Predictors of serum ferritin and serum soluble transferrin receptor in newborns and their associations with iron status during the first 2 y of life[1–3]

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ABSTRACT

Background: Adequate iron status at birth may prevent iron deficiency in early childhood.

Objectives: We aimed to identify predictors of serum ferritin (SF) and serum soluble transferrin receptor (sTfR) in healthy newborns and to relate these iron indexes to iron status in the first 2 y of life.

Design: Using bivariate correlations and linear regression, we related various factors in pregnancy to SF ($n = 363$) and sTfR ($n = 350$) in healthy, term infants. Measurements of cord SF and sTfR were compared with those of SF and sTfR at 6, 12, and 24 mo. All 4 measurements were available for 191 and 169 infants for SF and sTfR, respectively.

Results: Geometric mean (and 95% CI) cord SF and sTfR measurements were 159 (148, 171) μg/L and 7.3 (7.0, 7.6) mg/L, respectively. Cord SF correlated with sTfR ($\rho = -0.21$, $P < 0.001$). In regression analysis, cord SF correlated with smoking and the use of iron supplements during pregnancy (partial $r = -0.12$ and 0.16; $P < 0.05$ for both). Cord sTfR was associated with first trimester BMI, gestational age, and male sex (partial $r = 0.30$, 0.24, and 0.19, respectively; $P < 0.01$ for all). Cord SF correlated with SF at 6, 12, and 24 mo ($\rho = 0.45$, 0.31, and 0.16 respectively; $P < 0.05$ for all). At age 6 mo, 16 of 17 infants with SF <15 μg/L were boys.

Conclusions: Cessation of smoking and adequate iron prophylaxis during pregnancy may improve iron status in infancy. Cord SF is a predictor of iron status in the first 2 y of life. Boys are at particular risk of low iron status in early infancy. *Am J Clin Nutr* 2007;86:64–73.

KEY WORDS Iron status, iron deficiency, iron supplementation, serum ferritin, serum transferrin receptor, pregnancy, newborns, children, cord blood

INTRODUCTION

Adequate iron status is particularly important during pregnancy and during the child's first 2 y of life to ensure the optimal development of the brain and nervous system. Iron deficiency anemia in this period may delay or impair the mental and physical development of children (1). School-aged children with low iron status have been shown to perform worse on standardized math tests than do those with adequate iron status (2), and children with severe, chronic iron deficiency in infancy score lower in mental and motor functioning >10 y later, despite correction for iron deficiency (3). Studies in animal models have shown that iron deficiency affects brain development (4) and that prenatal and postnatal maternal iron deprivation is associated with behavioral effects in infant monkeys, even in the absence of iron deficiency (5). Studies of human infants indicate that iron deficiency may impair myelination in the central nervous system (6) and that the effects on transmission in the auditory and visual systems persist into childhood (7). A sufficient iron supply in pregnancy and the prevention of iron deficiency in infancy may therefore be of profound importance to the health and development of children.

Iron status usually is adequately assessed through the measurement of the concentrations of serum ferritin (SF) and serum soluble transferrin receptor (sTfR), which reflect storage iron and cellular iron needs, respectively. Combined with hematologic measurements, these 2 iron indexes are believed to provide a good picture of iron status (8). Indicators of iron deficiency are difficult to interpret in infants, however, because of the effect of coincident changes in physiology and metabolism during growth and development and because of frequent infections (9).

Cord SF has been shown to reflect neonatal iron stores (10). SF concentrations in the fetus increase throughout gestation (11), and at term, they are higher than those during most of postnatal life (12). However, the range of cord SF concentrations is quite wide (13), and normal reference limits are not available. The SF concentration changes markedly during the first year of life (14), although low cord SF has been associated with low SF later in infancy (15–17).

Studies of sTfR in the newborn are sparse, but cord sTfR is believed to reflect erythropoietic activity in the newborn (18). The value of cord sTfR in the assessment of iron status in the newborn has been questioned, however, because of the weak correlation to other iron indexes (19).

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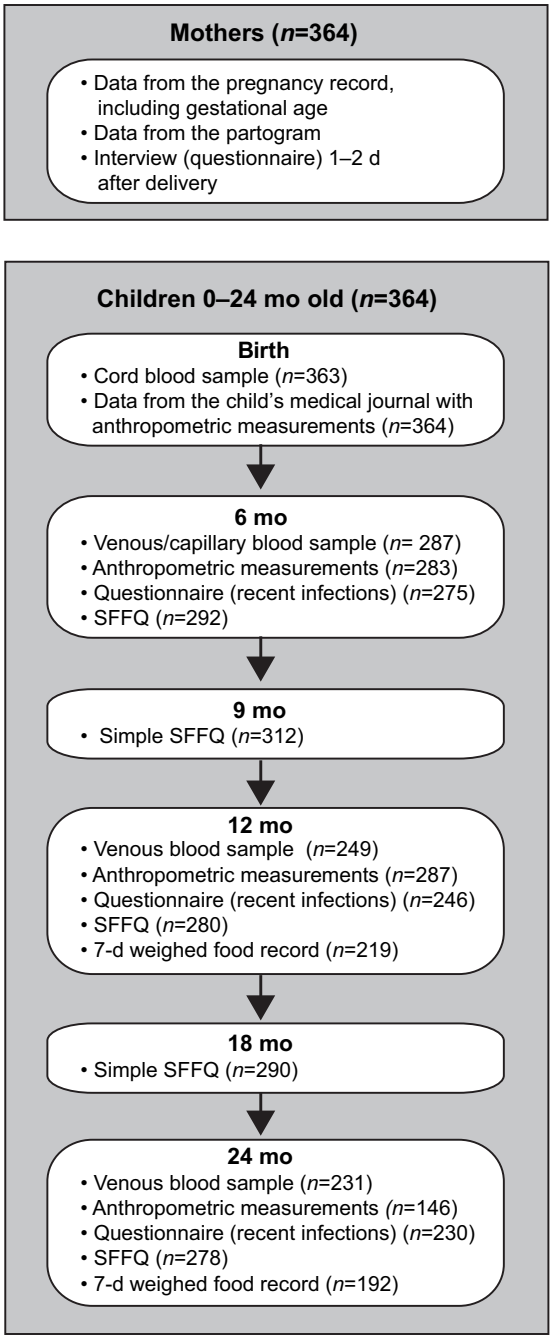

FIGURE 1. Flow of study participants. Overview of the various parts of the study, including the number of participants and the blood samples and data collected at birth and ages 6, 12, and 24 mo. SFFQ, semiquantitative food-frequency questionnaire.

In this study, we examined SF and sTfR in a group of apparently healthy newborn children, and we searched for predictors of these iron indexes at birth and their associations with iron status throughout the first 2 y of life.

SUBJECTS AND METHODS

Subjects

A flow diagram of the study is given in **Figure 1**. This longitudinal study followed Norwegian children from birth until 2 y of age (20). Invitations were sent to 471 pregnant women of Norwegian or other Nordic descent who were registered to deliver at Aker University Hospital, Oslo, Norway, between April and June 1997. By the time of delivery, 78% of the invited women agreed to participate. Another 67 women who had not received the invitation were recruited at the maternity ward when they were admitted to the hospital for delivery. A total of 364 women fulfilled the following criteria: singleton birth, gestational period of 37–43 wk, and birth weight over the 2.5 percentile [2600 and 2700 g for girls and boys, respectively, according to Norwegian growth charts (21)]. The subject families were invited to participate again when the children were 6, 9, 12, 18, and 24 mo of age; blood sampling was done at ages 6, 12, and 24 mo. If a child had fever that suggested an ongoing infection shortly before planned blood sampling, a new appointment was made. A common cold (without fever) was not considered a sufficient reason to postpone the blood sampling. A total of 197 children (54% of those included at birth) participated on all 4 occasions of blood sampling.

After each visit, the families were provided with free diapers and other infant products but no food products. After each blood sampling, each mother was informed of her child's iron status.

Written informed consent was obtained from each child's parent or parents. The study was approved by the Regional Committee for Research Ethics and the Norwegian Data Directorate.

Data collection

From the women's pregnancy records, we collected the following data: infant's gestational age and maternal smoking habits, body weight, height, SF concentration in early pregnancy, and lowest hemoglobin throughout pregnancy. Gestational age was based on estimated date of delivery by using an ultrasound scan carried out at the hospital 17–19 wk after the last menstruation. Smoking status was recorded as daily smoker, occasional smoker, or nonsmoker, and the number of cigarettes per day was registered. In the analyses, only 2 categories were used: daily smokers and nonsmokers (which included occasional smokers). Body mass index (BMI; in kg/m^2) was calculated. In the current study, we used only first-trimester BMI values, which were based on weight measurements taken no later than week 14 of gestation.

Information about each mother's background (ie, age, education, marital status, number of previous births, and number of years since last birth) and use of vitamin and mineral supplements during pregnancy was collected through interview and a questionnaire administered at the hospital 1–2 d after birth. The maternal intake of iron from supplements in each trimester was calculated with the use of a calculator on the basis of the collected information and product content. In the analyses, the average intake of iron from iron supplements during the second and third trimesters (or categories thereof) is reported, if not otherwise stated. Information on the child's birth weight, length, head circumference, and sex was collected from the child's medical record.

A questionnaire about sickness and fever in the child during the previous week or month was administered immediately before blood sampling at 6, 12, and 24 mo. Fever during the previous month was used as an indication of infection than may have an influence on SF values. Dietary assessment was performed at 6, 9, 12, 18, and 24 mo, but these data will be presented elsewhere.

Use of iron supplements in pregnancy and infancy

In Norway, there is no iron fortification of flour or other food items except baby foods. On the basis of SF measurements early in pregnancy, the pregnant women ($n = 327$) were given the following recommendations about iron prophylaxis (22, 23): *1*) in the case of iron deficiency anemia (ie, hemoglobin < 110 g/L and SF < 20 μg/L), iron doses up to 100 mg Fe/d were recommended; *2*) if SF concentrations were <20 μg/L, supplementation with 30–50 mg Fe^{2+}/d was recommended; *3*) if SF concentrations were 20–60 μg/L, supplementation with 30–50 mg Fe^{2+}/d starting in week 20 was recommended; and *4*) if SF concentrations were >60 μg/L, no extra iron was recommended.

Low iron status in the children at age 6 mo was defined as SF concentrations < 10 μg/L. At ages 12 and 24 mo, low iron status was defined as SF concentrations < 10 μg/L or as SF concentrations between 10 and 15 μg/L in combination with hemoglobin < 110 g/L (24). Low iron status was found in 2% (7/281) of infants at age 6 mo, 12% (29/249) of infants at age 12 mo, and 17% (38/229) of children at age 24 mo (20). It was recommended that these children be given a liquid iron preparation [(9 mg Fe/mL) Nycoplus Neo-Fer; Nycomed AS, Asker, Norway] at a dose of 2.5 mL twice a day—ie, 45 mg/d for 2 mo—to improve iron status. Women reporting use of iron supplements in pregnancy and children with low iron status are included in the statistical analyses, unless stated otherwise.

Blood sampling and blood analyses

At birth, cord blood samples ($n = 364$) were collected into serum separation tubes (Vacutainer SST; BD Diagnostic, Plymouth, United Kingdom) after the umbilical cord was clamped. The samples were placed in a refrigerator and centrifuged at 2500–3000 rpm for 10 min at room temperature (Model 203 centrifuge; Sigma Laborzentrifugen GmbH, Osterode, Germany), aliquoted, and frozen within 24 h. When the children were 6 ($n = 287$), 12 ($n = 249$) and 24 ($n = 231$) mo old, blood samples were drawn by hospital laboratory technicians and collected into Vacutainer SSTs and Vacutainer tubes containing EDTA (Vacutainer EDTA; BD Diagnostic). The blood samples were drawn from an antecubital vein after the use of an anesthetic cream (EMLA; AstraZeneca AS, Södertälje, Sweden). In a few cases ($n = 12$), a capillary sample was drawn from a fingertip when the child was 6 mo old. There was no significant difference in the mean iron indexes between the capillary and venous samples, and the capillary samples were thus included. Blood samples from the Vacutainer EDTA tubes were sent to the laboratory for measurements of the hematologic variables. The blood samples in the Vacutainer SSTs were kept at room temperature for $\leq$60 min and then centrifuged at 3000 rpm for 10 min at room temperature (Lavofuge 400; Heraeus GmbH, Osterode, Germany) and placed in a refrigerator. The serum fraction was collected and aliquoted within 24 h. The aliquots were stored at -70 °C until they were analyzed.

Analyses of iron indexes

Analyses of iron indexes were performed at Aker University Hospital; analyses of SF (180 Ferritin assay; Chiron Diagnostics ACS, Medfield, MA) were performed at the Central Laboratory, and those of sTfR (IDeA sTfR IEMA assay; Orion Diagnostica, Turku, Finland) were performed at the Hormone Laboratory. The number of measurements of SF and sTfR is lower than the total number of blood samples listed in Figure 1 because of limited sample volume in some cases. SF was measured in 363, 281, 249, and 229 children at 0, 6, 12, and 24 mo of age, respectively, and sTfR was measured in 350, 264, 242, and 226 children at those same ages. Measurements of SF and sTfR on all 4 occasions were available for 191 and 169 infants, respectively.

The between-day CV was $<5\%$ for the SF assay and 5–6% for the sTfR assay. When the children were 6, 12, and 24 mo old, red blood cell indexes including hemoglobin and mean corpuscular volume (MCV) were measured by using a Sysmex hematology instrument (model 8000/9000; Sysmex Corp, Kobe, Japan) with a between-day CV of $<1\%$. Red blood cell indexes were not measured in cord blood because the hematology instrument was not suitable for the high viscosity of the blood. The central laboratory regularly underwent quality-control evaluations (Labquality Ltd, Helsinki, Finland). Internal quality controls were used for the sTfR analyses.

Statistical analysis

Basic maternal and child characteristics are reported as means $\pm$ SDs or proportions. Because of the skewed distribution of SF and sTfR, these results are presented as geometric means (and 95% CIs). The geometric mean is calculated by back-transformation of the mean of log-transformed data. For comparison with previously published data, we have also included mean ($\pm$SD) and median (25th–75th percentile, or quartile 1–quartile 3 (Q1–Q3). Values of SF and sTfR were log transformed in the statistical analyses when parametric methods were used. Calculation of the ratio of sTfR to log ferritin provided the sTfR-F index, as reported in tables. Maternal intake of iron supplements was not normally distributed, and a substantial number of the mothers had not taken iron supplements. Thus, for this variable, we report the median and Q1–Q3 values and used nonparametric tests, or we used categories of the average iron intake from supplements in the second and third trimesters (0, 1–30, and >30 mg/d).

Student's *t* test and a chi-square test were used to compare independent groups. Bivariate correlations were examined by using the Spearman rank-order correlation test. Linear regression analyses and analyses of variance (ANOVA) were used to estimate the relative influence of various factors on cord SF and sTfR with control for potential confounders. Repeated-measures ANOVA was used for comparison of SF and sTfR in the different age groups. These statistical analyses were performed by using SPSS for WINDOWS software (version 12.01; SPSS Institute, Chicago, IL).

To assess the significance of the difference between 2 correlation coefficients, we employed Fisher's r-to-z transformation by using the VassarStats Web Site for Statistical Computation (Internet: http://faculty.vassar.edu/lowry/VassarStats.html). To study possible interactions between the age and the sex of the child for SF, we used a linear model for repeated measurements (linear mixed models). The interaction between categories of cord SF (in quartiles) and the age or the sex of the child for the proportion of those with SF < 15 mg/L was analyzed by an extension of logistic regression to repeated measurements [generalized linear mixed models (25)]. The interaction analyses were performed with the free R software (version 2.4.0; Internet: http://www.r-project.org/) by using the lme and lmer functions in the nlme package (26). Gaussian generalized additive regression models, as implemented in S-PLUS for WINDOWS software

TABLE 1
Characteristics of the population

	Subjects with available data	Value[1]
	n	
Mothers		
Age (y)	364	29.9 ± 4.4[2]
Living with partner [*n* (%)]	364	338 (92.9)
Education ≥12 y [*n* (%)]	364	262 (72)
Parity		
Para 0 [*n* (%)]		180 (49.5)
Para 1 [*n* (%)]	364	150 (41.2)
Para 2+ [*n* (%)]		34 (9.3)
Daily smoker [*n* (%)]	343	62 (17)
First trimester BMI (kg/m^2)	250	23.5 ± 3.6
Use of iron supplements		
At any time during pregnancy [*n* (%)]	364	270 (74.2)
Second trimester intake (mg)	363	9 (0–24)[3]
Third trimester intake (mg)	363	14 (0–33)
Early pregnancy ferritin (μg/L)	327	52 ± 34
Lowest pregnancy hemoglobin (mg/L)	356	112 ± 11
Newborns		
Boys [*n* (%)]	364	197 (54.1)
Gestational age (wk)	364	40.1 ± 1.2
Birth weight (g)	364	3673 ± 455
Birth length (cm)	351	50.8 ± 2.0
Head circumference (cm)	360	35.4 ± 1.3

[1] For normally distributed variables, mean ± SD values are given.
[2] $\bar{x}$ ± SD (all such values).
[3] Median; interquartile range (quartiles 1–3) in parentheses (all such values).

(version 6.2; Insightful Corporation, Seattle, WA), were used to generate a graphic representation of the nonlinear relation between cord SF and sTfR. P values < 0.05 were considered significant.

RESULTS

The characteristics of the mothers and newborns are listed in **Table 1**. Of the 364 mothers, 3 were 18–19 y old, and 5 were 40–42 y old. The mean birth weight was 3673 ± 455 g, and there was no significant difference between boys and girls. The mean birth length was 50.8 ± 2.0 cm, and there was a significant ($P < 0.001$) difference between the sexes: 51.2 ± 1.9 cm for boys and 50.4 ± 2.0 cm for girls.

Cord serum ferritin and serum soluble transferrin receptor in the total group and in boys and girls

Values of cord SF and cord sTfR are shown in **Table 2**, for the total group and for boys and girls separately. Geometric means (95% CIs) were 159 (148, 171) μg/L for SF and 7.3 (7.0, 7.6) mg/L for sTfR. The 5th–95th percentile reference intervals were 40–468 μg/L for cord SF and 3.8–14.9 mg/L for cord sTfR.

There was a significant difference in geometric mean cord sTfR between the sexes, with the boys having the higher values. Geometric mean cord SF did not differ significantly between the boys and the girls. However, significantly ($P = 0.013$) more boys than girls had cord SF values below the 5th percentile: 7.7% and 1.8%, respectively.

There was a negative correlation between cord concentrations of SF and sTfR ($\rho = -0.21$, $P < 0.001$), and low values of SF were thus associated with high values of sTfR. With SF values ≥ 100 μg/L, however, sTfR reached a plateau, as shown in **Figure 2**. Cord SF concentrations ≤ 100 μg/L were found in 19.0% of the samples; the proportion tended to be higher in boys than in girls (22.4% and 15.0%, respectively; $P = 0.068$).

Gestational age and anthropometric data at birth

Mean gestational age was 40.1 ± 1.2 wk, and there was no significant difference between the sexes. Gestational age was correlated with cord SF ($\rho = 0.13$, $P = 0.016$) and cord sTfR ($\rho = 0.24$, $P < 0.001$).

The values of cord SF, cord sTfR, and cord sTfR-F index (sTfR/log SF) and the weight and length of infants according to increasing lengths of gestation are shown in **Table 3**. There was a significant continuous increase in cord sTfR from gestational age 37–38 wk through gestational age 42 wk. There was a parallel increase in cord SF until week 41, which was followed by a drop in week 42. This sequence of changes according to the length of gestation probably explains why there was a significant difference in cord SF by ANOVA, but not by linear trend analysis.

TABLE 2
Cord serum ferritin (SF), serum soluble transferrin receptor (sTfR), and the ratio of sTfR to SF (sTfR/log SF) in boys and girls, separately and combined

	All	Boys	Girls	P[1]
SF (μg/L)				
n	363	196	167	
$\bar{x}$ ± SD	196 (127)	195 (135)	196 (117)	0.94
Geometric $\bar{x}$ (95 %CI)	159 (148, 171)	151 (137, 167)	168 (151, 187)	0.15
Median (Q1–Q3)	169 (114–242)[2]	169 (104–245)	169 (117–240)	0.65
sTfR (mg/L)				
n	350	187	163	
$\bar{x}$ ± SD	8.0 (4.1)	8.7 (4.6)	7.3 (3.2)	0.001
Geometric $\bar{x}$ (95% CI)	7.3 (7.0, 7.6)	7.8 (7.4, 8.3)	6.7 (6.3, 7.2)	0.001
Median (Q1–Q3)	7.1 (5.5, 9.6)	7.6 (5.8, 10.2)	6.5 (5.2, 8.5)	0.001
sTfR/log SF				
n	350	187	163	
$\bar{x}$ ± SD	3.8 (2.6)	4.3 (3.1)	3.3 (1.6)	<0.001
Geometric $\bar{x}$ (95% CI)	3.4 (3.2, 3.5)	3.6 (3.4, 3.9)	3.1 (2.8, 3.3)	0.001
Median (Q1–Q3)	3.2 (2.4–4.4)	3.4 (2.6–4.8)	2.9 (2.3–4.0)	0.002

[1] P for the difference between groups by Student's t test (for mean or geometric mean) or Mann-Whitney U test (for median).
[2] Interquartile range [quartile (Q) 1–3] in parentheses (all such values).

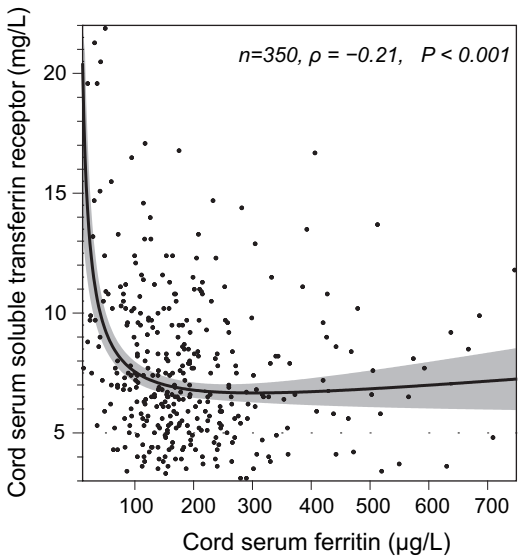

FIGURE 2. Association between cord serum ferritin and cord serum soluble transferrin receptor. Low values of cord serum ferritin were associated with high values of cord serum transferrin receptor. The curves were obtained by general additive regression models. Shaded area represents 95% CIs.

After adjustment for gestational age, there was no significant correlation between cord SF or cord sTfR and length, weight, or head circumference at birth.

Maternal factors

Iron indexes at birth were not correlated with the mother's age, the number of her previous childbirths, or the number of years since her last delivery. No significant difference in iron indexes was found between mothers living with their partner and single mothers or between mothers with high (≥12 y) and low (<12 y) education. Maternal first-trimester BMI was correlated with cord sTfR ($n = 240$; $\rho = 0.20$, $P = 0.001$) but not to SF. In a linear regression analysis, a significant association between first-trimester BMI and cord sTfR remained significant ($n = 229$; partial $r = 0.31$, $P < 0.001$) after adjustment for birth weight, birth length, and gestational age.

Maternal smoking habits

Infant birth weight was 3614 ± 480 g in the group of smokers ($n = 62$) and 3692 ± 444 g in the group of nonsmokers ($n = 281$) ($P = 0.22$). Gestational age was 39.9 ± 1.3 versus 40.2 ± 1.1 wk, respectively, in those 2 groups ($P = 0.16$). The lack of difference in the values in infants born to smoking and nonsmoking mothers may be due to the exclusion of premature and low-birth-weight infants.

Infants born to mothers who reported daily smoking in early pregnancy ($n = 61$) had lower cord SF than did infants born to nonsmoking mothers ($n = 281$), even after adjustment for gestational age and birth weight [geometric $\bar{x}$: 134 μg/L (95% CI: 112, 159 μg/L) and 166 μg/L (95% CI: 153, 180 μg/L), respectively ($P = 0.025$)]. Further analyses showed that there was no dose effect of smoking on cord SF in smokers. There was no difference in sTfR according to smoking status.

There was no significant difference in early pregnancy SF between smoking and nonsmoking women, but women who smoked during pregnancy had a slightly lower median and Q1–Q3 intake of iron from supplements [9.0 (0–22.8) mg/d] than did nonsmokers [14.0 (2.1–29.9) mg/d] ($P = 0.033$). In a regression model that included smoking, gestational age, birth weight, and categories of intake of iron from supplements, smoking had a significant, independent negative association with cord SF. The effect remained significant after adjustment for the use of cod liver oil as indicator of healthy lifestyle (27): the geometric mean cord SF was 135 (95% CI: 113, 161) μg/L and 166 (95% CI: 153, 180) μg/L in smokers and nonsmokers, respectively ($P = 0.035$).

Iron status in pregnancy

A total of 38 of 327 mothers (11.6%) with SF measurement had low iron stores, as indicated by SF < 20 μg/L. Of these 38, 17 also had a low hemoglobin (<110 g/L) at one point during pregnancy. Probably because of the selective iron prophylaxis, maternal SF concentrations in early pregnancy were not correlated with cord SF or with cord sTfR. Furthermore, there was no difference in cord SF or cord sTfR between infants born to mothers with low (SF < 20 μg/L) or adequate (>60 μg/L) iron stores in early pregnancy or between infants born to mothers with anemia (defined as hemoglobin < 110 g/L; n = 139) or without anemia [(1) n = 217] at ≥1 pregnancy check-ups. The lowest hemoglobin measurement in pregnancy was, however, weakly correlated to cord SF ($\rho = 0.11$, $P = 0.04$).

Intake of iron supplements in pregnancy

Infants born to mothers who had taken iron supplements during pregnancy ($n = 270$) had significantly ($P = 0.02$) higher cord SF concentrations than did infants born to mothers who had not taken iron supplements ($n = 93$). The geometric mean (and 95%

TABLE 3
Cord serum ferritin (SF), serum soluble transferrin receptor (sTfR), ratio of sTfR to SF (sTfR/log SF), birth weight, and birth length in relation to gestational age

	Gestational age (wk)											
	37+38		39		40		41		42		*P*	
	n	Value	*n*	Value	*n*	Value	*n*	Value	*n*	Value	ANOVA	Trend
SF (μg/L)	32	135 (106, 171)[1]	74	141 (120, 165)	116	163 (143, 184)	103	185 (162, 212)	38	141 (113, 175)	0.032	0.075
sTfR (mg/L)	31	6.7 (5.8, 7.7)	67	6.5 (5.9, 7.2)	113	7.0 (6.5, 7.5)	101	7.8 (7.2, 8.5)	38	9.0 (7.9, 10.3)	0.001	< 0.001
sTfR/log SF	31	3.1 (2.6, 3.7)	67	3.1 (2.8, 3.5)	113	3.2 (2.9, 3.5)	101	3.5 (3.2, 3.8)	38	4.3 (3.7, 5.0)	0.026	0.001
Weight (g)	32	3334 (3199, 3474)	74	3538 (3443, 3635)	116	3642 (3564, 3722)	104	3773 (3688, 3860)	38	3798 (3657, 3944)	0.026	< 0.001
Length (cm)	31	49.4 (48.7, 50.0)	70	50.0 (49.6, 50.5)	114	50.8 (50.5, 51.2)	99	51.3 (50.9, 51.7)	37	51.6 (51.0, 52.2)	< 0.001	< 0.001

[1] Geometric $\bar{x}$; 95% CI in parentheses (all such values).

CI) values were 168 (155, 183) μg/L and 134 (116, 154) μg/L, respectively.

In accordance with the recommendations for selective iron prophylaxis, the intake of iron from supplements differed according to maternal SF. In women with SF concentrations < 20 μg/L ($n = 38$), the median and Q1–Q3 intake of iron from supplements was 33 (17–82) mg/d, whereas it was 14 (3–27) mg/d in women with SF concentrations of 20–60 μg/L ($n = 192$). In the group with adequate iron stores (SF > 60 μg/L; $n = 96$), it was only 1 (0–14) mg/d. There were significant differences among the 3 groups both by Kruskal-Wallis test and by pairwise comparisons with the Mann-Whitney U test ($P < 0.001$ for all). Only 2 mothers with SF < 20 μg/L did not take iron supplements.

The intake of iron supplements during pregnancy did not predict cord sTfR. Cord SF, however, was positively correlated with iron intake from supplements ($\rho = 0.18$, $P < 0.001$), and there was a significant difference in cord SF according to 3 categories of iron intake ($P = 0.009$). In the group not taking iron supplements ($n = 97$), geometric mean (95% CI) cord SF was 133 (116, 152) μg/L. In the group taking 1–30 mg Fe/d ($n = 182$), cord SF was 166 (150, 183) μg/L, and, in the group taking >30 mg Fe/d ($n = 83$), it was 179 (154, 207) μg/L. Thus, infants born to women taking iron supplements had significantly ($P = 0.003$) higher cord SF concentrations than did infants born to women not taking supplements, despite the lower maternal SF. In contrast, there was no significant difference in cord SF between infants born to mothers with a high or a low intake of iron from supplements.

Predictors of serum ferritin and serum soluble transferrin receptor concentrations in multivariate analyses

In a stepwise linear regression ($n = 337$), we included the following factors that we found to influence cord SF: gestational age, sex of the child, smoking status (daily smokers versus nonsmokers), iron intake from supplements (3 categories), and lowest value of hemoglobin in pregnancy. For cord SF, a significant inverse association was obtained for smoking (partial $r = -0.12$, $P = 0.031$), and a positive association was found for iron intake from supplements (partial $r = 0.16$, $P = 0.004$). When cord sTfR was added to the model ($n = 324$), significant negative associations were found for smoking during pregnancy (partial $r = -0.12$, $P = 0.028$) and cord sTfR (partial $r = -0.32$, $P < 0.001$), and significant positive associations were obtained for gestational age (partial $r = 0.16$, $P = 0.005$) and iron intake from supplements (partial $r = 0.13$, $P = 0.016$).

In a stepwise linear regression analysis for sTfR, we included gestational age, sex, and first-trimester BMI ($n = 241$) in the model. Positive associations were obtained for gestational age (partial $r = 0.24$, $P < 0.001$), male sex of the child (partial $r = 0.19$, $P = 0.004$), and first-trimester BMI (partial $r = 0.30$, $P < 0.001$). The inclusion of cord SF in the model did not change these associations, but there was an independent negative association with cord SF (partial $r = -0.26$, $P < 0.001$).

Influence of iron status at birth on iron status at age 6, 12, and 24 mo

In both sexes, there was a significant ($P < 0.001$, repeated-measures ANOVA) decline in SF from birth to age 6 mo and a further but more modest decline to ages 12 and 24 mo (**Figure 3**). Likewise, sTfR concentrations declined significantly ($P < 0.001$) from birth to age 6 mo in both sexes and changed modestly thereafter. At 6 mo, but not at 12 and 24 mo, boys had significantly lower geometric mean SF and significantly higher sTfR concentrations ($P < 0.001$ for both) than did girls.

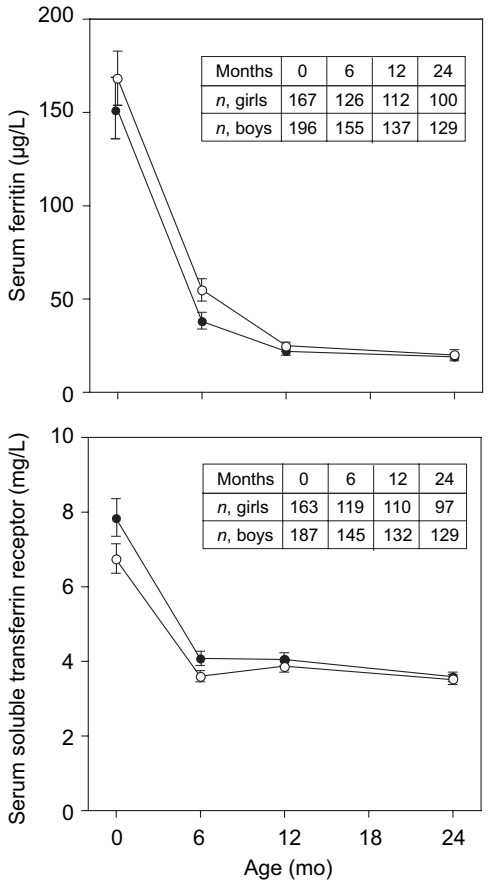

FIGURE 3. Geometric mean (95% CI) serum ferritin and serum soluble transferrin receptor from birth to age 24 mo in girls (○) and boys (●). Analyses used a linear model for repeated measurements. For serum ferritin ($n = 191$), there were significant results for the age ($P < 0.001$) and the sex ($P = 0.002$) of the child but no significant age × sex interaction ($P = 0.33$). For serum soluble transferrin receptor ($n = 169$), there were significant results for the age ($P < 0.001$) and the sex ($P = 0.002$) of the child but no significant age × sex interaction.

Cord sTfR did not correlate with SF or sTfR at age 6, 12, or 24 mo. Neither cord SF nor cord sTfR was correlated with hemoglobin or MCV at any age. A comparison of infants with cord SF < 100 μg/L and those with cord SF > 100 μg/L showed no difference in hemoglobin, MCV, or sTfR at age 6, 12, or 24 mo. In contrast, there was a strong positive correlation between cord SF and SF at ages 6, 12 and 24 mo (**Table 4**). The exclusion of children with fever during the month before blood sampling (25.2%, 41.3%, and 42.0% at ages 6, 12 and 24 mo, respectively) or of children with low iron status at 6 or 12 mo (2% and 12%, respectively) did not change the overall pattern. Hence, all children were included in the analyses.

Age 6 mo

The correlation between cord SF and SF at age 6 mo was significant in both sexes ($\rho = 0.37$ for girls and 0.55 for boys;

TABLE 4
Spearman correlations between cord serum ferritin (SF), serum soluble transferrin receptor (sTfR), ratio of sTfR to SF (sTfR/log SF), and SF or sTfR at 6, 12, and 24 mo[1]

	Cord SF			Cord sTfR			Cord sTfR/log SF		
	n	ρ	*P*	*n*	ρ	*P*	*n*	ρ	*P*
SF									
6 mo	280	0.45	< 0.001	270	−0.07	0.28	270	−0.18	0.003
12 mo	248	0.31	< 0.001	240	−0.07	0.28	240	−0.13	0.04
24 mo	228	0.16	0.017	218	−0.02	0.77	218	−0.06	0.39
6 vs 12 mo			0.062			1.00			0.57
6 vs 24 mo			< 0.001			0.58			0.18
12 vs 24 mo			0.085			0.60			0.45
sTfR									
6 mo	263	−0.16	0.011	253	−0.03	0.65	253	0.02	0.80
12 mo	241	0.01	0.87	233	0.04	0.57	233	0.03	0.64
24 mo	225	0.01	0.92	215	−0.02	0.80	215	−0.01	0.89
6 vs 12 mo			0.056			0.44			0.91
6 vs 24 mo			0.060			0.91			0.75
12 vs 24 mo			1.00			0.53			0.67

[1] sTfR/log SF is also called the sTfR-F index.

$P < 0.001$). At 6 mo, 17 of 281 infants (6%) had SF concentrations < 15 μg/L. Sixteen of 17 infants with SF < 15 μg/L were boys. Infants with cord SF concentrations < 100 μg/L were significantly ($P < 0.05$) more likely to have SF concentrations < 15 μg/L at 6 mo (7/50; 14.0%) than were infants with cord SF concentrations ≥ 100 μg/L (10/230; 4.3%), and the geometric mean SF in the former group also was significantly ($P < 0.001$) lower—29 μg/L (24, 35 μg/L) compared with 50 μg/L (46, 55 μg/L). The relation between cord SF and SF at age 6 mo was investigated further by comparing the quartiles of cord SF values with the proportion with SF < 15 μg/L at age 6 mo (**Figure 4**). Children born with cord SF in the lowest quartile had a significantly greater risk of low SF at age 6 mo ($P < 0.001$) than did those with cord SF in the highest quartile, a pattern that was most apparent in boys. Adjustment for cord sTfR did not change the finding.

Age 12 mo

The correlation between cord SF and SF at age 12 mo was significant in both sexes ($\rho = 0.35$ for girls and 0.30 for boys; $P < 0.001$). At age 12 mo, 53 of 249 infants (21.3%) had SF concentrations < 15 μg/L. There was no difference by sex in the proportion of infants with SF concentrations < 15 μg/L (21.4% of the girls and 21.2% of the boys). Only infants with cord SF in the highest quartile were protected from having an SF concentration < 15 μg/L at age 12 mo (Figure 2). Infants with cord SF concentrations < 100 μg/L were significantly ($P = 0.006$) more likely to have SF concentrations < 15 μg/L at age 12 mo (16/41; 39.0%) than were infants with cord SF concentrations > 100 μg/L (37/207; 17.9%), and the geometric mean SF at age 12 mo in the former group also was significantly ($P = 0.028$) lower—19 μg/L (16, 23 μg/L) compared with 24 μg/L (22, 26 μg/L).

Age 24 mo

The correlation between cord SF and SF at age 24 mo was significant in girls ($\rho = 0.31$, $P = 0.002$) but not in boys ($\rho = 0.08$, $P = 0.34$). At age 24 mo, 67 of 229 infants (29.3%) had SF < 15 μg/L. Boys were more likely than girls to have SF concentrations < 15 μg/L (34.1% and 23.0%, respectively), but this difference was not significant ($P = 0.065$). At age 24 mo, children with cord SF < 100 μg/L had low geometric mean (and 95% CI) SF concentrations [17 (14, 20) μg/L], whereas the rest of the group had SF concentrations of 20 (19, 22) μg/L ($P = 0.027$). The proportion of children (girls or boys) with SF < 15 μg/L at 24 mo did not differ significantly between those with cord SF < 100 or > 100 μg/L at birth.

DISCUSSION

We have searched for factors predicting SF and sTfR in the newborn child and investigated how these iron indexes are associated with iron status during the first 2 y of life.

Cord serum ferritin and serum soluble transferrin receptor

The mean cord SF concentrations observed in the present study agree with results from other studies (15, 28, 29). In the present cohort, 11% of subjects had cord SF concentrations < 76 μg/L—values that were associated in one study with lower mental and psychomotor test scores at age 5 y (30). Given that low iron status early in life may affect mental, neurologic, and motor functions later in childhood (1), the proportion of such subjects in the present study gives reason for concern, even though a causal relation between cord iron status and later neurodevelopmental outcome has not been established (13).

The cord sTfR concentrations observed in the present study were higher than those found in other surveys (18, 31, 32). This difference may be due to differences in methods, or it may reflect true differences in the population. As was reported by others (19, 33), we too found an inverse correlation between cord SF and cord sTfR. Our data reveal a sharp increase in sTfR when cord SF declines below 100 μg/L, which suggests that that value could be an appropriate cutoff for cord SF. In our healthy, term children, nearly 20% had cord SF concentrations below this threshold. Further studies are required to establish the association between iron status at birth and later health and development.

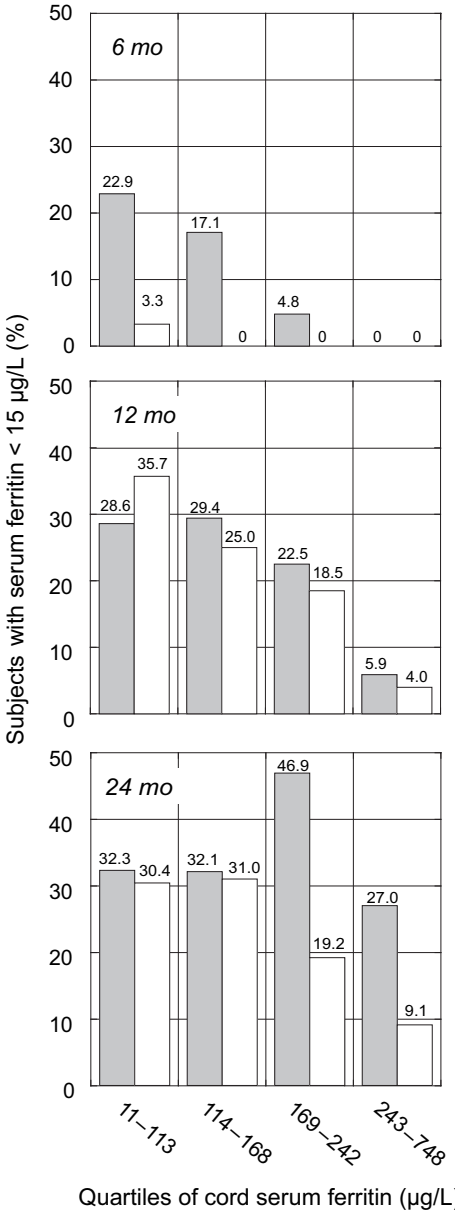

FIGURE 4. Proportions of boys (▨) and girls (□) with cord serum ferritin concentrations <15 μg/L at ages 6, 12, and 24 mo according to quartiles of cord serum ferritin in the total group. The number of boys and girls in each age group is shown in Figure 3. Analysis by generalized linear mixed models showed the following significant associations: age of the child ($P < 0.001$), sex ($P = 0.010$), and children with cord serum ferritin in quartiles 1 ($P < 0.001$), 2 ($P < 0.001$), and 3 ($P = 0.002$) relative to quartile 4. Furthermore, there was a significant interaction between the age of the child and quartile 1 ($P = 0.006$) and quartile 2 ($P = 0.043$) cord serum ferritin concentrations.

Length of gestation

We found an increase in sTfR throughout the last weeks of pregnancy. A positive association between sTfR and gestational length has been reported in some studies (32) but not in others (19, 33). An increase in the sTfR concentrations reflects the presence of a greater amount of transferrin receptors on cell membranes during periods of high erythropoietic activity (34). In fetal life, rapid cell proliferation and tissue growth affect transferrin receptor expression on all cell types, which is reflected in the cord sTfR concentration and which may explain the increase with greater gestational age (19).

As observed in other studies (11, 35, 36), cord SF concentrations increased with gestational age, except for weeks 42 and 43. The placenta plays an important role in the regulation of the accumulation of fetal iron stores (35). Toward the end of the third trimester, the placenta accumulates ferritin, which may advance placental iron delivery to the fetus (37). The decline in cord SF after gestation week 41 may be caused by degeneration of the placenta (38).

Sex and iron status at birth and early childhood

We found that boys had significantly higher cord sTfR concentrations than did girls, which may reflect greater erythropoietic activity in boys than in girls (18). During infancy, higher sTfR in boys than in girls has been found in some (31, 39) but not all (40) studies. Because the difference in sTfR is present at birth, we speculate that it could be due to hormonal factors: in male embryos, the testosterone concentration is high from early in gestation (41). The fact that the administration of sex hormones to adults changes sTfR values (42) indicates a hormonal effect on this variable.

In our study, cord SF concentrations in boys did not differ significantly from those in girls. This finding agrees with results from some (15, 18) but not all (43) studies. We observed, however, that low cord SF (<40 μg/L) was more prevalent in boys than girls, which suggests that boys are already at risk of low iron status at birth.

We found that cord SF was associated with SF at ages 6, 12, and 24 mo. In smaller studies, low SF in early infancy has been shown to persist later in infancy (15–17). Our data show that the risk of low SF at age 6 mo was most apparent in boys—in particular, boys born with cord SF concentrations below the median. At age 12 mo, the sex difference was no longer apparent, but in both sexes, the risk of low iron stores was influenced by cord SF. Thus, low iron stores at birth place children at greater risk of compromised iron status in the first years of life. In the present study overall, the cord sTfR concentration did not have the same predictive value as did the cord SF concentration in identifying those persons at risk of low iron stores later in infancy.

Previous reports showed that, in early childhood, girls have iron index values that are consistent with better iron status than those in boys (39, 44–46). That finding was also reported previously from the present cohort (20): at age 6 mo, the girls had significantly higher values of hemoglobin, MCV, and SF than did the boys. At ages 12 and 24 mo, the difference in MCV remained significant.

Maternal factors

First-trimester BMI was positively associated with cord sTfR. Even if not particularly strong, the association remained the most important maternal predictor of cord sTfR, even after adjustment for potential confounders. We have no explanation for this finding, but we can speculate that it is due to hormonal or lifestyle factors. This finding needs to be confirmed.

In line with previous studies (47, 48), we found that infants born to smoking mothers had significantly lower cord SF concentrations than did infants born to nonsmoking mothers. The various possible explanations include hypoxia leading to increased erythrocyte production (49, 50), impaired uterine blood

flow or interference with transplacental availability of iron (51, 52), shortening of gestational age, reduction in birth weight, and less healthy eating habits or less use of iron supplements (53, 54). In the present study, we found a modestly lower intake of iron from supplements in smoking women. The smoking effect did, however, remain significant after adjustment for potential confounders, which suggests an independent effect of smoking on cord SF.

Maternal iron status and iron supplement use

We did not find a significant association between maternal SF concentrations and cord SF or cord sTfR concentrations. This is not surprising, given that the women were advised to use iron supplementation according to their SF values. Thus, in the present study, low iron stores during pregnancy probably were compensated for by the use of iron supplements in the last 2 trimesters. The use of iron supplements during pregnancy has been debated. Iron supplementation improves maternal iron status and pregnancy outcome when the mother has low iron status; however, prophylactic supplementation of iron-replete women may increase the risk of complications and oxidative stress (55). Some reports suggest that it is only when the mother is severely iron deficient that her iron status or use of supplements affects her infant (9, 12). In the present population, however, with a fairly good overall iron status, maternal use of iron supplements was an independent predictor of cord SF concentrations, and the children of mothers not taking iron supplements had the lowest cord SF concentrations. The fact that the children with modestly low SF concentrations at birth remained at high risk of low SF concentrations during the first year of life suggests that the use of iron supplements by pregnant women with normal iron stores also should be considered.

Strengths and limitations of the study

The strengths of the present study include the size of the population, the data available from pregnancy, the measurements of both SF and sTfR, and the fact that most of the children were followed until age 2 y. Our study was confined to healthy term infants and excluded premature and low-birth-weight infants—ie, infants at greater risk of low iron status at birth (24). Thus, our findings cannot be generalized to these high-risk infants. Furthermore, this observational study can only show associations, which are no proof of causality. Some of the associations are relatively weak, but because they are related to lifestyle and they can potentially be modified, they may be important.

The use of iron supplements was recommended to pregnant women with low SF concentrations. Thus, we cannot properly evaluate the value of iron supplements during pregnancy. Information on maternal iron supplement use was collected 1–2 d after delivery. Retrospectively collected data are uncertain, but, if anything, poor data quality tends to weaken the associations.

The inclusion of measurements from children for whom iron supplements at age 6 or 12 mo were recommended to improve iron status, as well as from all children regardless of recent infections, may have weakened the associations. However, the exclusion of children with low iron status at age 6 or 12 mo or children with fever during the previous month at age 6, 12, or 24 mo did not alter the patterns.

Finally, statistical models showed that there was no significant interaction between iron status and sex, but that boys in general had poorer iron status than girls. The descriptive data, however, suggest that the sex differences in SF and sTfR were most apparent during the first 6 mo. Ascertainment of whether boys have lower iron status than girls from birth to age 2 y or only during a period of infancy will require larger studies.

In conclusion, these data suggest that the cord SF concentration is a strong predictor of iron status during the first 2 y of life, and that cessation of smoking and adequate iron prophylaxis during pregnancy may improve iron status at birth. Compared with girls, boys are at greater risk of low iron status at birth and in early infancy. Given the potentially serious consequences of either low or excess iron intake during pregnancy and infancy, our data suggest that selective low-dose iron prophylaxis during pregnancy, after measurement of the SF concentration, may be a valuable approach to optimizing the iron status of both mother and child.

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The authors' responsibilities were as follows—GH: design of the experiment, collection and analysis of data, and writing of the manuscript; HR: analysis of data and writing of the manuscript; AW: design of the experiment, analysis and interpretation of data, and critical revision of the manuscript; ELM: collection and analysis of data; EH: analysis of data; BB-I: design of the experiment, analysis and interpretation of the data, and critical revision of the manuscript; and all authors: reading and approval of the final manuscript. None of the authors had a personal or financial conflict of interest.

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