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Research report

An association between plasma ferritin concentrations measured 48 h after delivery and postpartum depression

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ABSTRACT

Context: Iron deficiency is the most common nutritional problem experienced by childbearing women, and postpartum depression (PPD) is the most common psychiatric disorder seen during the first year after delivery. The possible link between iron deficiency and PPD is not clear.
Objective: To evaluate whether iron status 48 h after delivery was associated with PPD. Our hypothesis was that iron deficiency would be associated with PPD.
Design: This was a prospective cohort study of depression-free women studied in the postpartum period.
Setting: Women who give birth at obstetric units in several general hospitals in Spain.
Participants: A subsample of 729 women was included in the present study after exclusion of women with high C-reactive protein (CRP) and other diseases known to interfere with iron metabolism.
Main outcome measures: We evaluated depressive symptoms at 48 h, 8 weeks and 32 weeks postpartum and used a diagnostic interview to confirm the diagnosis of major depression. A blood sample obtained 48 h after delivery was used to measure the following iron storage parameters: ferritin, transferrin (Tf), free iron and transferrin saturation (TfS) and the inflammatory marker CCRP.
Results: Overall, the women in the study had low iron concentrations (8.8 ± 6.9 μmol/L) and low TfS ($12.6 \pm 9.6\%$) but normal ferritin and Tf concentrations. A total of 65 women (9%) developed PPD during the 32 week postpartum period; these women also had a lower ferritin concentration (15.4 ± 12.7 μg/L vs. 21.6 ± 13.5 μg/L, $P = 0.002$). A strong association between ferritin and PPD was observed (odds ratio = 3.73, 95% CI: 1.84–7.56; $P = 0.0001$ for ferritin cutoff value of 7.26 μg/L). In our study, ferritin concentrations have a high specificity but low sensitivity in predicting PPD.
Conclusions: These findings support the role of iron in the etiology of PPD and the use of ferritin as a marker of iron deficiency in the postpartum period. We believe that this topic deserves further investigation.

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1. Introduction

Postpartum depression (PPD) is the most common psychiatric disorder experienced by women after childbirth (McGarry et al., 2009) with a prevalence of approximately 7% during the first three months postpartum (Garcia-Esteve et al., 2003; O'Hara, 2009);(Sanjuan et al., 2008). According to the DSM-IV criteria, PPD is indistinguishable from major depression with the exception that the symptoms must occur within weeks after delivery and that the symptoms cannot be better accounted for by the diagnoses of postpartum blues or postpartum psychosis (American Psychiatry Association, 1994). The condition can last from a few weeks to six months or more (Burt and Quezada, 2009) and, if untreated, can have a large economic impact on the patient's family as well as the public health infrastructure (Petrou et al., 2002), in addition to influencing mother–infant interactions and child development (Pearlstein et al., 2009). Genetic, hormonal, psychosocial, obstetric and biological factors have been associated with PPD (Brummelte and Galea, 2010; Garcia-Esteve et al., 2008; Leung and Kaplan, 2009; Sanjuan et al., 2008; Sibolboro Mezzacappa and Endicott, 2007).

Most authors have identified a history of a depressive episode and anxiety during pregnancy as the principal risk factors for PPD (O'Hara, 2009; Oppo et al., 2009). Some reports have demonstrated a link between PPD and deficiencies in micronutrients such as omega-3 fatty acids, zinc and iron (Bodnar and Wisner, 2005; Leung and Kaplan, 2009). Iron deficiency is the most common nutrient deficiency in the world, and it is especially prevalent in childbearing women (The World Health Organization, 2001). During the second trimester of pregnancy, iron requirements increase, and as a consequence, iron stores become depleted (Bothwell, 2000). The prevalence of iron deficiency during pregnancy ranges from 18 to 40% in developed countries (The World Health Organization, 2001) where iron supplementation is often offered to pregnant women (Pena-Rosas and Viteri, 2006); however, data on iron deficiency after delivery is scarce.

Iron is required by all tissues but is stored in the liver in a ferritin-bound state (60%) and also in muscle and the reticuloendothelial system (40%). In the plasma, circulating iron is primarily bound to transferrin (Tf). The hematological parameter "percent transferrin saturation" (TfS) (Fairbanks and Klee, 1999) is used as a marker of the amount of bioavailable iron in the plasma. The transferrin receptor-1 (TfR1) is produced in all types of cells and binds to the Fe–Tf complex. Thus, TfR1, ferritin and TfS are all markers of plasma iron stores and metabolism (The World Health Organization, 2001).

In the general population, iron deficiency has been classified into three stages according to severity; they are the following: (1) the depletion of iron stores, (2) marginal iron deficiency, and (3) iron deficiency anemia. Depletion of iron stores is characterized by ferritin <12 μg/L in the presence of normal circulating iron and hemoglobin concentrations. Marginal iron deficiency is characterized by depleted iron stores and reduced circulating iron concentration (TfS <16–20%) in the presence of normal hemoglobin levels. Iron deficiency anemia is characterized by reduced hemoglobin concentration (Brownlie et al., 2002). The clinical manifestations of iron deficiency anemia are well known in the general population; however, iron deficiency without anemia can also cause health problems (Khedr et al., 2008; Verdon et al., 2003). Iron is an essential micronutrient and plays important roles in oxidative metabolism, immunity and red blood cell synthesis (Munoz et al., 2009). In the brain, iron is involved in the synthesis of monoamine neurotransmitters and the myelination of axons (Beard, 2003; Beard and Han, 2009). There have been several studies published on the relationship between iron status and depression in the general population; however, the results are controversial (Baune et al., 2006; Hunt and Penland, 1999; Maes et al., 1996). Maternal iron deficiency anemia is associated with alterations in the mother's emotions and cognition as well as delayed infant development during the postpartum period (Beard et al., 2005; Murray-Kolb and Beard, 2009; Perez et al., 2005). There is a paucity of data, however, regarding the relationship between the depletion of iron stores (with or without anemia) and PPD. We hypothesized that depletion of iron stores would be associated with PPD. The purpose of the present study was to assess the possible relationship between iron status and PPD using iron deficiency markers collected 48 h after delivery when the mother and newborn child were still in the hospital.

2. Subjects and methods

2.1. Participants

Our study population was obtained from a larger multicenter prospective study of 1804 women that examined genetic and environmental factors associated with PPD; this study was conducted in Spain between December 2003 and October 2004 (Sanjuan et al., 2008).

The ethics committees at each of the participating hospitals approved the study. All participants volunteered, were of Spanish origin (Caucasian) and were >18 years old. Participants who were under psychiatric care during pregnancy were excluded from the study. The additional exclusion criteria in the present study were as follows: lack of plasma data (835 participants excluded), history of thyroid dysfunction according our previous study (Albacar et al., 2010) (25 women excluded) and severe systemic inflammation, which was defined as an elevated C-reactive protein (CRP) concentration ≥ 101.16 mg/L (90th percentile), and ferritin concentration ≥ 57.56 μL (90th percentile; 215 women excluded). In total, 729 women were included in the study. The 1075 excluded participants did not differ significantly from the individuals included in the study population with regard to the variables examined. Women with hemoglobin concentrations <12 g/L during pregnancy received iron supplementation based on the Spanish Gynecologic and Obstetrics Society guidelines. In the postpartum period, with the exception of the 16 weeks of paid maternity leave and the obstetric visit at 8 weeks postpartum, there are no special maternal support programs that exist for new mothers. Iron status after delivery is not measured unless the mother seeks medical care. Participants were assessed by the research teams (nurses, clinical psychologists and psychiatrists) at three time points: 48 h (obstetric ward), 8 weeks (obstetric unit) and 32 weeks postpartum (research unit, home or telephone visit). A blood sample was obtained 48 h

after childbirth to avoid the intrinsic physiological changes that occur as a result of delivery but still allow collection before the mother and newborn child left the hospital.

2.2. Assessment of depression

Depressive symptoms were assessed 48 h (baseline), 8 weeks and 32 weeks postpartum using the validated Spanish language version of the Edinburgh Postnatal Depression Scale (EPDS) (Garcia-Esteve et al., 2003). Women with scores higher than 9 on the EPDS at 8 or 32 weeks postpartum were identified as probable depression cases. The cutoff of 9 for major depression increases the sensitivity to 100% and the specificity to 89% (Navarro et al., 2007). Women scoring <9 on the EPDS were further evaluated using the Spanish language version of the Diagnostic Interview for Genetics Studies (DIGS) (Roca et al., 2007), which has been adapted to assess the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria for PPD; this was used to confirm the diagnosis. All interviews were conducted by clinical psychologists or psychiatrists who were previously trained in the DIGS using the same video case records. A reliability of kappa>0.8 was obtained among interviewers.

2.3. Blood samples and biochemical measurements

Fasting blood samples were collected in 10 mL tubes containing EDTA within 48 h postpartum at 8:00–9:00 AM, were quickly centrifuged to separate the plasma and serum from the cells and were then immediately frozen at −80 °C until analysis. All of the samples were analyzed in one laboratory using the same procedure. Serum ferritin concentration was measured using a microparticle enzyme immunoassay within an Axsym system (Abbott, Madrid, Spain). The CRP, plasma iron and Tf concentrations were determined using biochemistry procedures from Dimension AR (Dade Behring). According to the manufacturer's instructions for each assay, the sensitivity of the ferritin assay was 1.0 μg/L, with a normal range of 6.9–282.5 μg/L in women; the sensitivity of the CRP assay was 0.5 mg/L, with expected values for healthy individuals<3.0 mg/L; and the normal ranges of iron and Tf were 9.80–19.90 μmol/L and 2.0–4.0 g/L, respectively. We calculated TfS according to the method described by Fairbanks (Fairbanks and Klee, 1999).

2.4. Assessment of depletion of iron stores and marginal iron deficiency

Iron, Tf, TfS and ferritin were all used as markers of iron deficiency. We considered iron stores to be depleted when the serum ferritin concentration was <12 μg/L. Marginal iron deficiency was considered to be present when TfS was <16% and serum ferritin was <12 μg/L. These classifications were based on previously published descriptions of iron deficiency in the general population (The World Health Organization, 2001), as we excluded women with severe inflammation. Additionally, we used an iron deficiency cutoff for ferritin concentration of <7.26 μg/L (10th percentile).

2.5. Statistical analysis

Sociodemographic and obstetric variables (Table 1) were recorded. Qualitative variables were presented as percentages, and most quantitative variables (iron, ferritin, Tf, TfS and CRP) were presented as medians and standard deviations. Age was presented as the mean and SD. Because neither the raw quantitative variables nor the log-transformed quantitative variables were normally distributed, the non-parametric Mann–Whitney U test was used to compare these variables between the PPD and non-PPD groups. The chi-square test was used to compare the distribution of categorical qualitative variables across the PPD and non-PPD groups. Potential co-linearity between markers of iron metabolism and markers of inflammation was assessed using Spearman's correlation. A binary logistic regression model (Model 1) was created for each of the predictor variables (CRP, iron, ferritin, Tf, TfS and employment status during pregnancy). Based on the iron deficiency criteria, two multivariate logistic regression models were created (Models 2 and 3) to assess the relationship between PPD and risk factors for iron deficiency (ferritin and TfS), an inflammatory parameter (CRP), and employment status during pregnancy. In Model 2, the World Health Organization (WHO) definition of iron deficiency was used (i.e., ferritin<12 μg/; The World Health Organization, 2001). In Model 3, a cutoff level for ferritin of <7.26 μg/L (10th percentile for the total sample) was used. The Hosmer–Lemeshow chi-square test was used to assess the goodness of fit of these models. The Wald test was performed, and the associated odds ratios (ORs) and 95%

Table 1
Sociodemographic and obstetric characteristics of the total study population and of the PPD and non-PPD subgroups.

	Total sample n = 729	PPD n = 65	Non-PPD n = 664	P-value
Sociodemographic characteristics				
Age (years)	31.7 ± 4.7	31.2 ± 5.1	31.8 ± 4.6	0.32 [a]
Marital status (%)				
Partner	97.8	96.9	97.9	0.64 [b]
Without partner	2.2	3.1	2.1	
Employment status (%)				
Employed	76.7	63.1	78.0	0.009 [b]
Unemployed	23.3	36.9	22.0	
Education level (%)				
Primary school	31.7	40.0	30.9	0.23 [b]
Secondary school	41.3	40.0	41.4	
College degree	27.0	20.0	27.7	
Obstetric characteristics				
Lactation (%)				
Breast milk	87.1	92.3	86.6	0.38 [b]
Formula	11.4	6.2	11.9	
Both	1.5	1.5	1.5	
Caesarean section (%)				
Yes	12.2	12.3	12.2	1.00 [b]
No	87.8	87.7	87.8	
Parity (%)				
0	38.7	33.8	39.2	0.28 [b]
1	38.5	49.2	37.5	
2–4	21.4	15.4	22	
5–9	1.4	1.5	1.4	

Age is shown as the mean ± SD (standard deviation).
[a] Student's t-test.
[b] Chi-square test.

confidence intervals were calculated. The predictive value of the ferritin level with regard to PPD risk was calculated according to the methods described by Sackett et al. (2001). All two-tailed P-values <0.05 were considered to be statistically significant. We used SPSS version 15.0 for all statistical analyses.

3. Results

Of the 729 depression-free women included in the study, 19.2% scored >9 on the EPDS scale at 48 h postpartum, 12.4% at 8 weeks postpartum and 13.4% at 32 weeks postpartum. Sixty-five women (9%) experienced major depression during the 32-week postpartum period (detected either at the 8-week or 32-week time point evaluations). The sociodemographic and obstetric characteristics of the two groups are shown in Table 1 and were similar, with the exception of employment status during pregnancy. With regard to that parameter, there were more unemployed participants in the PPD group than in the non-PPD group (36.9% vs. 22%, respectively; P = 0.009).

Overall, the ferritin and transferrin concentrations of the participants were within the normal range, whereas the iron concentration and TfS were slightly below the lower limit of normal (Table 2). On the other hand, although severe inflammation cases (CRP ≥ 101.16 mg/L) were excluded, the CRP concentrations of the total study population were >3 mg/L, indicating the presence of moderate inflammation (Table 2).

In the PPD group, 38.5% of the women met the criteria for depleted iron stores, compared to 23.3% of women in the non-PPD group (P = 0.007). Overall, 24.7% of the women met the criteria for depleted iron stores. Iron deficiency was present in 14% of the women, and no difference was observed between the PPD and non-PPD groups (Table 2). Interestingly, the PPD group had a lower ferritin concentration than the non-PPD group (15.4 ± 12.7 μg/L vs. 21.6 ± 13.5 μg/L, respectively; P = 0.002), although this iron marker can be partially altered in the presence of moderate inflammation. Therefore, we explored the linear relationships between all biochemical variables using Spearman's correlation. The correlations between ferritin and Tf, ferritin and iron, Tf and CRP, iron and CRP, TfS and Tf or TfS and CRP were negative. Positive correlations were observed, however, between ferritin and CRP, Tf and iron and TfS and iron (Table 2). All of the correlation coefficients were less than 0.6, indicating that all of these biochemical variables could be introduced in the multivariate regression models.

The variables that differed in their distribution between the PPD and non-PPD groups (employment status and ferritin concentration) were assessed using a binary logistic regression model. There was an association between being unemployed during pregnancy and PPD (OR = 2.07, 95% CI = 1.21–3.45; P = 0.008) and between a low ferritin level and PPD (OR = 2.91, 95% CI = 1.51–5.58; P = 0.001) (Table 3).

To explore the relationship between the serum concentration of iron markers and PPD, we used a multivariate logistic regression analysis that took into account other factors (employment status and CRP). Ferritin persisted as the single iron marker associated with PPD in both models (OR = 2.30, 95% CI = 1.29–4.10 when a ferritin cutoff of <12 μg/L was used and OR = 3.73, 95% CI = 1.84–7.56 when a ferritin cutoff of <7.26 μg/L was used). Being unemployed during pregnancy was also associated with PPD in both

Table 2
Distribution of biochemical parameters in the total study population and in the PPD and non-PPD subgroups.

Distribution of ferritin, Tf, iron and CRP in the total sample and in the PPD and non-PPD groups					
	Total sample N = 729	PPD N = 65	Non-PPD N = 664	P-value[1,2]	Reference range[3]
Ferritin (μg/L)	21.3 ± 13.5	15.4 ± 12.7	21.6 ± 13.5	0.002	6.9–282.5
Tf (g/L)	2.8 ± 0.4	2.9 ± 0.5	2.8 ± 0.4	0.51	2.0–4.0
Iron (μmol/L)	8.8 ± 6.9	9.3 ± 6.7	8.8 ± 7.0	0.39	9.8–19.90
CRP (mg/L)	32.3 ± 22.4	33.0 ± 22.5	32.2 ± 22.5	0.51	<3.0
TfS (%)	15.0 ± 9.6	16.1 ± 10.6	14.9 ± 9.5	0.323	
Depletion of iron stores (ferritin <12 μg/L) (%)	24.7	38.5	23.3	0.007	
Marginal iron deficiency (ferritin <12 μg/L and TfS <16%) (%)	13.9	15.6	13.7	0.678	

Correlation between biochemical parameters		
	Rho	P-value
Ferritin-Tf	−0.43	<0.001
Ferritin-Iron	−0.17	<0.001
Ferritin-CRP	0.34	<0.001
Tf-Iron	0.19	<0.001
Tf-CRP	−0.11	<0.001
Iron-CRP	−0.25	<0.001
TfS-Iron	0.95	<0.001
TfS-Tf	−0.08	0.024
TfS-CRP	−0.23	<0.001

Data are presented as the median ± SD.
[1]Mann Whitney U test and [2]Chi-square test: non-PPD versus PPD.
[3]Range provided by the manufacturer in reference to the general population.

Table 3
Regression analyses assessing the possible relationship between iron parameters and other risk variables and PPD.

Regression model	Variables in the equation	Wald statistic	β	P-value	OR (95% CI)
Model 1. Binary logistic regression [a]	Ferritin	10.34	1.06	0.001	2.91 (1.51–5.58)
	Employment status	7.13	0.73	0.008	2.07 (1.21–3.45)
Model 2. Multivariate logistic regression [b] (ferritin <12 μg/L)	Ferritin	8.05	0.83	0.005	2.30 (1.29–4.10)
	Employment Status	7.23	0.75	0.007	2.11 (1.22–3.63)
	TfS	0.90	−0.26	0.34	0.77 (0.45–1.31)
	CRP	3.30	0.51	0.70	1.67 (0.96–2.91)
Model 3. Multivariate logistic regression [b] (ferritin <7.26 μg/L)	Ferritin	13.28	1.31	<0.001	3.73 (1.84–7.56)
	Employment Status	7.82	0.78	0.005	2.19 (1.26–3.80)
	TfS	1.45	−0.33	0.23	0.72 (0.42–1.23)
	CRP	3.32	0.53	0.07	1.70 (0.96–3.00)

[a] The "enter" method. Only variables with P-values <0.05 are shown.
[b] Hosmer–Lemeshow statistic, P = 0.39.

multivariate models (OR = 2.11, 95% CI = 1.22–3.64 for the model using a ferritin cutoff value of <12 μg/L and OR = 2.19, 95% CI = 1.26–3.80 for the model using a ferritin cutoff value of <7.26 μg/L). Finally, we explored whether or not ferritin concentrations were predictive of PPD in our patient population. When a ferritin cutoff of 12 μg/L was used, we found that it had a sensitivity (correct classification of a patient) of 38.5% (95% CI: 26.9–51.4) and a specificity (correct classification of the controls) of 76.7% (95% CI: 73.2–79.8) (Table 4). When a ferritin cutoff of <7.26 μg/L was used, the sensitivity fell to 21.9% (95% CI: 12.9–34.3), and the specificity rose to 91.2% (95% CI: 88.7–93.2) (Table 4). Moreover, a ferritin concentration <12 μg/L increased a patient's probability of developing PPD by a factor of 1.65, whereas a ferritin concentration <7.26 μg/L increased this probability by a factor of 2.50 (positive likelihood ratio, Table 4).

4. Discussion

The present study identified a strong association between ferritin concentration during the immediate postpartum period and PPD. Our initial hypothesis was that iron deficiency (including depletion of iron stores and marginal iron deficiency) would be associated with PPD. Consistent with this hypothesis, we found lower ferritin concentration and a higher percentage of women with depleted iron stores in the PPD group than in the non-PPD group. No differences were observed between the PPD and non-PPD groups with regard to TfS or the percentage of women fitting the criteria for marginal iron deficiency. On average, more women in the PPD group than in the non-PPD group had depleted iron stores without marginal iron deficiency. Given the strong association observed between PPD and serum ferritin concentration, a lower mean ferritin level could be expected in the PPD group. Taking into account the decrease in iron stores during pregnancy and delivery (Bothwell, 2000), the ferritin concentration in the postpartum period is expected to be low; however, the mean ferritin level of the total study population was >12 μg/L. This apparent anomaly can be explained by the inflammatory response that occurs after delivery. Even a non-traumatic delivery produces an acute inflammatory response in women (Mateos Gonzalez, et al., 2009), and it is known that ferritin and iron concentrations are altered as a result of this response (Munoz et al., 2009). Therefore, although iron stores can be depleted in the postpartum period, there is an elevation in the plasma ferritin concentration as a result of inflammation (Krafft et al., 2003). Although women with severe inflammatory responses were excluded from the present study, the elevated CRP concentration observed and the positive correlation with ferritin support the presence of a moderate inflammatory process. Similar results have been reported, and it is generally

Table 4
Predictive value of ferritin concentration in identifying patients with PPD.

	Ferritin <12 μg/L		Ferritin <7.26 μg/L	
Parameter	Value (%)	95% CI	Value (%)	95% CI
Patients correctly diagnosed	73.2	69.8−76.4	85.1	82.2−87.6
Sensitivity [a]	38.5	26.9−51.4	21.9	12.9−34.3
Specificity [b]	76.7	73.2−79.8	91.2	88.7−93.2
Positive predictive value [c]	18.9	9.4−20.0	19.4	11.4−30.8
Negative predictive value [d]	92.7	90.1−94.7	92.3	90.0−94.2
Positive likelihood ratio [e]	1.6	1.2−2.3	2.5	1.5−4.2
Negative likelihood ratio [f]	0.8	0.7−1.0	0.9	0.7−1.0

[a] Correct classification of patients.
[b] Correct classification of controls.
[c] Proportion of patients with a positive test result (ferritin concentration <12 or <7.26 μg/L) who were correctly diagnosed.
[d] Proportion of patients with a negative test result (ferritin concentration ≥12 or ≥7.26 μg/L) who were correctly diagnosed.
[e] True positives/false positives.
[f] False negatives/true negatives.

accepted that traditional markers of iron deficiency tend to be less reliable during pregnancy and the postpartum period. Still, no marker has been shown to be specific for iron deficiency during the postpartum period; as a result, general population iron deficiency markers are used (Akesson et al., 1998; Krafft et al., 2003). In the present study, ferritin was the only marker of iron deficiency associated with PPD. When we examined the positive predictive value of the ferritin level for diagnosing PPD in our sample, however, we found that it was a poor predictor of PPD. Still, a highly negative predictive value provides confirmation that the subject does not have the disease (i.e., PPD in our study) (Sackett et al., 2001). Low sensitivity with high specificity is a general feature of screening tests. Although there are different parameters that can be used to evaluate iron status, the ferritin level is one of the most sensitive and earliest indicators of iron deficiency (i.e., it can be altered prior to other changes in iron metabolism or anemia) (Beard and Han, 2009; Finch et al., 1986; The World Health Organization, 2001).

Iron deficiency has functional and metabolic consequences as well as clinical implications for affected patients. It is associated with unexplained fatigue (Verdon et al., 2003), and even iron deficiency without anemia can lead to lethargy, apathy, difficulty concentrating and body temperature dysregulation (Beard et al., 1990; Eftekhari et al., 2006). The brain is especially susceptible to iron bioavailability. During development, iron is required for proper myelination, and iron deficiency early in life can have irreversible consequences (Lozoff et al., 2000). Iron also plays an important role in the synthesis of various monoamine neurotransmitters, as it is a cofactor for tryptophan hydroxylase (which plays a role in serotonin synthesis), tyrosine hydroxylase (which plays a role in dopamine and norepinephrine synthesis) and monoamine oxidase. Therefore, the dopamine, serotonin and norepinephrine systems are all very sensitive to iron deficiency in the brain (Beard and Han, 2009).

Several studies have examined the relationship between iron status and depression in the general population; however, the results of these studies are controversial. Several authors have found higher ferritin concentrations in depressed inpatients with melancholic traits (Maes et al., 1996) and in young female students (Vahdat Shariatpanaahi, et al., 2007). On the other hand, others have found no relationship between iron deficiency and depression in premenopausal women (Hunt and Penland, 1999) or elderly patients with mild depression (Baune et al., 2006). These reports included both non-childbearing women and men, and this heterogeneity of study populations likely contributed to the divergent results observed between several of these previous reports and the current study. Moreover, few studies have examined the relationship between iron status and depression in the postpartum period. In a prospective double-blind study of South African mothers receiving iron therapy, Beard et al. (2005) found a relationship between iron deficiency anemia and anxiety, depression and cognitive dysfunction. In the same study population, an association was also found between iron deficiency anemia and a poor mother–infant relationship, which was improved with iron therapy (Murray-Kolb and Beard, 2009; Perez et al., 2005). In addition, we found an association between being unemployed during pregnancy and an increased risk of PPD. Being unemployed was also identified as a risk factor for PPD in a previous study (Posmontier, 2008).

Our report makes several new contributions to the body of evidence on this topic. First, it is the first study to examine the relationship between iron deficiency and PPD using measurements taken during the immediate postpartum period. All previous studies examined patients with iron deficiency anemia, and most of them evaluated iron status later in the postpartum period. Second, our patient sample was from a developed country, whereas most previous reports used patient samples from developing countries. Third, our sample size and homogeneity were remarkable. All 729 participants were Spanish and of Caucasian origin, which minimized heterogeneity in genetic background.

There are some limitations, however, to the present study. A single blood sample was taken immediately following delivery; however, iron status was not assessed during pregnancy or later in the postpartum period. Furthermore, only routine iron markers were analyzed, and it is possible that more sophisticated and expensive markers such as soluble TfR concentration would add more prognostic information (Akesson et al., 1998; The World Health Organization, 2001). The assessment of iron status peripartum is difficult, as even gold standard markers are not reliable. Different strategies have been used to adjust the iron nutritional status for the presence of inflammation (Beard et al., 2006). Others have proposed testing for iron status parameters that are influenced by inflammation to a lesser degree (Akesson et al., 1998). However, the perfect solution has not yet been found.

In conclusion, the present study identified an association between PPD and a low ferritin concentration after delivery. We propose that the continuous iron demand during pregnancy and the postpartum period (both directly, due to the demands of the developing fetus, and indirectly through breastfeeding) depletes iron stores, thereby altering these neurotransmitter and myelin metabolic pathways and increasing the risk of PPD in susceptible women. These results support both the role that nutrition plays in affective disorders and the importance of iron deficiency in the brain. They also highlight the importance of designing future studies that follow maternal iron status more closely during pregnancy and the postpartum period.

Role of founding source

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Conflict of interest

None of the authors had potential conflicts of interest related to this manuscript.

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