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ORIGINAL ARTICLE

Increased yet iron-restricted erythropoiesis in postpartum mothers

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Abstract Iron deficiency in the postpartum period is common and associated with impaired quality of life. Interpretation of ordinary laboratory parameters is considered to be simple in postpartum women, as normalization of pregnancy induced physiological changes is assumed to take place in the early postpartum period. We have studied changes in erythrocyte and iron parameters during the first 11 postpartum months. Erythrocyte parameters and iron markers, serum ferritin, and soluble transferrin receptor (sTfR), and an inflammation marker, neopterin, were investigated in healthy mothers 6 weeks ($n=104$), 4 months ($n=100$), and 11 months ($n=43$) after giving birth to a term infant. Healthy nonpregnant and nonlactating women ($n=61$) were included as controls. The hemoglobin level increased throughout the first 11 postpartum months and was significantly higher from 4 months on, compared to control women. At all time points, the mothers had significantly lower mean corpuscular volume (MCV) and higher erythrocyte count and percentage of hypochromic erythrocytes. sTfR levels were significantly higher over the whole serum ferritin distribution during the first 4 postpartum months compared to the controls, indicative of an increased cell production. At 6 weeks, postpartum mothers had higher neopterin levels and this was associated with markers of a low iron status, not including sTfR. Substantial changes in erythrocyte and iron parameters were observed in the postpartum period, consistent with an increased, but iron restricted erythropoiesis. The increased erythropoietic activity was reflected in higher sTfR concentrations. Given the vital role for iron in both mothers and infants, further studies are warranted for establishing proper cut off levels for sTfR as an iron marker in postpartum women.

Keywords Postpartum · Erythropoiesis · Iron status · Reticulocyte hemoglobin content · Hemoglobin

Abbreviations

BMI	Body mass index
CHr	Reticulocyte hemoglobin content
EPO	Erythropoietin
%Hypo	Percentage of erythrocytes with decreased amount of hemoglobin (MCHC<28 g/dl)
MCV	Mean corpuscular volume
RBC	Red blood cell
RDW	Red cell distribution width
sTfR	Soluble transferrin receptor

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Introduction

Iron deficiency in the postpartum period is a worldwide problem and associated with impaired quality of life due to reduced physical performance, cognitive dysfunction and depression [1]. Consequently, evaluation of iron status in postpartum women is important and prompt treatment of iron deficiency warranted.

While pregnancy is associated with a high demand for iron and a risk of iron deficiency, unless the mother is substituted [2, 3], the postpartum period is associated with low iron requirements [4], due to the lactation induced amenorrhea and a relatively low loss of iron in breastmilk (0.3 mg/day) [5]. In spite of this, postpartum anemia is considered to be common, due to low iron reserves prior to delivery and blood loss at delivery[4].

Women who are iron supplemented during pregnancy are less likely to develop postpartum anemia. A hemoglobin level below 11.0 g/dl is reported in 14 % of iron supplemented versus 24 % of nonsupplemented European women 1 week after delivery[1]. After 8 weeks, a low iron status defined as serum ferritin≤20 μg/l, was reported in 16 % of mothers who were iron supplemented during pregnancy and in 40 % of mothers who were not supplemented. Despite the high prevalence of low iron status, anemia, defined as a hemoglobin level below 12.0 g/dl, was observed in only 4 % of the non supplemented mothers[6].

Interpretation of ordinary laboratory parameters is considered to be easier in postpartum women compared to pregnant women, as normalization of pregnancy induced physiological changes is assumed to take place in the early postpartum period [6]. After delivery, hormonal and hemodynamic changes are considered to be reset to a prepregnancy status approximately 5 to 6 weeks postpartum [1]. Maternal serum erythropoietin (EPO) levels are reported to decline the first postpartum weeks, with a consequent reduction in erythrocyte mass to prepregnant levels [1].

Common biomarkers of iron status, serum levels of ferritin and soluble transferrin receptor (sTfR) are considered to be reliable 1 week after delivery [4]. sTfR is proportional to the receptor density on cells, determined by cellular iron needs, and to cell production. Consequently, a high sTfR level is associated with iron deficiency, as well as with increased erythropoiesis. sTfR is reported to increase steadily during pregnancy and decrease postpartum to levels equal to nonpregnant women after 5 weeks [7].

As iron is a vital part of hemoglobin, new erythrocyte parameters, such as reticulocyte hemoglobin content (CHr), a real-time parameter of iron status for the last 24–48 h, and the percentage of erythrocytes with decreased amount of hemoglobin (MCHC<28 g/dl), termed %Hypo, have proven useful in the evaluation of iron status, particularly in periods associated with many physiological changes [8].

Few reports have focused on changes in erythropoiesis and iron status after the puerperium [9–11]. We have studied mothers during the first 11 postpartum months and compared this to nonpregnant and nonlactating controls, in order to evaluate changes in erythrocyte and iron parameter in the later postpartum period.

Methods

Study population and design

Healthy mothers (n=104) who had given birth to a term baby 6 weeks before were recruited from a local health service in Western Norway from December 2004 through April 2006. They were all invited back at 4 months (n=100) and 11 months (n=43) postpartum. Healthy women below 40 years, who were not pregnant or breastfeeding (n=61), were recruited among first time blood donors at Haukeland University Hospital, Bergen, Norway during the same period and served as controls.

Nonfasting blood samples were obtained by antecubital venipuncture and a questionnaire on nutrition, iron supplementation, use of tobacco, current breastfeeding practice, weight, and length was completed at each visit.

Ethical approval of the protocol was granted by the local Committee on Medical Research Ethics, and the mother gave written, informed consent.

Blood sample collection and biochemical analyses

The blood samples for erythrocyte and reticulocyte indices were collected into EDTA vacutainer tubes (Becton Dickinson) and analyzed within 5 h with an automated hematology analyzer (ADVIA 120, Bayer Diagnostics). The reference interval for men and women ≥18 years was for CHr 31.5–35.5 pg and for %Hypo 0.1–1.1 %.

Serum was obtained by collecting blood into Vacutainer Tubes with no additive (Becton Dickinson). Blood was allowed to clot at room temperature for 30 min before the serum fraction was transferred to an empty glass vial. Serum ferritin was analyzed by Modular PP, Tina Quant (F. Hoffman–La Roche, Basel, Switzerland) with a reference interval for women of 15–160 μg/l. Serum sTfR was analyzed by Dade Behring (Marburg, Germany), N latex sSTfR method (Behring Nephelometer II, Dade Behring) with a reference interval of 0.84–1.54 mg/l.

Plasma was obtained by collecting blood into Vacutainer Tubes containing EDTA (Becton Dickinson), placed in ice water, and plasma was separated within 1/2 h and stored at −80°C until analysis. Plasma neopterin, a marker of cell-mediated immune activation [12], was analyzed by isotope dilution LC-MS/MS [13].

Reticulocyte indices and iron parameters were only available for a fraction of the mothers (reticulocyte parameters: 58/104 at 6 weeks, 71/100 at 4 months, and 38/43 at 11 months; iron parameters: 62/104 at 6 weeks, 82/100 at 4 months, and 38/43 at 11 months). Plasma neopterin was available for all controls and mothers at 6 weeks and 4 months, but none at 11 months.

Statistical analysis

Results are presented as mean (SD) and median (interquartile range). Means were compared by Student's *t*-test and medians with Mann–Whitney *U*-test. The association between two categorical variables was examined by the Chi-square test. Mann–Whitney *U*-test was used to compare sTfR levels in postpartum mothers according to serum ferritin distribution, categorized as <15, 15–30, and ≥30 μg/l.

Graphical illustrations of the dose–response relationship between CHr and ferritin level and sTfR and ferritin level were obtained by generalized additive models (GAM) [14].

GAMs were computed using the mgcv-package (version 1.4–1) in R (The R Foundation for Statistical Computing, version 2.8.1) [15], and the SPSS/PASW statistical package version 18 was used for the remaining statistical analyses. Two-sided *p*-values <0.05 were considered statistically significant.

Results

Demographics and nutrition

Demographic data at inclusion, 6 weeks postpartum, is presented in Table 1. The mothers were significantly older, had higher mean BMI, and were more often smokers compared to the controls (Table 1). Daily use of iron supplementation for shorter or longer periods was reported by 34/104 (33 %) mothers during pregnancy and by 15/100 (15 %) at 4 months and by 1/43 (2 %) at 11 months postpartum. Two of the mothers were vegetarians, the remaining mothers and all controls claimed to consume an omnivorous diet. The majority of the mothers and the controls were Caucasians (one mother was Chinese and one control was Arab).

All mothers reported an uncomplicated pregnancy and delivery, and they had all given birth to a term baby with a mean gestational age of 40 (SD 1) weeks, and appropriate for gestational age weight (mean 3573 (514) g). Information on blood loss during delivery was not available. The majority was breastfeeding at 6 weeks (98 %), 4 months (94 %), and 11 months (67 %). Of the mothers, 63 (61 %) had more than one child, while 49/61 (80 %) of the controls were nulliparous.

Erythrocyte parameters and iron status

Erythrocyte and iron parameters are presented in Table 2. During the first 11 postpartum months, mean hemoglobin level steadily increased and was from 4 months on significantly higher in the mothers compared to the controls. The number of anemic mothers, defined by a hemoglobin level <12.0 g/dl, was not significantly different from the control women at any time point. CHr and %Hypo improved during this period, but at all time points, the mothers had more, smaller, and hypochromic erythrocytes compared to the controls (Table 2).

The prevalence of mothers with iron deficiency, defined by either CHr <31.5 pg, %Hypo >1.1 %, ferritin <15 μg/l, or sTfR >1.54 mg/l, decreased during the postpartum period and was similar to the controls 11 months postpartum (Table 2). However, compared to the other iron markers, mean ferritin levels remained fairly stable during this period (Table 2), and the majority of the mothers had low iron reserves, defined as a ferritin level <30 μg/l [16], throughout the first 11 postpartum months (70 % at 6 weeks, 68 % at 4 months, and 79 % at 11 months).

sTfR levels were higher in mothers compared to controls over the whole ferritin distribution (<15, 15–30, and ≥30 μg/l) at 6 weeks ($p=0.004$, $p=0.03$, and $p=0.06$) and 4 months ($p=0.24$, $p<0.001$, and $p=0.007$), but less so at 11 months ($p>0.02$; Fig. 1).

We used GAM to obtain dose–response curves between CHr–ferritin and sTfR–ferritin (Fig. 2). Distinctly nonlinear relations were observed for both relations, with a change in slope at a ferritin level around 20 μg/l (Fig. 2).

Inflammation status

At 6 weeks, the mothers had significantly higher plasma neopterin levels compared to the controls [median 8.5 (range 7.2–10.8) vs. 7.3 (5.7–9.4), $p=0.001$]. At 4 months, maternal neopterin levels were decreased [median 8.0 (6.3–10.0)] and

Table 1 Demographic characteristics of control women and mothers 6 weeks postpartum

Parameters	Control women (*N*=61)	Postpartum mothers at 6 weeks (*N*=104)	*P*-value
Age, years, mean (SD)	25 (6)	31 (5)	<0.001[a]
BMI, mean (SD)	22.9 (3.1)	25.2 (3.9)	<0.001[a]
Daily iron supplementation, n (%)	1 (2 %)	18 (17 %)	0.004[b]
Daily smoking, *n* (%)	0	9 (9 %)	<0.001[a]

[a]Student's *t*-test

[b]Chi-square test

Table 2 Erythrocyte and iron parameters in control women and postpartum mothers[a]

Parameters	Control women (n=61)	Postpartum mothers			P-values of postpartum mothers 6 weeks/4 months/12 months vs. controls
		6 weeks (n=104)	4 months (n=100)	11 months (n=43)	
Hemoglobin, g/dl	13.0 (0.8)	13.3 (1.0)	13.5 (0.9)	13.7 (0.8)	0.10/0.002/0.04[b]
Hemoglobin<12 g/dl, %	8	10	5	2	0.76/0.42/0.21[c]
MCV, fl	92 (5)	88 (5)	88 (4)	90 (5)	<0.001/<0.001/0.04[b]
RDW, %	13.2 (0.7)	13.7 (1.7)	14.0 (1.6)	13.3 (0.7)	0.005/<0.001/0.24[b]
RBC×10^{12}/l	4.37 (0.27)	4.63 (0.35)	4.69 (0.33)	4.49 (0.28)	<0.001/<0.001/0.03[b]
Reticulocytes×10^{12}/l	0.049 (0.012)	0.048 (0.014)	0.054(0.016)	0.059 (0.020)	0.88/0.02/0.005[b]
CHr, pg	32.8 (32.1–33.8)	32.1 (30.7–33.0)	32.3 (31.2–33.3)	33.1 (31.9–34.0)	<0.001/0.006/0.80[d]
CHr<31.5 pg, %	13	36	29	13	<0.001/<0.001/1.00[c]
% Hypo	0.3 (0.2–0.7)	1.0 (0.4–2.2)	0.6 (0.3–1.3)	0.2 (0.1–0.5)	<0.001/0.005/0.01[d]
% Hypo>1.1, %	8	45	27	2	<0.001/0.005/0.21[c]
Serum ferritin, µg/l	27 (17–43)	23 (12–37)	21 (15–31)	23 (18–28)	0.06/0.04/0.16[d]
Serum ferritin<15 µg/l, (%)	20	30	19	10	0.18/0.95/0.16[c]
Serum sTfR, mg/l	1.1 (0.9–1.2)	1.4 (1.1–1.7)	1.3 (1.1–1.5)	1.2 (1.0–1.4)	<0.001/<0.001/0.03[d]
Serum sTfR>1.54 mg/l, %	8	35	23	14	0.001/0.02/0.35[c]

Reticulocyte data were available for 58 mothers at 6 weeks, 71 at 4 months, and 38 at 11 months. Ferritin and TfR data were available for 62 mothers at 6 weeks, 82 at 4 months, and 38 at 11 months

MCV Mean cellular volume, *RBC* red blood cell, *RDW* red cell distribution width, *CHr* reticulocyte hemoglobin content, *%Hypo* Percentage of erythrocytes with decreased amount of hemoglobin (MCHC<28 g/Dl), *sTfR* soluble transferrin receptor

[a] Mean (SD) or median (interquartile range)

[b] Student's t-test

[c] Chi-square test

[d] Mann–Whitney U-test

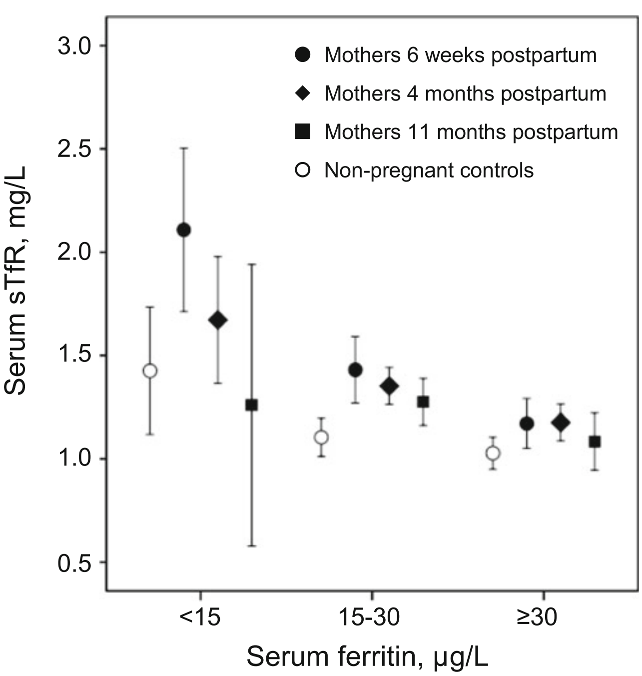

Fig. 1 sTfR in relation to serum ferritin in nonpregnant controls and mothers at 6 weeks, 4 months, and 11 months postpartum

no longer significantly different from the controls (p=0.06). Maternal neopterin levels were inversely correlated to MCV (r=-0.26, p=0.009), CHr (r=−0.25, p=0.06), and ferritin (r=−0.26, p=0.04), and positive correlated to %Hypo (r=0.25, p=0.06) at 6 weeks, but not at 4 months (all p>0.8). No significant correlations were observed between maternal neopterin levels and reticulocytes or sTfR at 6 weeks or 4 months (all p>0.4). We did not find any significant correlations between neopterin and erythrocyte and iron markers in the controls (all p>0.2).

Discussion

Substantial changes in erythrocyte parameters and iron markers consistent with an increased, but iron-restricted erythropoiesis, were seen in mothers during the first 11 postpartum months, indicative of an erythropoietic stimulus during this period. Higher sTfR levels were observed over the whole ferritin distribution during the first 4 months. Signs of cell-mediated immune activation, reflected by higher maternal neopterin levels, were observed at 6 weeks postpartum and was associated with markers of a low iron status, not including sTfR levels.

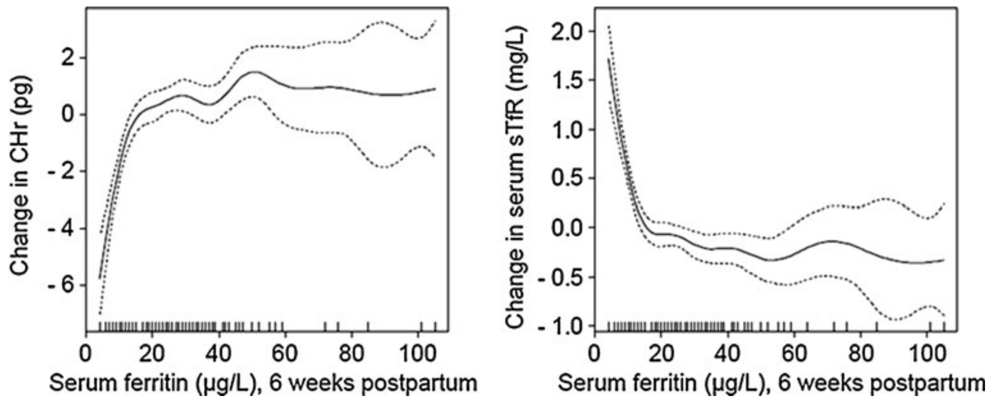

Fig. 2 Dose–response relationship between CHr and ferritin and between sTfR and ferritin in mothers 6 weeks postpartum by GAM

The controls were recruited among first time blood donors, and compared to the mothers, they were significantly younger, had a lower BMI, and the majority were nulliparous and nonsmokers. These discrepancies may increase the differences observed in erythrocyte parameters and iron status between postpartum women and the controls. The low response rate at 11 months may have introduced a selection bias. However, the same changes in the parameters were seen if the analysis were confined to the 43 mothers who were followed throughout the whole period (results not shown).

Despite a higher incidence of low iron status, there was not a significant difference in the prevalence of anemia between mothers and controls. Compared to the controls, the mothers had a higher mean hemoglobin level, as well as higher mean reticulocyte and erythrocyte counts throughout the first postpartum year. Maternal erythrocytes were, however, smaller and more hypochromic, indicative of an iron-restricted erythropoiesis.

While iron deficiency in adults is associated with a normal or decreased number of erythrocytes, a high red blood cell count is reported to be common in infants aged 6 to 48 months with iron deficiency anemia [17]. The reason for this difference according to age is not known. There might, however, be a common erythropoietic stimulus responsible for the high production of red cells, despite a marginal iron status, in both infants and postpartum mothers.

During pregnancy, there is a physiological, nonhypoxia-induced increase in EPO, which accounts for the expansion of red cell mass [10]. In addition to its role in erythropoiesis, EPO is an essential growth factor for endothelial cells, heart, gastrointestinal tract, and brain during the fetal and neonatal period [18]. EPO concentrations are reported to steadily increase in human milk during the lactation period, up to maximal levels seen at 12 months of lactation [18]. In animal studies, milk EPO levels have been shown to reflect maternal serum levels [19]. In humans, the mammary gland epithelium can produce EPO, but the entire source of EPO in human milk is still unknown [20]. The observed increased postpartum erythropoiesis could be an effect of an increased EPO production and high EPO blood levels in postpartum mothers, but as maternal EPO levels was not analyzed in this study, this hypothesis could not be tested.

Increased levels of various inflammation markers including neopterin have been reported during the first 4 to 6 postpartum weeks [21] and was confirmed in this study. Inflammation has been associated with higher EPO and reticulocyte levels in nonanemic states [22], something which may contribute to the observed increased erythropoiesis in the postpartum period. We did, however, not find any significant relation between neopterin and reticulocyte count, but at 6 weeks, we did observe a relation between maternal neopterin and markers of low iron status (MCV, CHr, ferritin, and %Hypo). As inflammation hampers the availability of iron for hemoglobin production [23], one could expect an inverse relation between neopterin and CHr, but possibly not with ferritin, as ferritin is known to increase during inflammation [24]. However, as both low iron status and higher neopterin levels are common in the early postpartum period [1], the inverse relation between neopterin and iron status could merely be a chance finding.

sTfR is reported to be unaffected by inflammation [9], something which has been confirmed in this study. sTfR is therefore considered to be a suitable parameter for evaluation of postpartum iron status [9]. sTfR levels have been reported to increase during pregnancy, as a result of increased erythropoiesis and iron deficiency [25]. In women with adequate iron stores, sTfR increased by 25 % during pregnancy, presumably due to increased erythropoiesis, but already 1 week after delivery, sTfR was considered to be a reliable iron indicator [26]. Our data do not confirm this observation. The increased erythropoietic activity from 6 weeks to 4 months postpartum was reflected in significantly higher sTfR concentrations over the whole serum ferritin distribution. Further, systematic studies are necessary in order to conclude whether there is a need for higher sTfR cut-off levels in postpartum mothers.

A ferritin level <15 µg/l is a reliable indicator of iron depletion, while a ferritin level <30 µg/l is associated with low iron reserves [16]. In accordance with this, we observed a change in slope of the GAM curves for the relation between

CHr- ferritin and sTfR-ferritin around a serum ferritin level of 20 μg/l. Below this, a decrease in ferritin was associated with a steep decrease in CHr and a steep increase in sTfR.

Although the requirement for iron increases substantially during pregnancy and lactation, iron supplementation during pregnancy remains controversial [2, 3, 27]. A study based on data from 40.000 pregnant Norwegian women during the period 2002–2005, showed that use of iron supplements improved iron intake, but not sufficiently to reach Nordic recommendations [28]. However, from 2005, routine iron supplementation during pregnancy is not recommended in Norway [29]. In our study population, a minority of the mothers were iron-supplemented during pregnancy and the postpartum period. The mean serum ferritin level remained stable during the first postpartum year, but 11 months postpartum, the prevalence of low iron stores (ferritin<30 μg/l) was substantial, 79 %. Serum ferritin levels reflect iron stores [30], but in postpartum women, it is probable that the augmented erythropoiesis will direct the newly absorbed iron to the bone marrow for hemoglobin production, leaving the ferritin stores essentially unchanged.

Conclusion

Substantial changes in erythrocyte and iron parameters were observed in the later postpartum period, consistent with an increased, but iron restricted erythropoiesis. The increased erythropoietic activity was reflected in higher sTfR concentrations. As the cut-off level for sTfR as an iron marker depend on the erythropoietic activity level, further studies on erythropoiesis and iron markers are warranted in postpartum women.

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Conflict of interest None.

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