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Effect of oral iron supplementation during pregnancy on maternal and fetal iron status

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The known increased need for iron during pregnancy, due to expansion of maternal red cell volume and the requirements of the developing fetus and placenta, appears to be met only in part by increased iron absorption and amenorrhea [12]. For this reason, considerable demands must be made on maternal iron stores, in particular in the last trimester of pregnancy when iron requirement rises to about 7 mg per day [10]. However, part of the iron is only borrowed by the maternal red cell mass and is largely returned after delivery.

Since available evidence suggests that a high proportion of apparently healthy women of childbearing age lack sufficient storage iron [3], pregnancy may be expected to cause iron deficiency in these women, which may also have a bearing on the iron status of the fetus and neonate [9]. Based on these considerations, prophylactic supplementation of dietary iron is advocated but remains a disputed issue [2, 5].

The present prospective and longitudinal study was undertaken to investigate changes in hematologic status, and in particular in iron stores, during the course of pregnancy in healthy women with and without oral iron supplements.

1 Patients and methods

The study involved 44 healthy Caucasian women with a singleton pregnancy who attended the Antenatal Clinic of the University Hospital Dijkzigt, Rotterdam. The women were selected on the basis of a hemoglobin concentration of at least 7.0 mmol per liter without iron supplementation at the time of their first visit between 8 and 14 weeks of amenorrhea.

After informed consent had been obtained, they were randomly assigned to a study group in which oral iron supplementation was given from the 16th week of amenorrhea until 6 weeks post partum (n = 21), and a control group without iron supplements (n = 23). The women in the study group took one tablet of a sustained release preparation of 525 mg of ferrosulfate* containing 105 mg of elemental iron daily at breakfast. They were asked at each prenatal visit how many tablets they had left and the women in the control group were asked if they had started taking any medication.

Venous blood samples were collected in iron-free containers in both groups at the start of the study at 16 weeks gestation, at 28 and 36 weeks, at the time of admission for delivery, and 6 and 12 weeks post partum. A sample of venous cord blood was collected immediately after delivery in all but three cases. All samples were allowed to clot at room temperature and the sera were stored at − 20 °C until analysis.

All patients had uncomplicated pregnancies, and were delivered vaginally of live healthy infants.

* FERO-GRADUMET (ABBOTT)

Blood loss at delivery was less than 1000 ml in all cases. Three women in the control group developed anemia with a hemoglobin concentration below 6.5 mmol/L, and three women of the study group decided to stop the iron supplementation for no obvious reason. These women were omitted from the study.

Serum iron concentrations were determined spectrophotometrically using the ferrozine reagent [15]. Serum transferrin was measured by the single radial immunodiffusion technique [15]. Serum ferritin was estimated with a specific solid-phase radioimmunoassay adopted from HALLIDAY et al. [4].

Since most variables did not show a GAUSSIAN distribution, appropriate non-parametric tests were used for statistical analysis, and 0.05 was taken as the level of significance.

2 Results

The results of the measurements of the various variables in maternal blood during the course of gestation in women with and without iron supplementation are summarized in Tab. I. There were no significant differences at the beginning of the study between women allocated to iron supplementation and women in the control group with regard to any of the variables studied.

Hemoglobin values in non-supplemented women determined at 28 weeks of amenorrhea were significantly reduced when compared to 16 weeks ($p < 0.05$). After 28 weeks a gradual increase in hemoglobin levels was observed, and at delivery there was no statistical difference with the values at 16 weeks. In iron supplemented women no significant changes in hemoglobin concentrations were observed.

Serum iron concentrations in untreated women showed a significant ($p < 0.01$) fall between 16 and 28 weeks of amenorrhea, and the concentrations remained at the same low level throughout pregnancy. In the supplemented group serum iron concentrations remained stable throughout pregnancy. No correlation between serum iron concentrations and hemoglobin levels could be demonstrated. Serum transferrin levels rose in the untreated as well as in the treated group. The increase was significant between 16 and 28 weeks, and between 28 and 36 weeks in both groups, but more pronounced in non-supplemented women. In both groups no significant correlation could be demonstrated between transferrin levels and serum iron, or hemoglobin concentrations.

The most marked changes occurred in the serum ferritin concentrations, which showed important variability between individuals in both groups. In untreated women the mean ferritin concentrations at 36 weeks were 30% and in iron supplemented women 71% of the initial values at 16 weeks, which means a significant fall in both groups. The differences between serum ferritin concentrations in treated and untreated women at 28 and 36 weeks, and at delivery, were highly significant ($p < 0.01$). No significant correlations were found between the concentrations of serum ferritin and serum iron, transferrin or hemoglobin levels.

Tab. I. Iron status in uncomplicated singleton pregnancies with (upper values, n = 18) and without (lower values, n = 20) oral iron supplements (means ± S.D.).

	16 weeks	28 weeks	36 weeks	At delivery	6 weeks p.p.	12 weeks p.p.
Hemoglobin (mmol/L)	8.0 ± 0.4 8.0 ± 0.5	7.8 ± 0.4 7.5 ± 0.4	7.8 ± 0.5 7.6 ± 0.6	8.0 ± 0.7 7.8 ± 0.7	8.5 ± 0.6 8.5 ± 0.6	8.8 ± 0.7 8.5 ± 0.5
Serum iron (μmol/L)	23.0 ± 5.1 22.4 ± 6.5	25.8 ± 9.8 15.4 ± 4.7**	22.9 ± 7.9 13.8 ± 5.9**	20.6 ± 11.4 14.0 ± 5.5*	19.8 ± 5.4 20.1 ± 7.2	19.5 ± 8.3 22.8 ± 5.8
Transferrin (μmol/L)	90.4 ± 17.0 95.0 ± 21.4	109.0 ± 21.0 125.2 ± 18.0*	123.0 ± 17.7 131.7 ± 20.2	122.7 ± 29.2 130.9 ± 32.5	89.8 ± 16.8 93.8 ± 16.4	94.7 ± 17.2 98.4 ± 23.9
Ferritin (μg/L)	74.5 ± 28.4 64.2 ± 38.0	66.4 ± 44.7 27.8 ± 20.7**	52.8 ± 32.0 19.2 ± 9.9**	45.2 ± 22.9 23.9 ± 9.9**	67.7 ± 35.9 48.3 ± 26.2	65.5 ± 42.1 37.8 ± 19.8*

* = $p < 0.05$ and ** = $p < 0.01$ between the study and the control group (WILCOXON rank-sum test, two-tailed).

Tab. II. Iron status in venous cord blood in the iron supplemented (n = 17) and non-supplemented (n = 18) group (means ± S.D.).

	Non-supplemented	Supplemented
Hemoglobin (mmol/L)	10.2 ± 0.7	10.3 ± 1.0
Iron (μmol/L)	32.5 ± 6.5	30.3 ± 11.4
Transferrin (μmol/L)	67.0 ± 10.3	67.5 ± 11.0
Ferritin (μg/L)	208 ± 83.5	190 ± 73.5

At six and 12 weeks post partum hemoglobin concentrations in both groups were significantly higher than in early pregnancy and serum iron concentrations were not significantly different from those at 16 weeks of amenorrhea. Post partum transferrin concentrations appeared to have returned to early pregnancy levels in both groups.

The ferritin concentration in serum at six and 12 weeks post partum was not different from that in early pregnancy in iron supplemented women, but it appeared to be still significantly lower in the untreated group.

The values obtained in venous cord blood are summarized in Tab. II. There were no significant differences between both groups. No significant correlations could be demonstrated between variables of the maternal and fetal iron status in iron supplemented women or in the control group.

3 Discussion

Physiologic changes during pregnancy have a marked effect on the variables used to assess the hematologic status. In pregnancy these variables cannot be judged by reference to nonpregnant standards. The relatively larger increase in plasma volume as compared with red cell mass can be calculated to cause a physiologic fall in hemoglobin concentration of approximately 12% of nonpregnant values in iron-sufficient pregnant women. The lowest hemoglobin values can be expected to occur around 34 weeks gestation, when plasma expansion is maximal [10].

In the present study we found that hemoglobin concentrations in non-supplemented pregnant women at 36 weeks were 10% lower than the levels determined six weeks post partum. Assuming that the latter concentration reflects nonpregnant values, the observed fall in hemoglobin concentration can be fully explained by physiologic hemodilution. Iron supplementation appeared to prevent the physiologic fall in hemoglobin concentration, presumably by elevating erythrocyte volume [13]. Iron supplements also prevented the decrease of serum iron concentration observed in non-supplemented pregnant women. However, no correlation was found between serum iron concentrations and hemoglobin levels. The reasons for normal fluctuations in serum iron are not understood, and serum iron levels are known to be affected by recent ingestion of iron [10].

It has been suggested that the rise in transferrin concentrations, observed in our study as well as by others [1], could be associated more closely with rising estrogen levels than with changes in iron status [6]. This concept is supported by the absence of a significant correlation between hemoglobin or serum iron concentrations and transferrin levels in our study, as well as by our finding that iron supplements did not prevent the increase in transferrin concentrations.

The concentration of ferritin in plasma or serum has been shown to be a sensitive and accurate indicator of mobilisable iron stores in nonpregnant individuals [7, 14]. Data from the literature suggest that a serum ferritin concentration of 1 μg/L represents 8 mg of storage iron [14]. However, it is not known how this data applies to pregnant women. The pregnant state might influence the overflow of ferritin from organ stores into the circulation and serum levels may be expected to fall due to physiologic hemodilution.

In our study serum ferritin levels showed a wide range of values. There was a gradual fall of serum ferritin levels between 16 weeks and term in both groups, but the decrease was significantly more pronounced in women without iron supplements. Even the 30% fall in ferritin levels in the supplemented group cannot be explained on the basis of hemodilution alone. Therefore, accepting that in pregnancy ferritin levels reflect, at least to some extent, iron stores, this data indicates that iron is

mobilized from the storage pool to meet the increased demand during pregnancy. Considering the fact that six and even 12 weeks after delivery ferritin levels in non-supplemented women without anemia were still significantly lower than in the first trimester of pregnancy, whereas in supplemented women they had returned to early pregnancy values, we conclude that iron supplementation prevents depletion of iron stores during pregnancy.

The relationship between the iron status of the mother and that of the fetus is still controversial. Like other investigators [8, 11] we found no relationship between maternal and fetal variables of the iron status, and in particular not between maternal and fetal ferritin levels. There was no difference in iron status between infants from iron supplemented and from non-supplemented women. Only KANESHIGE [9] reported a significant correlation between maternal and fetal ferritin levels at delivery. It should be realized that our results, like those of other investigators, were obtained in healthy, non-anemic women with a reasonable amount of storage iron at the beginning of pregnancy. We are not aware of studies on the pathophysiologic effects of severe and long-standing maternal iron depletion on the fetal hematologic status.

The results of our study indicate that prophylactic administration of iron raises hemoglobin levels during pregnancy and prevents depletion of iron stores. However, what is the actual benefit to the patient? Controlled studies have failed to provide evidence that the practice of screening the hemoglobin concentration of pregnant women at regular intervals and treating them when anemia is diagnosed, will have any adverse effect on the course of pregnancy, or on maternal or fetal health [5]. On the other hand, we found no correlation between hemoglobin concentrations within the normal range of values, and serum ferritin levels; a normal hemoglobin concentration is a poor indicator of iron stores. For this reason, the above practice of screening for low hemoglobin levels during pregnancy and treating only anemic patients will leave many women with low iron stores undetected and untreated. Our results show that depleted iron stores are still found three months after delivery. These women are at risk of anemia, which will usually be diagnosed after symptoms have appeared, since most women are not screened on a regular basis between pregnancies.

On the basis of these considerations we favor prophylactic iron supplementation in all pregnant women, from the beginning of the second trimester until delivery. Prescription of one tablet daily of a sustained release preparation, like that used in the present study, is well accepted by the patients and causes hardly any gastrointestinal side effects.

Summary

The known increased need for iron during pregnancy appears to be met only in part by increased iron absorption and amenorrhea. Considerable demands are made on maternal iron stores and, since many women lack sufficient storage iron, pregnancy may be expected to cause iron deficiency. This may lead to anemia in pregnancy and post partum and could also have a bearing on the iron status of the fetus and the neonate. Based on these considerations, prophylactic supplementation of dietary iron is advocated but remains a disputed issue. **In the present controlled, prospective and longitudinal study changes in hematologic status, and in particular in iron stores, during pregnancy were investigated in 44 healthy Caucasian women with uncomplicated pregnancies and deliveries.** They were randomly assigned to a study group (n = 21) receiving oral iron supplements from the 16th week of amenorrhea until 6 weeks post partum, and a control group (n = 23) without iron supplementation. **Maternal concentrations of hemoglobin, serum iron, serum transferrin and serum ferritin were determined at 16, 28 and 36 weeks of amenorrhea, at delivery, and 6 and 12 weeks post partum.** The same variables were determined in cord blood. Iron supplementation appeared to prevent the physiologic fall in hemoglobin and serum iron concentrations which occurred in the control group, but had little influence on the observed rise in transferrin concentrations. Ferritin levels in serum, which are known to reflect mobilisable iron stores, fell to 30 % of the initial values in the control group and to 70 % in the study group. Six and 12 weeks post partum ferritin levels were still low in the nonsupplemented group (Tab. I). No differences were found between the

hematologic variables in venous cord blood from infants from supplemented and nonsupplemented women (Tab. II). No correlations were found between the various variables of the maternal hematologic status, in particular not between hemoglobin concentrations and ferritin levels; a normal hemoglobin concentration appears to be a poor indicator of iron stores. We found no relationship between maternal and fetal iron status. Our study shows that depleted iron stores are still found three months following pregnancy without iron supplementation. **To prevent depletion of iron stores during pregnancy we favor prophylactic iron supplementation in all pregnant women from the beginning of the second trimester until delivery.**

Keywords: Ferritin, hematologic status, hemoglobin, iron supplementation, serum iron, transferrin.

Zusammenfassung

Einfluß einer oralen Eisengabe auf den mütterlichen und fetalen Eisenhaushalt während der Schwangerschaft

Der bekannte erhöhte Eisenbedarf während der Schwangerschaft kann wahrscheinlich nur zum Teil durch eine gesteigerte Eisenresorption sowie die Amenorrhoe kompensiert werden. Die mütterlichen Eisenspeicher werden in hohem Maße beansprucht; da viele Frauen ungenügende Eisenreserven haben, kann man erwarten, daß die Schwangerschaft einen Eisenmangel verursacht. Dies führt zu einer Anämie in der Schwangerschaft sowie post partum und könnte auch Auswirkungen auf den Eisenhaushalt des Feten bzw. Neugeborenen haben. Auf der Grundlage dieser Überlegungen wird zwar zu einer prophylaktischen oralen Eisengabe geraten, sie ist jedoch nicht unumstritten. **In der vorliegenden kontrollierten, prospektiven Longitudinalstudie untersuchten wir Veränderungen des hämatologischen Status und speziell der Eisenspeicher bei 44 gesunden Frauen der kaukasischen Rasse mit unkomplizierter Schwangerschaft und Geburt.** Nach dem Zufallsprinzip bildeten wir ein Kollektiv (n = 21), das orale Eisengaben von der 16. Woche nach Beginn der Amenorrhoe bis zur 6. Woche post partum erhielt, sowie eine Kontrollgruppe (n = 23) ohne jede Eisenmedikation. **Wir bestimmten die mütterlichen Konzentrationen von Hämoglobin, Serumeisen, Serumtransferrin und Serumferritin in der 16., 28. und 36. Woche nach Beginn der Amenorrhoe, bei der Geburt sowie 6 bzw. 12 Wochen post partum.** Die gleichen Parameter wurden im Nabelschnurblut gemessen. Die Eisengabe scheint den physiologischen Abfall der Hämoglobin- und Eisenspiegel, der in der Kontrollgruppe erfolgte, zu verhindern; sie hatte aber wenig Einfluß auf den beobachteten Anstieg der Transferrinkonzentration. Die Ferritinspiegel im Serum, die bekanntlich ein Maß für die mobilisierbaren Eisenspeicher darstellen, fielen auf 30 % der Ausgangswerte in der Kontrollgruppe bzw. auf 70 % der Ausgangswerte in dem behandelten Kollektiv zurück. 6 bzw. 12 Wochen post partum waren in der unbehandelten Gruppe die Ferritinspiegel immer noch niedrig (Tab. I). Bezüglich der hämatologischen Parameter im venösen Nabelschnurblut fanden sich keine singifikanten Unterschiede zwischen den Kindern behandelter bzw. unbehandelter Frauen (Tab. II). Die Variablen im mütterlichen hämatologischen Status, speziell die Hämoglobinkonzentration und der Ferritinspiegel veränderten sich nicht in Korrelation zueinander; ein normaler Hämoglobinwert läßt kaum eine Aussage über die Eisenspeicher zu. Wir fanden keine Zusammenhänge zwischen dem mütterlichen und fetalen Eisenhaushalt. Unsere Studie zeigt, daß noch 3 Monate nach der Schwangerschaft erschöpfte Eisenvorräte bei Frauen ohne Eisenmedikation gefunden werden. **Um eine Entleerung der Eisenspeicher während der Schwangerschaft zu verhindern, empfehlen wir eine prophylaktische Eisengabe an alle schwangeren Frauen vom Beginn des zweiten Trimesters bis zur Entbindung.**

Schlüsselwörter: Eisengabe, Ferritin, hämatologischer Status, Hämoglobin, Serumeisen, Transferrin.

Résumé

Effet sur l'équilibre martial de la mère et du fœtus d'une supplémentation orale en cours de grossesse

On connait le besoin accru en fer au cours de la grossesse; il semble n'être couvert que partiellement par l'augmentation de l'absorbtion martiale et par l'aménorrhée. Les réserves martiales maternelles sont utilisées de façon considérable, et, puisque de nombreuses femmes n'ont pas de réserves suffisantes, on peut s'attendre à ce que la grossesse soit responsable de carence martiale. Celle-ci peut conduire à une anémie de la grossesse ou du post-partum et peut également retentir sur l'équilibre martial du fœtus ou du nouveau-né. On préconise une supplémentation prophylactique du fer alimentaire, fondeé sur ces considérations, mais son intérêt demeure controversé. **Dans cette étude contrôlée, prospective et longitudinale, on a exploré au cours de la grossesse, chez 44 femmes caucasiennes en bonne santé sans complication gravidique ni lors de l'accouchement, les modifications de l'équilibre hématologique, et particulièrement les réserves martiales.** Ces femmes ont été apariées par randomisation à un groupe (n = 21) recevant une supplémentation orale en fer, de la 16ème semaine d'aménorrhée à la 6ème semaine du post-partum, et à un groupe contrôle (n = 23) sans supplémentation en fer. **On a déterminé les concentrations maternelles d'hémoglobine, de fer sérique et de ferritine à 16,28 et à 36 semaines d'aménorrhée, à l'accouchement, ainsi qu'à 6 et 12 semaines après l'accouchement.** Les mêmes paramètres ont été mesurés sur le

sang du cordon. Il apparaît qu'une supplémentation en fer prévient la chute physiologique de l'hémoglobine et du fer sérique qui survient dans le groupe témoin, mais qu'elle n'a qu'une petite influence sur l'élévation observée de la concentration de transferrine. Les taux sériques de ferritine qui sont connus pour refléter les réserves de fer mobilisable chutent à 30% des valeurs initiales dans le groupe témoin et à 70% dans le groupe étudié. Dans le groupe sans supplémentation, les taux de ferritine sont encore bas 6 à 12 semaines après l'accouchement (Tab. I). On n'a pas tronvé de différences au niveau des paramètres hématologiques du sang du cordon entre les enfants de mères avec et sans supplémentation (Tab. II). On n'a pas trouvé de corrélation entre les différentes variables de l'état hématologique maternel, en particulier entre la concentration d'hémoglobine et les taux de ferritine; une concentration normale en hémoglobine est un mauvais indicateur des réserves martiales. Nous n'avons pas trouvé de relation entre l'équilibre martial de la mère et du fœtus. Notre étude montre qu'une dépletion des réserves martiales se retrouve encore trois mois après la grossesse lorsqu'il n'y a pas de supplémentation en fer. **Nous sommes pour une supplémentation prophylactique en fer afin de prévenir une dépletion des réserves martiales au cours de la grossesse, chez toutes les femmes enceintes du début du second trimestre jusqu'à l'accouchement.**

Mots-clés: Equilibre hématologique, ferritine, fer sérique, hémoglobine, supplémentation en fer, transferrine.

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