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Thyroid status in pregnant women with pregnancy induced hypertension – A case control study

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Abstract

Introduction: Pregnancy induced hypertension (PIH) is an important cause of maternal and fetal morbidity and mortality affecting 5-10% of pregnancies. PIH is more frequently associated with elevated TSH (Thyroid-stimulating hormone). Thyroid dysfunction plays an important role in the development of gestational hypertension. However, this relationship remains unclear. The study was performed to evaluate the thyroid status in pregnant women with PIH and normal pregnant women.

Methodology: This was a hospital based observational case control study done in Dr M K Shah Medical College, Ahmedabad. Total 100 pregnant women were included, out of them 50 PIH women were included in the case study group and 50 normotensive healthy pregnant women were included in the control group. After taking written consent, thyroid profile (TSH, free T3 and free T4) were measured in all 100 subjects.

Results: Women with PIH had higher TSH levels and lower free T3 and free T4 as compared to normotensive pregnant women. There was a significant association between hypothyroidism and PIH cases. There was a significant positive correlation between TSH and systolic BP (r=0.42) and diastolic BP (r=0.52).

Conclusion: PIH women are at greater risk of decreased thyroid function. Therefore, PIH women should be monitored for thyroid levels regularly.

Keywords: gestational hypertension; preeclampsia; thyroid profile; subclinical hypothyroid; overt hypothyroid

Introduction

Pregnancy-induced hypertension (PIH) is defined as the new onset of hypertension in pregnant women after 20 weeks of gestation with systolic blood pressure (SBP) >140 mmHg and diastolic blood pressure (DBP) >90 mmHg, with or without protein excretion in urine [1]. PIH is a major factor in maternal and fetal morbidity and mortality [1]. This is still one of the top three causes of maternal morbidity and mortality worldwide. Hypertensive disorders of pregnancy include chronic hypertension, gestational hypertension (GH), preeclampsia, and eclampsia, with an estimated prevalence of 6–11% among pregnant women in India [2].

Thyroid hormones play an important role in controlling growth, metabolism, and many other body functions. Thyroid hormones are known to regulate neurodevelopment, probably from early fetal life. During pregnancy, the physiological changes of the thyroid gland are completely normal and incompatibility with

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these changes leads to dysfunction of the thyroid gland [3]. Naturally, thyroid hormones increase by 40–100% to meet the needs of both mother and fetus [4]. Many health-related effects have been shown to be due to inadequate levels of thyroid hormones in pregnant females and their newborns. The pathogenesis of hypothyroidism in PIH may be due to an alteration in nitric oxide release, which results in endothelial cell dysfunction of thyroid gland [5]. A reduction in levels of nitric oxide mainly causes vasoconstriction and arterial stiffness. It is known that placental dysfunction is more likely to occur in PIH cases at less than 34 weeks of gestation [6, 7], and early onset of PIH confers a substantially higher risk of thyroid, cardiovascular, respiratory, central nervous system, renal, and hepatic disorders [8, 9].

However, in most previous studies, thyroid hormones were measured before 20 weeks of gestation. The levels of thyroid hormones measured in the second half of pregnancy in different subtypes of PIH remained untouched and unclear. So this study was conducted to fill this lacuna.

The aim of the study was to evaluate thyroid status in pregnant women with PIH. The other objective was to find an association between the thyroid profile and PIH indicators.

Material and methods

A case control study was carried out at the Obstetrics and Gynecology Department at Dr. M. K. Shah Medical College and Research Centre, Ahmedabad, India. For the case and control groups, a total of 50 pregnant women were recruited in each group (100 pregnant women). The duration of the study was six months, from June 2019 to December 2019. The study commenced after obtaining ethical clearance from the Institutional Ethics Committee. Pregnant women with a diagnosis of PIH were included as cases. The diagnosis of pregnancy induced hypertension was made using current ACOG (The American College of Obstetricians and Gynecologists) guidelines. Blood pressure > 140/90 mm Hg on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with previously normal blood pressure recordings was labeled as PIH.

The serum TSH, free T3, and free T4 were estimated at the time of diagnosis of pregnancy induced hypertension using the enzyme linked immunosorbent assay method with a venous blood sample. The laboratory reference range of TSH, free T3, free T4 in pregnant women after 20 weeks of pregnancy are as below [10]: TSH - 0.30-3.0 micro IU/ml; free T3- 2.3-4.2 pg/ml; and free T4 -0.89-1.76 ng/dl.

This study excluded any pregnant women with a history of chronic hypertension or a prior history of thyroid dysfunction, thyroid surgery, or thyroid medication use. Pregnant women with a previous history of hepatic disease, renal disease, or any other coexisting medical illness were not included in the study.

After obtaining informed consent, data relating to name, age, symptoms, parity, height, and weight were recorded. Blood pressure was measured twice, six hours apart, in the semi-reclining position of the right arm. Blood pressures greater than 140/90 mm Hg on two or more occasions at least 6 hours apart are considered PIH cases [1]. A 5 ml of blood sample per patient was drawn in a red vacuette to separate serum by centrifugation at 3000 rpm for 10 minutes, and the separated serum (not haemolysed) was transferred to well-labeled aliquots and biochemical analysis was performed.

Free T3, free T4 and TSH were analyzed by two-dimensional immunoenzymometric test method in the TOSOH immunoassay hormone analyzer at the Central Clinical Biochemistry Laboratory. The laboratory reference ranges of TSH, free T3 and free T4 in pregnant women after 20 weeks of pregnancy are as follows [10]: TSH - 0.30-3.0 micro IU/ml; Free T3- 2.3-4.2 pg/ml; and Free T4 -0.89-1.76 ng/dl.

Statistical analysis

The primary explanatory variable was the study group. Mean and standard deviation were calculated for the descriptive analysis of quantitative variables, and categorical outcomes were compared between the study group and control group using the Chi square test. p value of less than 0.05 was considered statistically significant.

Results

A total of 100 pregnant women were included in the study, with 50 patients in the case and 50 patients in the control groups. Prior to the analysis of the results of this study, the absence of confounding factors between the case and control groups was confirmed.

The mean ages of pregnant women were 26.94±3.68 and 26.06±4.79 years, respectively, tabulated for the case and control groups (Table 1). The mean gestational age in the control group was 34.18±3.92 weeks, while in the case group it was 33.22±3.88 weeks. The p values of 0.3042 for pregnant women's age and 0.18 for gestational age indicate that there are no statistically significant differences between these two demographic features (Table 1). Systolic blood pressure recordings in the control group had a mean value of 124.12±8.56

mm Hg, while in the case group it was 155.04±9.08 mm Hg. while the diastolic blood pressure recorded in both groups had a mean value of 80.22±6.50 mm Hg for the control group and a mean value of 99.58±10.97 mm Hg for the case group. Both systolic and diastolic blood pressure recordings were significantly higher in the case group based on p value (< 0.0001). The mean TSH of controls was 1.90 + 0.92(mIU/L), while the mean TSH (mIU/L) of cases was 4.43±1.8. This difference was highly statistically significant (p value <0.05). The mean free T3 in the control group was 3.22±0.75 (pg/mL), while it was 2.66±0.75 (pg/mL) in the case group and the difference was significant (p<0.05). The mean free T4 was 1.29±0.23 (ng/dL) in the control group and 0.84±0.25 (ng/dL) in the case group, which was also significant (p<0.05) among the two groups.

Table 1: Comparison of demographic variables between cases and controls.

Variables	*Cases (n=50) Mean ± SD*	*Controls (n=50) Mean ± SD*	*p value*
Pregnant women's age (years)	26.94±3.68	26.06±4.79	0.30
Gestational age (weeks)	33.22±3.88	34.18±3.92	0.18
Primigravida	34	31	>0.05
Multigravida	16	19	>0.05
Systolic BP (mm Hg)	155.04±9.08	124.12±8.56	<0.05
Diastolic BP (mm Hg)	99.58±10.97	80.22±6.50	<0.05
Mean arterial BP (MAP)* (mm Hg)	118.06±9.57	94.85±5.01	<0.05
TSH (micro lU/ml)	4.43±1.8	1.90±0.92	<0.05
Free T3 (pg/mL)	2.66±0.75	3.22±0.53	<0.05
Free T4 (ng/dL)	0.84±0.25	1.29v0.23	<0.05

Abbreviations: SD: Standard deviation; S. TSH: Serum thyroid stimulating hormone;

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; *MAP (Mean arterial blood pressure) = Diastolic pressure + 1/3 (Systolic BP-Diastolic BP).

The patients in the control and case groups underwent laboratory testing for various blood markers, and the results were compared (Table 2). The mean difference in hemoglobin (g/dL) levels between normotensive and pregnant women with PIH was statistically insignificant (p value = 0.6223). The mean values for blood urea (mg/dL) were (16.87±6.76) in controls and (16.79±6.47) in cases, with the difference being statistically insignificant (p = 0.9278). The mean values of serum creatinine levels (mg/dL) in controls were (0.68±0.18) and in cases (0.66±0.19) which was statistically insignificant. (p value = 0.3920).

For serum total protein (g/dL) levels, mean values were 5.25±0.50 (g/dL) in controls and 5.10±0.52 (g/dL) in cases, with a difference being statistically insignificant (p value = 0.4012). Also, a statistically insignificant difference (p value = 0.123) was seen between the mean serum albumin 3.40±0.38 (g/dL) among controls and 3.22±0.43 (g/dL) among cases.

Table 2: Comparison of biochemical markers between cases and control groups.

Variables	*Control (n=50) Mean ± SD*	*Cases (n=50) Mean ± SD*	*p– value*
Hb (g/dL)	11.36±1.18	11.42±1.78	0.6223
B. Urea (mg/dL)	16.87±6.76	16.79±6.47	0.9278
S. creatinine (mg/dL)	0.68±0.18	0.66±0.19	0.3920
S. total protein (g/dL)	5.25±0.50	5.10±0.52	0.4012
S. albumin (g/dL)	3.40±0.38	3.22±0.42	0.123

Table 3 shows the distribution of cases of pregnancy induced hypertension. It shows that our study includes 15 cases of gestational hypertension and 35 cases of preeclampsia (n=50).

Table 3: Distribution of cases of pregnancy-induced hypertension in our study.

Type of PIH	*Number of cases*
Gestational hypertension	15
Preeclampsia	35
Eclampsia	00
Total cases	50

Table 4 shows the distribution of thyroid between cases and controls, which shows the maximum percentage of patients having overt hypothyroidism belongs to the group of PIH (both gestational hypertension and preeclampsia) and the maximum percentage of patients having euthyroidism belongs to the control group.

Table 4: Distribution of thyroid status between controls and PIH cases (gestational hypertension and preeclampsia).

	Euthyroidism	*Hypothyroidism (Subclinical & Overt)*	*Total*
Control Group	44	06	50
PIH cases	30	20	50
Total	74	26	100

Note: The chi-square statistic is 10.18. The p-value is 0.0014, which is very significant.

Table 5 shows comparison of thyroid status among controls, gestational hypertension and preeclampsia. The mean value of S. TSH (mIU/ml) among gestational hypertension cases was 3.84±1.48; in preeclampsia was 5.81±1.76; and that of the control group was 1.90±0.92. This difference was statistically significant ($p < 0.05$). In comparison to the control group, free T4 was on the lower side in the PIH group (gestational hypertension and preeclampsia). Free T4 was lowest in the preeclampsia cases and borderline decreased in the gestational hypertension cases when compared among the three groups ($p < 0.05$). It showed that there was a definitive trend of increased TSH from the control group to gestational hypertension and finally to preeclampsia. Since this difference was statistically significant.

Table 6 shows the correlation of systolic and diastolic BP with TSH, free T3, and free T4 in the PIH group. It demonstrates that systolic and diastolic BP have positive and significant correlations with TSH ($p < 0.05$) and poor negative correlations with Free T3 and Free T4 ($p < 0.05$).

Discussion

With comparable age and gestational age in the case and control groups, hypothyroidism in PIH women was found to be significantly higher, with 40% of cases having serum TSH > 3.5 mIU/ml compared to 12% in normotensive pregnant women. Serum albumin levels were significantly lower in the hypertensive group, with 22.44% of cases having serum albumin 3.0 g/dL compared to 15% of patients in the normotensive group having serum albumin 3.0 g/dL. It was found that the mean serum TSH level increased and Free T4 decreased as the pathology of PIH progressed along the spectrum of gestational hypertension from non severe to severe preeclampsia, which showed a stronger association of hypothyroidism with the severity of PIH. Sardana et al found that TSH was significantly increased in cases of preeclampsia [5]. Rafeeinia et al reported the level of thyroid hormones in preeclampsia women in Gorgan and reported findings similar to our study [11]. These findings are similar to those of our study.

The negative correlation between the serum albumin and serum TSH levels showed both values were independent of each other. There has been no correlation found at all between the two values in certain studies before. Other

Table 5: Comparison of thyroid profile among controls, gestational hypertension, and preeclampsia.

Variables	*TSH (micro lU/ml)*	*Free T_3 (pg/mL)*	*Free T_4(ng/dL)*	*p value*
Controls (n=50)	1.90±0.92	3.22±0.53	1.29±0.23	<0.05
Gestational hypertension (n=15)	3.84±1.48	2.84±0.75	0.90±0.24	<0.05
Preeclampsia (n=35)	5.81±1.76	2.23±0.60	0.69±0.22	<0.05

Table 6: Correlation of blood pressure with thyroid profile in the PIH group.

Systolic BP			*Diastolic BP*		
Parameter	r value	p value	Parameter	r value	p value
TSH	0.42	0.001	TSH	0.52	0.001
Free T3	-0.23	0.40	Free T3	-0.16	0.24
Free T4	-0.24	0.32	Free T4	-0.27	0.15

blood parameters were also compared between the case and control groups. Hemoglobin, blood urea, and serum creatinine values did not vary significantly between the two groups. Platelets, total proteins, and serum albumin were significantly lower in the hypertensive group.

High endothelin levels and soluble-FMS like tyrosine kinase 1 (SFLT-1) are caused by endothelial dysfunction, seen in PIH in particular. They contribute to the spread of vasospasm and abnormalities in many organs, including the fetoplacental unit in PIH. SFLT-1 and endothelin (potent vasoconstrictor) are believed to be responsible for decreased capillary flow to thyroid gland which could lead to hypothyroidism and the corresponding increase in TSH levels in PIH cases. Decreased thyroid function may be due to anti-angiogenic factors in PIH that reduce nitric oxide production [12, 13]. Hypothyroidism in pregnancy is a risk factor for the premature rupture of membranes (PROM), intrauterine growth restriction (IUGR) and low birth weight (LBW) [14, 15].

Limitation

We have studied thyroid profile of PIH women in third trimester only. We have not set any follow up study for these patients which can be useful to identify the long term complications after delivery. Larger studies in future may throw light on this subject.

Conclusion

The findings of this study suggest that thyroid function is deteriorated in PIH patients. It suggests that each PIH patients should be monitored for thyroid levels regularly. Identification of such patients and managing timely with appropriate measures in terms of possible thyroid hormone replacement is beneficial for both mother and fetus to prevent complications related with hypothyroidism.

Conflicts of interest

Authors declare no conflicts of interest.

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