《原　著》

Gestational Anemia and Serum Ferritin

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Abstract Serial observations for serum ferritin levels were made on healthy pregnant women with and without iron supplement from early pregnancy until 6 months postpartum. Without iron supplement, serum ferritin levels fell to less than 10 ng/m*l* during the latter half of pregnancy, and did not return to the early pregnancy levels even at 6 months postpartum. These results indicate that without iron supplement the storage iron was exhausted during the latter half of pregnancy and was not replenished after pregnancy. With 800 mg of iron supplement, serum ferritin levels at late pregnancy and at 6 months postpartum did not differ from those at early pregnancy, suggesting that most of the supplemented iron was effectively utilized by the mother and fetus and the storage iron did not decrease while gravid. Our observations demonstrated that gestational anemia is mainly due to iron deficiency, and that iron supplement is an effective method for the prevention of gestational anemia.

Introduction

While gestational anemia is a common disorder during pregnancy, its etiology has been disputed for many years. To elucidate its pathophysiology in relation to iron metabolism, the investigation of both hemoglobin and storage iron is required. Until recently, however, there was no simple way to estimate storage iron levels.

Since Addison *et al.*[1] first reported a sensitive radioimmunoassay for determination of serum ferritin, it has been shown that the levels of serum ferritin correlate well with those of storage iron[2]. In this report, to assess the storage iron levels during pregnancy and after parturition, serial observations for serum ferritin levels were made on healthy pregnant women with and without iron supplement from early pregnancy until 6 months postpartum.

Subjects and Methods

Thirty-two pregnant women, visiting the Nagoya University Branch Hospital/Obstetrical Clinic, were studied during pregnancy and after parturition. All pregnancies and deliveries were uncomplicated, and newborn children were healthy. Twenty women (Group A) had received no iron supplement throughout this study. Twelve women (Group B) received 800 mg of elemental iron as iron-chondroitinsulfate colloid (Blutal^{R}, Dainippon Pharmaceutical Co., Ltd., Osaka, Japan) intravenously, divided into four biweekly doses of 200 mg, starting at the 22nd week of pregnancy. At intravenous infusion, iron-chondroitin sulfate colloid was diluted in 500 m*l* of physiologic saline and given at about 50 drops per minute. No side effect was observed.

Venous blood samples were obtained between 9:00 and 11:00 a.m. during early (7th to 11th week), mid (28th to 32nd week), and late (36th to 39th week) pregnancy, at 1 month postpartum and finally at approximately 6 months postpartum. In twenty-one subjects cord blood samples were also obtained at delivery.

Blood hemoglobin (Hb) and hematocrit (Ht) were determined with a Coulter Counter Model S. Total iron binding capacity (TIBC) and unsaturated iron binding capacity (UIBC) of the serum were determined by the radioassay methods

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Table 1 Serum ferritin and other parameters of the iron status during and after pregnancy in no iron supplemented (group A, n=20) and 800 mg of iron supplemented (group B, n=12) women. Means and standard deviations are given.

Analysis	Group	Pregnancy			Postpartum	
		Early (7th–11th wk)	Mid (28th–32nd wk)	Late (36th–39th wk)	1 month	6 months
Hb (g/dl)	A	12.2±0.8	11.0±0.8*	11.1±1.1*	12.1±0.7	13.0±0.7
	B	*13.0±0.3*	*12.4±1.0*	*13.2±1.0*	*13.6±1.1*	*13.7±0.6*
Ht (%)	A	36.8±2.5	34.1±2.6*	34.4±3.2*	37.6±1.9	37.9±2.1
	B	*39.8±1.6*	*36.9±2.9**	*38.9±3.3*	*39.6±2.9*	*39.4±1.5*
TIBC (μg/dl)	A	320±48	494±53**	524±73**	377±41**	341±34
	B	333±53	*414±65*	*446±60***	*309±52*	307±64
SI (μg/dl)	A	112±34	65±25*	56±24*	77±27*	85±30
	B	107±37	*118±36*	*114±39*	*107±22*	93±30
T-Sat (%)	A	36.3±12.2	13.4±5.6*	11.0±6.0*	20.0±6.8*	25.1±9.0
	B	32.4±10.9	*28.9±7.8*	*26.5±11.7*	*36.1±11.7*	30.9±9.1
Serum ferritin[1] (ng/ml)	A	23 (10–53)	4 (2– 6)*	4 (2– 6)*	6 (3–14)*	8 (4–14)*
	B	14 (4–44)	*53 (30–95)***	*18 (11–31)*	*57 (30–108)***	*27 (12–60)*

The means of group B which are significantly different from the means of group A are in *italics* ($p<0.001$)

[1]Logarithmic mean values with±1 SD range in parentheses

*indicates value below early pregnancy level ($p<0.001$)

**indicates value above early pregnancy level ($p<0.001$)

described previously[3,4]. Serum iron (SI) was obtained by subtracting UIBC from TIBC, and transferrin saturation (T-Sat) was obtained dividing SI by TIBC. The assay of serum ferritin concentration was performed by a 2-site immunoradiometric assay method (SPAC Ferritin Kit, Daiichi Radioisotope Laboratory, Tokyo, Japan).

Statistical comparisons were made using the "t" test at $p<0.001$ level. Analyses of serum ferritin values were performed on logarithmic values, as serum ferritin concentrations are normally distributed on a logarithmic scale[5].

Results

The serum ferritin and other parameters of iron status determined during and after pregnancy in the two groups are summarized in Table 1.

At early pregnancy, when no iron was supplemented, there was no significant difference in serum ferritin between the two groups (Table 1).

Serial individual changes in serum ferritin during and after pregnancy for groups A and B are depicted in Fig. 1 and 2, respectively.

Group A: At mid and late pregnancy marked falls of serum ferritin were observed as compared with values at early pregnancy, and all women in group A showed serum ferritin levels below 10 ng/ml (Fig. 1). In addition, at mid and late pregnancy there were significant decreases in Hb, Ht, SI and T-Sat, and significant increases in TIBC, when compared with values at early pregnancy (Table 1).

After pregnancy, Hb returned to early pregnancy levels by 1 month postpartum. However, serum ferritin at 6 months postpartum still remained lower than that at early pregnancy (Table 1).

Group B: A marked increase of serum ferritin at mid pregnancy was observed (Fig. 2). However, at late pregnancy serum ferritin decreased, and no significant difference was found between levels determined at early and late pregnancy (Table 1). Ht at mid pregnancy and TIBC at late pregnancy in group B also showed significant decrease and increase, respectively. However, Hb, SI and T-Sat showed little change during pregnancy (Table 1).

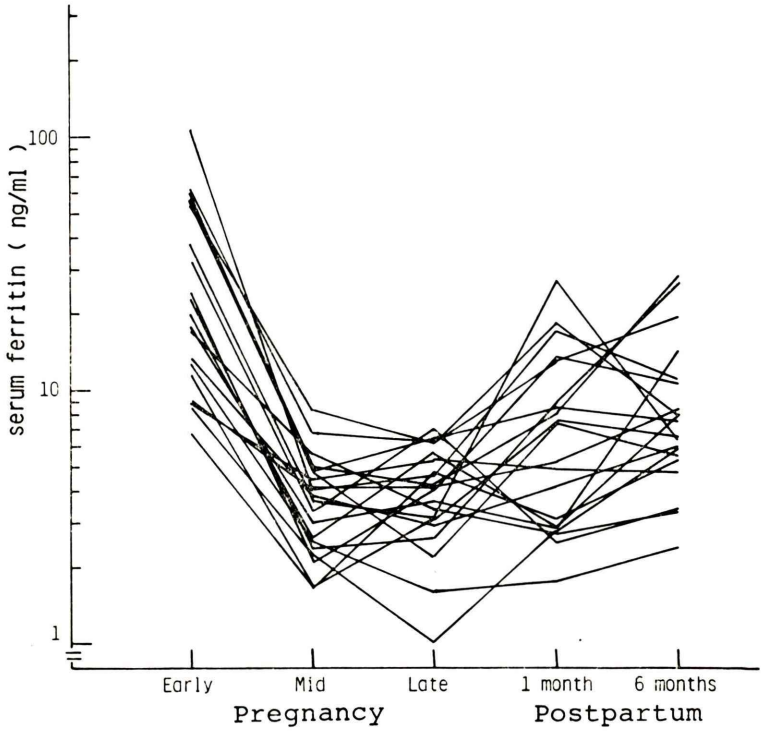

Fig. 1 Serial observations for serum ferritin during and after pregnancy in no iron supplemented women (group A).

Table 2 Cord blood serum ferritin and other parameters of the iron status in relation to iron supplement (Mean±SD)

	Hb (g/dl)	Ht (%)	TIBC (μg/dl)	SI (μg/dl)	T-Sat (%)	Serum ferritin[1] (ng/ml)
Group A* (n=11)	15.9±1.3	48.8±4.8	208±24	150±42	72±16	108 (64–184)
Group B** (n=10)	15.2±1.4	45.8±4.4	206±50	128±30	64±14	99 (66–147)

[1]Values in parentheses are the limits of ±1 SD

*Without iron supplement

**With 800 mg of iron supplement

After pregnancy, serum ferritin increased again at 1 month postpartum. However, at 6 months postpartum a second fall in serum ferritin was observed, and no significant difference between levels determined at early pregnancy and 6 months postpartum was found (Table 1). In group B, Hb, Ht, TIBC, SI and T-Sat after pregnancy showed no significant differences, when compared with values at early pregnancy.

Cord blood: The serum ferritin and other parameters of iron status determined in cord blood samples for the two groups are shown in Table 2. There was no significant difference between cord blood serum ferritin in group A and B, nor between other parameters of iron status in cord blood.

Relationships between the cord and maternal (at late pregnancy) parameters of iron status were examined. As shown in Fig. 3, no correlation was found between the cord and maternal ferritin concentrations, nor between other parameters in

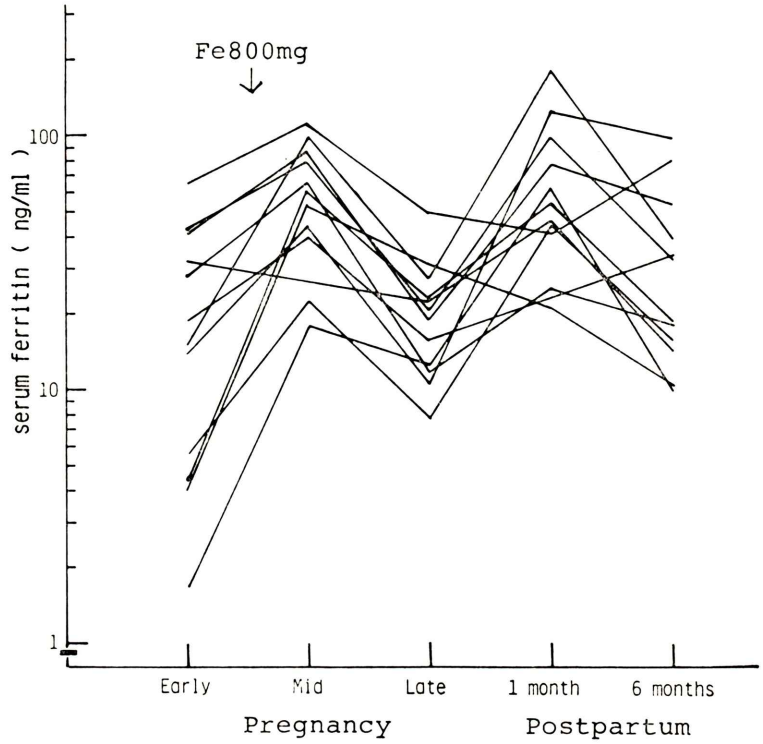

Fig 2 Serial observations for serum ferritin during and after pregnancy in 800 mg of iron supplemented women (group B).

cord and maternal blood.

Discussion

While storage iron as reserve in adult women has been estimated at about 200 to 300 mg[6], total iron loss and requirements in pregnancy have been calculated to be approximately 800 and 1,100 mg respectively[7]. Accordingly, it has been suggested that gestational anemia is due to iron deficiency. However, because there is a greater increase in plasma volume than in red-cell volume during pregnancy, gestational anemia has often been attributed to hydremia.

Hytten and Leitch[8] wrote, "Perhaps the critical information needed to decide the interpretation of the 'physiological anemia of pregnancy' is whether or not the average young woman has a sufficiency of 'storage iron': the falling concentration of haemoglobin could hardly be attributed to iron deficiency if there were demonstrable stores in the body of unused iron." In the present study, observation of storage iron during and after pregnancy was made for this purpose, using the recently developed immunoassay for serum ferritin.

At first, pregnant women without iron supplement were studied. With a fall in the concentration of hemoglobin, serum ferritin fell to less than 10 ng/m*l*, a generally accepted criterion of exhausted iron stores[9], during the latter half of pregnancy, which are consistent with the findings reported by Taft *et al.*[10]. As mentioned above, the increase in maternal red-cell volume physiologically occurs due to pregnancy. Accordingly, if the serum ferritin returned to the early pregnancy level after pregnancy, the decrease of serum ferritin during pregnancy could be attributed to a shift of iron from the storage pool to the hemoglobin pool. The fact is that, though hemoglobin returned to the early pregnancy level after pregnancy, serum ferritin was not corrected at 6 months postpartum. Therefore, it must be concluded that without iron supplement storage iron is actually exhausted

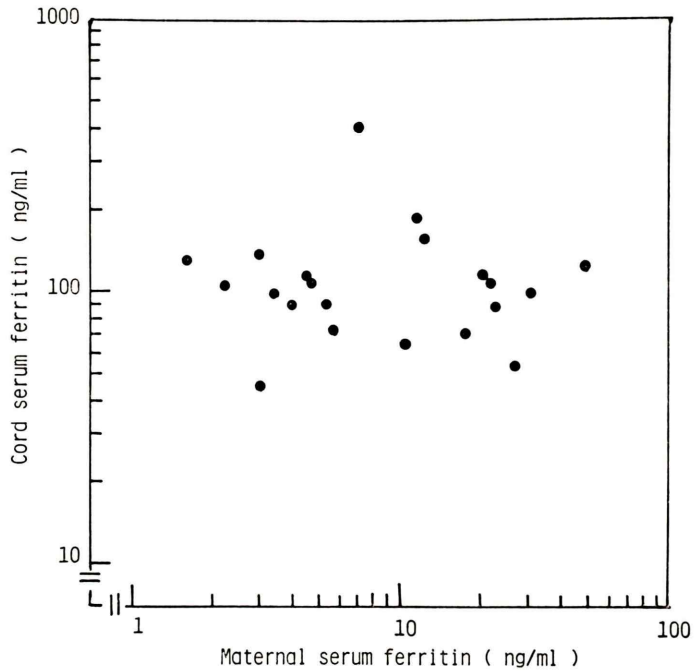

Fig. 3 Correlation between maternal (at late pregnancy) and cord serum ferritin in 21 subjects. The regression equation between logarithmic values of maternal serum ferritin (X) and those of cord serum ferritin (Y) is $Y=-0.024X+2.04$, and the correlation coefficient is -0.05 ($p>0.05$).

during the latter half of pregnancy and is lost by one pregnancy. Furthermore, these findings support the view that the falling concentration of hemoglobin during pregnancy is due to iron deficiency.

As reported previously[11], hemoglobin levels during the latter half of pregnancy can be improved by iron supplement. This may be taken as supporting evidence to indicate that gestational anemia is due to iron deficiency. Therefore, pregnant women received 800 mg of elemental iron, which has been estimated to be the total iron loss in one pregnancy[7], were studied. In this group, the serum ferritin increased markedly at mid pregnancy, due to a transient build up of the storage iron following intravenous iron administration[12]. However, at late pregnancy serum ferritin decreased to the early pregnancy level, indicating that the bulk of supplemental iron has been utilized. After pregnancy, serum ferritin increased again at 1 month postpartum, probably due to decrease of red-cell volume with return of iron to the stores after pregnancy. However, at 6 months postpartum serum ferritin declined to the early pregnancy level, indicating that with 800 mg of elemental iron supplement storage iron is neither lost nor replenished by one pregnancy.

Likewise in the group without iron supplement, the decrease in Ht at mid pregnancy was also observed in the group with iron supplement. Therefore, the development of gestational anemia may be partly attributed to hydremia. However, Ht at mid pregnancy in the iron supplemented group was within normal limit.

From the present study, it may be safe to say that iron deficiency is the main cause of gestational anemia, and that iron supplement is an effective method for the treatment or prevention of gestational anemia.

In addition, we also tested whether the iron status of the mother influences that of the newborn infant. No significant difference in the cord serum ferritin and other parameters between the groups with and without iron supplement was observed.

It, therefore, may be concluded that gestational anemia does not affect the iron status of the newborn infant.

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要　旨

妊娠貧血と血清フェリチン

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妊娠貧血の病態を鉄代謝の側面より解明すべく，鉄剤非投与妊婦(A群)，鉄剤800 mg投与妊婦(B群)について，妊娠初期より分娩後6か月にわたり，貯蔵鉄の指標となる血清フェリチンをRIA法にて測定した．①A群の血清フェリチン値は妊娠中期・後期に激減し，妊娠中期以降の貯蔵鉄の枯渇が明らかとなった．また，分娩後6か月に至るも血清フェリチン値は依然低値を示し，妊娠による貯蔵鉄の損失が示唆された．②一方，従来より一回の妊娠による鉄損失量と推定されている800 mgの鉄剤を投与したB群では，妊娠初期と妊娠後期・分娩後6か月の血清フェリチン値に変動なく，投与された鉄が有効に利用され，妊娠による貯蔵鉄の損失は防がれたと考えられた．

Key words: Pregnancy, Ferritin, Iron, Maternal-fetal exchange.