ORIGINAL RESEARCH

Study of maternal thyroid hormone status in preeclampsia and normal pregnancy

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ABSTRACT
Aim: The present study is being done to evaluate thyroid hormones status in normal pregnancy andpreeclamptic women and correlate it with the severity of preeclampsia.**Materials and Methods:** A case control study was done on age and parity matched 100 preeclamptic women and 100 normotensive women in their third trimester. Serum free T3, T4, TSH were evaluated in both the groups. Their prevalence and their association with the severity of pre-eclampsia was also seen.**Results:** Most of the patient in cases group were primigravida i.e.,-53% vs 43% in controls. In this study, Prevalence of thyroid dysfunction in preeclamptic women is 48%.Among these patients, 42% patients had subclinical hypothyroidism, 4% had over thypothyroidism and 2% had hyperthyroidism. Severe preeclampsia was seen is 17 (17%) patients, out of which 10 (58.8%)were subclinical hypothyroid, 3 (17.6%) were overt hypothyroid and 1 (0.05%) was of hyperthyroid. The mean TSH value in the preeclamptic group (PE) is more than the controls in our study (2.91±1.69 Vs 2.33 ± 1.33) and is significant (p=0.007) The mean free T4 values in our study in preeclampsia Vs controls is 0.97 ±0.29 Vs1.07 ±0.40 which is significant.**Conclusions:** Hypothyroidism maybeamodifiableriskfactorforpreeclampsia. Maternal markers of hypothyroidism should be controlled at early stages of pregnancy to minimize risk for not only hypothyroidism but also for development of preeclampsia.

Key words: Hypothyroidism, preeclampsia

INTRODUCTION

Thyroid dysfunction is one of the commonest endocrine disorders encountered duringpregnancy after diabetes mellitus. Pregnancy develops major changes in hypothalamic pituitary thyroid axis, iodine metabolism and the immune function. During pregnancy, there is an increased thyroid demand and increased iodine uptake and synthesis of thyroid hormones. Estrogen induces a rise in serum TBG and the placenta releases several thyroid stimulatory factors in excess. e.g., hCG. Alpha subunit of hCG is identical to that of TSH and has weak thyrotropic activity. The proper maternal thyroid function is important for both mother and fetus, especially during early pregnancy.Thyroid dysfunction during pregnancy has been shown to be associated with a number of adverse outcomes that can have an important consequences as much for the mother as for the fetus e.g. Spontaneous abortion, placental insufficiency, hypertension, anemia, postpartum hemorrhage and increased frequency of low birth weight and congenital malformation. Although, pregnancy is usually associated with very mild hyperthyroxinemia which is the presence of a free thyroxin (FT4) value above the 2.5thpercentile with a thyrotropin (TSH) level within the reference range. Women complicated with preeclampsia have high incidence of hypothyroidism that might correlate with the severity of preeclampsia. Preeclampsia is a pregnancy specific syndrome defined as: a disorder of widespread vascular endothelial malfunction and vasospasm that occurs after 20 weeks gestation and can present as late as 4-6 weeks postpartum. It is clinically presented by new onset hypertension and proteinuria, with or without pathologic edema. It can affect virtually every organ system and it continues to be a leading cause of maternal morbidity and perinatal morbidity and mortality especially in developing countries. Hypothyroidism has been observed as one of the causes of high blood pressure. 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. In preeclampsia, there is failure of oestrogen production and placental dysfunction resulting in low levels of TBG, TT3, TT4. In preeclampsia, an increase in the superoxide anion, which may inactivate NO, leading to reduced relaxation and increased vasoconstriction. Experimental studies have indicated that release of NO is altered in hypothyroidism and the resulting endothelial cell dysfunction might be a pathogenetic mechanism for hypothyroidism in preeclampsia. In pre-eclampsia, the most affected organs are liver, kidneys and brain and due to autointoxication, functional disorders in these organ systems are evidential. As liver, kidneys and muscles are the main organs of peripheral deiodination of T4 to T3, the serum concentration of T4 and T3 may differ in pre-eclampsia than that of normal pregnancy.

MATERIALS AND METHODS

This prospective observational study was done in the department ofObstetrics and Gynecology, S.M.G.S (Shri Maharaja Gulab Singh) Hospital Jammu, over a period of one year from November 2021 to October 2022 after proper institutional ethical approval and informed written consents from the participants. It was a case control study where total 200 pregnant women in the third trimester were taken who were divided into two groups 100 preeclamptic women as cases and 100 healthy normotensive pregnant women as controls. Cases were enrolled according to the inclusion criteria-diagnosed case of preeclampsia, previously normotensive and exclusion criteria-previous H/O medical renal, metabolic, hepatic disease, endocrine disorders, RHD, chronic hypertension, women in first and second trimester of pregnancy, not on any chronic drugs, medication that might affect thyroid function, multiple gestation, molar pregnancy, history of thyroid surgery or treatment with radioactive iodine.

The Controls were the patients with matched age, parity, healthy normotensive pregnant women in the third trimester. Serum free T3, T4, TSH was evaluated in the diagnosed preeclamptic women. Further, depending upon the fT4 and fT3 values, all women were classified as Subclinical hypothyroidism, Euthyroid, Subclinical hypothyroidism, Overt hypothyroidism, Hyperthyroidism. Women were also classified according to the severity of pre-eclampsia into mild and severe. 10ml venous blood sample was taken from the cubital vein of preeclamptic women, after the diagnosis was made but before the initiation of the antihypertensive treatment, and before the delivery and each control subject as well for thyroid hormone analysis FT3, FT4, TSH. It will be measured using Chemiluminescent assay. All women were followed up through their antenatal, intrapartum and postpartum period. They will be especially observed for the development of the symptoms and signs of hypo/hyperthyroidism. Statistical comparison between cases and controls was done using Chi square test, student t test and p value below 0.05 was considered significant.

RESULTS

Most of the patients in the study ranged from 21- 30 years age group. There were increased number of cases in the age group 30-40 years compared to controls. The mean age in the study group was 27.3±5.19 vs 29±5.75 in the control group.

Table1: Obstretic history in the study group

OBS. Score	Cases	Controls
Primi	53	43
Multi with prev LSCS	22	19
Multi with prev NVD	17	31
Multi with prev abort	8	7
Total	100	100

There were more of primigravida both in case 53% and control 43% group than multigravidas.

Table2: Gestational Age at Admission

Gestational Age	Case	Controls
37-38	44	24
38-39	31	29
39-40+	25	47
Total	100	100

Most of the cases in the study were admitted prior to 38 weeks gestational age and in control group majority of them were admitted after 39 weeks. Also comparing entire population of patients, 34% were admitted at 37-38 weeks of gestation, followed by 30% at 38-39 weeks and 36% at 39-40 weeks.

Table3: Mode of Labour

Mode of Labour	Cases	Controls
Induction of Labour	46%	27%
Spontaneous Labour	32%	54%
Elective RPT LSCS before Labour	22%	19%

In this study induction of labour was done in 46% of study group compared to that of 27% in control group with significance p<0.005.

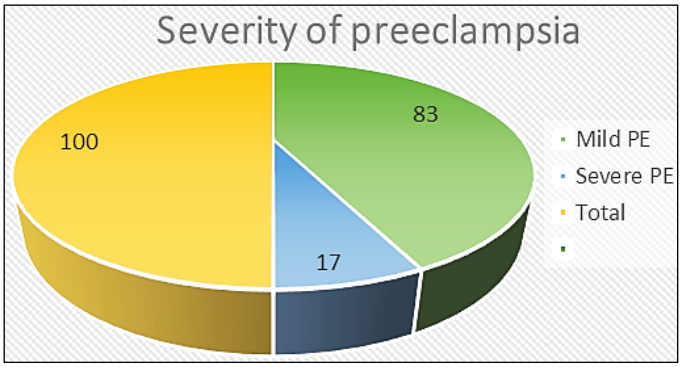

Fig1: Pie Chart Showing Severity of Preeclampsia

83% of cases had mild preeclampsia and were started on Tab Labetalol 100 mg BD, BP monitored twice daily, while Severe PE constituted 17% ofcases were started with drug regimen(Tab Labetalol 200 mg tds)and BP was monitored 4 hrly.

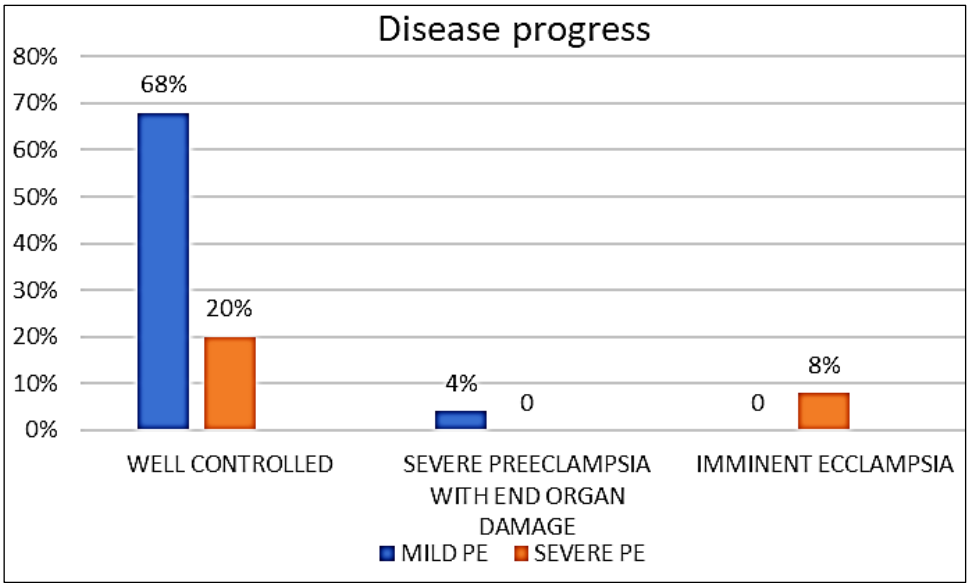

Fig2: Bar Diagram Showing Progression of Disease

Out of 17 severe PE patients 20% were controlled with drug, 8% developed features of imminent Eclampsia. In the Mild PE 68% of patients were controlled with anti-HT drugs, while 4% progressed to severe PE.

Table4:TSH, FT4 and FT3 Values

Mean ± SD	Cases	Control	p value
TSH	2.91±1.69	2.33±1.33	0.0076
FT3	3.04 ± 1.36	3.19± 1.44	0.44
FT4	0.97± 0.29	1.07±0.40	0.04

The mean TSH value in the preeclamptic group (PE) is more than the controls in our study (2.91±1.69 Vs 2.33 ± 1.33) and is significant (p=0.007) The mean free T4 values in our study in preeclampsia Vs

controls is 0.97 ±0.29 Vs1.07 ±0.40 which remains within the normal trimester specific range of FT4. However, the PE group had a mean FT4 level which was lower than the controls and the difference was significant statistically (p=0.04). The mean free T3 values in our study in preeclampsia Vs controls is (3.04±1.36 Vs 3.19±1.44). However, the difference is not statistically significant (p>0.05)

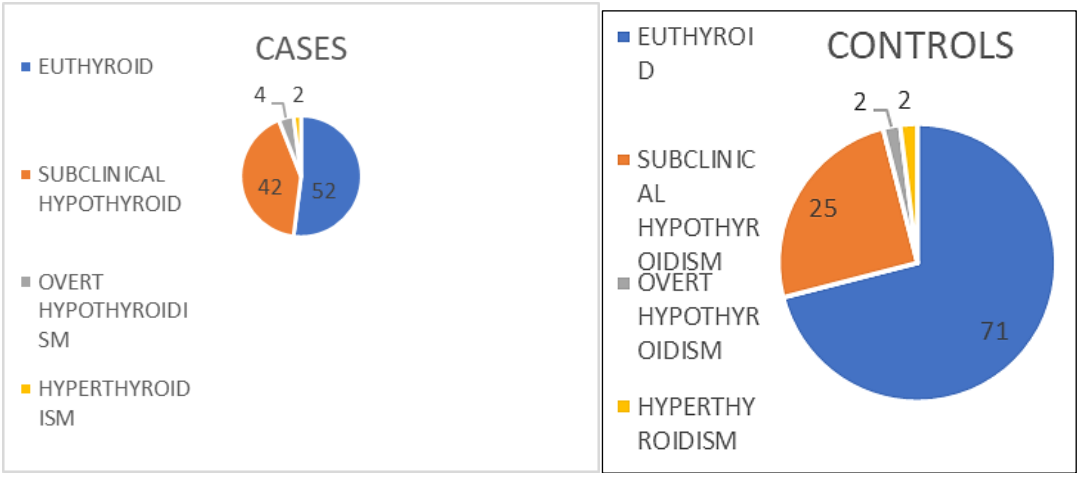

Fig3: Classification on the Basis of TSH Levels in Both Groups

The prevalence of thyroid dysfunction in preeclamptic women is 48%. The prevalence of subclinical hypothyroidism is 42% of Preeclampsia women and 25% of Normotensive women and Overt hypothyroidism contributing to 4% in Preeclamptic group while 2% in Normotensive group.

Table5: Prevalence

Classification	Frequency	Percentage
Euthyroid	123	62%
Subclinical Hypothyroidism	67	33.5%
Overt Hypothyroidism	6	3%
Hyperthyroidism	4	1.5%
Total	200	100%

This table shows the prevalence of hypothyroidism in the total study is 36.5%.Of the totally screened patients 33.5% of them are sub clinically hypothyroid, 3% of them are overt hypothyroid. Chi sq. & p value 0.04 which is significant. Only 1.5% are hyperthyroid.

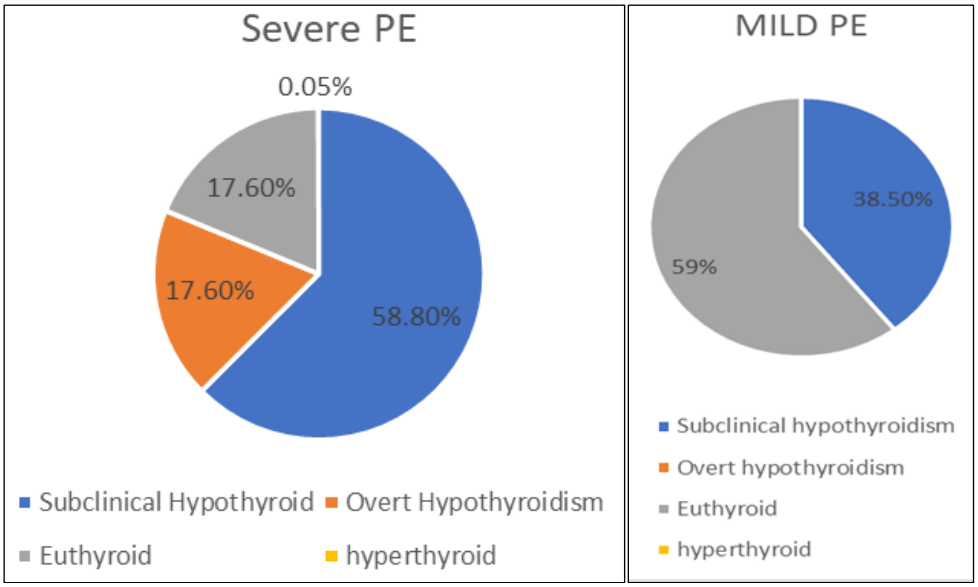

Fig4: Diagram Showing Correlation of Thyroid Status with Severity of Preeclampsia

In group of Severe PE, Subclinical hypothyroidism constitutes 58.8% (10 of 17 cases), overt hypothyroid were 17.6%(3of 17 case), Hyperthyroid were 0.05% (1 of 17 cases) and remaining were Euthyroid 17.6% (3 of 17cases). In group of mild PE(59% are Euthyroid, and 38.5% are Subclinical hypothyroid, 0.012% are overt hypothyroid and 0.012% are hyperthyroid. Thus, comparing the Severe PE and Mild PE groups incidence of Subclinical hypothyroidism is more in Severe PE than in mild PE (58.8% vs 38.5%) and is statistically significant ($p<0.005$).

DISCUSSION

The prospective case control observational study was conducted on 200 pregnant women in their third trimester who attended Obstetrics OPD or were admitted in labour room of the department at the post graduate department of Obstetrics and Gynaecology, SMGS Hospital Government Medical College, Jammu from November 2021 to October 2022. The patients were divided into two groups; one group containing 100 preeclamptic patients and the control group of 100 normotensive subjects. Maternal thyroid status via serum TSH, FT4, FT3 was studied in both the groups.The patients were followed up till the termination of pregnancy and outcome of the study was assessed. The age distribution of patients included in our study ranged from 18 to 40 years. Majority of them belonged to the 21-30 years in both the groups. The mean age of the patients in study and control group was 29±5.75 and 27.3±5.19 years respectively, which was comparable and statistically significant($p=0.05$). In a similar study done by Ashokkumar *et al*. (2005), comparing preeclamptics with normotensive women, the mean (± SD) age of the study group and the control group was 28.4 ± 6.24 years and 27.5±5.91 years respectively which is quite similar to our study. The mean (± SD) parity of the study group and the control group were25±19.5 and 25±15.4 respectively and there was no significant difference between the two groups ($p>0.05$). Comparing the two groups, preeclamptic women group consisted of more primigravia compared to normotensive women (53% vs 43%). The results were similar to the findings of Khanam M*et al*. (2013) that the mean (±SD) parity of the study group and the control group were 1.28± 0.90 and 1.30± 0.88 respectively and there was no difference between two group ($p> 0.05$). In this study the mean (±SD) gestational age at the time of admission was 38.3 ± 0.81 in the study group and 38.7 ± 0.81 was in the control group. The difference between the groups was statistically significant ($p<0.05$). Similarly, Kharb *et al*. (2013) found that the mean (± SD) gestational age was 37.7± 1.7 in the cases and 39.03± 1.3 in the control group, which was statistically significant.

The mean TSH value in the preeclamptic group is more than the controls in our study (2.9±1.69 Vs 2.33 ± 1.33) and is statistically significant ($p=0.007$). The mean free T4 values in our study in preeclampsia Vs controls is 0.97±0.29 Vs 1.07 ±0.40 which remains within the normal trimester specific range of FT4 ($p<0.05$). However, the PE group had a mean FT4 level which was lower than the controls and the difference was significant statistically ($p =0.04$). The mean free T3 values in our study in preeclampsia vs controls is (3.04±1.36 Vs 3.19±1.44) and not significantly significant ($p>0.05$). In a study done by, B Shanthirani*et al*. (2021) the mean TSH value in the preeclampsia group is more than the controls in our study (2.4 ± 1.3 vs. 1.8 ± 0.9) and the PE group had a mean FT4 level lower than the controls (0.93 ± 0.28 versus 1.07 ± 0.33) and the difference was statistically significant ($P < 0.0001$) which is comparable to our study. In another Indian study by Khaliq f *et al*. (1999) where mean TSH titres in the preeclamptic pregnancies has been reported to be 3.8±0.53mIU/ml while in the normal pregnancies it was 2.3±0.24mIU/ml which again is comparable to the present study. In the calcium for preeclampsia prevention cohort, the mean TSH values were increased 2.42 times above baseline in the PE group as compared with a1.48 times increase in controls (Richard J Levin *et al*. 2009). This study thus suggests PE as a possible risk factor for hypothyroidism and the mechanisms could be one mediated through s-fms like tyrosine kinase. On the other hand there are few studies arguing against any relationship between hypothyroidism and preeclampsia and one of them is a study done by Qublan*et al*. (2003) where he observed no significant difference in the levels of FT4, FT3 and TSH between normal pregnancy and pre-eclamptics, therefore concluded that thyroid function is not altered in preeclampsia. This difference in the results of present study could be due to various geographical areas, different races and different diets.

The prevalence of subclinical hypothyroidism in our entire study group is 33.5% (21% in Preeclampsia women and 12.5% in Normotensive women) and Overt hypothyroidism contributing to 2% in Preeclamptic group while 1% in Normotensive group. The results were comparable to the study done by Wilson KL *et al*. (2012) where women with subclinical hyperthyroidism had an incidence of hypertensive disorders of 6.2% as compared with 8.5% of euthyroid women and 10.9% of subclinical hypothyroid women. After adjusting, only women with subclinical hypothyroidism were at increased risk for severe preeclampsia (adjusted OR, 1.6; 95% CI, 1.1 to 2.4; $P = 0.031$) pointing towards a causal role.

In our study, out of the 100 preeclamptic patients, 17 belonged to the severe and 83 belonged to the mild preeclampsia group. The TSH was significantly more in the 17 severe preeclampsia group as compared to mild preeclampsia (4.1±2.83 Vs 3.6 ±0.38); ($p<0.05$). The values of free T4 are (4.19± 2.83Vs 2.6 ±1.26) less in severe preeclampsia than mild preeclampsia and difference was statistically significant

(P<0.0001). These findings strongly suggest an association between the severity of preeclampsia and hypothyroidism. In a similar study done by Deshpande *et al*. (2015) where he observed association of thyroid hormone status with severity of preeclampsia was statistically significant (p=0.02). Odds ratio indicates that severe preeclampsia group have 2.87 times more incidence of thyroid hypofunction.In another study by, B Shanthirani*et al*. (2021) TSH was significantly more in the severe preeclampsia group as compared to mild preeclampsia (2.8 ± 1.67 vs. 2.4 ± 1.33); P < 0.0001), which is comparable to the present study. According to Ghalia Ashoor *et al*. (2010), measurement of maternal serum TSH can improve the prediction of late-PE provided by a combination of factors in the maternal history and the measurements of mean arterial pressure and uterine artery pulsatility index.

CONCLUSION

These findings indicate that there is state of hypothyroxinemia in normal pregnancy and in preeclampsia. It may be concluded that 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. These results provide insights into optimizing clinical decision-making strategies that should provide thyroid screening in women with preeclampsia.

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