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Pregnancy outcomes in women with iron deficiency detected in the first trimester: A Retrospective, single-center Study

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Abstract

Background: The aim of present study was to investigate the association between iron deficiency (ID) detected in the first trimester and pregnancy outcomes.

Methods: In a retrospective cohort study, 482 pregnant women were included in the analysis. Blood samples were investigated for hematological status and serum ferritin in the first trimester, and for hemoglobin before and after delivery. Pregnancy outcomes were compared between women with ID diagnosed in the first trimester (ID group; n = 147), and women without ID (non-ID group; n = 335). The adverse maternal and perinatal outcomes were determined. Medical data were extracted from clinical records of pregnant women who attended antenatal care and delivered at the University Hospital Basel between 2017 and 2019. Iron substitution was started in the second or third trimester in pregnant women with ID.

Results: Excluding macrosomia, ID detected early in pregnancy was not associated with adverse maternal and neonatal outcomes in women. Macrosomia was increased significantly in women with ID, but there was not a concomitant increase in gestational diabetes mellitus (6.5% [10/153] vs. 1.7% [6/347, P = 0.005). Emergency cesarean section doubled in women with normal iron status (8.2% [12/147] vs. 17.0% [57/335], P = 0.011).

Conclusion: Excluding macrosomia, ID detected in the first trimester was not associated with adverse maternal and neonatal outcomes in iron-supplemented women.

Introduction

Iron deficiency (ID) in pregnancy is a common syndrome for which effective diagnosis and therapy exist, but little is known about the effects of maternal ID in the first trimester on maternal and neonatal outcomes [1]. Assessing the impact that maternal ID has on pregnancy outcomes and on early childhood development is more complex than it might seem at first. While there are few prospective studies that have proven routine screening and iron supplementation have benefits, numerous evidence-based reports indicate that ID in mothers and infants causes significant morbidity [2]. During mild maternal ID, iron is prioritized to the fetus [3]. However, during moderate and severe ID, the entire maternal-placental-fetal unit becomes deficient in iron, with significant consequences to the fetus in the short and long term.

Fetal, neonatal, and childhood brain growth and development require iron; deficiencies have adverse effects on myelination, neurotransmitter synthesis, and brain programming [2]. Low maternal serum ferritin concentrations are associated with ID in neonates [4]. ID in neonates has been associated with a significant increase in both cognitive and behavioral abnormalities that are long lasting, detectable up to 19 years of age [2,5]. According to the World Health Organization (WHO), serum ferritin is the most effective single test for ID in pregnancy; its concentration during early pregnancy reliably indicates ID [6]. Based on a recent systematic review of serum ferritin thresholds for ID in pregnancy, most researchers have used values of 12–15 µg/l, but some used thresholds as high as 30 µg/l [7]. It has been estimated that a ferritin threshold at 30 µg/l is 98% specific and 92% sensitive for ID [8].

To the best of the authors' knowledge, no previous study has explored the effect of maternal ID on adverse pregnancy outcomes. In this retrospective single-center study, the effect of maternal ID detected in the first trimester on the pregnancy outcomes was investigated in pregnant women treated with iron supplementation starting in the second or third trimester.

Methods

A retrospective cohort study was conducted at the Department of Obstetrics and Antenatal Care, University Hospital Basel, Switzerland, to examine the association between adverse pregnancy outcomes and ID detected in the first trimester of pregnancy. For this study, data on pregnant women who attended antenatal care and delivered at University Hospital Basel from January 2017 to December 2019 were used. The inclusion criteria for pregnant women with ID (ID group) were as follows: serum ferritin < 30 µg/l and hemoglobin (Hb) levels ≥ 110 g/l in the first trimester. Pregnant women without ID (non-ID

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Table 1. Characteristics of pregnant women with and without iron deficiency (ID). The data are expressed as mean ± standard deviation (range) or n (%)

	Women with ID	Women without ID	*P* Value
	(n = 147)	(n = 335)	
Maternal age (years)	30.8 ± 5.6	31.6 ± 6.0	0.170
Parity	1.8 ± 1.1 (1–6)	1.8 ± 1.1 (1–7)	1.000
BMI (kg/m²)	29.0 ± 5 (20–54)	28.8 ± 5 (15–47)	0.686
Previous abortion	45/147 (30.6)	75/335 (22.4)	0.055
Primipara	63/147 (42.9)	167/335 (49.9)	0.157
Multiples	5/147 (3.4)	12/335 (3.6)	0.921
Previous cesarean delivery	31/147 (21.1)	57/335 (17)	0.287
Gestational age at delivery (week)	39/3 ± 1.5	39/3 ± 2.3	1.000
< 37 (%)	5/147 (3.4)	23/335 (6.9)	0.134

BMI- Body Mass Indexing.

group) included women with normal hematologic parameters and normal iron status in the first trimester (serum ferritin levels ≥ 30 µg/l and Hb levels ≥ 110g/l). Pregnant women with a documented refusal, women under the age of 18, or women with communication barriers were excluded. In pregnant women with ID diagnosed in the first trimester, iron substitution was started in the second or third trimester. The study received ethical approval from the Swiss local ethics committee in Basel (ID 2020-02033) and was registered at http://www.ClinicalTrials.gov (NCT05262634) on 23 March 2022.

The gestational age was assessed according to the last menstruation date or adjusted through a first trimester ultrasound if the discrepancy was more than ± 5 days. The maternal demographic data, hematological data and delivery mode were investigated.

The following maternal outcomes were examined: Hb before and after delivery; iron infusion in pregnancy; and complications (the definitions used for each complication are provided in the cited references) such as pre-eclampsia/eclampsia and pregnancy induced hypertension; abnormal placentation; peripartum hemorrhage; anemia in pregnancy and postpartum; gestational diabetes mellitus (GDM); intrahepatic cholestasis; infections during pregnancy; puerperal infection or sepsis; subinvolution uteri; and manual placenta removal [9-14].

The following neonatal outcomes were investigated: birth weight; preterm delivery < 37 weeks of gestation; preterm premature rupture of membranes (PPROM, which occurs at < 37 weeks of gestation); macrosomia; intrauterine growth restriction (IUGR); Apgar score at 1 min and Apgar score < 5 at 5 min as a criterion for poor neonatal adaptation; umbilical arterial and venous pH; fetal acidosis defined as arterial pH < 7.00; stillbirth; and neonatal death [15,16]. Arterial and venous pH was measured in all newborns.

Hematologic assessment: Blood samples were checked for hematologic status and serum ferritin in the first trimester, and for Hb before and after delivery. All blood measurements (blood count, C-reactive protein (CRP), and ferritin) were conducted at the Department of Laboratory Medicine, University Hospital Basel. A hematology analyzer measured Hb, the red blood cell count (RBC), the mean corpuscular volume (MCV), the mean corpuscular hemoglobin (MCH), reticulocytes, reticulocyte hemoglobin (CHr), hypochromic red blood cells (HRC), and red blood distribution width (RDW). The MCH was automatically calculated from the Hb and RBC values. Serum ferritin was assessed by a chemiluminescence immunoassay and CRP was assessed by immunoturbidimetry.

Statistical analysis: Statistical analysis was conducted by using STATA 15.1 (Stata Corporation College Station, TX, USA). Student's t-test for different sample sizes was used for group comparisons of normally distributed variables, and the Wilcoxon rank-sum test was used for group comparisons of non-normally distributed variables. Group comparisons of nominal and categorical variables were carried out with the χ^2 test. The level of statistical significance was set at $P < 0.05$. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for infant and maternal outcomes and variables as well as the delivery mode.

Results

A total of 508 pregnant women were recruited for this study (155 pregnant women with ID and 353 pregnant women without ID). Due to missing pregnancy outcomes for 26 pregnant women, the final analysis was conducted with 482 women (147 in the study group and 335 in the control group).

The demographic and clinical characteristics of the groups are shown in **Table 1.** There were no differences between women with and without ID with respect to maternal age, parity, and body mass index (BMI). Although there was no difference in Hb between the groups in the first trimester (125 ± 7.9 vs. 126 ± 8.1, $P = 0.079$), there were significant differences in parameters of ID erythropoiesis, including MCV, MCH, HRC, RDW and CHr (**Table 2**).

The delivery mode is shown in **Table 3**. Vaginal delivery was significantly higher in pregnant women with ID than in women without ID (110/147 [74.8%] vs. 219/335 [65.4%], $P = 0.044$). There was a significant difference regarding the rate of cesarean sections between the groups (37/147 [25.2%] vs. 116/335 [34.6%], $P = 0.040$). Moreover, delivery by emergency cesarean section (CS) was significantly higher in pregnant women without ID (12/147 [8.2%] vs. 57/335 [17.0%], $P = 0.011$, OR 0.43, 95% CI 0.20–0.85). Excluding macrosomia (10/153 [6.5%] vs. 6/347 [1.7%], $P = 0.005$), the groups did not differ significantly

Table 2. Hematological data and serum iron status of pregnant women with and without iron deficiency (ID) in the first trimester. The data are expressed as mean ± standard deviation (range) or median (range)

	Women with ID (n = 147)	Women without ID (n = 335)	*P* Value
Hb (g/l)	125 ± 7.9 (110–145)	126.4 ± 8.1 (110–155)	0.079
RBC (× 10^6/µl)	4.24 ± 0.3 (3.51–4.96)	4.16 ± 0.3 (3.42–5.1)	0.007
MCH (pg)	29.4 ± 1.8 (24.4–34.3)	30.4 ± 1.5 (27–34.2)	< 0.001
MCV (fl)	85.8 ± 4.5 (72-97)	87.7 ±4.0 (78-98)	<0.001
HRC (%)	0.4 (0–13.2)	0.2 (0–5.1)	< 0.001
RDW (%)	14.2 ± 1.4 (12.4–21.4)	13.4 ± 0.9 (11.7–21.2)	< 0.001
CHr (pg)	31.6 ± 1.9 (21.7–31.6)	32.5 ± 1.6 (28.9–35.8)	< 0.001
Reticulocytes (‰)	17.9 ± 4.7 (10–33)	18.3 ± 4.9 (7–40)	0.403
Ferritin (µg/l)	21 (6–29)	62 (30–436)	< 0.001
CRP (mg/l)	4.2 (0.3–21.4)	3.6 (0.3–90)	0.598

CHr- Reticulocyte hemoglobin; CRP- C-reactive protein; Hb-Hemoglobin; HRC-Hypochromic red blood cells; MCH- Mean corpuscular hemoglobin; MCV- Mean corpuscular volume; RBC- Red blood cell count; RDW- Red blood distribution width.

Table 3. Delivery mode. The data are expressed as n (%)

	Women with ID	Women without ID	OR (95% CI)	*P* Value
	(n = 147)	(n = 335)		
Vaginal delivery	110/147 (74.8)	219/335 (65.4)	1.57 (1.00–2.51)	0.0436
Operative vaginal delivery	27/147 (18.4)	64/335 (19.1)	0.97 (0.68–1.37)	0.849
Cesarean section	37/147 (25.2)	116/335 (34.6)	0.64 (0.40–0.99)	0.040
Elective cesarean section	25/147 (17.0)	59/335 (17.6)	0.96 (0.55–1.64)	0.872
Non-elective cesarean section	12/147 (8.2)	57/335 (17.0)	0.43 (0.20–0.85)	0.011

Table 4. Neonatal outcomes. The data are expressed as mean ± standard deviation (range) or n (%)

	Women with ID	Women without ID	O. R. (95% CI)	*P* Value
	(n=153)	(n=347)		
Birth weight (g)	3220 ± 594	3158 ± 600		0.286
PPROM	2/153 (1.3)	11/347 (3.2)	0.40 (0.04-1.89)	0.228
IUGR	15/153 (9.8)	29/347 (8.4)	1.19 (0.57-2.38)	0.599
Macrosomia	10/153 (6.5)	6/347 (1.7)	3.97 (1.28-13.52)	0.005
Apgar score at 1`	8.1 ± 1.7 (0-10)	7.9 ± 1.8 (0-10)		0.245
5-minutes Apgar <5	3/153 (2.0)	4/347 (1.2)	1.72 (0.25-10.3)	0.479
Umbilical artery pH	7.25 ± 0.07	7.25 ± 0.08		1.000
Umbilical artery pH ≤ 7.00	0/153 (0.0)	3/347 (0.9)	n.a.	
Neonatal death	0/153 (0.0)	2/347 (0.6)	n.a,	
Stillbirth	1/153 (0.7)	0/347 (0)	n.a.	

n.a.- None.

in any other variable related to neonatal outcomes (**Table 4**). Although macrosomia was significantly higher in pregnant women with ID, there was no difference in GDM between the groups.

The maternal outcomes are shown in **Table 5**. Because of iron supplementation in pregnancy, there was no difference regarding Hb prior to delivery between groups (126 ± 12 vs. 125 ± 11, $P = 0.372$). Iron infusion during pregnancy was administered more often in women with ID (19/147 [12.9%] vs. 21/335 [6.3%], $P = 0.015$; OR 2.21, 95% CI 1.09–4.49). Due to the significantly higher number of cesarean sections in pregnant women without ID, Hb after delivery was significantly lower in that group (109 ±13 g/l vs. 106 ± 15 g/l, $P = 0.036$).

Discussion

To our knowledge, there is no study that has investigated the effect of maternal ID on adverse pregnancy outcomes. In present study, the effect of ID verified in the first trimester on the pregnancy outcome has been studied.

There were no differences in neonatal and maternal outcomes between the groups, except for more macrosomia in pregnant women with ID. This finding is in accordance with our previous study [17] in which there was a higher incidence of macrosomia in women with depleted iron stores (11.4%) and with ID anemia (16%). Interestingly, macrosomia was more often only in women with depleted iron stores or ID anemia in that study, but not in anemic women with normal iron status [17] . Our first hypothesis for macrosomia in women with ID is that ID early in pregnancy and not anemia *per se* could induce placental hypertrophy. Huang, *et al.* found placental hypertrophy in women with ID anemia [18]. Early non-excessive placental hypertrophy in women with ID or ID anemia might lead to increased nutritional support in later pregnancy and, consequently, cause macrosomia. However, the placenta was not investigated in the present study. Therefore, futher studies must determine whether placental hypertrophy occurs in women with ID or ID anemia in the first trimester.

The second hypothesis that could explain higher rates of macrosomia in women with ID is iron supplementation. Women with ID in the first trimester are routinely given oral iron supplements as first-line therapy. However, for oral iron supplementation to have a sufficient effect, good compliance for about two or three months is required. Iron status is routinely monitored in gestational weeks 28-30. In the case of persistent ID, iron infusion as second-line therapy is indicated. In the present study, there was significantly more iron infusion in pregnant women with ID. Elevated maternal iron concentration after iron infusion is unphysiologically high for the first two-three weeks after iron administration. Due to this high iron levels after iron infusion, GDM could develop later in pregnancy without being recognized by GDM screening performed between gestational weeks 24 and 28. This is also the hypothesis as to why the incidence of GDM was not increased in pregnant women with fetal macrosomia in the present study. More and more studies suggest that an elevated iron concentration is associated with the development of GDM. A systematic review and meta-analysis by Fernandez-Cao *et al.* provided evidence that elevated iron status is positively associated with the risk of developing GDM [19]. Likewise, it has been shown that ferritin levels increase the risk of GDM by more than twofold in the third trimester of pregnancy [19-22]. On the other hand, a high concentration of maternal ferritin might also induce metabolic alternations leading to fetal hyperinsulinemia due to oxidative damage [23,24].

Another possible reason for macrosomia in pregnant women without GDM could be early metabolic changes leading to a normal maternal plasma glucose through fetal insulin. In a previous study, the authors reported that fetal hyperinsulinemia could suppress the peak of plasma glucose in pregnant women [25]. Consequently, oral glucose

Table 5. Maternal outcomes. The data are expressed as mean ± standard deviation (range) or n (%)

	Women with ID	Women without ID	O. R. (95% CI)	*P* Value
	(n=147)	(n=335)		
Hb prior to delivery	126 ± 12 (70-156)	125 ± 11 (87-158)		0.372
Iron infusion in pregnancy	19/147 (12.9)	21/335 (6.3)	2.21 (1.09-4.49)	0.015
Gestational diabetes	21/147 (14.3)	56/335 (16.7)	0.83 (0.46-1.46)	0.503
Infection in pregnancy	19/147 (12.9)	43/335 (12.8)	1.01 (0.53-1.85)	0.979
Intrahepatic cholestasis	7/147 (4.8)	20/335 (6.0)	0.79 (0.27-1.99)	0.595
Hypertensive disorders	4/147 (2.7)	9/335 (2.7)	1.01 (0.22-3.70)	0.983
Pre-eclampsia/Eclampsia	1/147 (0.7)	9/335 (2.7)	0.25 (0.01-1.82)	0.155
Abnormal placentation	5/147 (3.4)	8/335 (2.4)	1.44 (0.36-5.09)	0.527
Vaginal bleeding in pregnancy	0/147 (0.0)	9/335 (2.7)	n.a.	
Peripartal hemorrhage	9/147 (6.1)	26/335 (7.8)	0.78 (0.31-1.76)	0.523
Manual placenta removal	4/147 (2.7)	18/335 (5.4)	0.49 (0.12-1.53)	0.199
Subinvolution uteri	8/147 (5.4)	11/335 (3.3)	1.70 (0.58-4.73)	0.262
Hb after delivery	109 ± 13 (68-140)	106 ± 15 (55-144)		0.036
Anemia postpartum	75/147 (51.1)	192/335 (57.3)	0.78 (0.52-1.17)	0.201
Infection postpartum	1/147 (0.9)	4/335 (1.2)	0.57 (0.01-5.80)	0.608

Hb- Hemoglobin; n.a- None.

tolerance test results in those pregnant women might be mistaken for normal.

In the present study, there was a significantly higher rate of vaginal delivery in women with ID. It was mentioned previously that placental hypertrophy is due to ID anemia early in pregnancy. This result might lead to better adaption to stress during delivery, and could explain the lower rate of CSs in women with ID.

Our study has some limitations that must be considered when we present these data, and the results must be used with care. First, it employs a retrospective design, which is also why many important data are missing or were not investigated. Example is the lack of information on placenta, GDM screening or diurnal blood sugar profile in the third trimester in women with and without iron infusion, the lack of the sample size estimation with power-analysis and so on. Second, the iron supplementation given in pregnant women with ID must be taken into consideration. However, it would be unethical not to treat ID diagnosed in the first trimester because its effects on pregnancy outcomes are unknown. On the other hand, it is important to note that the aim of this study was to determine the effect of ID only in the first trimester, namely in the most vulnerable phase of fetal development.

In the future, well-powered longitudinal studies are required to examine the effects of ID on pregnancy outcomes, to verify the effects of ID on placental development, to investigate the possible effects of iron supplementation on the development of GDM in pregnancy and the consequential incidence of macrosomia.

Conclusion

Excluding macrosomia, ID detected in the first trimester was not associated with adverse maternal and neonatal outcomes in iron-supplemented women.

Disclosure Statement

The authors report no conflicts of interest in relation to the present study.

Consent for publication

The manuscript has been read and approved by all authors.

Availability of data

The material contained in this manuscript has not been published, has not been submitted or is not being submitted elsewhere.

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Authors` contribution

Selina Dörig collected the data and drafted the article. Tilo Burkhardt conducted the statistical analysis. Gwendolin Manegold-Brauer reviewed the manuscript. Gabriela Amstad designed the study, reviewed and edited the manuscript.

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