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Original article

ASSOCIATION BETWEEN IRON AND THYROID STATUS IN PREGNANT WOMEN

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ABSTRACT

Purpose: Pregnancy is often complicated by iron deficiency, affecting negatively thyroid gland physiology. The aim of our study is to investigate parameters of iron and thyroid status during I, II and III trimester of pregnancy in order to establish potential correlations in their dynamics.

Materials and methods: The study involved 61 pregnant women and 43 controls. Their iron and thyroid status was determined by measuring hemoglobin (Hb), serum ferritin (SF), serum transferrin receptor (sTfR), thyroxine (FT4) and thyroid-stimulating hormone (TSH).

Results: Significant differences between pregnant women and the control group were found, indicating an iron deficiency risk: sTfR level was higher, while Hb, ferritin and FT4 levels were lower in pregnant women. Thyroxine correlated positively with Hb ($p = 0.016$) and ferritin ($p = 0.003$) in pregnant women. In the I trimester, there was a negative association between sTfR and FT4 ($p = 0.013$), and in the III trimester, there was a positive association between sTfR and TSH ($p < 0.0001$).

Conclusions: sTfR represented the relationship between iron and thyroid status in the I and III trimester. Iron deficiency was expressed in the III trimester with a positive association between sTfR and TSH. The increased maternal iron requirement (sTfR) correlated with increased TSH secretion induced by decreased thyroxine.

Keywords: iron deficiency, pregnant women, ferritin, sTfR, thyroxine, TSH,

INTRODUCTION

The mechanism relating iron homeostasis with thyroid status still remains unclear. It has been previously reported that iron deficiency may affect thyroid function [1, 2]. Iron deficiency in rat embryos and neonatal rats reduces thyroid hormone-responsive gene mRNA levels in the hippocampus and cerebral cortex [3]. On the other hand, there is experimental evidence revealing the effect of thyroid hormones on ferritin expression. High levels of triiodothyronine (T3) are related to increased expression of ferritin in K562 cells but do not affect the expression of the transferrin receptor [4]. The administration of T3 in hypothyroid individuals causes a significant increase in the level of serum ferritin [5] and is explained as a positive correlation of thyroid hormones with serum ferritin [6].

The first step of thyroid hormones synthesis is iodine oxidation catalyzed by the iron-containing enzyme thyreoperoxidase (TPO), which is activated by TSH. Iron deficiency can impair TPO activity and thyroid metabolism and may cause decreased production of thyroid hormones [7-9]. Additional administration of iron improves the efficacy of the iodine-enriched salt in goitrous and iron-deficient children [10, 11], which is essential in the treatment of children with often overlapping deficiencies [12]. Some studies report that iron supplementation in hypothyroidism also requires additional administration of thyroxine to correct the thyroid hypofunction [13]. Researches on patients with iron deficiency anemia and subclinical hypothyroidism reveal that oral administration of ferrous *iron salts* alone is not sufficient to restore normal functions of the thyroid gland and only a combined treatment of levothyroxine and iron salts has a therapeutic effect [14, 15].

Iron deficiency is often observed in pregnant women, and it has negative effects on thyroid gland metabolism [16]. Impaired function of the maternal thyroid gland during pregnancy may cause retardation in the development of the neonatal nervous system. In a comprehensive clinical study during the third trimester of pregnancy, Zimmermann et al. have found that the parameters for evaluation of iron homeostasis – serum ferritin, transferrin receptor and body iron stores predict changes in thyroid status [17].

The aim of our study is to investigate the parameters of iron homeostasis (Hb, SF and sTfR) and thyroid status (FT4 and TSH) during I, II and III trimester of pregnancy in order to establish the associations in their dynamics and to define the most sensitive marker for detection of iron deficiency and thyroid dysfunction during the different trimesters of pregnancy.

MATERIALS AND METHODS

The iron and thyroid status in healthy pregnant women and clinically healthy women was determined by measuring Hb, SF and sTfR, FT4 and TSH. The research was approved by the Ethics Committee at Medical University of Plovdiv (protocol No.4/18.07.2013) according to the Declaration of Helsinki. Voluntary participation of the human subjects was documented with signed informed consent. The study involved 61 healthy pregnant women admitted to the department of Obstetrics and Gynaecology, MPHAT – Asenovgrad, Bulgaria. The mean age of pregnant women was 27.6 ± 4.6 years compared to 43 clinically healthy women as a control group with the mean age of 28.8 ± 5.2 years.

Blood was collected in monovettes via venipuncture. The blood samples were immediately centrifuged at 1000 × g for 15 min at 4°C and stored at - 20°C prior analysis. Thyroxine and TSH levels in human sera were determined with commercial ELISA kits (Globe Diagnostics, Milan, Italy), following the manufacturer's protocol. Hb levels in blood were measured on hematology analyzer STKS Coulter, USA and Sysmex 9500, Kobe, Japan. ELISA was used to determine serum ferritin and sTfR levels with commercially available kits (BioVendor, Brno, Czech Republic) according to the manufacturer's instructions. Serum levels of C-reactive protein (CRP) were measured by an immunturbidimetric, endpoint method via automated analysis (Konelab 60i, Thermo Scientific, Finland) and samples with CRP > 10 mg/L were omitted.

Statistical software package SPSS 17.0 for Windows (SPSS Inc.) was used. Results are given as Mean ± standard deviation (SD) or as Median (95% CI). Quantitative variables were tested for normality of data distribution using Kolmogorov-Smirnov test (One-Sample Kolmogorov-Smirnov D-Test) and Shapiro-Wilk's tests. The difference between means of two independent groups with Gaussian distribution was evaluated with Student t-test, and for comparison of non-Gaussian distributed variables, Mann-Whitney U test was used. Pearson and Spearman correlation analysis was used depending on the distribution of the parameters. Statistical significance was defined as $p < 0.05$.

RESULTS

Parameters of iron homeostasis

According to the WHO guidelines, the lower threshold value for Hb in pregnancy is 110 g/L [18]. The mean of Hb in the control group was significantly higher in comparison to pregnant women: 131.58±5.38 g/L (n = 43) and 114.64±11.21 g/L (n = 61), ($p < 0.0001$). In 26% of pregnant women (n = 16) Hb level was below 110 g/L, which indicated iron deficiency during pregnancy. In pregnant women, a significant decrease of serum ferritin was observed - 95% CI 12.84-20.1 µg/L, compared to the control group - 95% CI 29.17-53.07 µg/L ($p = 0.001$). In 65.6% of pregnant women (n = 40) SF was below 15 µg/L, which was indicative of an iron deficiency during pregnancy. Compared to the control group, the levels of sTfR were significantly higher. The median of pregnant women group was 1.44 µg/mL (95% CI 1.48-2.03) and the median of the control group was 0.68 µg/mL (95% CI 0.66-0.89), ($p < 0.0001$). Almost in half of the pregnant women (49.2%, n = 30) sTfR was above 2.9 µg/mL that was the upper limit according to the manufacturer.

The levels of Hb and serum ferritin were decreased after the first trimester of pregnancy, while sTfR levels increased with pregnancy progression. Statistically significant differences in serum ferritin and sTfR were found comparing the first trimester with the second and the third one. The levels of sTfR were significantly higher in the third trimester of pregnancy compared to the first trimester (table 1).

Table 1. Comparison of iron homeostasis parameters in trimesters

Trimesters	Hb [c] g/L	SF [b] g/L	sTfR [b] µg/mL
I (n = 9)	120.78±9.08	24.93(18.34-55.06)	0.77 (1.09-1.62)
II (n = 19)	117.89±12.77	13.73 (11.85-22.29)	1.21 (1.19-2.01)
	p=0.507	p = 0.032 [a]	p =0.068
I (n = 9)	120.78±9.08	24.93(18.34-55.06)	0.77 (1.09-1.62)
III (n = 33)	114.64±9.68	9.38(9.12-12.12)	2.17 (1.81-2.35)
	p =0.019[a]	p = 0.0001[a]	p=0.008[a]
II (n = 19)	117.89±12.77	13.73 (11.85-22.29)	1.21 (1.19-2.01)
III (n = 33)	114.64±9.68	9.38(9.12-12.12)	2.17 (1.81-2.35)
	p =0.031[a]	p=0.04[a]	p= 0.076

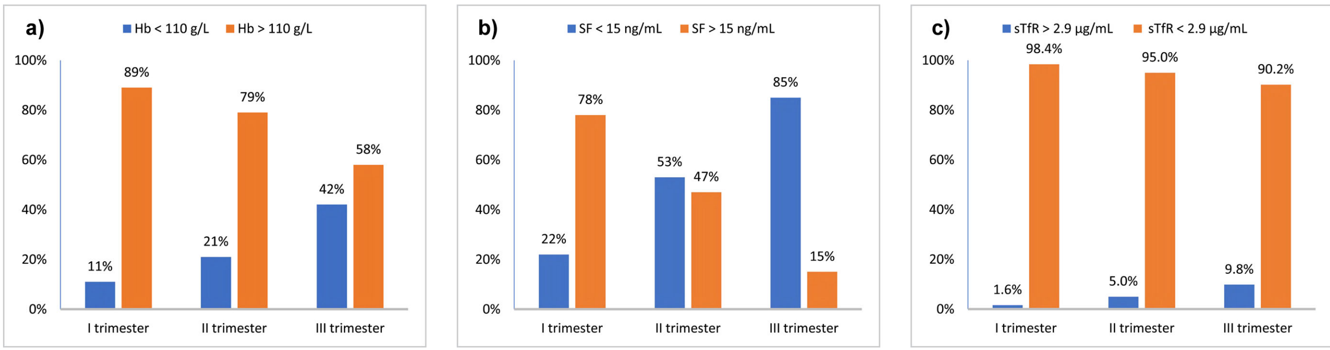
[a] statistical significance

[b] SF and sTfR have non-Gaussian distribution, the evaluation was based on the median value of the parameters, Median (95% CI) - Mann-Whitney U Test

[c] Mean±SD - Independent Samples t-test

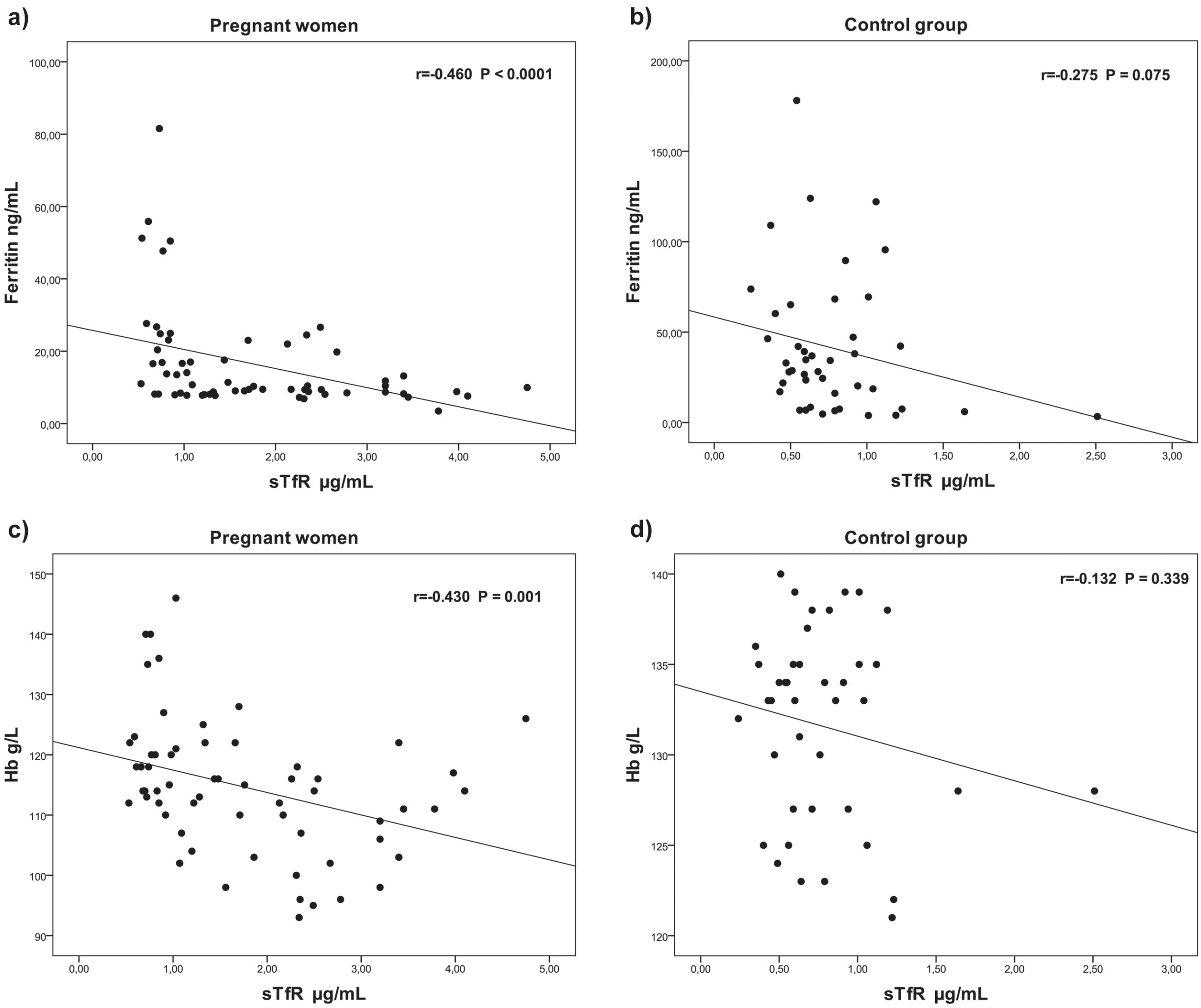
The distribution of pregnant women (%) in trimesters is shown in fig. 1. The subjects were divided into two groups according to the level of Hb, SF and sTfR. The first group corresponds to an iron deficiency condition, and the second to normal iron homeostasis. The results indicate an increase in iron deficiency with the progression of pregnancy.

Fig. 1. Distribution of pregnant women (%) in trimesters according to the levels of: **a.** Hb < 110g/L and > 110g/L; **b.** SF < 15 ng/mL and > 15 ng/mL; **c.** sTfR > 2.9 µg/mL and < 2.9 µg/mL



In the group with pregnant women, there was a significant negative correlation between sTfR and SF and between sTfR and Hb (fig. 2). These associations were not observed in the control group. A statistically significant correlation between SF and Hb was not found in both groups.

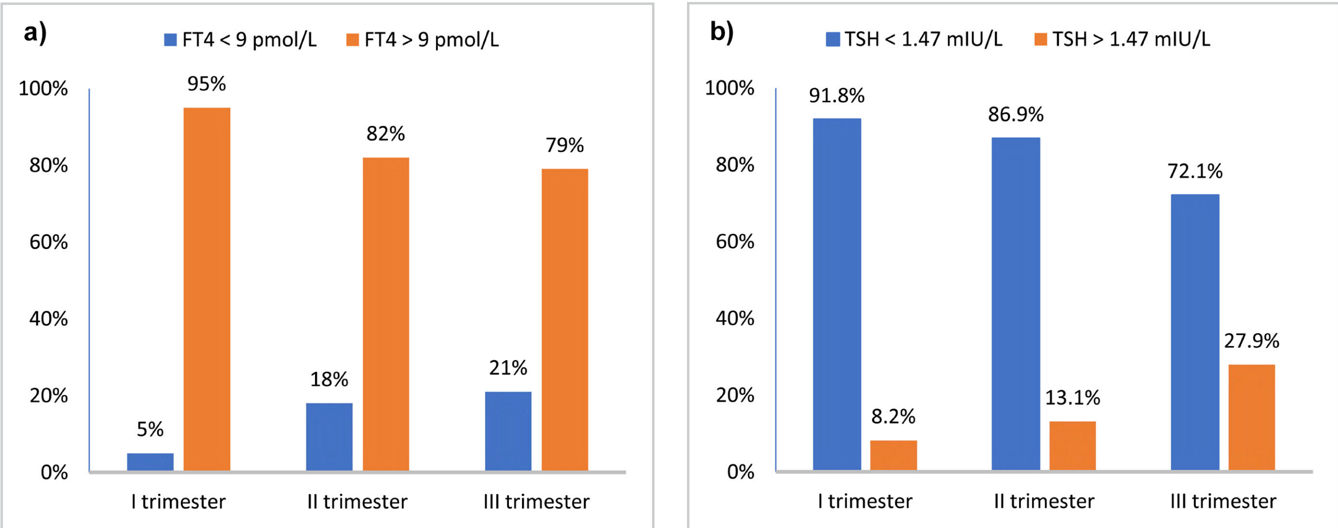
Fig. 2. Correlations between iron homeostasis parameters in pregnant women and control group (a, b, c, d)



Parameters of thyroid status

The level of free thyroxine in the control group was significantly higher compared to pregnant women: mean FT4 in pregnant women was 9.27 ± 1.79 pmol/L, and in the control group, it was 13.83 ± 2.26 pmol/L ($p < 0.0001$). TSH level was lower in the control group compared to pregnant women: median TSH in pregnant women was 1.47 mIU/L (95% CI 1.59-2.25), and in the control group, it was 1.15 mIU/L (95% CI 1.18-1.74). The difference was not statistically significant, p = 0.141. The levels of FT4 and TSH were higher in the early months of pregnancy and decreased gradually, but a statistically significant difference in the concentration of the hormones in the different trimesters was not found. The results on thyroxine levels show that the women in the I trimester had mean FT4 9.89 ± 0.91 pmol/L, in the II trimester 8.88 ± 0.41 pmol/L, in the III trimester 9.33 ± 0.26 pmol/L, and the difference in the hormone levels was not statistically significant. In 22.9% of pregnant women (n = 14), FT4 was below the lower limit, 3 of the subjects were in the I trimester, 4 in the II trimester and 7 in the III trimester. The women with normal FT4 level were 6 in the I semester, 15 in the II and 26 in the III trimester. According to Zimmerman et al. [17], TSH above 4 mIU/L indicates mild subclinical hypothyroidism. Median TSH in trimesters was as follows: I trimester 2.39 (95% CI 0.26-1.98), II trimester 1.28 (95% CI 1.08-2.15) and III trimester 1.58 (95% CI 1.67-2.36). In the entire group, 11.5% of women (n = 7) had TSH above 4 mIU/L. Six of the subjects were in the third trimester, and one was in the first trimester. TSH in trimesters was expressed as Median. The distribution of pregnant women (%) in trimesters according to the FT4 level < 9 pmol/L and > 9 pmol/L is shown in Fig. 3a, and according to TSH level < 1.47 mIU/L and > 1.47 mIU/L is shown in fig. 3b.

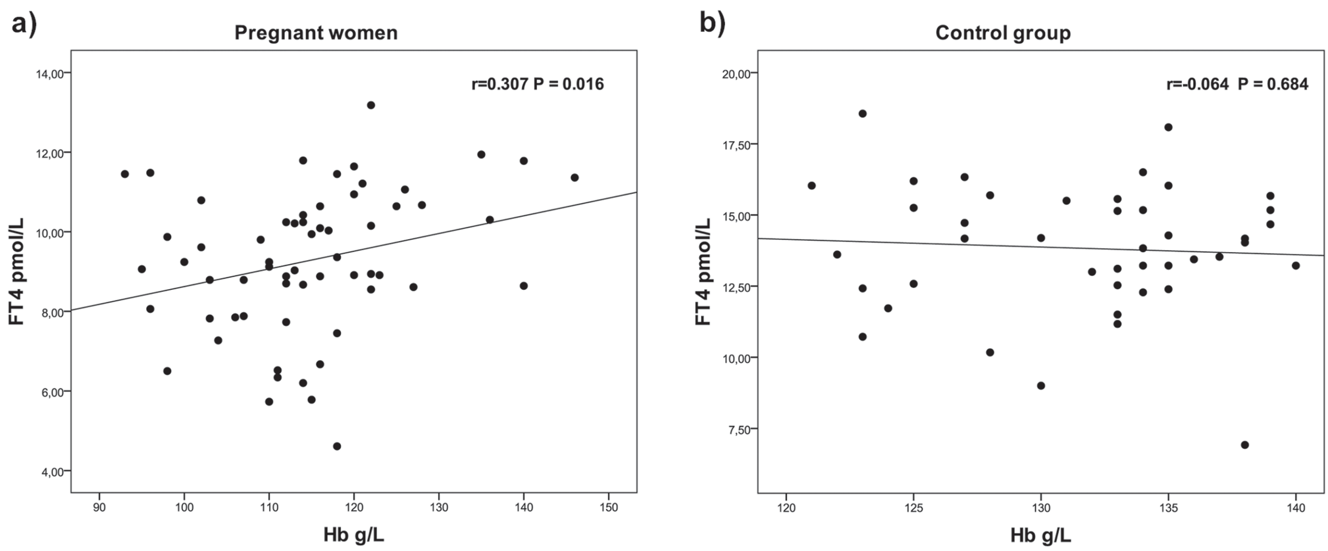
Fig. 3. Distribution of pregnant women (%) in trimesters according to the level of: **a.** FT4 < 9 pmol/L and > 9 pmol/L; **b.** TSH < 1.47 mIU/L and > 1.47 mIU/L

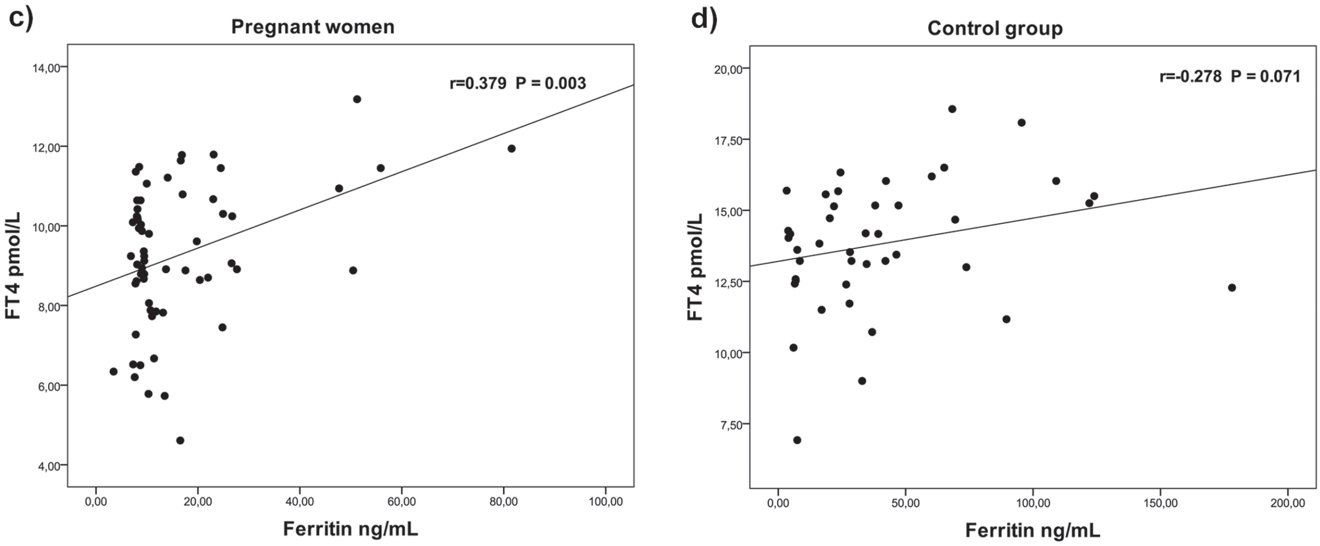


Correlations between iron homeostasis parameters and thyroid status

A significant positive correlation between Hb level and FT4 and also between SF and thyroxine was found in pregnant women. In the control group, these associations were not observed (fig. 4). No significant correlation between sTfR and thyroxine was found in the target groups - pregnant women and the control group.

Fig. 4. Correlations between Hb, ferritin and FT4 in pregnant women and control group (a, b, c, d)





In the first trimester of pregnancy, a strong negative correlation between thyroxine and sTfR and a positive correlation between thyroxine and serum ferritin were observed (table 2). During the second trimester, there was a trend for a positive correlation between FT4 and Hb and for a negative correlation between TSH and Hb that also suggested a dependence of thyroxine levels on iron supply (table 2). During the third trimester, strong positive correlations between TSH and sTfR and FT4 and SF were observed. They indicated a parallel increase of sTfR together with TSH secretion, induced by decreased thyroxine concentration (table 2).

Table 2. Correlations between parameters of thyroid and iron status in trimesters

	I trimester		II trimester		III trimester	
	r	p	r	p	r	p
TSH/sTfR	0.360	0.342	0.107	0.663	0.597	<0.0001[a]
FT4/sTfR	- 0.783	0.013[a]	0.171	0.483	- 0.279	0.115
FT4/Hb	0.496	0.174	0.397	0.092	- 0.004	0.980
TSH/Hb	0.067	0.864	- 0.408	0.083	- 0.024	0.895
TSH/SF	- 0.217	0.576	0.369	0.120	- 0.279	0.116
FT4/SF	0.738	0.023[a]	0.037	0.880	0.432	0.012[a]

[a] statistical significance

Table 3 presents the number of pregnant women with normal and deviating from the normal values of the parameters of iron and thyroid status and their correlations in the two groups.

Table 3. Correlations between thyroid status hormones and iron homeostasis parameters at normal and deviating values

	*with low SF (*n = 40*)*		*with normal SF (*n = 21*)*	
	r	p	r	p
TSH/sTfR	0.554	<0.0001[a]	- 0.093	0.688
TSH/Hb	- 0.358	0.023[a]	0.064	0.782
FT4/Hb	0.339	0.033[a]	0.181	0.431
	*with low Hb (*n = 19*)*		*with normal Hb (*n = 42*)*	
	r	p	r	p
TSH/sTfR	0.614	0.011[a]	0.273	0.069
FT4/sTfR	- 0.198	0.463	- 0.208	0.170
FT4/Hb	- 0.375	0.152	0.410	0.005[a]
FT4/SF	0.379	0.148	0.379	0.010[a]

	*with high sTfR (*n = 10*)*		*with normal sTfR (*n = 51*)*	
	r	p	r	p
FT4/Hb	0.652	0.041[a]	0.205	0.148
FT4/SF	0.381	0.277	0.361	0.009[a]
	*with high TSH (*n = 27*)*		*with normal TSH (*n = 34*)*	
	r	p	r	p
TSH/sTfR	0.736	0.050[a]	0.169	0.221
FT4/Hb	0.021	0.965	0.320	0.018[a]
FT4/SF	0.391	0.386	0.383	0.004[a]
	*with low FT4 (*n = 27*)*		*with normal FT4 (*n = 34*)*	
	r	p	r	p
TSH/sTfR	0.332	0.091	0.382	0.026[a]
FT4/sTfR	- 0.222	0.265	- 0.446	0.008[a]
FT4/Hb	0.273	0.168	0.485	0.004[a]
FT4/SF	0.316	0.108	0.416	0.014[a]

[a] statistical significance

The results indicate that in deficiency of SF and Hb, there was a significant positive correlation between TSH and sTfR that was also observed in the group with high TSH (table 3). In pregnant women with Hb deficiency, there was a positive correlation only between TSH and sTfR and associations between FT4 and iron homeostasis parameters were not observed (table 3). In pregnant women with high sTfR, there was a positive correlation only between FT4 and Hb. In pregnant women with normal sTfR levels, there was a positive correlation between FT4 and SF (table 3). In pregnant women with high TSH, there was a significant positive correlation between TSH and sTfR, while in the group with normal TSH, there was a positive correlation between FT4 and Hb and between FT4 and SF (table 3). Only in pregnant women with normal FT4, there were significant correlations between FT4 and iron homeostasis parameters; in the same group, a significant positive correlation between TSH and sTfR was observed (table 3).

DISCUSSION

Our previous studies report iodine and iron deficiency during pregnancy [19, 20]. The present research involves pregnant women from risk groups living in iodine deficient regions compared to healthy controls at the same age. Pregnant women were distributed in two subgroups – with normal and deviating values of iron homeostasis parameters, FT4 and TSH and the variations of these parameters in trimesters were investigated in order to assess iron deficiency and changes in thyroid status. The correlations of iron homeostasis parameters with FT4 and TSH were also determined.

The results showed significant statistical differences between pregnant women and the control group that indicate an iron deficiency risk: sTfR level was significantly higher, while Hb and ferritin levels were significantly lower in pregnant women. This finding is in agreement with previous studies on iron deficiency during pregnancy [21, 22]. A significant difference was also observed in thyroxine level but not in the TSH level.

In pregnant women, there were significant negative correlations between sTfR and serum ferritin and also between sTfR and Hb (fig. 2). These associations were not statistically significant in the control group. We found that all parameters of iron homeostasis were significantly different from the normal levels in the third trimester of pregnancy compared to the first one (table 1, fig. 1 and fig. 3). These results indicate the increased iron requirements related to fetal nutrition and growth and a trend for an iron deficiency that was most prominent during the last trimester of pregnancy. In pregnant women, a significant positive association between Hb and thyroxine and between SF and FT4 was found, which was not observed in the control group (fig. 4). The parallel change of FT4 in relation to SF and Hb confirms the association between thyroid status and iron stores and the dependence of thyroxine synthesis on iron supply. This finding is in agreement with Gur et al., who report that Hb correlated positively with FT4 in pregnant women with and without hypothyroidism [23].

In order to explain better the relationship between iron metabolism and thyroid status, the group with pregnant women was separated into subgroups according to the level of SF, Hb, sTfR, TSH and FT4. In pregnant women with low Hb level, there was a positive correlation between sTfR and TSH (table 3), which suggested a parallel control in the regulation of tissue iron supply and thyroid hormones synthesis. Tong et al. [27] have found that the elevation of sTfR and its negative association with the severity of congenital hypothyroidism suggested the presence of a self-regulating mechanism. In pregnant women with normal FT4, we found that there was a positive correlation between TSH and sTfR, regardless of thyroxine concentration, that indicated a permanent mechanism responsible for the correspondence between iron supply and thyroid hormones synthesis (table 3).

Serum ferritin is a parameter for the amount of iron stores, but its increased level is also a factor of inflammation. Therefore, pregnant women with higher than normal levels of SF were excluded. Serum ferritin levels were decreased after the first trimester of pregnancy, while sTfR levels were increased, which was indicative of a progressive decrease of iron stores during pregnancy. sTfR was a more sensitive marker for the increased iron requirement than Hb since there was a significant correlation between SF and sTfR ($p < 0.0001$) and between Hb and sTfR ($p = 0.001$), and no significant association between SF and Hb was found (fig. 2). In pregnant women with ferritin levels lower than normal, a positive correlation between sTfR and TSH was observed (table 3). This suggests an adaptive mechanism stimulating parallel iron uptake and thyroxine synthesis.

The distribution of pregnant women according to TSH and thyroxine level confirmed the correlations observed between the parameters of iron homeostasis and thyroid status. TSH levels were related to the parameters of iron metabolism in order to respond to the intensity of thyroid hormones production: normal TSH values corresponded to a positive correlation between thyroxine and ferritin and also between thyroxine and Hb. The increased values of TSH correlated only with sTfR, and therefore the combined determination of the two parameters would be more informative for the detection of the risk of hypothyroidism and iron deficiency (table 3). In pregnant women with low Hb and SF and high TSH, there was a positive correlation between TSH and sTfR, indicating an adaptive mechanism for simultaneous compensation of iron and thyroxine deficiency (table 3). This correlation (TSH/sTfR) was significant in the last trimester of pregnancy ($p < 0.0001$) (table 2).

The results presented in Table 3 showed that only in pregnant women with ferritin deficiency, which indicates decreased iron stores, there was a negative correlation between TSH (stimulus for FT4 production) and Hb (reflected hematopoiesis abilities). The positive correlation between iron homeostasis parameters (Hb and SF) and FT4 was not preserved in pregnant women with low Hb. The results suggest disorders in the regulatory mechanisms associated with iron supply and thyroid hormones synthesis (table 3).

The studies regarding the relationship between parameters of iron homeostasis and thyroid status in the different trimesters of pregnancy are rather scarce. Our findings indicate that in the first trimester when maternal stores are not depleted, there is a strong negative correlation between sTfR and thyroxine levels that proves the association between iron and thyroid status in pregnant women. Such association was not observed in the II trimester. Iron deficiency was mainly expressed in the third trimester with a strong positive association between TSH and sTfR that was also observed in the subgroups with low SF, low Hb, high sTfR and high TSH. sTfR represented the relationship with thyroid status in the I and III trimester. Serum ferritin was positively associated with FT4, and the correlation was statistically significant in the I and III trimester.

The present study enhances our knowledge of iron deficiency during pregnancy and its effect on the maternal thyroid gland function. These findings contribute to the understanding of the dynamics in the serum levels of iron and thyroid status parameters and their relationships in the different periods of pregnancy.

The first limitation of our study is the relatively smaller number of pregnant women in the I trimester of pregnancy compared to the II and III trimester. Another limitation is the lack of information on the pre-pregnancy iron and thyroid status of the participants.

CONCLUSIONS

The study has demonstrated, for the first time, that the association between iron and thyroid status in pregnant women was changed with progression of pregnancy and it was most prominent in the last trimester. We found that in pregnant women the higher iron requirement (sTfR) related with the increasing maternal blood volume and the iron needs of the fetus correlated with elevated TSH secretion induced by decreased thyroxine. Our results indicate that the combined determination of sTfR and TSH is necessary during pregnancy for the assessment of iron deficiency and the risk of hypothyroidism.

Abbreviations

Hb - hemoglobin
SF - serum ferritin
sTfR - serum transferrin receptor
FT4 - thyroxine
TSH - thyroid-stimulating hormone

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