deliveries, caesarean section rate, gestational age, and educational level) (Table 1).

Fig. 1 shows the results of the EPDS questionnaire completed at 6 weeks postpartum by participants treated with intravenous ferric carboxymaltose, intravenous ferric derisomaltose or oral ferrous sulphate. Fig. 2 compares the differences in EPDS scores before treatment (at inclusion) and after treatment (six weeks postpartum). Data are presented as median values with interquartile intervals and maximum and minimum values. The treatment modality of postpartum anaemia did not have a statistically significant effect on the EPDS score six weeks after treatment ($p = 0.10$), nor did it have a statistically significant effect on the difference in EPDS scores before and after treatment ($p = 0.68$).

Table 1
Comparison of baseline characteristics of study population.

	Ferric carboxymaltose (n = 94)	Ferric derisomaltose (n = 93)	Ferrous sulphate (n = 91)	p-value
Maternal age, years	31 (± 8)	30 (± 7)	31 (± 9)	0.38
BMI before conception, kg/m^2	24 (± 6)	24 (± 5)	23 (± 6)	0.59
BMI at delivery, kg/m^2	28 (± 7)	30 (± 5)	29 (± 6)	0.52
Multiple pregnancies, n (%)	6 (2 %)	6 (2 %)	2 (1 %)	0.32
Nulliparity, n (%)	63 (23 %)	67 (24 %)	51 (18 %)	0.07
Gestational age at delivery, completed weeks of gestation	39 (± 2)	39 (± 2)	39 (± 2)	0.53
Caesarean section, n (%)	28 (10 %)	22 (8 %)	31 (11 %)	0.30
Education*	7 (± 4)	7 (± 4)	8 (± 4)	0.51

Data are presented as median with interquartile range or n (%); BMI body mass index; * educational attainment using the Statistical Office of the Republic of Slovenia grading (from 0, no education; 12, Ph.D. degree).

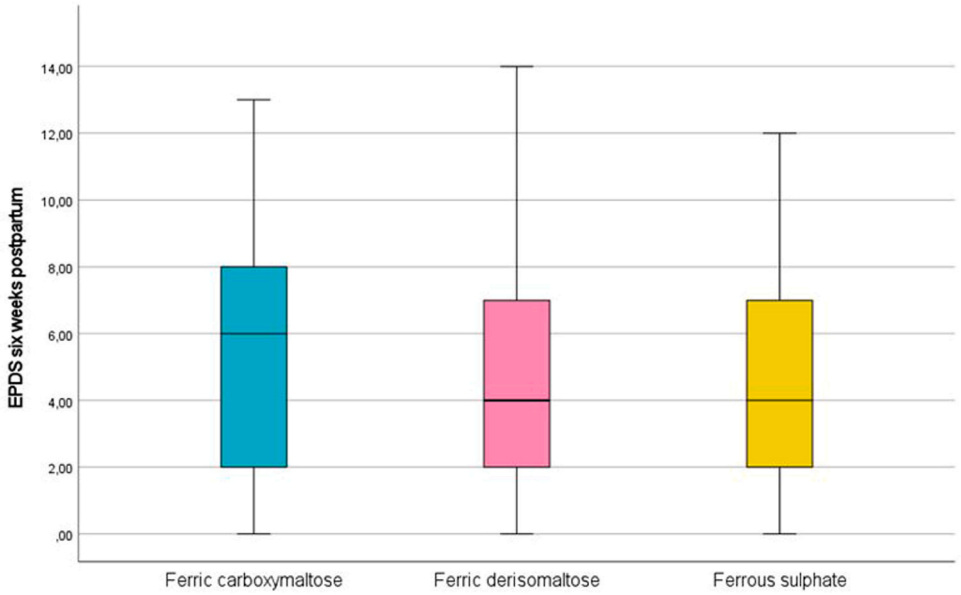

Fig. 1. Comparison of Edinburgh Postnatal Depression Screening Questionnaire (EPDS) scores at six weeks postpartum.

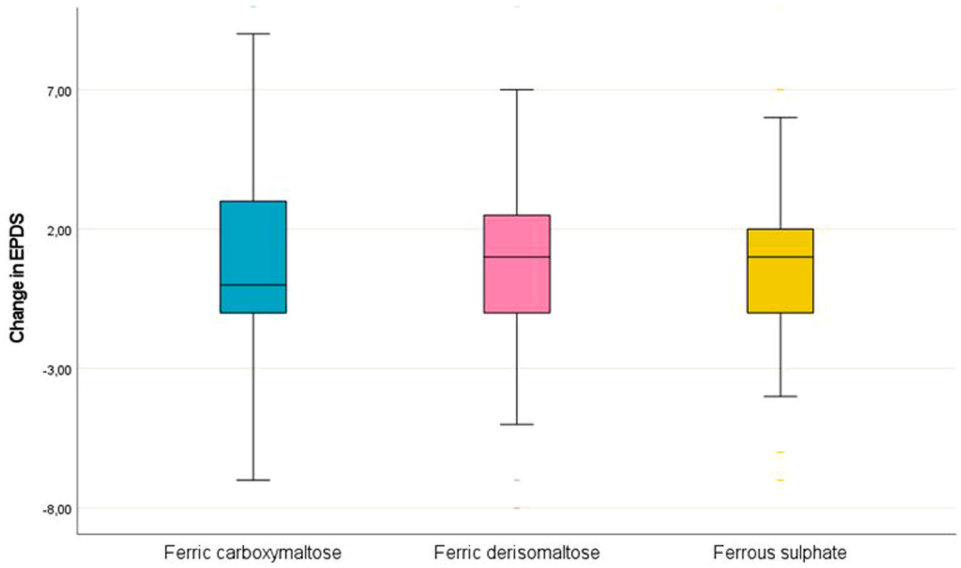

Fig. 2. Comparison of changes in Edinburgh Postnatal Depression Screening Questionnaire (EPDS) scores before and after anaemia treatment.

In the ferric carboxymaltose group, 12 (10 %) participants scored 10 or more points on the EPDS, 12 (4 %) participants in the ferric derisomaltose group, and 9 (3 %) in the ferrous sulphate group. The proportions of participants who scored 10 or more points on the EPDS scores at six weeks postpartum were not statistically different between the groups ($p = 0.79$).

The proportions of participants who responded positively to the question on the presence of suicidal ideation were statistically significantly different between groups ($p < 0.001$). The proportion of participants who responded positively to the EPDS question on the presence of suicidal ideation was significantly higher in the ferric carboxymaltose-treated group (6 (3 %)) than in the ferric derisomaltose-treated group (2 (1 %)) or in the ferrous sulphate-treated group (1 (1 %)).

The proportion of participants with an EPDS score of 10 or more at six weeks postpartum in the total study population was compared with the proportion reported by Koprivnik et al. [10] in their 2005 study. In the total population of participants in our study, 33 (12 %) had an EPDS score of 10 or more, whereas Koprivnik et al. reported 21 % of such women (78 out of 366) [10]. The difference in proportions was statistically significant ($p < 0.001$).

5. Comment

We have demonstrated that there are no significant differences in the incidence of postpartum depression between groups of anaemic participants treated with different iron supplements. There was a marked decrease in the proportion of women with EDPS scores ≥ 10 six weeks after delivery (12 %) compared with 20 % immediately after delivery. This decrease was similar in all three study groups. Given that postpartum anaemia is an important risk factor for the development of postpartum depression, the decrease in the proportion of participants with higher EDPS scores indicates the importance of appropriate detection and treatment of postpartum anaemia. The first EPDS measurement was performed in the first two days postpartum, when postpartum "baby blues" begins, which can affect 50–80 % of women, peaking around 72 h postpartum [10], whereas the incidence of

postpartum depression only peaks between the second and third month postpartum. The higher EPDS results in the first two days after delivery suggest that postpartum baby blues was already prominent in 20 % of the women included.

We found a statistically significant difference in the proportion of participants who responded positively to the question about suicidal ideations six weeks after childbirth. In the ferric carboxymaltose group, the proportion of mothers who answered positively to the EPDS question on the presence of suicidal ideation was significantly higher than in the other groups. This result is most likely due to the small number of participants who answered positively to the question on the presence of suicidal ideation and should be interpreted as a likely consequence of a type I (alpha) statistical error due to the random distribution of the small number of female subjects with suicidal ideation between the groups.

The findings of our study are comparable to those conducted on the population of participants worldwide and nationally. The prevalence of postpartum depression worldwide ranges between 7 % and 23 % [10]. One international study using the EPDS questionnaire at 6 weeks postpartum was conducted in Israel in 2000 and reported a 23 % incidence of postpartum depression, which is higher than the 12 % observed in our study [11]. The largest study to date examining the association between anaemia in pregnant women and postpartum depression was conducted in a tertiary centre in Japan. It included 1128 pregnant women and found that anaemia in the postpartum period was significantly associated with an increased risk of postpartum depression [6].

In contrast, the incidence of postpartum depression among women with postpartum anaemia in our study was significantly lower compared to previously reported overall incidence in the country [10]. In the present study, 12 % of participants scored 10 or more on the EPDS at 6 weeks postpartum, while Koprivnik et al. reported a higher proportion (21 %) in the unselected population of postpartum women in Slovenia in 2005 [10]. These data were used in our analysis to compare the level of depression in the population of anaemic participants after appropriate treatment with the general population, due to the relatively similar methodology. It has to be noted, however, that in order to definitively conclude that anaemic pregnant women after appropriate iron supplementation treatment are at no higher risk of postpartum depression than the general population, we would need to have data for the whole population over the same time period, i.e. 2020–2022.

5.1. Strengths and limitations

Our study has several limitations. The sample includes only participants recruited in a single tertiary-care perinatal centre. As a result, the sample may not be representative for the whole population of women postpartum and the results should not be generalised. We also did not include participants with severe chronic illnesses, who may be at an even higher risk of postpartum depression. Although our findings on the prevalence of postpartum depression are comparable to those of previous studies, the exclusion of participants who did not speak Slovenian well enough to complete the EPDS questionnaire may mean that our results are not valid for women with other linguistic or socio-cultural background. Another limitation of the study is the relatively small sample size of participants, but given the very small differences in EPDS scores between groups, it is unlikely that these differences would be statistically significant even with a larger sample size.

In addition to its limitations, our research also has some strengths. It is the first randomised trial to investigate possible differences in the incidence of postpartum depression after the treatment of postpartum anaemia with different iron supplements. Of the few studies that have looked at clinically-relevant, patient-centered outcomes of postpartum anaemia treatment, none has compared the three iron preparations used in the study. Another strength is the high response rate, with 91 % of the women returning for follow-up six weeks after delivery.

6. Conclusions

In anaemic participants postpartum, the choice of iron supplementation has no significant effect on the risk of postpartum depression. Participants with postpartum anaemia who are adequately treated with either oral or intravenous iron preparations are not at a higher risk of postpartum depression than the general population at six weeks postpartum. Diagnosing and treating postpartum anaemia can reduce the incidence of postpartum depression regardless of the iron preparation used.

Data sharing information

a. Will individual participant data be available (including data dictionaries)?	• Yes
a. What data in particular will be shared?	• Demographic and baseline characteristics, main and secondary outcomes
a. What other documents will be available (e.g., study protocol, statistical analysis plan, etc.)?	• N/A
a. When will data be available (start and end dates)?	• Data will be available on request from publication onward for at least 15 years
a. How will data be shared (including with whom, for what types of analyses, and by what mechanism)?	• Data will be shared on request in the format requested.

Declaration of Competing Interest

L.B.T. and M.L. received fees from Ewopharma for leading an anemia in pregnancy and postpartum workshop in Slovene after study completion (Anaemia Talks 2022, June 8th, local meeting, Ljubljana, Slovenia). Other authors declare report no conflict of interest. The study received no specific funding. Pharmaceutical companies manufacturing or marketing iron preparations used in the study had no role in study design, data collection, data analysis, data interpretation or writing of the report.

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