

The Correlation between Iron Deficiency Anemia and Hypothyroidism during Pregnancy

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Abstract

Background: Pregnant women are often iron deficient, and this has adverse effects on thyroid metabolism. Impaired maternal thyroid function in pregnancy may cause neurodevelopmental delay in the offspring. **Objectives:** To investigate if maternal iron status is a determinant of thyroid stimulating hormone (TSH) and/or free T4 (FT4) concentrations during pregnancy. **Materials and Methods:** A case-control study was conducted in the Department of Obstetrics and Gynecology at Azadi Teaching Hospital, Kirkuk, Iraq over a period of 7 months from February 1st to September 1st, 2020. It included 80 pregnant women with singleton pregnancy in the obstetric outpatient clinic and labor room. Verbal consent was obtained. They were divided into: (1) case group: it included 40 cases of iron deficiency (ID) anemic pregnant women with hemoglobin level of 105 g/L and less in the second and third trimesters. (2) Control group: It included 40 cases of healthy pregnant women. Estimation of gestational age was done depending on the date of last menstrual cycle, and/or early ultrasound scan. **Results:** In this study, 80 pregnant women in their second and third trimesters participated. Fifty percent were anemic, had elevated serum soluble transferrin receptor and negative body iron stores, 35% had a free T4 less than 7.5 pmol/L, and 47.5% had a TSH more than 4.0 mIU/L. 47.5% who were hypothyroid had negative body iron store. Serum ferritin, soluble transferrin receptor, and body iron stores were highly significant predictors of thyroid status. **Conclusions:** Poor maternal iron status predicts both higher TSH and lower free T4 concentrations during pregnancy. On the basis of results, we had there may be a correlation between ID anemia of pregnant women and their thyroid status.

Keywords: Anemia, hypothyroidism, pregnancy, soluble transferrin receptor (sTfR)

INTRODUCTION

Anemia in pregnancy affects almost half of all pregnant women worldwide and is prevalent in developing countries. The two most common causes of anemia during pregnancy and puerperium are iron deficiency and acute blood loss.^[1] Iron requirements for pregnancy, the fetus and delivery are substantial, with the average woman requiring at least 1250mg. Western diets typically afford 15mg/day, of which 10% is absorbed. During pregnancy, absorption rises to around 30% by 30 weeks but this is often insufficient to meet demand. Furthermore, many women start pregnancy already iron depleted, due to poor diet, increased need, menstruation and previous pregnancies within 2 years. Iron is one of the important elements required for normal functioning of thyroid gland. Iron is stored in the body in the form of ferritin and it is an intracellular protein. All the cells of the body

contain ferritin and act as a reserve of iron and small amounts are secreted into the serum for the formation of hemoglobin and other heme proteins.^[2]

Iron deficiency (ID) is the most prevalent of all micronutrient deficiencies worldwide.^[3] Numerous studies have shown that ID can impair thyroid hormone synthesis and metabolism. It decreases plasma T4 and T3 concentrations by impairing two initial steps catalyzed by heme-dependent thyroid peroxidase (TPO) enzyme in thyroid hormones synthesis, And ID appears to decrease thyroid stimulating hormone (TSH)

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response to thyrotropin-releasing hormone (TRH), reduce the peripheral conversion of T4 to T3 and increase circulating TSH.^[4] Patient with thyroid disease have shown altered serum ferritin levels. Similarly changes in thyroid hormone levels have reflected if there is an alteration in the concentration of serum ferritin. Furthermore, there is an increase in the concentration of serum ferritin level after starting treatment for hypothyroid patient.^[5]

As in clinical practice, most studies use serum ferritin as an indicator on ID in pregnancy. However, the validity of this measure can be questioned as inflammation, infection, and the physiological hemodilution in pregnancy influence the ferritin concentration.^[6]

Transferrin receptor 1 (TfR1) plays a major role in iron delivery to nearly all cells in the human body. After iron binds to plasma protein transferrin (TfR), the iron-transferrin complex associates with the specific membrane receptor and induces cellular iron endocytosis in the internal vesicles. Trans membrane TfR1 is expressed on probably all dividing, iron-requiring cells with the exception of mature erythrocytes and some other terminally differentiated cells. Its rate of synthesis is closely linked to the requirements of the cell for iron.^[7] In contrast to serum ferritin and transferrin concentrations, sTfR has been shown to be unaffected by concomitant chronic disease and inflammation. Therefore, it may be useful in distinguishing between anemia of chronic disease (ACD) and iron deficiency anemia (IDA), and extremely valuable in identifying mixed IDA + ACD, because serum sTfR concentrations are expected to rise in IDA, but not in ACD.^[8]

The objective of this study was to find whether maternal iron status during pregnancy by the mean of serum ferritin, soluble transferrin receptor and body iron store is a determinant of serum TSH and/or serum free T4 in the second and third trimester of pregnancy and correlation with demographic characteristics.

MATERIALS AND METHODS

This study is a case-control study that was conducted in the Department of Obstetrics and Gynecology at Azadi Teaching Hospital, Kirkuk, Iraq over a period of 7 months from February 1st to September 1st, 2020.

The study protocol was approved by scientific council of obstetrics and gynecology/IRAQI Board for medical specializations.

The study includes 80 pregnant women with singleton viable pregnancy at gestational age (16–40) weeks attending the obstetric outpatient and labor room of the hospital. They were informed about the nature of the study and verbal consent was obtained from them. They were divided into two groups:

1. Case group: include 40 cases of ID anemic pregnant patients with hemoglobin level was 105 g/L and less in the second and third trimester.^[9]
2. Control group: include 40 cases of healthy pregnant patients.

Assessment and estimation of gestational age were done relaying on the date of last menstrual cycle, and/or early ultrasound scan.

Both groups were compared to the thyroid status in second and third trimester of pregnancy.

Women included in this study were aged 16–45 years, gestational age 16–40 weeks, no history of thyroid disorder, singleton viable pregnancy, no history of anemia of chronic disease, and had given acceptance to participate.

Exclusion criteria included women with:

Age less than 16 years and more than 45 years; first trimester of pregnancy; history of thyroid disorder and or current use of thyroid medication; twin pregnancy; pregnant women with history of chronic anemia, history of hemolytic anemia, history of medical disorders (preeclampsia, duodenal ulcer, DM), and women who refuse to participate.

7 mL of venipuncture blood was collected, and hemoglobin (HB), mean corpuscular volume, serum ferritin, free T4, and TSH were measured. Of these 2 mL of blood was put into the plain tube and samples were allowed to clot for 2 h at room temperature or overnight at 4°C before centrifugation for 15 min at 1000×g. Serum and assay were removed immediately or aliquot and store samples at –20°C or –80°C. Repetitive freeze-thaw cycles were avoided.

ID was defined as SF less than 15 g/L or sTfR more than 8.5 mg/L.

Body iron (TBI) was calculated, from sTfR and serum ferritin (SF) concentrations by using the following formula:

$$TBI(\text{mg/kg}) = - \left[\log_{10} (sTfR * 1000/SF) - 2.8229 \right] / 0.1207.$$

Positive values of TBI indicate the quantity of iron in stores, and negative values indicate the deficit in tissue iron.^[10]

TSH level 4.0 mIU/L and more indicating subclinical hypothyroidism and free T4 less than 7.7 pmol/L indicating hypothyroxinemia.^[11]

Statistical analysis

The data were analyzed using Statistical Package for Social Sciences (SPSS, IBM Company, Chicago, IL, USA) version 25.0. The data were presented as mean, standard deviation, and ranges. Categorical data were presented by frequencies and percentages. Independent *t* test (two

tailed) was used to compare the continuous variables accordingly. Pearson's correlation test (r) was used to assess correlation between continuous variables accordingly. Receiver–operating characteristic (ROC) curve analysis was used for sTfR as predictor of hypothyroidism in anemic pregnant ladies. A level of P value < 0.05 was considered significant.

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients verbal and analytical approval before sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee according to the document number 20 dated December 18, 2022.

RESULTS

The total number of studied patients was 80. All of them were pregnant women in the 2nd or 3rd trimester. They were divided into two groups: case group included 40 pregnant women diagnosed with ID anemia and control group included 40 healthy pregnant women.

The distribution of study groups by age is shown in general characteristics in Table 1. Study patients' age was ranging from 16 to 45 years with a mean of 31.1 years and a standard deviation (SD) of ± 7.05 years. The highest proportion of study patients in case and control groups was aged ≥ 35 years (both were between 40%–42.5%). Regarding body mass index (BMI) level, the highest proportion of women in case group were overweighted (47.5%); while half of control groups had normal level.

Table 1: Comparison between study groups by certain characteristics

Variable	Study groups		P-value
	Case Mean $\pm$ SD	Control Mean $\pm$ SD	
Age (years)	31.45 $\pm$ 7.6	30.75 $\pm$ 6.6	0.66
BMI (kg/m ²)	23.89 $\pm$ 3.1	23.64 $\pm$ 2.5	0.704
Gravida	4.4 $\pm$ 1.9	3.77 $\pm$ 1.6	0.12
Space interval (year)	1.3 $\pm$ 0.9	1.73 $\pm$ 0.8	0.027

BMI = body mass index

Table 2: Comparison between study groups by hematological parameters

Hematological parameters	Study groups		P-value
	Case Mean $\pm$ SD	Control Mean $\pm$ SD	
Hemoglobin (gm/dL)	9.78 $\pm$ 2.4	11.47 $\pm$ 2.7	0.004
S. Ferritin (μ g/L)	11.28 $\pm$ 1.1	17.71 $\pm$ 1.7	0.001

We noticed that 81.3% of the pregnant women were multigravida in both groups.

Concerning space interval after last pregnancy, it was less than 2 years in 72.5% of case group and ≥ 2 years in 68.4% of control group. Regarding gestational age (GA), 55% of case group were in the 2nd trimester whereas 67.5% of control group were in the 3rd trimester.

Mean of space interval after last pregnancy was significantly lower in patients of case group than that in controls (1.3 vs. 1.73 years, $P = 0.027$).

There were no statistically significant differences ($P \geq 0.05$) between the study groups in age, BMI, and gravida.

Table 2 shows the comparison in hemoglobin and serum ferritin levels between study groups. Means of hemoglobin and serum ferritin levels were significantly higher in control group than that in case group (11.47 $\pm$ 2.7 vs. 9.78 $\pm$ 2.4 gm/dL, $P = 0.004$; and 17.71 $\pm$ 1.7 vs. 11.28 $\pm$ 1.1 μ g/L, $P = 0.001$ respectively).

We noticed that 47.5% of case group and 20% of controls were diagnosed with hypothyroidism. In case group, mean of free T4 level was significantly lower and mean of TSH level was significantly higher than that in controls (7.83 vs. 9.78 pmol/L, $P = 0.002$; and 4.55 vs. 3.45 mIU/L, $P = 0.006$ respectively) as shown in Table 3.

Table 4 shows the comparison in soluble transferrin receptor between study groups. Mean of sTfR was

Table 3: Comparison between study groups by thyroid function test

Thyroid function test	Study groups		P-value
	Case group Mean $\pm$ SD	Control group Mean $\pm$ SD	
Free T4 (pmol/L)	7.83 $\pm$ 2.7	9.78 $\pm$ 2.9	0.002
TSH (mIU/L)	4.55 $\pm$ 1.8	3.45 $\pm$ 1.7	0.006

TSH = thyroid stimulating hormone

Table 4: Comparison between study groups by sTfR

Soluble transferrin receptor (mg/L)	Study groups		P-value
	Case Mean $\pm$ SD	Control Mean $\pm$ SD	
	11.2 $\pm$ 0.95	5.7 $\pm$ 0.72	0.001

Table 5: Comparison in sTfR according thyroid status of case group

Soluble transferrin receptor (mg/L)	Thyroid status		P-value
	Hypothyroidism Mean $\pm$ SD	Euthyroid Mean $\pm$ SD	
	11.83 $\pm$ 1.5	10.26 $\pm$ 1.5	0.002

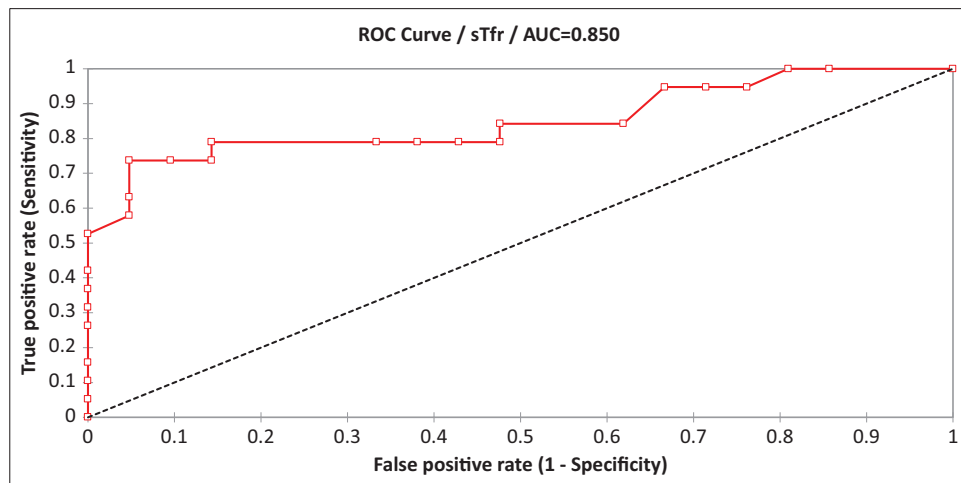


Figure 1: ROC curve for sTfR as predictor of hypothyroidism in anemic pregnant

Table 6: Diagnostic accuracy for sTfR level						
sTfR level (mg/L)	cutoff value	Sensitivity	Specificity	PPV	NPV	Accuracy
	11.4	73.7%	95.2%	93.3%	80%	85%

PPV: Positive predictive value; NPV: Negative predictive value

Table 7: Association between TBI and thyroid status				
TBI status	Thyroid status		Total (%) n = 80	P-value
	Hypothyroidism (%) n = 27	Euthyroid (%) n = 53		
Positive	8 (20.0)	32 (80.0)	40 (50.0)	0.009
Negative	19 (47.5)	21 (52.5)	40 (50.0)	

TBI: total body iron store

significantly higher in case group than that in controls (11.2 vs. 5.7 mg/L, $P = 0.001$).

Table 5 shows the comparison in soluble transferrin receptor according thyroid status of case group. Mean of sTfR was significantly higher in anemic patients diagnosed with hypothyroidism than that in anemic patients with euthyroid status (11.83 vs. 10.26 mg/L, $P = 0.002$).

ROC analysis was constructed for sTfR as predictor of hypothyroidism in anemic pregnant. As shown in Figure 1 and Table 6, the cut point of sTfR was 11.4 mg/L, so sTfR > 11.4 mg/L is predictive for hypothyroidism in anemic pregnant as a large significant area under the curve (AUC = 85%) indicating significant association between higher level of sTfR level and prediction of hypothyroidism in anemic pregnant.

Soluble transferrin level was 73.7% sensitive, 95.2% specific, and 85% accurate as a predictor for hypothyroidism in anemic pregnant.

Body iron (TBI) was calculated, from sTfR and SF concentrations. The association between TBI status and thyroid status is shown in Table 7. In this study, 80% of

patients with positive TBI were in euthyroid status with a significant association ($P = 0.009$) between TBI status and thyroid status.

DISCUSSION

Regarding the general characteristics of our sample study patients. The age was ranging from 16 to 45 years, the mean of age in case group was 31.45 ± 7.6 whereas that of control group was 30.75 ± 6.6 . P value between the two groups was (0.66); this was statistically non-significant. An agreement observed in study done by Zimmerman *et al.*^[12] which was a cross-sectional study involving 365 pregnant women through which the age of the patients was ranging from 16 to 42 years the mean of age was 29.6 ± 4.2 in case group and 29.8 ± 4.8 in control group. Another study done by He *et al.*^[13] which was also across sectional study involving 209 pregnant women, the age of studied group was between 18 and 40 years and the mean of age was 27.54 ± 4.6 in case group and 27.20 ± 3.8 in control group.

The gestational age of studied group was between 16 and 40 weeks, the mean of gestational age in the case group were 27.90 weeks in contrast to control group 29.944 weeks. The P value between the two groups was (0.106); this was statistically non-significant. This was comparable to a study done by Zimmermann *et al.*^[12] in which the mean of gestational age was 26.7 ± 2.1 weeks in case group and $31.9 \pm 4.4 \pm 3.1$ in control group. In contrast to a study done by He *et al.*^[13] 2018 the mean of GA in case group was 19.33 ± 3.4 weeks whereas in control group, it was 16.88 ± 3.2 weeks.

Regarding the BMI, the mean was 23.89 ± 3.1 kg/m² in case group while in control group it was 23.64 ± 2.5 kg/m². P value was 0.704. This was statistically non-significant. Nearly similar to our result, a study was done by He *et al.*^[13] in which the mean of BMI was 21.08 ± 3.25 kg/m² in case group and 21.28 ± 3.59 kg/m² in control group. In contrast to a study done by Iqbal *et al.*^[14] which involved

120 pregnant women; the BMI was higher $27.0 \pm 2.7 \text{ kg/m}^2$ in case group and $25.6 \pm 4.0 \text{ kg/m}^2$ in control group.

The mean of space interval after last pregnancy (<2 years) was significantly lower in patients of case group than that in controls (1.3 vs. 1.73 years, $P = 0.027$). This was statistically significant.

Regarding the hematological parameters the anemic patients in our study were 40 cases (50%) which was similar to study done by Bivolarska *et al.*^[15] which involved 128 pregnant cases, in which 36.7% of them were anemic. Another study done by Iqbal *et al.*^[14] which involved 80 pregnant cases in which 68.8% were anemic patients.

The mean value of hemoglobin in case group was $9.78 \pm 2.4 \text{ g/L}$, whereas that of control group was 11.47 ± 2.7 . P value is 0.004 which is statistically significant. Our results were nearly similar to a study done by He *et al.*^[13] showed the mean and SD of Hb were $11.40 \pm 1.09 \text{ g/L}$ in case group and 12.9 ± 2.05 in control group. Another study done by Bivolarska *et al.*^[15] which was a cross-sectional study involved 128 pregnant women the mean and SD of Hb level $11.49 \pm 1.79 \text{ g/L}$. It was in disagreement with the study of Zimmerman *et al.*^[12] who demonstrated higher mean of HB $12.1 \pm 1.0 \text{ g/L}$ in case group and $12.3 \pm 1.2 \text{ g/L}$ in control group.

While the mean and SD of ferritin level was in case group $11.28 \pm 1.1 \text{ } \mu\text{g/L}$ and in control group $17.71 \pm 1.7 \text{ } \mu\text{g/L}$, this was statistically significant the P value was (0.001). Low s. ferritin during pregnancy was mainly due to the increased iron requirement and plasma volume expansion. A study done by Teng *et al.*^[16] which was a cross-sectional; that study involved 723 pregnant women in the second and third trimester of pregnancy which was nearly similar to our study. The mean and SD of s. ferritin was $14.26 \pm 9.29 \text{ } \mu\text{g/L}$ in case group and $26.16 \pm 8.4 \text{ } \mu\text{g/L}$ in control group. Another study done by Iqbal *et al.*^[14] the mean and SD of s. ferritin level was $15.09 \pm 5.59 \text{ } \mu\text{g/L}$ in case group and 24.14 ± 3.46 in control group. Disagreement observed in a study done by Bivolarska *et al.*^[15] the mean and SD of ferritin was $23.85 \pm 27.27 \text{ } \mu\text{g/L}$ in case group and $49.17 \pm 36.64 \text{ } \mu\text{g/L}$ in control group this deference may be due to deferent area of study.

Regarding thyroid status in our study, the hypothyroidism was present in 47.5% in case group and 20% in control group. The study done by Agrawal *et al.*^[17] involved 110 pregnant cases, in which hypothyroidism was present in 31.81% in case group.

In case group, mean of free T4 level was significantly lower and mean of TSH level was significantly higher than that in controls (7.83 ± 2.7 vs. $9.78 \pm 2.9 \text{ pmol/L}$, $P = 0.002$; and 4.55 ± 1.8 vs. $3.45 \pm 1.7 \text{ mIU/L}$, $P = 0.006$, respectively).

Regarding the mean of FT4, our study results agreed with a study done by Baghel *et al.*^[18] in which the mean of

FT4 was $6.56 \pm 5.1 \text{ pmol/L}$ in case group and $17.37 \pm 3.9 \text{ pmol/L}$ in control group. This study disagreed with a study done by He *et al.*^[13] in which the mean and SD of FT4 were normal in case group $14.26 \pm 1.45 \text{ pmol/L}$ and 14.81 ± 1.56 in control group. Also, a disagreement was observed in study done by Bivolarska *et al.*^[15] the mean and SD of FT4 $13.68 \pm 2.9 \text{ pmol/L}$.

Regarding the TSH level in our study was similar to study done by to He *et al.*^[13] show the mean of TSH level higher in case group $3.25 \pm 1.72 \text{ mIU/L}$ and normal in control group $2.18 \pm 1.33 \text{ mIU/L}$. In contrast to Zimmerman *et al.*^[12] the mean of sTSH ($1.5 \pm 1.3 \text{ mIU/L}$). Another study done by Yo *et al.*^[19] The mean of TSH level was $1.82 \pm 1.55 \text{ mIU/L}$ in case group and $1.79 \pm 1.61 \text{ mIU/L}$ in control group.

Regarding sTfR between study groups, the mean level in case group was higher than that of control group ($11.2 \pm 0.95 \text{ mg/L}$) and ($5.7 \pm 0.72 \text{ mg/L}$), respectively. This level statistically was highly significant; the P value was 0.001. The higher level which observed when there is ID anemia reflects an increase in transferrin receptor at cellular level whereas in Zimmerman *et al.*^[12] the comparison of sTfR was $7.2 \pm 2.5 \text{ mg/L}$ in the 2nd trimester and 8.6 ± 3.0 in the 3rd trimester. The mean was lower in study by Bivolarska *et al.*^[15] $1.83 \pm 1.05 \text{ mg/L}$. Another study done by Teng *et al.*^[16] the mean and SD of case group was 3.60 ± 2.1 and 2.58 ± 3.2 in control group. Also, the mean of sTfR was lower than our results in a study done by Yo *et al.*^[19] which showed comparable level of the sTfR between pregnant and non-pregnant women; the level was 2.67 mg/L and 3.11 mg/L , respectively.

Iron is a nutritional element which is not only needed for the synthesis of hemoglobin but is also essential for enzymes involved in neurochemical reaction^[20] such as myelin formation, brain energy metabolism, and some neurotransmitters and enzymes metabolism such as monoaminoxidase and aldehyde oxidase.^[21] Several studies showed that ID anemia affects thyroid function via several mechanisms. ID decreases serum total and free T3, T4 concentrations, and heme-dependent TPO activity^[21] ID decreases pituitary TSH response to TRH, decreases the activity of hepatic T4 deiodination and T3 turnover rates, and increases peripheral type III deiodinase activity resulting in high T4 and T3 clearance rate. Impaired maternal thyroid function during pregnancy may cause neurodevelopmental delays in the offspring. ID blunts the efficacy of iodine prophylaxis,^[22] and iron repletion improves the efficacy of iodized salt in goitrous children with ID. Thyroid hormones play an important role in kidney development and physiology, through their actions on growth, renal blood flow, and maintenance of kidney homeostasis. Thyroid dysfunctions have an important effect on renal function, as well as cardiovascular alterations.^[23]

CONCLUSIONS

On the basis of the results which were obtained we can draw the conclusion that there may be an important relationship between the thyroid hormone and iron status during the second and third trimesters of pregnancy. Poor maternal iron status predicts both higher TSH and lower free T4 concentrations during pregnancy in an area of borderline iodine deficiency.

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Conflicts of interest

There are no conflicts of interest.

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