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Association between non-anemic iron deficiency in early pregnancy and perinatal mental health: A retrospective pilot study

Takuma Ohsuga[1], Miho Egawa[1], Misato Kii[2], Yumie Ikeda[1,3], Akihiko Ueda[1], Yoshitsugu Chigusa[1], Haruta Mogami[1] and Masaki Mandai[1]

[1]*Department of Gynecology and Obstetrics, Kyoto University Graduate School of Medicine, Kyoto, Japan*
[2]*Faculty of Medicine, Kyoto University, Kyoto, Japan*
[3]*Department of Health Informatics, Kyoto University School of Public Health, Kyoto, Japan*

Abstract

Aim: Postpartum anemia and iron deficiency are reportedly involved in postpartum depression, but the association between perinatal depression and iron deficiency with or without anemia is poorly documented. This pilot study retrospectively investigated the relationship between non-anemic iron deficiency (NAID) in early pregnancy and perinatal depressive symptoms.

Methods: This study included 31 non-anemic women among patients who received perinatal care with preserved residual serum from routine antenatal checkups in Kyoto University Hospital. All participants gave informed consent for research. The ferritin concentration in their preserved serum was measured. The hemoglobin (Hb) and ferritin in early pregnancy, as well as the Edinburgh Postpartum Depression Scale (EPDS) at mid-pregnancy and 1 month after childbirth were analyzed. Iron deficiency was defined as a serum ferritin concentration < 30 ng/mL.

Results: Based on the ferritin level in early pregnancy, 13 women (41.9%) had NAID, whereas 18 were normal. The mean Hb and ferritin were 12.7 ± 0.6 g/dL and 18.5 ± 5.8 ng/mL in the NAID group and 12.8 ± 0.9 g/dL and 74.7 ± 39.2 ng/mL in the normal group, respectively. The median EPDS scores at mid-pregnancy and 1 month postpartum, respectively, were 2.0 (2.0–3.3) and 5.0 (4.0–6.6) in the NAID group and 4.5 (2.3–7.3) and 4.5 (2.3–5.7) in the normal group. EPDS scores increased significantly from mid-pregnancy to 1 month postpartum in the NAID group only.

Conclusion: NAID in early pregnancy was highly prevalent and was suggested to reduce resilience to depression during the perinatal period.

Key words: anemia, early pregnancy, ferritin, non-anemic iron deficiency, postpartum depression.

Introduction

Perinatal depression is a mood disorder that occurs during pregnancy (prenatal depression) and after childbirth (postpartum depression [PPD]). This disease has a significant impact on the physical and mental health of both mother and child, including the physical development of the child. The prevalence of prenatal depression and PPD in Japan, respectively, is 5.6% and 5.0%.[1] There are many risk factors for perinatal depression, including physiological, psychological, socio-economical, and obstetrical factors.

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Correspondence: Miho Egawa, Department of Gynecology and Obstetrics, Kyoto University Graduate School of Medicine, 54 Shogoin-kawahara-cho, Sakyo-ku, Kyoto, Japan.
Email: megawa@kuhp.kyoto-u.ac.jp

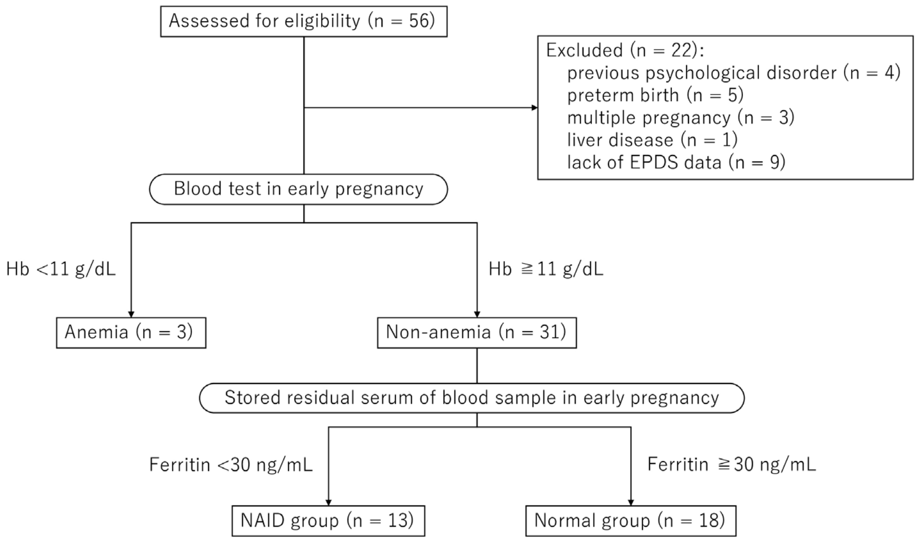

FIGURE 1 Study flowchart. EPDS, the Edinburgh Postpartum Depression Scale; NAID, non-anemic iron deficiency.

Therefore, it is important for the mothers' family members and healthcare providers to identify the mother's depressive signs early on and initiate care and treatment if necessary. In Japan, to provide seamless mental health support even before the onset of perinatal depression, public health centers and obstetrics facilities usually ask pregnant women to answer the Edinburgh Postpartum Depression Scale (EPDS), and individualized care is provided to detected high-risk women through multidisciplinary collaboration. Alternatively, from a public health perspective, it is necessary to recognize the risk factors that can be detected in earlier stages. These can be corrected or countered to prevent the development of perinatal depression.

Iron deficiency remains a common and significant health problem among women of reproductive age. If the iron supply does not meet its demand, a decrease in stored iron first occurs, and the hemoglobin (Hb) level is maintained. However, after the stored iron is depleted, the Hb level drops, resulting in iron deficiency anemia. Although iron deficiency without anemia, a condition that precedes anemia, is a potential risk factor, it is neither treated nor detected in our current clinical practice because it cannot be diagnosed

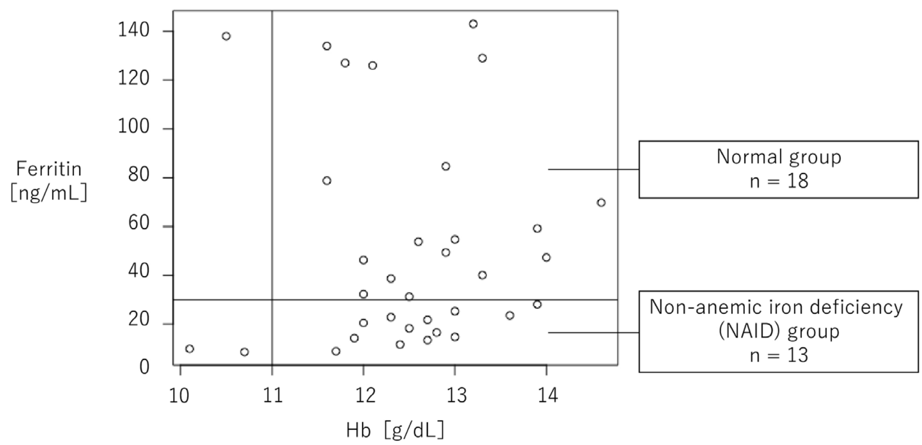

FIGURE 2 Distribution of hemoglobin and ferritin levels in early pregnancy. Anemia and iron deficiency in early pregnancy were defined as hemoglobin (Hb) concentration < 11 g/dL and ferritin concentration < 30 ng/mL. Out of 31 women without anemia included in the analysis, 13 (41.9%) were classified into the NAID group (iron-deficient with ferritin <30 ng/mL), whereas the other 18 (58.1%) were classified into the normal group. Hb, hemoglobin; NAID, non-anemic iron deficiency.

only by screening Hb levels. In Japan, the Hb levels of all pregnant women are routinely checked in the early, middle, and late stages of pregnancy, whereas ferritin, which is the most useful biomarker of iron deficiency,[1] is not usually measured during screening.

Recently, PPD has been reported to be associated with postpartum iron deficiency with or without anemia,[2–5] but its relationship with iron deficiency during pregnancy is poorly documented. From a public health perspective, the earlier detection of risk factors is helpful for considering preventive interventions for perinatal depression. Since iron deficiency anemia after childbirth is known to be a risk factors of PPD, we believe that it necessary to focus on its preceding condition, iron deficiency without anemia (i.e., non-anemic iron deficiency [NAID]), at the earliest stage of the perinatal period. The purpose of this pilot study is to explore whether NAID in early pregnancy, which is not usually recognized in clinical practice, is associated with perinatal mental health conditions.

Methods

Definition of anemia and iron deficiency

Anemia in early pregnancy is defined as having a Hb level < 11 g/dL.[6] On the other hand, the threshold of serum ferritin level for the diagnosis of iron deficiency in pregnancy varies from study to study, with reports using 12, 15, and 30 ng/mL.[7] In this study, we defined iron deficiency as a serum ferritin concentration < 30 ng/mL based on the criteria of the British Society of Haematology (UK guidelines) on the management of iron deficiency in pregnancy.[6]

Participants

The residual serum of routine blood tests of all pregnant women who underwent antenatal checkups between February 2018 and March 2019 at Kyoto University Hospital was stored frozen at −20°C.

In this study, we assessed 56 women who had blood test data in early pregnancy, delivered at our hospital, and underwent a 1 month postpartum checkup. We excluded 13 women for obstetrical complications or systemic comorbidities, some of which are risk factors for perinatal depression: previous psychological disorder ($n = 4$), preterm birth ($n = 5$), multiple pregnancy ($n = 3$), and liver disease ($n = 1$). Furthermore, nine more women were excluded because of lack of EPDS data. Finally, three women who exhibited anemia (Hb < 11 g/dL) in early pregnancy were excluded. The remaining 31 subjects were analyzed and classified into two groups based on their iron status in early pregnancy: those with ferritin levels < 30 ng/mL (NAID group) and ≥30 ng/mL (normal group) (Figure 1).

Clinical data (e.g., EPDS at mid-pregnancy and 1 month postpartum) was obtained from the patients' electronic medical records. We did not conduct additional questionnaires or further blood sampling in this study.

TABLE 1 Background and obstetrical characteristics of the NAID and normal groups

	NAID	Normal
	$n = 13$	$n = 18$
Age, median (IQR) [years]	33.0 (31.0–38.0)	32.0 (30.0–34.8)
BMI, median (IQR)	20.3 (17.7–22.6)	19.2 (18.2–20.3)
Parity, *n* (%)		
Nulliparity	8 (61.5)	13 (72.2)
Multiparity	5 (38.5)	5 (28.8)
ART, *n* (%)		
Yes	4 (30.8)	2 (11.1)
No	9 (69.2)	16 (88.9)
Gestational week of delivery, median (IQR) [weeks]	39.0 (38.0–40.0)	38.5 (38.0–39.0)
Birth weight, median (IQR) [g]	3090 (2786–3338)	2833 (2546–2950)
Mode of delivery, *n* (%)		
Normal vaginal delivery	7 (53.8)	9 (50.0)
Assisted delivery	1 (7.7)	5 (27.8)
Cesarean delivery	5 (38.5)	4 (22.2)
Elective cesarean section	4 (30.8)	2 (11.1)
Emergency cesarean section	1 (7.7)	2 (11.1)
Intrapartum hemorrhage, median (IQR) [g]	878 (600–930)	567 (325–792)
Iron preparation during pregnancy, *n* (%)		
Yes	4 (30.8)	2 (11.1)
No	9 (69.2)	16 (88.9)
Iron preparation after delivery, *n* (%)		
Yes	4 (30.8)	5 (27.8)
No	9 (69.2)	13 (72.2)

Abbreviations: ART, assisted reproductive technology; BMI, body mass index; IQR, interquartile range; NAID, non-anemic iron deficiency. [Correction added on 26 August 2022, after first online publication: Table 1 legends have been updated.]

TABLE 2 Ferritin, Hb, MCV, MCH, and MCHC levels of the NAID and normal groups

	NAID $n = 13$	Normal $n = 18$	Difference (95% CI)
In early pregnancy			
Ferritin (ng/mL)	18.5 ± 5.8	74.7 ± 39.2	−56.2 (−75.9 to −36.6)
Hb (g/dL)	12.7 ± 0.6	12.8 ± 0.9	−0.1 (−0.7 to 0.40)
MCV (fL)	87.6 ± 4.3	90.0 ± 3.3	−2.4 (−5.3 to 0.6)
MCH (pg)	29.9 ± 1.8	31.1 ± 1.2	−1.2 (−2.4 to 0.0)
MCHC (%)	34.2 ± 1.0	34.6 ± 0.7	−0.2 (−1.1 to 0.3)
In mid-pregnancy			
Hb (g/dL)	10.9 ± 1.2	11.4 ± 0.9	−0.5 (−1.3 to 0.4)
MCV (fL)	90.3 ± 5.3	93.6 ± 4.6	−3.3 (−7.0 to 0.5)
MCH (pg)	30.0 ± 2.5	31.5 ± 1.7	−1.5 (−3.1 to 0.2)
MCHC (%)	33.2 ± 1.1	33.6 ± 0.9	−0.4 (−1.1 to 0.5)
In late pregnancy			
Hb (g/dL)	11.0 ± 0.9	11.4 ± 0.9	−0.4 (−1.1 to 0.3)
MCV (fL)	87.6 ± 6.2	90.1 ± 5.0	−2.5 (−6.7 to 1.9)
MCH (pg)	29.1 ± 2.7	30.0 ± 2.4	−0.9 (−0.9 to 0.7)
MCHC (%)	33.1 ± 1.0	33.2 ± 1.2	−0.2 (−2.8 to 1.0)

Plus–minus values: means ± SD. and Abbreviation: CI, confidence interval; Hb, hemoglobin; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; NAID, non-anemic iron deficiency.

Collection of blood test data

Complete blood counts were routinely checked at early (before 16 weeks of gestation), mid- (24–34 weeks of gestation), and late (after 35 weeks of gestation) pregnancy in our hospital. Hb, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) levels were extracted from the electronic medical records. We measured ferritin levels in the stored residual serums that were obtained on the same day of blood sampling in early pregnancy described above.

Evaluation of perinatal depressive symptoms

In our hospital, the Japanese version of EPDS is routinely used in all mothers for the early detection of depressive symptoms at mid-pregnancy (i.e., after 16 weeks of gestation) and 1 month after delivery to provide optimal perinatal care. The EPDS is a 10-item self-reported measurement tool that is widely used for screening of PPD.[8] The Japanese version of the EPDS has been validated for reliability in mothers in the first postpartum month, with a cutoff value of 8/9 points.[9] In this study, EPDS scores at mid-pregnancy and 1 month postpartum were extracted from the

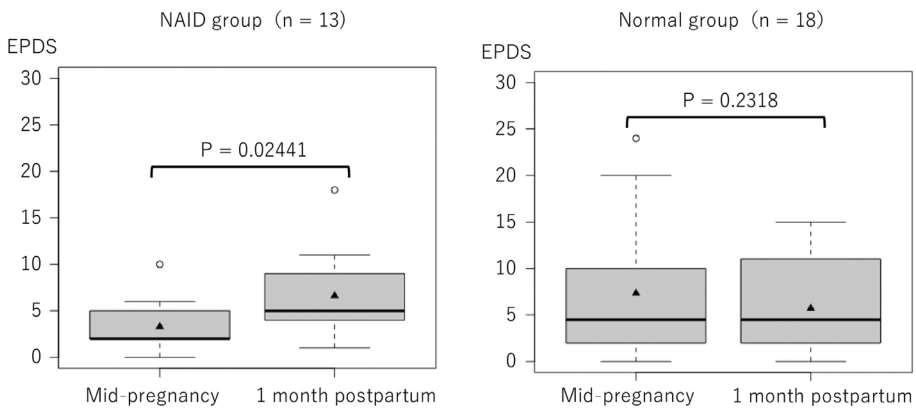

FIGURE 3 Comparison of Edinburgh Postpartum Depression Scale at mid-pregnancy and 1 month postpartum in the non-anemic iron deficiency and normal groups. The bold bars indicate the median, whereas the black triangles indicate the mean. EPDS scores at mid-pregnancy and 1 month postpartum were compared using exact the Wilcoxon signed-rank test. EPDS, the Edinburgh Postpartum Depression Scale; NAID, non-anemic iron deficiency.

electronic medical records to assess perinatal mental health.

Statistical analysis

The background characteristics, laboratory values (i.e., Hb, MCV, MCH, MCHC, and ferritin), and EPDS score at mid-pregnancy and 1 month postpartum of both groups are presented as the mean ± SD or median (interquartile range). The laboratory values were compared between groups using an independent-sample *t* test. EPDS scores at mid-pregnancy, and 1 month postpartum values were compared using the exact Wilcoxon signed-rank test, which is a nonparametric test that is used to compare two paired groups. *p*-Values < 0.05 were considered statistically significant. Statistical analyses were conducted using the R software for Mac.

Ethical consideration

The preservation and usage of the residual serums of routine antenatal blood tests were approved by the Kyoto University Medical Ethics Committee (G0325-5), and written informed consent was obtained from all subjects. An analysis of the correlation between the biomarker and mental status was approved by the same committee (R2586), and informed consent was obtained in an opt-out manner on the website. All research procedures were consistent with the ethical standards of the World Medical Association Declaration of Helsinki.

Results

The flowchart of this study is shown in Figure 1, and the distribution of Hb and ferritin levels in early pregnancy is shown in Figure 2. Among the 31 non-anemic women included in the analysis, 13 (41.9%) had iron deficiency with ferritin <30 ng/mL and were referred to as the NAID group, whereas the other 18 (58.1%) were referred to as the normal group.

The background and obstetrical characteristics of both groups are shown in Table 1. Age, body mass index, parity, use of assisted reproductive technology, gestational week of delivery, birth weight, mode of delivery, intrapartum hemorrhage, and prescription of iron preparation during the perinatal period were similar between the two groups.

The mean ferritin, Hb, MCV, MCH, and MCHC levels of the NAID and normal groups are shown in Table 2. In early pregnancy, the mean Hb and ferritin levels, were 12.7 ± 0.6 g/dL and 18.5 ± 5.8 ng/mL in the NAID group and 12.8 ± 0.9 g/dL and 74.7 ± 39.2 ng/mL in the normal group, respectively. The mean MCV, MCH, and MCHC levels in early, mid-, and late pregnancy were lower in the NAID group, although there was no significant difference.

The EPDS scores of both groups are shown in Figure 3. The median EPDS scores in the NAID group were 2.0 (2.0–3.3) at mid-pregnancy and 5.0 (4.0–6.6) at 1 month postpartum. In the NAID group, the EPDS score significantly increased from

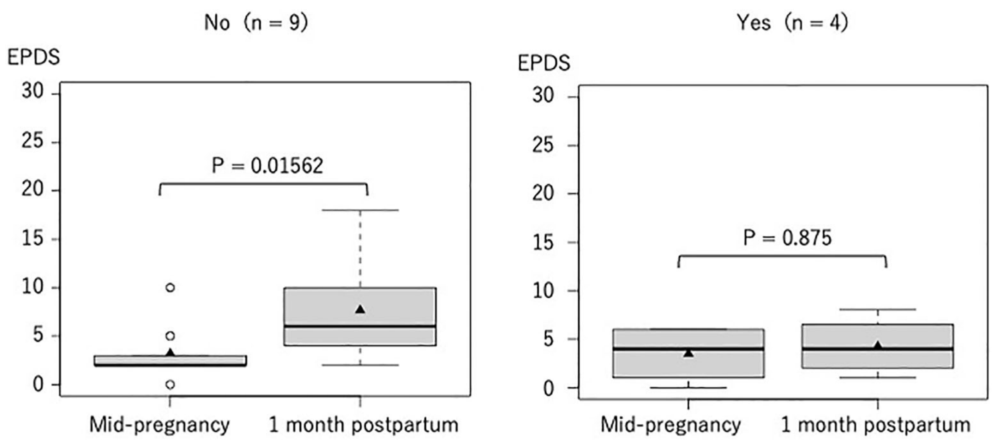

FIGURE 4 Comparison of the Edinburgh Postpartum Depression Scale at mid-pregnancy and 1 month postpartum when divided by the "yes" or "no" iron prescription groups during pregnancy within the NAID group. The bold bars indicate the median and black triangles indicate the mean. EPDS scores at mid-pregnancy and 1 month postpartum were compared using the exact Wilcoxon signed-rank test. EPDS, Edinburgh Postpartum Depression Scale; NAID, non-anemic iron deficiency.

mid-pregnancy to 1 month postpartum. On the other hand, the normal group had a median EPDS score of 4.5 (2.3–7.3) at mid-pregnancy and 4.5 (2.3–5.7) at 1 month postpartum. In the normal group, there was no significant difference between EPDS scores at mid-pregnancy and 1 month postpartum. In the comparison between the two groups, the median EPDS scores of both mid-pregnancy and 1 month postpartum showed no significant difference, while the scores of mid-pregnancy in the NAID group were lower than those of the 1 month postpartum group.

The NAID group had a higher iron prescription percentage during pregnancy; therefore, iron deficiency restoration was possible because of the iron prescriptions. Consequently, 13 subjects in the NAID group were divided based on iron prescriptions ("yes" or "no") during pregnancy, and changes in the EPDS scores were examined from mid-pregnancy to 1 month postpartum. The comparison results are presented in Figure 4. The "yes" group comprised four women, all of whom had a Hb level of <10.0 g/dL in mid- or late pregnancy, and the median EPDS scores were 4.0 (1.5–6.0) at mid-pregnancy and 4.0 (2.5–5.8) at 1 month postpartum, without significant difference in the exact Wilcoxon signed-rank test. The "no" group comprised nine women, of whom one had a Hb level of <10.0 g/dL in mid- or late pregnancy, and the median EPDS scores were 2.0 (2.0–3.0) at mid-pregnancy and 6.0 (4.0–10.0) at 1 month postpartum, with a significant increase in the exact Wilcoxon signed-rank test.

Discussion

To the best of our knowledge, this is the first report focusing on the association of early-pregnancy NAID with perinatal mental health. Although iron status is not usually addressed nor examined when Hb value is within normal range, we found a high prevalence of early-pregnancy NAID. We also found that only the NAID group showed a mild increase in EPDS score from mid-pregnancy to 1 month postpartum. These findings suggest that early-pregnancy NAID may be a cause of mental health vulnerability during the perinatal period. The EPDS score at mid-pregnancy, which was the baseline in this study, was lower in the NAID group than the normal group, but increased postpartum, despite depression during pregnancy being a well-known risk factor of PPD.[10] Based on these results, we hypothesized that iron deficiency progresses during the latter half of the perinatal period unless recognized and compensated accordingly. This can contribute to worsening depressive symptoms of mothers. Increased EPDS scores from mid-pregnancy to 1 month postpartum, especially in the NAID subgroup not prescribed iron during pregnancy, is consistent with this hypothesis. The increased rate of cesarean section (CS) in the NAID group should be noted regarding the possible PPD confounding risk factors although without significant difference. CS is considered a risk factor for PPD; however, elective CS has been shown to have a milder risk than emergency CS.[11] Four of the five CSs in our current analysis were performed as elective operations. Therefore, we can only presume minimal contribution of CS to EPDS score elevation in the NAID group in our study. Contrastingly, the rate of assisted reproductive technology (ART) was also increased in the NAID group although previous studies reported that ART is unrelated to PPD.[12,13]

NAID poses two risks. First, NAID is a precursor of iron deficiency anemia, which is considered a risk factor for PPD. Second, the iron-deficient state itself, with or without anemia, may negatively affect the biosynthesis of neurotransmitters, such as serotonin and noradrenaline, which are involved in the pathogenesis of depression.[10]

Several reports have demonstrated that postpartum anemia or NAID is a risk factor for PPD. A large prospective observational study by Maeda et al. showed that postpartum anemia was associated with an increased risk of PPD.[5] Moreover, Albacar et al. ran a prospective cohort of 729 postpartum mothers and reported that low ferritin levels at 48 hours postpartum were associated with PPD up until 32 weeks postpartum.[2] This study was well-designed to exclude subjects showing inflammatory signs with high C-reactive protein levels, since inflammation can increase ferritin levels, making them a poor iron deficiency markers in such patients. Sheikh et al. also conducted a randomized controlled trial in postpartum women without anemia with an EPDS score ≥ 11 at 7 days postpartum. Iron supplementation was demonstrated to improve EPDS scores better than the placebo.[10] Meanwhile, Hameed et al. carried out a case–control study of 150 postpartum women with PPD (EPDS score ≥ 10) on postpartum day 30 and found that body iron status, calculated from the levels of ferritin and soluble transferrin receptors (sTfR), was associated with an increased risk of PPD. In that study, the PPD group was found to have significantly lower ferritin levels than the control group.[14] Despite this currently available information, however, no previous study has demonstrated the association of iron deficiency in early pregnancy with PPD.

The demand for iron increases during pregnancy due to increased circulating blood volume, growth and development of the fetus, and high metabolic activity of the placenta. Iron loss also occurs due to hemorrhage during delivery and postpartum breastfeeding.[15] There is a chance that the depletion of iron stores is not recognized by Hb-only screening in early pregnancy, or that iron supplementation is not properly advised to meet its increased demand. These would lead to the development of iron deficiency anemia manifesting itself after the final antenatal checkup or at 1 month postpartum checkup, being overlooked. Therefore, the assessment of iron status throughout the perinatal period is considered essential from a preventive medicine perspective. However, research is limited on the association between PPD and antenatal iron deficiency with or without anemia. Due to the physiological hemodynamic changes associated with pregnancy, the interpretation of some biomarkers during the antenatal period could pose an issue. Taking this into consideration, we specifically focused on early-pregnancy iron deficiency using the ferritin value as a biomarker before the occurrence of hemodynamic changes. It is assumed that the iron status in early pregnancy almost resembles that of the latest menstrual cycle immediately before conception. Preconception iron deficiency, which is presumably caused by deficit nutrient intake and/or intestinal absorption as well as large iron loss caused by menstruation, possibly indicates a potential risk of its progression. Our observations in the current study address the importance of awareness for iron deficiency, even without anemia, in the earliest stage of pregnancy, giving great insight into preconception healthcare with emphasis on iron deficiency that is widely prevalent in women of reproductive age.

This study has several limitations. This is a retrospective pilot study with a small sample size and limited available preserved specimens. We also did not measure socio-economic factors that may confound with both iron deficiency and perinatal depression. Moreover, there may be a selection bias because the field of enrollment (our hospital) is a tertiary medical institute wherein many women with potential medical risks receive antenatal care, even if we excluded abnormal obstetrical courses and comorbidities with mental illness in the current analysis. Such an exclusion was one of the reasons why the analyzed sample size was small. Recognizing the sample size limitation, we attempted to focus on the change of depressive symptoms between the two points of each subject using the exact Wilcoxon signed-rank test. Additionally, the presence of minute inflammations could not be assessed using other biomarkers because of the limitation of available specimens. The serum ferritin level is often affected by many conditions and is especially elevated by inflammation; therefore, iron deficiency cannot be completely ruled out even if the ferritin level appears adequate. Subjects with iron deficiency may be hidden, even among the group of patients with a ferritin level of ≥30 ng/mL, referred to as the “normal” group. Finally, EPDS is a screening tool that does not allow for the diagnosis of major depression by itself, and most of the subjects examined in the current study are within the subclinical state of depression. Based on our findings, however, iron deficiency is likely involved in the vulnerability for depression. Thus, maintaining sufficient iron status may enhance the resilience of maternal mental health, which is important from the perspective of preventive healthcare. To confirm the hypothesis above and further investigate whether NAID has a potent risk for perinatal depression, a larger number of subjects should be enrolled with an appropriate psychiatric diagnosis and examined in well-designed future research. This may provide valuable insight into the improvement of preconceptional healthcare, especially in terms of nutritional intake and menstruation control among adolescents and young adults. Further research is needed to establish antenatal NAID management based on some reports that show associations between high serum ferritin levels or prophylactic iron supplementation and other increased pregnancy outcomes, such as gestational diabetes[16] and hypertensive disorders of pregnancy,[17,18] although the causal relationship and mechanism remain unclear.

In conclusion, this study demonstrated a high prevalence of NAID in early pregnancy among noncomorbid women. Unless given intervention, NAID in early pregnancy may be a potent risk factor for worsening mental health during the perinatal period. Although only exploratory, this study highlights a meaningful clinical implication regarding the necessity of identifying NAID in early pregnancy, or especially during preconception, to promote perinatal mental health. Further research is needed to provide high-quality evidence on the association between perinatal depression and iron deficiency in early pregnancy.

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Conflict of interest

The authors declare no conflict of interest.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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