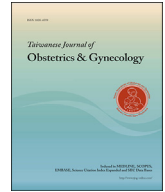




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## Original Article

## Parity-based assessment of anemia and iron deficiency in pregnant women

Kimitoshi Imai

Imai OB/GYN Clinic, Suehiro-cho 117-1, Aoi-ku, Shizuoka, 420-004, Japan

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## ABSTRACT

**Objective:** This study aimed to separately evaluate the prevalence of anemia and iron deficiency in nulliparous and multiparous women.

**Materials and methods:** We retrospectively examined data of women who delivered in our clinic from January 2016 to December 2018. Inclusion criteria were delivery occurring at  $\geq 36$  weeks and singleton pregnancy. Pregnant women with severe medical disorders were excluded. We estimated complete blood count (CBC) and serum ferritin (SF) in the first trimester and only CBC in the late second trimester. Data of nulliparas and multiparas were analyzed separately. Statistical significance was set at  $p < 0.05$ . **Results:** Totally, 481 nulliparas and 603 and multiparas were enrolled. Mean hemoglobin values in the first trimester were  $12.6 \pm 1.0$  and  $12.4 \pm 1.0$  g/dl ( $p < 0.001$ ), while median SF values were 42.7 (12.2, 108.2) and 27.7 (8.0, 72.6) ng/ml ( $p < 0.001$ ) in nulliparas and multiparas, respectively. Hemoglobin in the late second trimester was  $11.2 \pm 0.9$  and  $10.7 \pm 1.0$  g/dl ( $p < 0.001$ ) in nulliparas and multiparas, respectively. Low ferritin levels (SF  $< 12$  ng/ml) were more frequently found in multiparas than in nulliparas (111/603 vs. 46/481,  $p < 0.001$ , Odds ratio [OR] = 2.13). Anemia in the first trimester (hemoglobin  $< 11.0$  g/dl) was found in 3.5% (17/481) and 8.8% (53/603) ( $p < 0.001$ ; OR, 2.63), while that in late second trimester (hemoglobin  $< 10.5$ ) was observed in 21.0% (101/481) and 36.3% (219/603) ( $p < 0.001$ , OR = 2.15) nulliparas and multiparas, respectively. Non-anemic women (hemoglobin level  $\geq 11.0$ ) with low ferritin levels (SF  $< 12$  ng/ml) in the first trimester showed higher rate of anemia development in the second trimester than those with both normal hemoglobin and ferritin levels, irrespective of parity (51.3% [19/37] vs. 16.2% [69/427],  $p < 0.001$  in nulliparas and 76.9% [60/78] vs. 26.5% [125/472],  $p < 0.001$  in multiparas).

**Conclusion:** Anemia and low SF levels occurred more commonly in multiparous than in nulliparas. Further, low SF was a risk factor for anemia development in later pregnancy.

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## Introduction

Anemia is still a worldwide health problem, not only in developing, but also in developed countries [1–5] and is one of the most common medical disorders encountered during pregnancy [6,7]. The frequency of gestational anemia varies among nations, is influenced by socioeconomic status, and increases the risk of adverse pregnancy outcomes in both affected women and their offspring [8,9]. Iron deficiency anemia (IDA) is considered the commonest type of gestational anemia [6] and is a late manifestation of iron deficiency (ID) [10]. Anemia in pregnancy is defined as a hemoglobin level of  $< 11$  g/dl in the first trimester and that  $< 10.5$  g/dl in the second and/or third trimesters [11]. Serum ferritin

(SF) is a good marker of iron storage in the body, and its concentration in early pregnancy is usually a reliable indicator of ID [12]. In this single center study, we retrospectively examined the prevalence of iron deficiency and anemia among pregnant women and aimed to attract physician's more attention to this silent disease.

## Materials and methods

## Patients

We retrospectively collected and examined data of women who delivered in our clinic from January 2016 to December 2018. The study center is a private obstetrics/gynecology clinic located in Shizuoka city in central Japan. The city has a population of about 700,000. Enrollment criteria included: i)  $\geq 36$ -week gestational

E-mail address: [imai3k@yr.tnc.ne.jp](mailto:imai3k@yr.tnc.ne.jp).

period before delivery, and ii) singleton pregnancy. As this clinic accepted mainly low-risk pregnancy and delivery cases, pregnant women with serious medical comorbidities such as maternal heart disease, thyroid disorder, mental illnesses, and morbid obesity were excluded. This study was approved by the Local Ethics Committee (No. 19003).

### Estimation of ID

Complete blood count (CBC), SF, and serum iron (Fe) levels were examined in the first trimester. Anemia in pregnancy was defined as a hemoglobin level of <11 g/dl in the first trimester and that <10.5 g/dl in the second and/or third trimesters. Further, a SF level <12 ng/ml was used to determine the presence of ID, in this study [13]. A CBC test was repeated again in the late second trimester. Data obtained from nulliparous and multiparous women were analyzed separately.

### Statistical analysis

The hemoglobin concentration was expressed as mean  $\pm$  standard deviation (SD), while SF and serum Fe were expressed as median with 10th and 90th percentile values. All statistical analyses were performed using the SPSS version 22.0 for Windows (IBM Japan, Tokyo, Japan) software. A P-value of <0.05 was considered statistically significant.

## Results

We enrolled 481 and 603 nulliparous and multiparous women, respectively, in this study. The demographic characteristics of all study patients are summarized in Table 1. The mean hemoglobin concentration in the first trimester was  $12.6 \pm 1.0$  and  $12.4 \pm 1.0$  g/dl in nulliparas and multiparas, respectively. The first trimester SF values were 42.7 (12.2, 108.2) vs. 27.7 (8.0, 72.6) ng/ml ( $p < 0.001$ ) in nulliparous and multiparous women, respectively. The corresponding median Fe concentration values were 108.0 (61.0, 161.8) vs. 108.0 (51.0, 162.0)  $\mu\text{g/dl}$  ( $p = 0.242$ ), in nulliparous and multiparous study subjects, respectively.

The mean hemoglobin levels in the late second trimester dropped to  $11.2 \pm 0.9$  and  $10.7 \pm 1.0$  g/dl ( $p < 0.001$ ) in nulliparous and multiparous women, respectively. The fall in hemoglobin concentration in the second trimester, as compared to that in the

first, was observed to be greater in multiparas than in nulliparas ( $-1.6 \pm 0.9$  vs.  $-1.5 \pm 0.9$  g/dl,  $p = 0.002$ ) (Table 1).

In the first trimester, anemia was detected in 3.5% (17/481) vs. 8.8% (53/603) nulliparas and multiparas, respectively ( $p < 0.001$ ). In the second trimester, anemia was observed to affect 21.0% (101/481) vs. 36.3% (219/603) ( $p < 0.001$ ) nulliparous and multiparous women, respectively (Table 2A, B).

Low SF level was observed more frequently in multiparas than in nulliparas (68.2% [411/603] vs. 9.6% [46/481],  $p < 0.001$ , Table 2C). Our findings show that irrespective of parity, pregnant women with normal hemoglobin ( $\geq 11.0$  g/dl) and correspondingly low ferritin ( $< 12$  ng/ml) levels in the first trimester, were more likely to develop anemia in the second trimester as compared to those with both normal first-trimester hemoglobin and ferritin ( $\geq 12$  ng/l) levels (Table 3 A, B).

We also found that the decrease in hemoglobin concentration from first to second trimesters was greater when SF was low in the first trimester in multiparous women (Table 4B). However, this finding did not apply to the nulliparous women in our study (Table 4A).

## Discussion

This study showed that the prevalence of anemia and iron deficiency was higher in multiparas than in nulliparous women

**Table 2**  
Rates of occurrence of anemia (A, B) and low ferritin (C) in study subjects.

	(+)	(-)	p-value	OR	95%CI
A. Anemia in early pregnancy <sup>a</sup>					
Nulliparas(n = 481)	17(3.5%)	464	<0.001	2.63	1.50–4.61
Multiparas(n = 603)	53(8.8%)	550			
B. Anemia in mid-pregnancy <sup>b</sup>					
Nulliparas(n = 481)	101(21.0%)	380	<0.001	2.15	1.63–2.83
Multiparas(n = 603)	219(36.3%)	384			
C. Low ferritin <sup>c</sup>					
Nulliparas(n = 481)	46(9.6%)	435	<0.001	2.13	1.48–3.08
Multiparas(n = 603)	111(18.4%)	492			

P-value: Fisher's exact test.

<sup>a</sup> Hemoglobin concentration < 11.0 g/dl.

<sup>b</sup> Hemoglobin concentration < 10.5 g/dl.

<sup>c</sup> Serum ferritin level < 12.0 ng/ml.

**Table 1**  
Clinical and laboratory findings in pregnant women.

Demographic data	Nulliparas (n = 481)	Multiparas (n = 603)	p-value
Age	30.2 $\pm$ 4.4	32.9 $\pm$ 4.1	<0.001 <sup>a</sup>
Height (cm)	158.5 $\pm$ 5.5	158.1 $\pm$ 5.1	0.228 <sup>a</sup>
Body weight (kg)	50.9 $\pm$ 6.5	52.0 $\pm$ 7.6	0.019 <sup>a</sup>
Body mass index (kg/m <sup>2</sup> ) <sup>c</sup>	20.3 $\pm$ 2.3	20.8 $\pm$ 2.7	0.002 <sup>a</sup>
First blood sampling (weeks)	9.1 $\pm$ 1.0	9.2 $\pm$ 1.1	0.315 <sup>a</sup>
Hemoglobin (g/dl)	12.6 $\pm$ 1.0	12.4 $\pm$ 1.0	<0.001 <sup>a</sup>
Fe ( $\mu\text{g/dl}$ )	108.0 [61.0, 161.8]	108.0 [51.0, 162.0]	0.242 <sup>b</sup>
Ferritin (ng/ml)	42.7 [12.2, 108.2]	27.7 [8.0, 72.6]	<0.001 <sup>b</sup>
Mean corpuscular volume (fl)	88.5 $\pm$ 4.2	87.9 $\pm$ 5.0	0.027 <sup>a</sup>
Second blood sampling (weeks)	28.5 $\pm$ 0.7	28.5 $\pm$ 0.7	0.238 <sup>a</sup>
Hemoglobin (g/dl)	11.2 $\pm$ 0.9	10.7 $\pm$ 1.0	<0.001 <sup>a</sup>
$\Delta$ Hemoglobin (g/dl) <sup>d</sup>	-1.5 $\pm$ 0.9	-1.6 $\pm$ 0.9	0.002 <sup>a</sup>

Data are presented as mean  $\pm$  standard deviation or as median [10th and 90th percentile].

<sup>a</sup> Unpaired t test.

<sup>b</sup> Mann–Whitney U test.

<sup>c</sup> Body weight (kg)/height(m)<sup>2</sup>.

<sup>d</sup> (hemoglobin at second blood sampling)–(hemoglobin at first blood sampling). Women who were prescribed iron tablets after the first blood sampling (4 nulliparous and 13 multiparous women) were excluded.

**Table 3**

Rate of occurrence of anemia in mid-pregnancy among women who were non-anemic in the first trimester.

No anemia in the first trimester <sup>a</sup>	Anemia in mid-trimester (+) <sup>b</sup>	Anemia in mid-trimester (–)	p-value	OR	95%CI
A. Nulliparous women					
Low ferritin <sup>c</sup> (n = 37)	19(51.3%)	18	<0.001	5.48	2.74–11.0
Normal ferritin (n = 427)	69(16.1%)	358			
B. Multiparous women					
Low ferritin <sup>c</sup> (n = 78)	60(76.9%)	18	<0.001	9.25	5.26–16.28
Normal ferritin (n = 472)	125(26.5%)	347			

P-value: Fisher's exact test.

OR: odds ratio, CI: confidence interval.

<sup>a</sup> Hemoglobin concentration  $\geq 11.0$  g/dl.<sup>b</sup> Hemoglobin concentration  $<10.5$  g/dl.<sup>c</sup> Ferritin level  $<12.0$  ng/ml.**Table 4**

Estimation of decrease in hemoglobin concentration among non-anemic women in the first trimester.

A. Nulliparous women	Low ferritin <sup>b</sup> (n = 37)	Normal ferritin (n = 427)	p-value
$\Delta$ Hemoglobin <sup>a</sup>	$-1.7 \pm 0$	$-1.5 \pm 0.9$	0.155
B. Multiparous women	Low ferritin <sup>b</sup> (n = 78)	Normal ferritin (n = 472)	
$\Delta$ Hemoglobin <sup>a</sup>	$-2.3 \pm 0.7$	$-1.6 \pm 0.8$	<0.001

P-value: Unpaired t-test.

<sup>a</sup> (Hemoglobin concentration in mid-pregnancy)–(hemoglobin concentration in the first trimester).<sup>b</sup> Ferritin level  $<12.0$  ng/ml in the first trimester.

(Table 2) and that all pregnant women with normal hemoglobin and low ferritin levels in the early antenatal period, irrespective of parity, showed higher likelihood of developing anemia later in the pregnancy than those with normal levels (Table 3). The decrease in hemoglobin concentration (presented in Table 1 as  $\Delta$ Hb) was higher in multiparas than in nulliparas, and higher  $\Delta$ Hb correlated with low first-trimester ferritin levels in multiparous women (Table 4B).

Gestational anemia is defined differently in various reports and guidelines. According to the new UK guidelines released in 2019, anemia in pregnancy is defined as a hemoglobin level  $<11.0$  g/dl in the first trimester or that  $<10.5$  g/dl in the second and/or third trimester [11]. WHO defines anemia in pregnancy as hemoglobin level  $<11$  g/dl throughout the gestational period [14]. While Centers for Disease Control and Prevention (CDC) defines anemia as hemoglobin concentration  $<11.0$  g/dl and  $<10.5$  g/dl in the first and second trimesters, respectively (as in UK guidelines), an extended criterion of hemoglobin concentration  $<11.0$  g/dl is applied to define gestational anemia in the third trimester [15]. In the Asia–Pacific region, anemia is defined as hemoglobin level  $<10.5$  g/dl and  $<10.0$  g/dl during pregnancy and in the postpartum period, respectively [16]. An acceptable lower limit of hemoglobin during pregnancy of 10.0 g/dl was also described [15]. In this study, the normal hemoglobin cutoff values as defined by UK guidelines were employed, considering the occurrence of physiological hemodilution during pregnancy, which causes decrease in hemoglobin concentration [11].

Normal SF levels in pregnancy also differ across studies [13]. SF levels of 12, 15, or 30 ng/ml have been proposed as the cutoff value in earlier studies. Serum ferritin is not only a sensitive and specific indicator of iron storage, but is also an acute phase reactant [17]. Patients with inflammatory diseases such as chronic kidney disease, inflammatory bowel disease, and infections have elevated ferritin levels, even though their iron stores maybe low [18]. Therefore, a cutoff serum ferritin value of 12 ng/ml (the lowest

defined figure) was employed in this study, to avoid decreasing specificity of the estimation.

Anemia may be classified as microcytic, normocytic and macrocytic anemia according to mean corpuscular volume (MCV), and IDA typically presents microcytic [19]. But Gupta et al. reported low sensitivity of MCV as a screen for IDA [20]. Seward et al. also showed low sensitivity of MCV for detecting the cause of anemia [21]. The presence of microcytosis does not necessarily imply ID and can be produced by other anemias [22]. Therefore, MCV was not employed as a parameter for evaluating anemia in this study.

Prevalence of anemia in pregnant women is estimated to be 38% globally, ranging from 24% in the Western Pacific region to 49% in South-East Asia [2,23]. However, this report did not assess anemia prevalence in nulliparous and multiparous women, separately. Our study findings show that anemia and low SF was found more frequently among multiparous women than in nulliparas, in the first trimester (2), suggesting that the iron stores spent in the preceding pregnancies and deliveries had not been adequately supplemented before the current gestation. Mei et al. also reported that pregnant women with parity  $\geq 2$  had higher prevalence of ID compared with pregnant women with parity  $\leq 1$  [24]. Short intervals between consequent pregnancies is another risk factor for gestational anemia [25].

Anemia in pregnancy is associated with several maternal and perinatal complications, such as preterm delivery, low birth weight, preeclampsia, gestational hypertension [8,9], maternal death, stillbirth [8], and postpartum depression [26]. Maternal ID leads to low iron levels in neonates and infants [27,28]. As iron is essential for neuronal development, this decrease may negatively affect behavior, cognition, and eventually academic development [29]. Neonatal ID may also be associated with increased risk of autism, attention deficit/hyperactivity disorders, and intellectual disability [30].

As women with normal hemoglobin and associated lower ferritin levels in early antenatal period were highly likely to develop anemia later during pregnancy (Table 3), it is advisable to consider iron supplementation in such non-anemic but iron-deficient subjects. Crispin et al. also reported on the importance of detecting pregnant women with low ferritin in the first trimester as candidates for prophylactic iron therapy [31]. This early-antenatal, non-anemic, iron-deficient status has recently attracted a lot of attention as a disease entity [10,32–35]. However, the positive effect of iron supplementation in affected women remains to be clarified. While the United States Preventive Task Force did not recommend iron supplementation in all pregnant women due to lack of sufficient clinical data [36], Auerbach et al. have strongly advised it, based on their findings [37].

This study has some limitations. Firstly, SF levels were not measured in the second blood sampling performed in the second trimester. If data of ferritin levels in the mid-gestational period had

been available, more detailed analyses might be possible. Secondly, parameters such as soluble transferrin receptor concentration and hepcidin levels indicative of iron stores in the body [38,39] were not evaluated. Using these markers in combination with SF, could help us assess ID in pregnant women more accurately. But SF measurement is still an excellent test of iron deficiency, and is recommended to all pregnant women [40].

In conclusion, anemia and ID are more common in multiparas than in nulliparous women. Furthermore, development of ID anemia in late pregnancy can be predicted and possibly prevented, by estimating serum ferritin levels in the first trimester.

## Declaration of competing interest

None.

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