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Original Research Article

Thyroid dysfunction in preeclampsia and related fetomaternal outcomes

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ABSTRACT

Background: Changes in thyroid function in normal pregnancy are well-documented but in complicated pregnancy like preeclampsia, very little is known. Studies have shown evidences of hypothyroidism in preeclampsia necessitating thyroid function tests to be done in preeclampsia. The study was done to analyze the fetomaternal outcome of preeclampsia with coexisting thyroid dysfunction.
Methods: A cross-sectional analytical study was done over 18 months on 95 preeclamptic patients admitted at the antenatal ward and fetomaternal outcomes were analyzed according to thyroid status.
Results: Out of 95 patients with preeclampsia, 42 (44.2%) had thyroid dysfunction. Among these 42 patients, 37 (38.9%) patients had subclinical hypothyroidism, 4 (4.2%) had overt hypothyroidism and 1 (1%) had hyperthyroidism. Severe preeclampsia was seen in 64.3% of the patients with thyroid dysfunction compared with 39.6% in euthyroid patients. The mean thyroid stimulating hormone (TSH) level was significantly higher and means free thyroxine (fT4) level was significantly lower in severe preeclampsia compared with non-severe preeclampsia. Complications like abruption, intrauterine fetal death (IUD), intrauterine growth restriction (IUGR), oligohydramnios, preterm deliveries, postpartum hemorrhage (PPH), low birth weight babies, birth asphyxia in babies and subsequent neonatal intensive care unit (NICU) admissions were significantly higher ($p < 0.05$) in the preeclampsia patients with thyroid dysfunction in comparison with euthyroid ones.
Conclusions: Hypothyroidism may be a modifiable risk factor for preeclampsia. Thyroid screening early in pregnancy may be helpful in predicting the occurrence of preeclampsia and timely thyroid hormone administration can reduce the maternal and perinatal morbidity and mortality associated with preeclampsia.

Keywords: Fetomaternal outcome, Hypothyroidism, Preeclampsia

INTRODUCTION

Pregnancy is associated with maternal physiological adaptation of different organ systems which include circulatory, metabolic and endocrine changes.[1] Hypertensive disorders of pregnancy are one of the most significant and intriguing unsolved problems of obstetrics with preeclampsia being the most dangerous entity.

Preeclampsia can affect virtually every organ system and complicates 3-8% of pregnancies.[2] The risks posed by preeclampsia to the mother include placental abruption, cerebrovascular accidents, postpartum hemorrhage (PPH), pulmonary edema etc. and those to the fetus include intrauterine growth restriction (IUGR), intrauterine fetal demise (IUD), preterm birth (iatrogenic or spontaneous) and birth asphyxia.[3]

Thyroid hormone plays a role in placental development and is an important regulator of various metabolic and inflammatory processes. During normal pregnancy, changes in thyroid function are well-documented, but information about thyroid function in complicated pregnancy is scanty.

Maternal hypothyroidism is the most common disorder of thyroid function in pregnancy and is associated with fetal effects such as fetal loss, preterm birth, low birth weight, increased neonatal respiratory distress, low intelligence quotient (IQ) of off-springs and adverse maternal outcomes such as pregnancy induced hypertension, postpartum haemorrhage and placental abruption.[4] Although pregnancy is usually associated with mild hypothyroidism, preeclamptic patients have higher incidence of hypothyroidism that might correlate with the severity of the condition.[5]

The probable explanations for the association of preeclampsia with hypothyroidism have been found in many studies. Reduced thyroid hormones in preeclampsia have been explained to be due to the loss of thyrotropin and protein bound hormones in the urine.[6] Hypothyroidism can cause vascular smooth muscle contraction in systemic and renal vessels leading to increased diastolic pressure and peripheral vascular resistance thereby decreasing tissue perfusion.[7]

The present study was undertaken to determine the frequency of thyroid dysfunction in preeclamptic patients and analyze the consequent fetomaternal outcomes.

METHODS

A cross-sectional analytical study was conducted in the Department of Obstetrics and Gynecology, Regional Institute of Medical Sciences (RIMS), Imphal, Manipur from September 2016 to February 2018. Of all women attending the antenatal clinic, a total of 95 preeclamptic patients fulfilling the inclusion and exclusion criteria were recruited for the study.

Inclusion criteria

- Preeclamptic pregnant women between 18-45 years of age with more than 20 weeks of gestation admitted at the antenatal ward of the Department of Obstetrics and Gynecology, RIMS, Imphal, Manipur, India.

Exclusion criteria

- Age <18 years and >45 years
- Patients with gestational hypertension without proteinuria
- Women with history of chronic hypertension
- Other medical conditions like chronic kidney disease, chronic liver disease and autoimmune diseases.

After obtaining an informed written consent, a comprehensive history was taken from each patient followed by general physical and gynecological examination. All routine and specific investigations for preeclampsia were done. A fasting venous sample of 2ml was withdrawn by antecubital venepuncture for the estimation of serum levels of thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4).

The trimester specific normal range of TSH[8]

- First trimester: 0.1-2.5 mIU/L
- Second trimester: 0.2-3 mIU/L
- Third trimester: 0.3-3 mIU/L

According to the reports of the thyroid function tests or on the basis of history of thyroid disease already on medication or not, those preeclamptic patients were divided into 2 groups- one with thyroid dysfunction and the other euthyroid preeclamptic patients. The fetomaternal outcomes were determined and analyzed in both the above mentioned groups.

Statistical analysis

Data was analysed using SPSS version 21.0 IBM. Descriptive statistics like mean, percentage, standard deviation (SD) were used. For inferential statistics, Chi square test, Fisher's exact test and independent sample t-test were utilized and p value <.05 was taken as statistically significant.

RESULTS

Out of 95 preeclamptic patients, 42 (44.2%) were found to have thyroid dysfunction with 37 (38.9%) patients having subclinical hypothyroidism, 4 (4.2%) overt hypothyroidism and 1 (1%) hyperthyroidism (Table 1).

Table 1: Distribution of patients according to thyroid status.

Thyroid status	No. of patients (n=95)	%
Euthyroid	53	55.8
Thyroid dysfunction	42	44.2
Hypothyroid (subclinical)	37	38.9
Hypothyroid (overt)	4	4.2
Hyperthyroidism	1	1.1

Majority of the patients, that is, 62.3% of euthyroid preeclamptic patients and 57.1% preeclamptic patients with thyroid dysfunction were in the age group of 26-35 years respectively. There was no statistical significance in the age distribution in the two groups (p=0.375). The mean age of patients with thyroid dysfunction was 29.86±5.68 years which was not statistically different

(p=0.470) from that of the euthyoid ones, that is, 30.70±5.55 years (Table 2).

Table 2: Age distribution of patients according to thyroid status.

Age in years	Thyroid status		Total (n=95)	p value
	Thyroid dysfunction (n=42)	Euthyroid (n=53)		
18-25	11 (26.2%)	8 (15.1%)	19 (20%)	0.375
26-35	24 (57.1%)	33 (62.3%)	57 (60%)	
36-45	7 (16.7%)	12 (22.6%)	19 (20%)	
Chi-Square Test				

Nullipara accounted for 45.2% of the preeclampsia patients with thyroid dysfunction and 45.3% of euthyroid preeclampsia patients. There was no statistically significant difference in parity (p=.068) in the two groups (Table 3).

Table 3: Parity distribution in relation to thyroid status of patients.

Variables	Thyroid status		Total (n=95)	p value
	Thyroid dysfunction (n=42)	Euthyroid (n=53)		
Para 0	19 (45.2%)	24 (45.3%)	43 (45.3%)	0.068
Para 1	14 (33.3%)	14 (26.4%)	28 (29.5%)	
Para 2	5 (11.9%)	15 (28.3%)	20 (21.1%)	
Para 3	2 (4.8%)	0 (0%)	2 (2.1%)	
Para 4	2 (4.8%)	0 (0%)	2 (2.1%)	
Chi-Square/Fisher's Exact Test				

It was found that severe preeclampsia was seen in 64.3% of the patients with thyroid dysfunction compared with 39.6% in euthyroid patients which was statistically significant (Table 4).

Table 4: Distribution of severity of preeclampsia in relation to thyroid status of patients.

Severity of preeclampsia	Thyroid status		Total
	Thyroid dysfunction	Euthyroid	
Non severe	15 (35.7%)	32 (60.4%)	47 (49.5%)
Severe	27 (64.3%)	21 (39.6%)	48 (50.5%)
Total	42 (100%)	53 (100%)	95 (100%)
p=0.0017, Chi-Square Test			

The mean TSH level was significantly higher and mean free T4 level was significantly lower in the preeclamptic patients having severe disease than those without severe features. Mean free T3 level did not differ significantly in the two groups (Table 5).

Antenatal complications [placental abruption, anaemia, gestational diabetes mellitus (GDM), IUD, IUGR, oligohydramnios, premature rupture of membrane (PROM), disseminated intravascular coagulation (DIC), pulmonary edema, etc] were seen in 76.2% of preeclampsia patients with thyroid dysfunction compared with 50.9% of euthyroid preeclamptic patients which was statistically significant (Table 6). Abruption was seen in 9.5% preeclampsia patients with thyroid dysfunction compared to 5.7% in the euthyroid group. IUD was seen in 7.1% patients with thyroid dysfunction and in 3.8% euthyroid patients. Oligohydramnios was seen in 4.8% of preeclampsia patients with thyroid dysfunction compared to 3.8% euthyroid patients. Pulmonary edema was found in 4.8% patients with thyroid dysfunction whereas it was not found in euthyroid preeclampsia patients. DIC and septic shock were however not noted in patients with thyroid dysfunction but each of them was present in 1.1% euthyroid patients.

Table 5: Comparison of the mean fT3, fT4 and TSH among severe and non-severe preeclampsia.

Thyroid status	Severe preeclampsia n=48	Non-severe Preeclampsia n=47	p-value
fT3(pg/mL)	1.617±0.82	1.82±0.90	.43
fT4(pg/mL)	0.80±0.31	1.09±0.53	.02
TSH(mIU/L)	6.49±3.24	4.46±2.71	.02
Independent sample t-test			

Table 6: Antenatal complications in relation to thyroid status of patients.

Antenatal complications	Thyroid status		Total (n=95)
	Thyroid dysfunction (n=42)	Euthyroid (n=53)	
Nil	10 (23.8%)	26 (49.1%)	36 (37.9%)
Yes	32 (76.2%)	27 (50.9%)	59 (62.1%)

p= 0.012, Chi-Square Test

Table 7: Period of Gestation (POG) at delivery according to thyroid status.

POG at delivery	Thyroid status		Total
	Thyroid dysfunction	Euthyroid	
<37 weeks	19 (45.2%)	14 (26.4%)	33 (34.7%)
37-40 weeks	22 (52.4%)	34 (64.2%)	56 (58.9%)
>40 weeks	1 (2.4%)	5 (9.4%)	6 (6.3%)
Total	42 (100%)	53 (100%)	95 (100%)
p= 0.099, Fisher's Exact Test			

It was observed that 45.2% of preeclamptic patients with thyroid dysfunction had preterm deliveries compared with only 26.4% in euthyroid patients though not statistically significant (p=.099, Table 7). Complications were noted in 45.2% of preeclampsia patients with thyroid dysfunction compared with only 15.1% euthyroid

patients and this difference was found to be statistically significant (p=.001).

Table 8: Intraoperative/intrapartum complications in relation to thyroid status.

Intraoperative/ intrapartum complications	Thyroid status		Total (n=95)
	Thyroid dysfunction (n=42)	Euthyroid (n=53)	
Nil	23 (54.8%)	45 (84.9%)	68 (71.6%)
Yes	19 (45.2%)	8 (15.1%)	27 (28.4%)
Atonic PPH	18 (42.9%)	7 (13.2%)	25 (26.3%)
Biood transfusion	18 (42.9%)	8 (15.1%)	26 (27.4%)
ICU admission	1 (2.4%)	0 (0%)	1 (1.1%)
Peripartum hysterectomy	0 (0%)	2 (3.8%)	2 (2.1%)
Morbidly adherent placenta	0 (0%)	1 (1.9%)	1 (1.1%)
p=0.001, Chi-Square Test			

Table 9: Distribution of birth weight of babies in relation to thyroid status of mothers.

Birth weight (kg)	Thyroid status		Total
	Thyroid dysfunction	Euthyroid	
<2.5	26 (61.9%)	17 (32.1%)	43 (45.3%)
≥2.5	16 (38.1%)	36 (67.9%)	52 (54.7%)
Total	42 (100%)	53 (100%)	95 (100%)
p<0.005, Chi-square test			

Low birth weight babies were born in 61.9% of preeclamptic mothers with thyroid dysfunction compared with 32.1% of the euthyroid mothers which was statistically significant (p< .005, Table 9).

Table 10: Apgar score of babies in relation to thyroid status of mothers.

Apgar score at 5 minutes	Thyroid status		Total
	Thyroid dysfunction	Euthyroid	
<7	17 (40.5%)	9 (17%)	26 (27.4%)
≥7	25 (59.5%)	44 (83%)	69 (72.6%)
Total	42 (100%)	53 (100%)	95 (100%)
p=0.011, Chi-Square Test			

It was also found that 40.5% of preeclamptic mothers with thyroid dysfunction gave birth to babies with Apgar score less than 7 at 5 minute of birth compared with only 17% of euthyroid preeclamptic mothers and the difference was statistically significant (p= .011, Table 10). Moreover, 45.2% of the babies of preeclamptic mothers with thyroid dysfunction were admitted at NICU at birth compared only 13.2% of babies of euthyroid mothers and the difference was statistically significant (p<.001).

DISCUSSION

Preeclampsia is a multisystem disorder of unknown aetiology unique to human pregnancy. It may be associated with hypothyroidism that carries a higher risk of adverse obstetric outcomes. A number of biochemical markers have been proposed to predict preeclampsia but with inconsistent reliability and poor predictive value for routine use. Understanding the frequency of thyroid dysfunction in preeclampsia and its impact on fetomaternal outcomes may be helpful in predicting the occurrence and severity of preeclampsia.

A total of 95 preeclamptic patients were studied in the present study; out of which 42 (44.2%) were found to have thyroid dysfunction with 37 (38.9%) patients having subclinical hypothyroidism and 4 (4.2%) patients with overt hypothyroidism and 1 (1%) hyperthyroidism. Bankowska EM et al, found that 78.2% of patients with pregnancy induced hypertension had thyroid dysfunction and concluded that subclinical hypothyroidism as the most common thyroid dysfunction in the tested group supporting the findings of the present study.[9] Kharb S et al, also observed that 55% of preeclamptic patients had hypothyroidism.[10] Deshpande S et al, also found that there was a significant association between preeclampsia and thyroid hypofunction (p= .0406).[11] However, contrary to this, thyroid function changes were not found in preeclamptic patients in the study of Khadem M et al.[12]

In the present study, majority of the patients i.e 57.1% of the preeclamptic patients with thyroid dysfunction and 62.3% of euthyroid preeclampsia patients were in the age group of 26 to 35 years. Nulliparity accounted for 45.2% of the preeclamptic women with thyroid dysfunction and 45.3% of the euthyroid ones. There was no significant difference in age and parity in the two groups showing that both the groups were comparable. This can be explained by the fact that in our institution, most of the patients getting admitted and delivered are nulliparous and primigravidae. The numbers of multiparous and especially grand multiparous women are reducing due to increased use of family planning techniques. As a whole, 45.3% of the preeclamptic patients were nulliparous which is supported by other studies like Singh A et al, who reported nulliparity as a risk factor for severe preeclampsia.[13]

Severe preeclampsia was seen in 64.3% of the patients with thyroid dysfunction compared with 39.6% in the euthyroid patients which was found to be statistically significant. Similarly, Kharb S et al, and Wilson KL et al, found a significant association between severity of

preeclampsia and hypothyroidism.[10,14] Kharb S et al, also found that preeclamptics with raised TSH levels had significantly higher mean arterial pressure as compared with preeclamptic patients with normal TSH levels (p<.001).[10] There are a number of observations that support the biological plausibility of this association. These include the cardiovascular effects of abnormal concentration of thyroid hormones like ventricular hypertrophy leading to heart failure.[15] These aberrations follow long term exposure to excessive or decreased thyroid hormones.[16] Subclinical hypothyroidism might cause endothelial dysfunction characterised by diminished nitric oxide production with impaired vasorelaxation which might cause hypertension.[17] Hypothyroidism might also cause vascular smooth muscle contraction, leading to increased diastolic hypertension, peripheral vascular resistance and decreased tissue perfusion.[18]

In the present study, the mean S.TSH level was significantly higher and mean free T4 level was significantly lower in the preeclamptic patients having severe disease than those without severe features. Mean free T3 level did not differ significantly in the two groups. Thus, thyroid hormone level might be correlated with the occurrence of preeclampsia and also with its severity. Kharb S et al, reported that there was a state of biochemical hypothyroidism that correlated with severity of preeclampsia and influenced obstetric outcome in women with preeclampsia.[10] Despande S et al, also reported that severe preeclampsia patients had 2.87 times more chances of thyroid hypofunction.[11] Wilson KL et al, reported that women with subclinical hypothyroidism in pregnancy have an increased risk of severe preeclampsia when compared with euthyroid women.[14] In contrast, Sheela SR et al, reported that changes in the thyroid hormones did not correlate with the severity of preeclampsia.[19]

It was observed that antenatal complications like abruption, anemia, GDM, IUD, IUGR, oligohydramnios, PROM, DIC, pulmonary edema were seen in 76.2% of preeclampsia patients with thyroid dysfunction compared with 50.9% of euthyroid preeclampsia patients which was found to be statistically significant (p= .012). Abruption was seen in 9.5% preeclampsia patients with thyroid dysfunction compared to 5.7% in the euthyroid group. IUD was seen in 7.1% patients with thyroid dysfunction and in 3.8% euthyroid patients.

Sravani M et al, found that in hypothyroid women with hypertension, abruption was seen in 6%, IUD in 10% and IUGR in 14% of the patients supporting the findings of our study.[20] These findings suggest that thyroid dysfunction in preeclampsia has a role to play in increasing the complications associated with it significantly needing timely detection and treatment for better outcomes.

In the present study, 45.2% preeclampsia patients with thyroid dysfunction had preterm delivery which was more than that in euthyroid patients (26.4%). Sravani M et al, also found higher incidence of preterm deliveries (10%) in patients with hypothyroidism complicated with hypertension.[21] This may be secondary to the increased severity of preeclampsia associated with raised thyrotropin levels as found in the above-mentioned studies and thus increasing the neonatal morbidity due to prematurity.

Intrapartum or intraoperative complications like atonic PPH, blood transfusions, ICU admission were noted in 45.2% of the preeclampsia patients with thyroid dysfunction compared with only 15.1% euthyroid patients and this difference was found to be statistically significant (p=.001) which can be explained by the increased occurrence of antenatal complications and need for emergency LSCS in the women with thyroid dysfunction than the euthyroid ones.

Low birth weight babies were seen in 61.9% of preeclamptic mothers with thyroid dysfunction which was significantly more than that seen in euthyroid mothers (32.1%). Similarly, Sardana D et al, found a significant negative correlation between birth weight and TSH level (p<.001) in patients with preeclampsia.[21] Kharb S et al, found that birth weight was significantly lower in preeclamptic women having high TSH levels as compared to euthyroid preeclampsia patients (p<.001) and commented that this might be explained by placental dysfunction in preeclamptic patients causing failure in estrogen production, leading to a decrease in TBG, total T3 and total T4 levels with simultaneous growth failure of the fetus.[10]

In the present study, 40.5% of the patients with thyroid dysfunction had babies with Apgar score less than 7 at 5 minute of birth compared with only 17% of the babies of euthyroid mothers. Again, 45.2% of the babies of preeclamptic mothers with thyroid dysfunction were admitted at NICU at birth compared with only 13.2% of babies of euthyroid mothers. These findings showed the unfavourable outcomes of preeclampsia complicated with thyroid dysfunction. Sunanda K et al, also found that preeclamptic patients with raised TSH had increased perinatal mortality and morbidity in terms of abnormal Apgar score at birth and NICU admissions compared with euthyroid preeclamptic patients.[5]

CONCLUSION

Preeclamptic patients with thyroid dysfunction were found to be at greater risk of adverse fetomaternal outcomes like preterm delivery, abruption, IUGR, IUD, PPH, low birth weight babies, birth asphyxia and subsequent NICU admission than euthyroid preeclampsia patients.

Thus, hypothyroidism may be a modifiable risk factor for preeclampsia. Thyroid screening early in pregnancy may be helpful in predicting the occurrence of preeclampsia, and undertaking timely interventions and appropriate measures in terms of possible thyroid hormone administration to reduce the severity of the morbidity and mortality associated with preeclampsia. However, to conclusively prove the hypothesis of our study, randomized controlled trials with larger sample size are required.

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