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Testing the Tormenting TRIO: A Study of Thyroid Autoimmunity, Iron Deficiency and Thyroid Diseases in the First Trimester of Pregnancy

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Abstract

***Introduction:** Anaemia is a worldwide leading health problem affecting women, which is still more common during pregnancy as the demand for iron increases. A review of the most recent literature reveals that the link between Iron deficiency and thyroid diseases is controversial. A few studies have shown that Iron deficiency anaemia can cause thyroid hypofunction by reducing Thyroid peroxidase (TPO) enzyme activity[1]. Hence this study was taken up with the objectives of 1) To evaluate the association between Iron deficiency and thyroid disorders in the first trimester of pregnancy, and 2) to evaluate the association between thyroid autoimmunity and Iron deficiency in early pregnancy.*

***Material and methods:** This was a cross-sectional study conducted between Jan 2017 and June 2019 at JSS Hospital, Mysuru. 500 pregnant women were recruited. Under aseptic precautions, venous blood was sent for analysis of Hb, TSH, T3, T4, Anti-TPO antibody and Serum Ferritin. Chi-square analysis was done to analyse any association between Iron deficiency and Hypothyroidism.*

***Results:** Out of 500 women, 9 were excluded because of preanalytical error, hence there were 491 pregnant women in the first trimester of pregnancy. Among 491 pregnant women, 156 (31.77%) were hypothyroid and 7 (1.42%) had thyrotoxicosis. Among 156 Hypothyroid women, 9 (5.76%) had overt hypothyroidism and 147 (94.23%) had subclinical hypothyroidism. Among 491 pregnant women, 128 (29.22%) had iron deficiency, 82 (18.72%) had iron deficiency anaemia, 228 (52.05%) had normal Hb and ferritin. 53 (10.79%) women were excluded as they had low Hb but normal ferritin, hence three groups were made for analysis. TSH was higher in the iron deficiency anaemia group compared to the other 2 groups but it was not statistically significant. There was no difference in the rates of thyroid dysfunction among different groups.*

***Conclusion:** The prevalence of hypothyroidism was very high (31%) in our setting compared to that seen in earlier published reports. There was no association found between hypothyroidism and iron deficiency in this study contrary to previous studies. There was no association found between thyroid autoimmunity and iron deficiency in this study.*

***Key words:** Subclinical hypothyroidism, anaemia, thyroid antibodies, gestation.*

Introduction

Anaemia is a worldwide health problem affecting 33% of non-pregnant women and 38% of pregnant women[2]. As pregnancy progresses, the prevalence of anaemia also increases. Iron deficiency anaemia (IDA) accounts for 75% of anaemia during pregnancy[3,4]. The prevalence of anaemia in pregnant women is 50.3% and in non-pregnant women is 52.2%, in India (NFHS-4)[5]. Pregnant women are highly susceptible to iron deficiency anaemia as there is increased demand for iron during pregnancy[6]. Recently the prevalence of hypothyroidism is seen to be increasing among women. The causes are unknown, when thyroid antibodies are negative in them. Some studies have noted that iron deficiency anaemia can cause thyroid hypofunction by reducing Thyroid peroxidase (TPO) enzyme activity[1]. Iron deficiency was linked to a twofold rise in hypothyroidism[7,8]. Women with thyroid dysfunction were more likely to have anaemia compared with euthyroid women[9]. Iron deficiency (ID) is related to a high prevalence of thyroid autoimmune disease (TAI), higher serum thyroid-stimulating hormone (TSH), and lower free thyroxine (FT4) levels during the first trimester of pregnancy[10]. A clinical study that involved 15,000 Chinese pregnant women showed that subclinical hypothyroidism was not related to anaemia, whether treated or not[11]. Sahu *et al*[12] and Wang *et al*[13] also drew the same conclusion. There were only a few studies in India regarding this issue, hence this study was taken up.

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Aims and objectives

1. To evaluate the association between iron deficiency and thyroid disorders in the first trimester of pregnancy.
2. To evaluate the association between iron deficiency and thyroid autoimmunity in the first trimester of pregnancy.

Methodology

This was a cross-sectional study conducted between January 2017 and June 2019 at JSS Hospital, a tertiary care teaching and research hospital attached to JSS Medical College in Mysuru city, South India. 500 consecutive pregnant women aged 18 - 45 years in the first trimester of pregnancy were recruited. Informed written consent was taken from all women. Ethical Clearance was obtained from JSS Medical College Institutional Ethics Committee. (JSSMC/IEC/14/6047/2016-17).

Pregnant women who had any past or present history of thyroid dysfunction/disease, family history of thyroid disease, previous head or neck irradiation, usage of drugs such as levothyroxine, methimazole, iodide, lithium, amiodarone and corticosteroids, patients diagnosed with autoimmune and connective tissue diseases were excluded from the study. Detailed history and clinical examination were recorded in clinical proforma. Under all aseptic precautions, venous blood of about 5 ml was drawn and sent for analysis of Hb, TSH, T3, T4, Anti-TPO antibody and serum ferritin. T3, T4, TSH, Anti-TPO antibody and serum ferritin were measured by chemiluminescence method for all pregnant women. TSH value >2.5 μIU/ml but less than or equal to 10 with normal T4 were considered to have subclinical hypothyroidism (SCH), TSH value >10 μIU/ml irrespective of T4 values and TSH value >2.5 μIU/ml with low T4 values were considered to have overt hypothyroidism[14] (American Thyroid Association and National Guidelines). Serum ferritin less than 20 was considered as iron deficiency and pregnant women having both Hb < 11g/dl and serum ferritin < 20 ng/ml were considered to have iron deficiency anaemia. All parameters were compared and statistically evaluated for significant association between groups.

Statistical analysis

Data collected were entered in Microsoft Excel and analysed using SPSS version 22.

Descriptive statistical measures like percentage, mean and standard deviation were calculated. Inferential statistical tests like the Chi-square test, two-way ANOVA were used wherever relevant and statistical significance was considered at a p-value of < 0.05.

Results

Out of 500 subjects in the study, 9 were excluded because of preanalytical error, hence data of the remaining 491 pregnant women were analysed. Most of them, 403 (82%) were in the age group 21 - 30 years, the majority - 363 (74.75%) belonged to the urban category, most, i.e., 481 (98%) were literate and 466 (95%) were homemakers. 412 (84%) had married when aged between 18 - 25 years age, 407 (83%) had a non-consanguineous marriage, 228 (46%) were primigravida and 263 (53%) were multigravida, only 4 (0.8%) had previous caesarean section and 51 (10%) had a previous history of irregular menstrual cycles. 370 (75%) were non-vegetarians, 418 (85%) had an intake of cauliflower and cabbage weekly once. 227 (46%) had normal BMI, 107 (21%) were overweight, 65 (12%) were obese and 92 (18%) were underweight.

Among 491 pregnant women, 128 (29.22%) had iron deficiency, 82 (18.72%) had iron deficiency anaemia, 228 (52.05%) had normal Hb and ferritin and 53 (10.79%) were excluded as they had low Hb but normal ferritin, hence three groups were made for analysis as shown in Table I. Age, weeks of pregnancy and BMI were similar among the three groups. There was variation in SBP between groups with a significant p-value - 0.02, SBP was less in the iron deficiency anaemia group.

The predominant symptom of the iron deficiency anaemia group was fatigue (26.82%) followed by hair loss (24.39%) (Table II).

Table I: Comparison of clinicodemographic variables among different groups according to iron status.

Groups	n	Age (years)	Weeks of Pregnancy	BMI (Kg/m^2)	Pulse (bpm)	SBP (mm Hg)	DBP (mm Hg)	Hb (g/dl)	Serum Ferritin (ng/ml)
ID	128 (29.22%)	23.00 ± 3.60	8.26 ± 2.35	21.67 ± 3.39	80.41 ± 6.87	112.43 ± 10.53	78.56 ± 7.17	12 ± 0.84	13.05 ± 4.87
IDA	82 (18.72%)	22.93 ± 3.00	8.54 ± 2.10	21.77 ± 3.46	83.06 ± 9.73	106.95 ± 11.62	69.75 ± 7.19	9.62 ± 1.07	9.41 ± 5.39
Normal	228 (52.05%)	23.90 ± 4.05	8.66 ± 2.14	22.10 ± 3.67	81.98 ± 9.00	111.16 ± 11.38	71.68 ± 7.96	12.23 ± 0.75	47.19 ± 33.88
p-value		0.125	0.258	0.512	0.077	0.02	0.189	< 0.0001	< 0.0001

Table II: Comparison of symptoms among different groups according to iron status.

Symptoms	Iron deficiency anaemia	Iron deficiency	Normal	p value
Tiredness	22 (26.82%)	49 (38.28%)	84 (36.84%)	0.19
Feeling Cold	5 (6.09%)	27 (21.09%)	44 (19.29%)	0.01
Dry Skin	5 (6.09%)	8 (6.25%)	17 (7.45%)	0.87
Hair Loss	20 (24.39%)	55 (42.96%)	69 (30.26%)	0.009
Poor Memory	1 (1.21%)	2 (1.56%)	4 (1.75%)	0.94
Constipation	0 (0%)	6 (4.68%)	6 (2.63%)	0.12
Weight Gain	1 (1.21%)	3 (2.34%)	4 (1.75%)	0.83

Among 491 pregnant women, 156 (31.77%) were hypothyroid and 7 (1.42%) had thyrotoxicosis. Among 156 hypothyroid women, 9 (5.76%) had overt hypothyroidism and 147 (94.23%) had subclinical hypothyroidism. The prevalence of hypothyroidism was very high in this study due to the low TSH cut-off value used according to recent ATA guidelines whereas previous studies have used TSH >4 μIU/ml.

Predominant symptom in hypothyroid women was fatigue (35.6%) followed by hair loss (31.7%), cold intolerance (16.9%), dry skin (6.72%), constipation (2.65%), weight gain (2.24%) and poor memory (2.04%). Goitre was present in 10 women.

The thyroid function indices are compared in Table III. TSH was higher in the iron deficiency anaemia group compared to the other 2 groups but it was not statistically significant. T3.T4 and Anti-TPO antibody were similar in all groups with no statistical significance.

Table III: Comparison of thyroid status among different groups according to iron status

Groups	n	TSH (μIU/ml)	T3 (ng/ml)	T4 (μg/dl)	Anti-TPO Ab (IU/ml)
ID	128	1.63 ± 1.60	1.41 ± 0.34	8.87 ± 2.55	16.70 (9.91, 24.60)
IDA	82	2.01 ± 1.50	1.41 ± 0.39	9.33 ± 3.04	14.75 (10.22, 21.85)
Normal	228	1.77 ± 1.70	1.45 ± 0.76	9.39 ± 2.39	16.87 (12.19, 22.27)
p-value		0.536	0.791	0.173	0.793

2.34% of pregnant women had overt hypothyroidism and 26.56% had SCH in the ID group. 29.26% of women had SCH in the IDA group. Overt hypothyroidism was not found in the IDA group. There was no difference in the rates of thyroid dysfunction and thyroid autoimmunity among different groups as in Table IV.

Subgroup analysis was done, as depicted in Table V, and it did not show any association between iron deficiency and SCH.

Table IV: Comparison of thyroid dysfunction among different groups according to iron status.

Groups	Overt Hypothyroidism	SCH	Hyperthyroidism	TPO Ab Positivity
ID	3 (2.34%)	34 (26.56%)	3 (2.34%)	6 (4.68%)
IDA	0 (0%)	24 (29.26%)	1 (1.21%)	5 (6.09%)
Normal	6 (2.63%)	66 (28.94%)	2 (0.87%)	13 (5.70%)
p value	0.34	0.91	0.54	0.88

Table V: Subgroup analysis.

Groups	SCH 1 TSH >4 but < 10	SCH 2 TSH >4.5 but < 10
ID (128)	13 (10.1%)	9 (7.03%)
IDA (82)	11 (13.41%)	9 (10.9%)
Normal (228)	16 (0.07%)	11 (8.59%)
p value	0.26	0.201

Discussion

Iron is a very essential micronutrient and a major component of haemoglobin, myoglobin and various enzymes such as thyroid peroxidase and myeloperoxidase. Iron also has a role in the regulation of immune and thyroid function. Iron deficiency results in impairment of cognitive performance and behaviour, immune function, thermoregulation and exercise/work capacity. Iron deficiency (ID) remains a worldwide problem, affecting about 20% of the world's population. In industrialised countries, the prevalence of iron deficiency in pregnancy ranges from 24 - 44%[3,15]. The prevalence of anaemia in India is above 40% and in Karnataka, it is 75.9%[3]. The prevalence of anaemia in pregnant women is 50.3% and in non-pregnant women is 52.2% according to NFHS-4[5]. Pregnant women are highly susceptible to IDA as there is increased demand for iron. Iron deficiency anaemia in pregnancy can lead to various complications like preterm birth, low birth weight, post-partum haemorrhage and unhealthy neurodevelopment in the foetus.

Recent research suggests that iron deficiency with or without anaemia impairs thyroid function[17]. It decreases plasma T4 and T3 concentrations by impairing two initial steps catalysed by heme-dependent thyroid peroxidase (TPO) enzyme in thyroid hormone synthesis and ID appears to decrease TSH response to TRH, reduce the peripheral conversion of T4 to T3 and increase circulating TSH[17]. However, in all these studies, there was no association found between ID and subclinical hypothyroidism[16,17]. ID can adversely influence thyroid hormone metabolism by altering control of the central nervous system (CNS)[21] and decreasing the binding of T3 to hepatic nuclear receptors[22]. ID could also impair thyroid metabolism through lowered

oxygen transport[23]. It is likely that these mechanisms jointly contribute to the impairment of thyroid function in iron deficiency anaemia[17].

There are a few published articles which have studied the association between iron deficiency and hypothyroidism in pregnant women; a few have positive association and a few have shown no association, which are discussed below.

ID was found in 35% of the women in the study by Veltri *et al*, which included 1,900 pregnant women. Thyroid autoimmunity (TAI) and SCH were substantially more common in the ID group than in the non-iron deficiency group (10% vs 6% and 20% vs 16%; P = 0.011 and 0.049, respectively). After controlling for confounding factors, ID remained linked with TAI in the logistic regression model (P = 0.017). During the first trimester of pregnancy, ID was more common, and it was linked to a higher incidence of TAI, higher serum TSH, and lower FT4 levels[10].

In a study done in China by Li *et al*, ID could lead to hypothyroidism during early pregnancy which could be explained by TAI. 2,654 pregnant women were enrolled, the positive rate of TPO antibody was higher in the IDA group rather than mild ID and controls with $p < 0.05$. They also observed that pregnant women in mild ID and IDA groups have higher TSH and lower FT4 levels than in the control group, the rate of hypothyroidism or SCH in the IDA group was significantly higher than in mild ID and controls group ($p < 0.01$)[17].

In both pregnant and non-pregnant women, the prevalence of mild and severe hypothyroxinaemia was considerably higher in women with ID than in women without ID, according to Yu *et al* study (p 0.01). Logistic regression analysis demonstrated that ID was an independent risk factor for both mild and severe hypothyroxinemia in pregnancy, independent of the effects of iodine and TAI. ID might be a causal factor for hypothyroxinaemia in pregnant women during the first trimester[18].

In research by Zhang *et al*, 7,463 first-trimester pregnant women were included which showed that the ID group had lower serum FT4 levels than the control group ($p < 0.01$), while the ID group's median TSH level was similar to the control group's[19].

In a study done by Sahu *et al*, 633 women in the second trimester from India were enrolled and found that the percentage of anaemia was more in SCH, but it was statistically insignificant[12].

In a study by Wang *et al*, which enrolled 756 first-trimester pregnant women, no link was found between SCH and other obstetrical issues such as gestational hypertension, premature delivery, anaemia, post-partum haemorrhage, low newborn Apgar scores, or low birth weight[13].

Yang *et al* (2015) observed no statistically significant difference in the incidence of placental abruption, anaemia or foetal distress between the SCH-treated and untreated groups in a trial of 2,042 women in early pregnancy with SCH[11].

In the present study, the prevalence of hypothyroidism was very high due to the low TSH cut-off value used (TSH > 2.5 μIU/ml) in the study according to recent ATA and National Guidelines[14] contrary to previous studies which used TSH > 4 μIU/ml.

In the present study, 128 (29.22%) women had ID and 82 (18.72%) had IDA. 2.34% of pregnant women had overt hypothyroidism and 26.56% had SCH in the ID group, 29.26% of women had SCH in the IDA group. Overt hypothyroidism was not found in the IDA group. None had severe IDA. There was no difference in rates of thyroid dysfunction among different groups in the current study, hence no association was found between ID and thyroid dysfunction in this study. There was no difference in Anti-TPO antibody levels among different groups, hence no association was found between ID and TAI in this study.

Overt hypothyroidism and TPO antibody-positive status were found to be risk factors for gestational anaemia in a meta-analysis published in 2020, however SCH and hyperthyroidism were not[20]. In the current study, the prevalence of SCH (94.23%) was more compared to overt hypothyroidism (5.76%) this might be the cause that the present study could not find any association between ID and hypothyroidism.

The strength of the study is that a large number of pregnant women were recruited; this was a larger study compared to previous studies and the association between TAI and ID was also studied.

Limitations of the study: The results of the study are limited by the fact that it was a single-centre cross-sectional study.

Conclusion

The prevalence of hypothyroidism was very high in our setting compared to that seen in earlier published reports. There was no association found between hypothyroidism and ID in this study contrary to previous studies. There was no association found between TAI and ID in this study.

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