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A Comparative Study of Thyroid Function in Non-Severe and Severe Preeclampsia in a Hospital Based Study in Manipur

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Abstract: Several studies from different parts of India reported increased TSH in preeclampsia and variable FT3 and FT4 levels. Also, the association between thyroid hormones and severity of preeclampsia are less well studied. This case control study aims to measure thyroid hormones level in non-severe and severe preeclampsia in RIMS, Manipur on 45 diagnosed case of preeclampsia and 46 healthy normotensive pregnant women in the age group of 18-40 years and >20 weeks gestation. Preeclamptic women were grouped as non-severe (n=23) and severe (n=22). Thyroid hormone assay was done by ELISA. Comparison was done by unpaired t-test and correlation by Pearson correlation test. A *p*-value less than 0.05 were considered significant. The TSH level in severe preeclampsia (6.49±3.24) compared to non-severe preeclampsia (4.46±2.71)(p=0.02) was significantly higher and FT4 (0.80±0.31 vs 1.09±0.53)(p=0.02) was significantly lower in severe preeclampsia. FT3 (1.61±0.82 vs 1.82±0.90) (p=0.43) of severe preeclampsia was non-significantly lower compared to non-severe preeclampsia. The TSH level in preeclamptic patients were significantly higher (5.50 ± 3.12 mIU/L) compared to normotensive pregnancy (2.03 ± 0.78 mIU/L)(p=0.0001). FT4 (0.94 ± 0.45ng/dl, 0.94 ± 0.34 ng/dl) (p=0.99) showed no change in preeclampsia and FT3 (1.71 ± 0.86 pg/ml, 1.73 ± 0.83 pg/ml) (p=0.92) was non-significantly lower in preeclampsia compared to normal pregnancy. This suggests the role of TSH in the pathogenesis and development of severity of preeclampsia. Early detection of thyroid abnormalities may help in better management of the disease in established preeclamptic women.
Keywords: TSH, FT3, FT4, ELISA, severity preeclampsia.

INTRODUCTION

Preeclampsia is best described as a pregnancy specific syndrome that can affect virtually every organ system [1]. In India, it affects approximately 5-15% of all pregnancies [2]. Preeclampsia is defined by National High Blood Pressure Education Program Working Group as a blood pressure ≥140/90mmHg measured twice 4-6 hours apart and 24 hours proteinuria ≥300gm/day or a protein: creatinine ratio of ≥ 0.3 and onset at >20 weeks gestation in previously normotensive non proteinuric pregnant women.

According to the recommendations of the Task Force on Hypertension in Pregnancy convened by the American College of Obstetrics and Gynaecologists [14] preeclampsia is classified into nonsevere preeclampsia ("mild" and "moderate") and severe preeclampsia. Non- severe classification includes mild and moderate but these have not been specifically defined. Criteria for severe preeclampsia include DBP≥100mmHg, SBP≥160mmHg, proteinuria none to positive, presence of headache, visual disturbances, upper abdominal pain, oliguria, convulsion, elevated serum creatinine, thrombocytopenia, marked elevation of serum transaminase, obvious fetal growth restriction and presence of pulmonary edema[3].

Pre-eclampsia is a multisystem disorder of unknown cause that is unique to human pregnancy. Numbers of biochemical markers have been proposed to predict which women are likely to develop preeclampsia. However, data for the reliability of these markers in indicating preeclampsia have been inconsistent, and many markers are not specific or predictive enough for routine use in clinical practice [4].

Pregnancy is usually associated with very mild hyperthyroxaemia [1]. Thyroid stimulating hormone (TSH) decreases during the first half of pregnancy due

to negative feedback from peripheral T3 and T4 secondary to thyroid gland stimulation by human chorionic gonadotropin (hCG)[5].

The association between thyroid hormones and severity of preeclampsia is not well studied. Conflicting reports are found in the literature regarding thyroid hormones level in severe and non-severe preeclampsia. It has been suggested that there may be an existence of mutual influences between preeclampsia and thyroid function.

Therefore, the present study was aimed to compare thyroid function in non-severe and severe preeclampsia in a hospital based study in RIMS, Manipur (India).

EXPERIMENTAL SECTIONS/ MATERIALS AND METHODS

It was a case control study carried out in the Department of Physiology in collaboration with the Department of Obstetrics & Gynecology, Regional Institute of Medical Sciences, Manipur (Impalal) from January 2016 – October 2017. The study consisted of 45 diagnosed case of preeclampsia and 46 healthy normotensive pregnant women in the age group of 18-40 years and >20 weeks gestation. Preeclamptic women were grouped as nonsevere (n=23) and severe (n=22).

Inclusion Criteria

Includes diagnosed case of preeclampsia between 18-40 years of age and >20 weeks gestation, history of iodised salt intake and healthy pregnant women between 18-40 years and >20 weeks gestation

Exclusion criteria

Includes history of thyroid dysfunction /thyroid surgery, multiple gestation, diabetes/ chronic liver/ kidney disease/ chronic hypertension and history of intake of any medications that might affect thyroid function.

After written informed consent, 2ml of venous blood was drawn. Serum obtained was centrifuged and stored at 2º to 8º C. Estimation of serum FT3, FT4 and TSH was done using BioChek, Inc Enzyme Immunoassay (ELISA) method. Data was analyzed using Statistical package for the social sciences (SPSS) software version 21. Descriptive statistics like Mean, SD and Percentages were used. Independent t test was used to test significance between two means. Pearson correlation test was used to test correlation between severity of preeclampsia and thyroid hormone levels. P value of <0.05 was taken statistically significant. Study was conducted after approval from the Research Ethics Board, Regional Institute of Medical Sciences (RIMS), Imphal.

RESULTS

This study was conducted among 91 pregnant women of which 45 were preeclamptic and 46 were normotensive. Among the preeclamptic pregnant women, 23 were non-severe preeclamptic and 22 were severe preeclamptic.

Table no.1 shows the characteristics of the study population in normotensive pregnancy and preeclampsia. Statistically significant higher systolic blood pressure (SBP), diastolic blood pressure (DBP) and BMI were found in preeclamptic cases when compared to normotensive women. However, gestational weeks, age and parity shows no significant differences. The study is gestational weeks, age and parity matched.

Table-1: Characteristics of the study population in normotensive pregnancy and preeclampsia

Characteristics (mean±SD)	Normotensive (n=46)	Preeclampsia (n=45)	P-value
SBP (mmHg)	112.43±9.66	164.40±21.98	0.00***
DBP(mmHg)	71.69±7.89	105.55±6.92	0.00***
BMI (Kg/m^2)	25.83±3.08	28.91±3.62	0.00***
Duration of pregnancy (weeks)	33.4±3.55	34.7±4.26	0.11
Age (years)	27.98±5.08	30.18±6.34	0.07
Parity	1.72±0.45	1.71±0.45	0.94

***p<0.001: Highly Significant.

Table no.2 shows serum TSH, FT3 and FT4 level comparison between preeclampsia and normotensive pregnancy. Statistically significant higher TSH and a non-significant lower FT3 and no change in FT4 were found in preeclampsia compared to normotensive pregnancy.

Table-2: Comparision of TSH, FT3 and FT4 between normotensive pregnancy and preeclampsia (Mean±SD)

Parameters	Normotensive (n=46)	Preeclampsia (n=45)	P-value
TSH (mIU/ml)	2.03±0.78	5.50±3.12	0.00***
FT3 (pg/ml)	1.73±.83	1.71±0.86	0.92
FT4 (ng/dl)	0.94±0.34	0.94±0.45	0.99

***Preeclampsia compared to normotensive p<0.0001

Table no.3 shows serum TSH, FT3 and FT4 level comparison between non-severe and severe preeclampsia. Statistically significant higher TSH and lower FT4 were found in severe preeclampsia when compared to non-severe preeclampsia.

Table-3: Comparision of TSH, FT3 and FT4 between non-severe and severe preeclampsia (Mean±SD)

Parameters	Non severe (n=23)	Severe (n=22)	P-value
TSH (mIU/ml)	4.46±2.71	6.49±3.24	0.02*
FT3 (pg/ml)	1.82±0.90	1.617±0.82	0.43
FT4 (ng/dl)	1.09±0.53	0.80±0.31	0.02*

* Severe preeclampsia compared to nonsevere p<0.05

Table no. 4 shows correlation between severity of preeclampsia and thyroid functions. TSH showed significant positive correlation with severity. FT4 showed significant negative correlation with severity. FT3 failed to show any significant correlation.

Table-4: Correlations between severity of preeclampsia and Thyroid functions

Correlations between Severity and Thyroid functions						
Parameter	Serum FT3		Serum FT4		Serum TSH	
	r	p	r	p	r	P
Severity	-0.100	0.51	-0.351	0.01*	0.364	0.01*

* Correlation is significant at the 0.05 level (2 tailed)
Pearson Correlation (r) test

DISCUSSION

In a study by Kumar S [6] on same ethnic population on thyroid hormone levels across different trimesters, it was reported that statistically significant increase in mean TSH was seen in second and third trimester. Due to increased thyroxine requirement and reduced availability of iodine during pregnancy, the TSH levels are raised to meet the increased demand.

In the present study, it was observed that TSH was higher in preeclampsia which was statistically significant and serum FT3 and FT4 did not differ significantly between preeclampsia and normotensive pregnant women. Similar findings in agreement with the present study were reported in earlier studies by Levine RJ *et al*.[1] , Manjunatha S *et al*.[7], Kumar A *et al*.[8], Satyanarayan K A *et al*.[9].

The effect of pre-eclampsia on thyroid function may be mediated by sFlt-1(soluble fms-like tyrosine kinase-1). These sFlt-1 acts by inhibiting Vascular Endothelial Growth Factor (VEGF) and placental growth factor (PIGF) signalling, preventing their role in endothelial preservation. The presence of this protein creates an angiogenically imbalanced vascular environment and contributes to the endothelial insult occurring in preeclampsia [1].

Reduced thyroid hormones had been postulated to be due to the loss of protein bound hormones in the urine and TSH is acting as a tissue specific angiogenesis [7]. Alteration in thyroid hormones were due to stress factor, decreased plasma albumin concentrations, Nitric Oxide that regulates secretion of thyroid hormones by modulating regional blood flow and faulty estrogen production due to placental dysfunction in preeclampsia[8]. Hypothyroidism can cause vascular smooth muscle contraction both in systemic and renal vessels, which leads to increased diastolic hypertension, peripheral vascular resistance, and decreased tissue perfusion[9].

Elhaj ET *et al*. [10] reported significantly lower mean TSH and significantly higher FT3 and FT4 in preeclampsia compared to normotensive pregnant women. No changes in serum TSH, FT3 and FT4 have been reported by Dekker RR *et al*.[11] and Qublan HS *et al*.[12]. These differences with the present study may be due to different geographical areas, ethnicity and diet.

It was also observed that the mean TSH was significantly higher and FT4 was significantly lower in severe preeclampsia when compared to non-severe preeclampsia. FT3 showed no significant changes.

Similar findings in agreement with the present study were reported in earlier study by Basbug M *et al*.[13] and Kharb S *et al.* [14]. Despande S *et al.* [2] reported that preeclampsia group have chance of higher TSH (>4.8 mIU/L) by 2.19 times (95% confidence intervals= 1.0223 –4.6934). The association between severity of pre-eclampsia and thyroid hypofunction (subclinical and overt hypothyroidism) was found to be statistically significant (p= 0.02717). Odds ratio indicating that severe preeclampsia group have 2.87 times more chance of thyroid hypofunction. Wilson KL *et al*.[15] reported there was a significant association between subclinical hypothyroidism and severe preeclampsia (adjusted odds ratio 1.6, 95% confidence interval 1.1-2.4; p=.03).

In contrast, Al-Naqeeb AA [16] reported significantly higher TSH and FT4 in mild preeclampsia

when compared to severe preeclampsia. Sheela SR *et al*.[17] reported that changes in the thyroid hormones did not correlate with the severity of preeclampsia between mild and severe pre-eclampsia groups. Thyroid hormones level might be correlated with occurrence of severity of preeclampsia.

The limitations of the study were that fasting was not mandatory for pregnant participants in our study. Although fasting is not necessary for thyroid tests and the reference interval for pregnant woman has been used regardless of the fasting status, a preanalytical factor related to the fasting status has been proposed to affect the results. Thyroid hormone levels were measured irrespective of antihypertensive medication status. Some studies reported that antihypertensive therapy with alpha-methyldopa may have an effect on the synthesis and/or release of placental proteins in pregnancies complicated by preeclampsia and that this effect may be independent of its known antihypertensive action. Baseline thyroid profile in the study population was not undertaken. However, in our previous study by Kumar S *et al*.[6] on the same ethnic population, it was found that in the second and third trimesters the mean values of thyroid function tests were within the normal range.

CONCLUSION

This study shows that the mean TSH value was significantly higher and the mean FT4 value was significantly lower in severe preeclampsia when compared to non-severe preeclampsia. Also, mean TSH value was significantly higher in preeclamptic women compared to normotensive pregnancy. This suggests the role of TSH in the pathogenesis and development of severity of preeclampsia. Early detection of thyroid abnormalities may help in better management of the disease in established preeclamptic women.

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