

Serum transferrin receptor: a specific marker of iron deficiency in pregnancy¹⁻³

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ABSTRACT

Background: Current markers of iron deficiency tend to be less reliable in pregnancy.

Objective: Our aim was to study the usefulness of soluble serum transferrin receptor (sTfR) as a marker for iron deficiency during early and late gestation and to define iron status in 254 pregnant Swedish women.

Design: We performed a cross-sectional and longitudinal evaluation of sTfR in comparison with concentrations of serum ferritin and hemoglobin in blood collected around gestational weeks 11 and 36.

Results: The specificity of sTfR was 100%. The sensitivity in relation to both anemia and depleted iron stores was $\approx 70\%$, but this figure is less reliable because of few samples. sTfR in early pregnancy was low: 11% of women had a value below the reference interval. sTfR increased significantly from early to late pregnancy even in the group of women with persisting iron stores. In late pregnancy, 14% of women developed tissue iron deficiency and 5% had iron deficiency according to a combination of all 3 markers.

Conclusions: sTfR seems to be a specific and sensitive marker of iron deficiency in pregnancy and may have advantages over serum ferritin and hemoglobin. The low sTfR concentration in early gestation seems to be caused by reduced erythropoiesis, whereas the increase from early to late pregnancy reflects increased erythropoiesis, and in case of iron deficiency, also tissue iron deficiency. Further studies are needed to verify whether decreased erythropoiesis reduces the possibility of detecting iron deficiency during early gestation by sTfR. *Am J Clin Nutr* 1998;68:1241-6.

KEY WORDS Pregnancy, iron, iron deficiency anemia, soluble serum transferrin receptor, serum ferritin, hemoglobin, erythropoiesis, parity, women, Sweden

INTRODUCTION

Between 10% and 40% of fertile women in Sweden have depleted iron stores (1-6) and are at risk of developing iron deficiency during pregnancy. The iron requirement during the first 10 wk of gestation is less than that for nonpregnant women, but increases severalfold during the last 10 wk (7). Because iron deficiency may affect pregnancy outcome (8), iron status should be assessed during gestation. Available markers of iron deficiency,

however, tend to be less reliable in pregnancy because they either are not sensitive enough or are altered by gestation, independent of iron status. For instance, despite an increase in red cell and hemoglobin mass, the blood hemoglobin concentration often decreases during pregnancy as a result of an even greater and earlier expansion of plasma volume (9). Furthermore, because values for nondeficient and deficient subjects overlap, hemoglobin is not a sensitive index of mild iron deficiency anemia and is not specific for anemia caused by iron deficiency (9-11). Despite this, hemoglobin measurements are fast, simple, and suitable for screening. Serum ferritin is generally considered to be a more sensitive index of iron status because low concentrations correlate well with depleted iron stores (12-18). Nevertheless, serum ferritin does not identify those with functional iron deficiency and concentrations are often reduced after the first trimester of pregnancy, even when iron balance is positive (19-21).

The soluble transferrin receptor in serum (sTfR) seems to correlate well with the amount of receptor expressed at the cell membrane, which in turn reflects the cellular need for iron (22, 23). sTfR increases with tissue iron deficiency and with increased erythropoiesis (22, 24-28). It does not appear to be elevated by inflammatory diseases (27-29) and a low biological and analytic variability has been reported (30). Previously reported studies of sTfR in pregnancy are either limited to one trimester (31) or constitute cross-sectional studies of different women at different periods of gestation (32). There are also a few studies based on selected individuals, eg, from countries with a high prevalence of anemia (33-35).

The aim of the present study was to further elucidate the usefulness of sTfR as a marker for iron deficiency during early and late gestation and to define iron status in a group of pregnant Swedish women by using serum ferritin, sTfR, and hemoglobin.

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Assessing sTfR in combination with serum ferritin and hemoglobin may further characterize iron status and provide a spectrum ranging from adequate iron stores through depleted iron stores and tissue iron deficiency to iron deficiency anemia.

SUBJECTS AND METHODS

Subjects and blood sampling

As a part of the public health care system in Sweden, essentially all pregnant women visit antenatal care units (ACUs) regularly. Pregnant women who had their primary appointment at any of the 3 ACUs in the town of Solna between October 1994 and January 1996 (15 mo) and were knowledgeable in the Swedish language were invited to participate in the study. In total, 254 of 618 pregnant women who were registered at the ACUs fulfilled the enrollment criteria and agreed to participate. Maternal age ranged from 20 to 45 y (median: 30.8 y). The total number of pregnancies (including the present one) ranged from 1 to 8 (median: 2) and parity ranged from 0 to 3 (median: 0). Four women carried twins. Gestational age was determined by ultrasound or, in 9% of women, from the date of the last menstrual period.

As was customary at the ACUs, the women were advised to take iron supplements in the form of 18 mg Fe (2.4 mg heme iron and 16 mg Fe as iron fumarate) daily from gestational week (GW) 20. If needed, the therapy was gradually increased to a maximum of 54 mg or changed to 100 mg FeSO₄/d. However, no individual data on iron supplementation were collected.

Venous blood samples were drawn twice, at a median of GW 11 (range: 7–21) and GW 36 (range: 34–40). Serum samples were analyzed for ferritin and sTfR. Data on hemoglobin in capillary blood were obtained from the ACU file. If there were more than 8 d between the sampling dates for hemoglobin and serum, the hemoglobin value was excluded, which resulted in relatively few hemoglobin results at GW 36 (Table 1). Reasons for quitting the study included miscarriage ($n = 17$), interruption of pregnancy ($n = 2$), delivery before second blood sampling ($n = 5$), and change of ACU ($n = 25$). Other reasons included samples not being collected or analyzed. The study was approved by the ethics committee at the Karolinska Institutet.

Analytic methods

Serum ferritin was measured by using a noncompetitive fluorescence immunoassay (DELFLIA; Wallac, Turku, Finland), calibrated according to a human liver ferritin standard (WHO 80/602). The total CV was <6%. Serum ferritin values ≤ 12 $\mu\text{g/L}$ were considered to reflect depleted iron stores.

sTfR was measured by using a kit based on a polyclonal antibody in a quantitative sandwich enzyme immunoassay (ELISA; Ramco Laboratories, Inc, Houston). To ascertain analytic quality, all standards, controls, and samples were analyzed in duplicate and all duplicates with a CV >10% were reanalyzed. The supplied controls, representing a high and a normal sTfR concentration, were analyzed as 32 duplicates in 8 different analytic runs and gave results well within the stated range (CVs = 8.6% and 9.7%, respectively). To assess the interassay variability, a serum sample was analyzed twice in each run throughout the series (CV = 7.9%). Values <3.0 mg/L were considered indicative of decreased erythropoiesis and values >8.5 mg/L were indicative of tissue iron deficiency according to the manufacturer.

TABLE 1

Number of samples collected and analyzed at gestational week (GW) 11, GW 36, and both GW 11 and 36 (paired samples)¹

	GW 11	GW 36	GW 11 and 36
Serum ferritin	246	147	143
sTfR	224	145	132
Hb	216	99	88
All 3 markers	192	97	80 ²

¹sTfR, soluble serum transferrin receptor; Hb, hemoglobin.

²No statistical analyses were performed on all 3 markers at GW 11 and 36.

Capillary hemoglobin was measured at the ACU by using a colorimetric method (HemoCue; HemoCue AB, Ångelholm, Sweden). According to the World Health Organization, values <110 g/L are considered to represent anemia (36). Because capillary hemoglobin, which was measured in the present study, tends to be lower in pregnant women than venous hemoglobin (37), a value of 105 g/L was used as the cutoff instead.

Statistical analyses

Sensitivity was defined as $\text{TP}/(\text{TP} + \text{FN}) \times 100$ and specificity as $\text{TN}/(\text{TN} + \text{FP}) \times 100$, where TP is true positive, FN is false negative, TN is true negative, and FP is false positive. Positive predictive value was defined as $\text{TP}/(\text{TP} + \text{FP}) \times 100$ and negative predictive value as $\text{TN}/(\text{TN} + \text{FN}) \times 100$.

Nonparametric statistical methods were used when data were not normally distributed (serum ferritin and sTfR). To detect differences between paired samples, Student's *t* test (hemoglobin) or Wilcoxon's signed-rank test (serum ferritin and sTfR) was used. To determine differences between 2 independent groups, Student's *t* test (hemoglobin) or the Mann-Whitney test (serum ferritin and sTfR) was used; to detect differences between several independent groups, one-way analysis of variance (hemoglobin) or the Kruskal-Wallis test (serum ferritin and sTfR) was used. Correlation coefficients were calculated by Spearman's method for ranked values (r_s). All statistical analyses were conducted with SPSS version 7.5 (SPSS Inc, Chicago).

RESULTS

In an overall comparison, sTfR was evaluated in relation to serum ferritin and hemoglobin, irrespective of gestational age. All women with sTfR >8.5 mg/L, indicating tissue iron deficiency, had a serum ferritin concentration <8 $\mu\text{g/L}$ (Figure 1); thus, specificity for sTfR in relation to depleted iron stores was 100%. The specificity, sensitivity, positive predictive value, and negative predictive value of sTfR in relation to iron deficiency status as defined by serum ferritin and hemoglobin are shown in Table 2.

When the markers were evaluated in relation to gestational age, there was a general trend toward a deterioration in iron status with time (Table 3). Notably, samples with sTfR <3.0 mg/L were present only during early gestation. The fraction of women with a combination of depleted iron stores (serum ferritin ≤ 12 $\mu\text{g/L}$), tissue iron deficiency (sTfR >8.5 mg/L), and anemia (hemoglobin <105 g/L) increased from none at GW 11 to 5% at GW 36. There was a significant decrease in serum ferritin with increasing time of pregnancy during the first period of blood sampling, ie, from GW 7 to GW 21 ($r_s = -0.19$, $P = 0.002$), but no change in the other 2 markers.

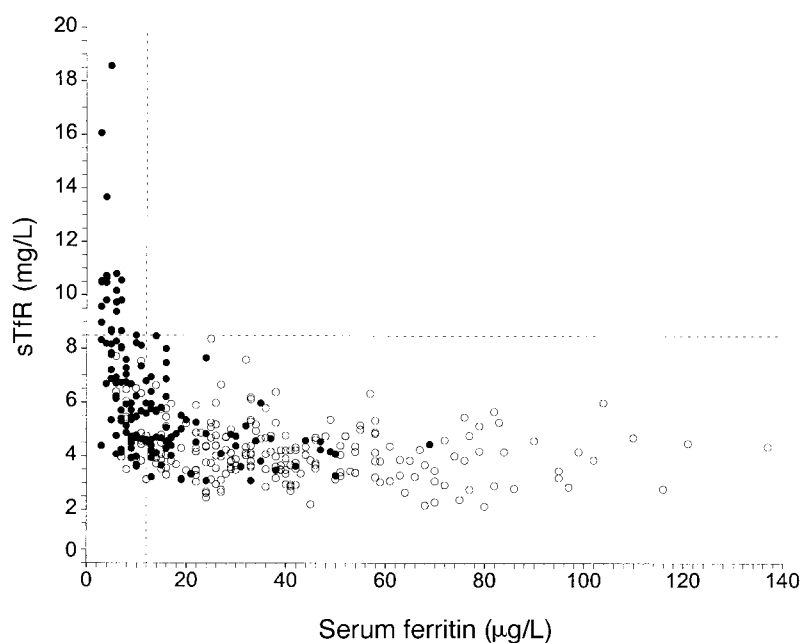


FIGURE 1. Soluble serum transferrin receptor (sTfR) in relation to serum ferritin during early and late gestation (369 samples). ○, gestational week (GW) 11; ●, GW 36. Dotted lines inside graph represent 12 µg serum ferritin/L (vertical line) and 8.5 mg sTfR/L (horizontal line). Note that most women are represented twice. $r_s = -0.26$ at GW 11 and -0.64 at GW 36 ($P < 0.001$).

sTfR was evaluated longitudinally on the basis of data from women with results from both GW 11 and 36 (paired observation, **Figure 2**). There was a significant increase in sTfR ($P < 0.001$) and a significant decrease in serum ferritin and hemoglobin ($P < 0.001$) between GW 11 and GW 36. The women who quit the study did not differ significantly with respect to any of the 3 markers from those who continued the study and the fractions of samples outside the reference intervals were about the same as in Table 3. Of the women with depleted iron stores at GW 11 according to serum ferritin ≤ 12 µg/L ($n = 20$), 90% also had depleted iron stores at GW 36 and 45% developed tissue iron deficiency as defined by sTfR > 8.5 mg/L.

The markers were evaluated in relation to parity before the start of iron supplementation (GW 11). There was a significant difference in serum ferritin between groups of women with no,

1, or 2–3 children ($P < 0.001$; **Figure 3**). The same was true for sTfR ($P = 0.023$), but not for hemoglobin. The change in serum ferritin and sTfR with increasing parity was not due to a later blood sampling with respect to gestational age for women with previous children. As shown in Figure 3, serum ferritin decreased from a median of 39 µg/L in women with no children to 33 µg/L in those with 1 child and to 23 µg/L in those with 2–3 children (\bar{x} : 2.2 children). The corresponding results for sTfR were 3.9, 4.3, and 4.4 mg/L, respectively.

To evaluate a possible influence on sTfR of factors other than iron status, women were divided according to iron stores. sTfR in women with serum ferritin concentrations consistently < 20 µg/L (at both GW 11 and 36) and in women with serum ferritin concentrations consistently ≥ 20 µg/L was evaluated within and between groups (**Table 4**). The longitudinal evaluation of sTfR

TABLE 2

Specificity, sensitivity, negative predictive value (PV $-$), and positive predictive value (PV $+$) of soluble serum transferrin receptor (sTfR) in all samples collected in pregnant women (gestational weeks 11 and 36)¹

	Not iron deficient ($n = 216$)	Iron deficient ($n = 7$)
Specificity	216/216 + 0 (100%)	—
Sensitivity	—	5/5 + 2 (71%)
PV $-$	216/216 + 2 (99%)	—
PV $+$	—	5/5 + 0 (100%)

¹Calculations are related to the absence of iron deficiency (serum ferritin > 12 µg/L and hemoglobin ≥ 105 g/L) or the presence of iron deficiency (serum ferritin ≤ 12 µg/L and hemoglobin < 105 g/L). Specificity is the fraction of women without iron deficiency that sTfR predicts correctly, sensitivity is the fraction of women with iron deficiency that sTfR predicts correctly, PV $-$ is the fraction of negative results according to sTfR that are true negatives, and PV $+$ is the fraction of positive results according to sTfR that are true positives.

TABLE 3

Concentrations of serum ferritin, soluble serum transferrin receptor (sTfR), and hemoglobin (Hb) in all samples collected during pregnancy

	Concentration	Percentage outside reference interval ¹
		%
Gestational week 11		
Serum ferritin (µg/L)	34 (22–52) ²	10
sTfR (mg/L)	4.1 (3.5–4.8)	11, 0
Hb (g/L)	130 (123–138)	0.9
Gestational week 36		
Serum ferritin (µg/L)	10 (7–16)	58
sTfR (mg/L)	5.4 (4.5–7.4)	0, 14
Hb (g/L)	120 (113–128)	7.1

¹The reference intervals were as follows: serum ferritin, ≤ 12 µg/L; sTfR, < 3.0 mg/L and > 8.5 mg/L, respectively; and Hb, < 105 g/L.

²Median; interquartile range in parentheses.

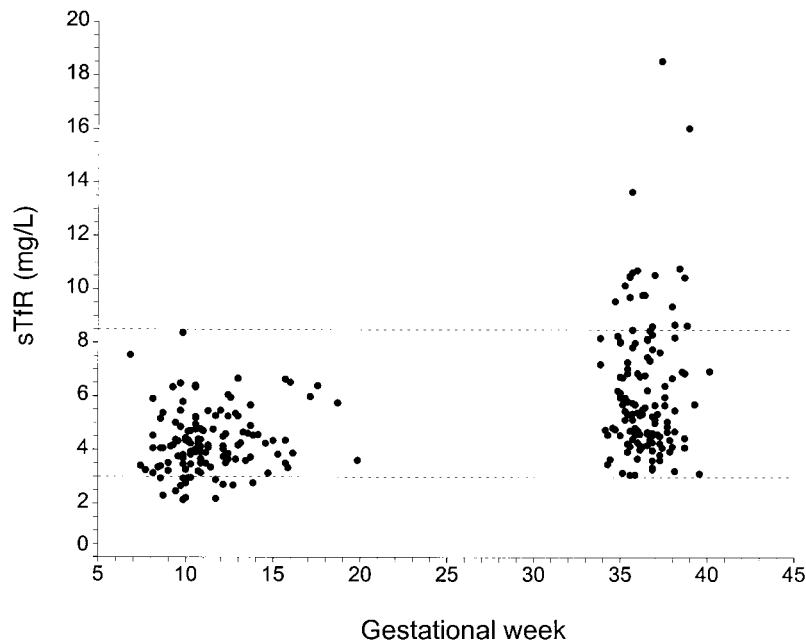


FIGURE 2. Soluble serum transferrin receptor (sTfR) in relation to gestational age for paired samples in 132 pregnant women. The horizontal dotted lines represent 3.0 and 8.5 mg sTfR/L.

showed a 74% increase from early to late pregnancy in women with serum ferritin $<20 \mu\text{g/L}$ and a 25% increase in women with serum ferritin $\geq 20 \mu\text{g/L}$.

DISCUSSION

This work includes a cross-sectional and a longitudinal evaluation of sTfR as a marker of iron deficiency compared with serum ferritin and hemoglobin in pregnant women. To our knowledge, this is the first assessment of paired samples of sTfR

during early and late gestation in well-nourished women, providing the opportunity to study the diagnostic usefulness of sTfR and to evaluate a possible influence of gestation on this index.

We must emphasize that neither hemoglobin nor serum ferritin can serve as the ultimate gold standard for sTfR because each of the 3 markers represents a different aspect of iron status (26). It would therefore be misleading to base the sensitivity and negative predictive value of sTfR on data on depleted iron stores alone. Instead, the accuracy of sTfR was evaluated in relation to both serum ferritin and hemoglobin, indicating either the absence or presence of iron deficiency. Unfortunately, because of the limited number of samples, the estimated sensitivity of 71% was less reliable. The value for sensitivity was likely an underestimation because our data indicated a low specificity of the hemoglobin measurements. Two of 9 women with hemoglobin $<105 \text{ g/L}$ had serum ferritin concentrations $\geq 20 \mu\text{g/L}$ (data not shown), which can probably be attributed to uncertainties in the hemoglobin measurement as mentioned previously. In addition, capillary sampling is known to affect the accuracy of the results (37). On the other hand, it cannot be ruled out that serum ferritin was falsely elevated in these 2 women because serum ferritin can be raised in connection with inflammation (3, 16, 18, 38). Thus, no firm conclusions can be drawn regarding the sensitivity of sTfR in this study. In addition, the effect of iron supplementation cannot be elucidated and needs to be studied. Nevertheless, the findings indicate a good accuracy of sTfR compared with serum ferritin and hemoglobin and support observations from earlier studies that sTfR is not elevated above the reference interval by hormonal alterations in pregnancy or by receptors of placental origin (31). Furthermore, because a large portion of the women with depleted iron stores did not have functional iron deficiency and a large portion of the women (10 of 15) with tissue iron deficiency did not have low hemoglobin concentrations, it can be concluded that sTfR may be of particular value in detecting mild iron deficiency of recent onset.

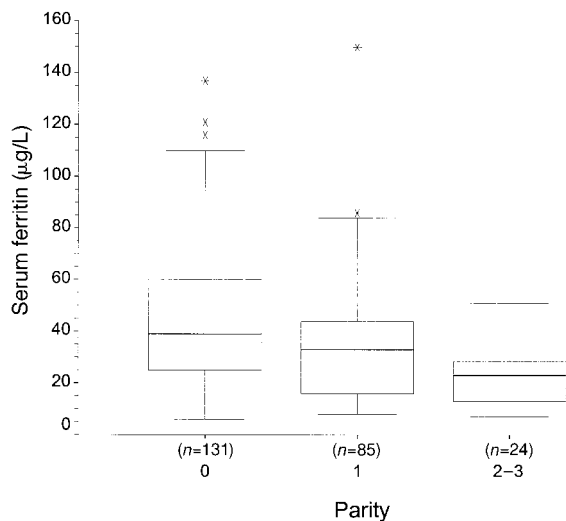


FIGURE 3. Box plots of serum ferritin (gestational weeks 7–21) in relation to parity. The boxes contain 50% of all values (25th to 75th percentiles). The horizontal line inside the boxes represents the median; the lines extending from the boxes represent the highest and the lowest values, excluding outliers (*).

TABLE 4

Result from longitudinally paired samples grouped according to serum ferritin concentration < or $\geq 20 \mu\text{g/L}$ ¹

Group	Gestational week 11	Gestational week 36	<i>P</i> ¹
Serum ferritin <20 $\mu\text{g/L}$ on both occasions			
sTfR (<i>n</i> = 29)	4.7 (3.1–7.5) ^{2,3}	8.2 (4.6–18.6) ³	<0.001
Serum ferritin	11	5	<0.001
Serum ferritin $\geq 20 \mu\text{g/L}$ on both occasions			
sTfR (<i>n</i> = 21)	3.6 (2.1–5.3)	4.5 (3.1–6.0)	0.003
Serum ferritin	58	32	0.001

¹Significance of difference between gestational weeks 11 and 36.²Median; range in parentheses.³Significantly different from the group in which serum ferritin was $\geq 20 \mu\text{g/L}$ on both occasions, *P* < 0.001.


In early pregnancy, 10% of the women had depleted iron stores (serum ferritin $\leq 12 \mu\text{g/L}$) and 16% had serum ferritin concentrations < $16 \mu\text{g/L}$, a limit also used to represent depleted iron stores (3). Note that the absence of some menstrual periods and the accompanying decrease in iron requirements during early gestation may improve iron status and raise serum ferritin concentrations (39). Thus, most likely, >10% had serum ferritin concentrations $\leq 12 \mu\text{g/L}$ before pregnancy, which compares with the 10–40% of nonpregnant Swedish women reported to have depleted iron stores (1–6). Essentially all women with serum ferritin concentrations $\leq 12 \mu\text{g/L}$ at GW 11 had depleted iron stores at GW 36, and about half had developed tissue iron deficiency according to sTfR. This illustrates the importance of entering pregnancy with sufficient iron stores, as well as the need for effective and well-tolerated iron supplementation. In total, 14% of women in the third trimester had tissue iron deficiency and 5% developed iron deficiency according to combined criteria of all 3 markers.

Both serum ferritin and sTfR were influenced by parity. Thus, despite the general Swedish advice of iron supplementation during pregnancy, each full-term pregnancy seemed to result in an iron deficit in the mother.

In late pregnancy, sTfR ($6.1 \pm 2.5 \text{ mg/L}$; $\bar{x} \pm \text{SD}$) was similar to both that observed in American women at GW 36–40 [$6.2 \pm 2.0 \text{ mg/L}$ (31)] and that observed in healthy control women and men from the United States [mean values: 5.4–5.7 mg/L (25, 27, 40)]. However, in early pregnancy, sTfR seemed lower (\bar{x} : 4.2 mg/L) than that observed in the healthy control subjects. In fact, 11% of women had sTfR concentrations below the reference interval (3.0 mg/L). This was not due to a systematic analytic error because all samples were analyzed randomly, but may indicate decreased erythropoiesis in early pregnancy. Also, after iron stores were controlled for, sTfR was found to be significantly lower at GW 11 than at GW 36. Unfortunately, because of the limited number of subjects with adequate iron stores at GW 36, a complete adjustment for serum ferritin could not be obtained (although it remained $> 20 \mu\text{g/L}$). There is, however, no reason to believe that sTfR, at persisting iron stores, would increase $\approx 25\%$ from early to late gestation because of iron deficiency. The most likely explanation for the difference is increased erythropoiesis. The 74% increase between GW 11 and GW 36 at low serum ferritin concentrations seems to be the result of a combination of increased erythropoiesis and a concurrent development of tissue iron deficiency.

Still, sTfR values during early gestation seemed lower than expected, independently of iron status. Similar results were observed in pregnant Belgian women, who had lower sTfR val-

ues together with blunted erythropoietin production during the first 2 trimesters compared with the third trimester or to values in nonpregnant women (32). Such reduced erythropoiesis is further supported by a reduction in reticulocytes (39) during early gestation, concomitant with decreased iron absorption (7). Whether decreased erythropoiesis in early pregnancy masks iron deficiency, as detected by sTfR, is not known. If so, the reference interval needs reevaluation. In a study of Jamaican anemic women (hemoglobin: 80–110 g/L), sTfR was elevated at GW 14–22 [mean values: 7.2–8.6 mg/L, range not reported (33)]. The question is whether sTfR would have been even more elevated at similar degrees of iron deficiency in late pregnancy or in nonpregnant women. In the present study, no woman had an sTfR value above the reference interval at GW 11, which probably indicates the absence of tissue iron deficiency because no woman had both depleted iron stores and anemia.

In conclusion, sTfR seems to be a specific and sensitive marker of iron deficiency in pregnancy. The major advantage of sTfR over serum ferritin is that it can distinguish individuals with iron deficiency from those with only depleted iron stores. The advantage of sTfR over hemoglobin is mainly related to an earlier detection of iron deficiency, ie, increased sensitivity. It is reasonable to assume that the low sTfR in early pregnancy reflected a somewhat decreased red cell production, whereas the increase from early to late gestation reflected increased erythropoiesis during the course of pregnancy, and, when the increase was extended above the reference interval, also tissue iron deficiency. Further studies are needed to clarify the specific effect on sTfR during early gestation of reduced erythropoiesis compared with iron deficiency. 

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