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Thyroid hormones: As biomarker of preeclampsia and an influencer in outcome of pregnancy

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Abstract
The literature regarding reports of altered thyroid hormones are lacking in conditions of preeclampsia. The present study was carried out in 100 patients of preeclampsia (50 mild and 50 severe preeclampsia) and 100 normotensive pregnant women (control) admitted or attending the Outpatient Department of Obstetrics and Gynaecology in Nestiva Jay Arogyam Hospital, Patna, in the third trimester of pregnancy (between 28 and 36 weeks). Fifty healthy volunteers served as controls (healthy volunteers comprised of healthy employees of the institute and medical and nursing students). T_3 levels were lower in preeclampsia, while Thyroid-stimulating hormone (TSH) and T_4 levels were higher in mild preeclampsia as compared with severe preeclampsia. Mean arterial pressure (MAP) was significantly raised in preeclamptic females with higher TSH levels and were also associated with low birth weight. The observations were significant enough to indicate the state of biochemical hypothyroidism that correlates with severity of preeclampsia and influences obstetric outcome in these females.

Keywords: Preeclampsia, thyroid-stimulating hormone, mean arterial pressure

Introduction
Alteration in physiological levels of thyroid hormones, such as increased total thyroxine (T_4), have been observed and reported in abundance during normal pregnancy. But, the literature regarding reports of altered thyroid hormones are lacking in conditions of preeclampsia. Preeclampsia is a condition during pregnancy where there is a sudden rise in blood pressure and swelling, mostly in the face, hands, and feet. Kaya *et al* mentioned about the occurrence of biochemical hypothyroidism (raised thyroid-stimulating hormone [TSH]) in preeclampsia[1]. The direct correlation between hypothyroidism and high blood pressure was mentioned by Endo *et al*. [2]. Retardation of foetal growth has been documented in pre-eclamptic females due to decreased production of estrogen on account of placental dysfunction causing lowered TBG (Thyroid Binding Globulin), T_3, and T_4 [3]. Relationship between birth weight and thyroid hormonal status has been controversially reported with few mentioning a significant relation [4] while others didn't observe any correlation.
Similar controversy can be observed regarding the correlation of TSH levels in pregnancy, especially in the second part. Although, reports have been documented for transient fall in TSH level in the serum during second and third months of pregnancy. On the other hand, an increased serum concentration of TSH in the presence of normal serum levels of T_4 and triiodothyronine (T_3), termed as subclinical hypothyroidism, is associated with an increased risk for pregnancy complications and adverse neuropsychological development of the child. Thyroid dysfunction is associated with pregnancy complications such as hypertension, pre-term birth, low birth weight, placental abruption and fetal death [4, 5]. These pregnant females are at an increased risk for severe preeclampsia when compared with euthyroid women. Hence, it becomes important to accurately interpret the alteration in serum levels of TSH during pregnancy.
The present study was planned to study thyroid hormones in mild and severe preeclamptic women and normotensive women and correlate them with outcome of pregnancy as there is a lack of evidence showing between subclinical hypothyroidism and pregnancy outcomes

Materials and Methods
The present study was carried out in 100 patients of preeclampsia (50 mild and 50 severe preeclampsia) and 100 normotensive pregnant women (control) admitted or attending the

Outpatient Department of Obstetrics and Gynaecology in Nestiva Jay Arogyam Hospital, Patna, in the third trimester of pregnancy (between 28 and 36 weeks). Fifty healthy volunteers served as controls (healthy volunteers comprised of healthy employees of the institute and medical and nursing students). The subjects in the three groups were age, body mass index and gravidity matched. Informed consent was obtained from all the subjects and the study was approved by the ethical committee of the institute.

Inclusion criteria for preeclampsia were

Blood pressure > 140/90 mmHg on at least two occasions 6 h apart and/or proteinuria, and diagnostic criteria of the American College of Obstetrics was followed[6].

Exclusion criteria were

History of chronic hypertension, any chronic illness, renal disease, endocrinal disorder metabolic disorder or medication known to affect thyroid function, subject in labor.

Study samples were drawn from overnight fasting subjects before starting any treatment. Serum samples were separated for radioimmunoassay for thyroid hormones (T_3, T_4, TSH)[7]. Immunoradiometric assay (IRMA) kit were used for TSH, T_4 and T_3 analysis. The Endocrine Society Clinical Practice Guidelines of 2007 were followed for cut-off values for TSH, T_3 and T_4 (based on pregnancy-specific and trimester-specific) reference ranges. Patients were followed till delivery for outcome of pregnancy. Data so obtained were analyzed using student's t-test and regression analysis was carried out.

Observations & Results

In the present study, preeclamptic women had raised TSH and T_4 levels, as compared with normotensive pregnant and non-pregnant women [Table 1]. TSH and T_4 levels were higher in mild preeclampsia as compared with severe preeclampsia (P<0.001 and P<0.01, respectively). T_3 levels were lower in preeclampsia (more so in severe preeclamptics) as compared with normotensive pregnant and non-pregnant women [Table 1]. TSH, T_3, and T_4 levels were lower in normotensive pregnant women as compared with non-pregnant women (P<0.001, P<0.001 and P<0.05, respectively).

Table 1: Thyroid function tests in various groups (mean ± S. D.)

Parameters	Non-pregnant (n=50)	Normotensive pregnant (n=100)	Mild preeclampsia (n=50)	Severe preeclampsia (n=50)	Preeclampsia (n=50)
T_3	113.32 ± 21.02	131 ± 32.38	128.32 ± 34.12	112.87 ± 31.87 [a, ##]	118.11 ± 37.32 [#]
T_4	8.6 ± 11.20	11.87 ± 3.03	11.32 ± 3.37 [#]	8.21 ± 1.67 [b, ###]	7.84 ± 3.01 [#]
TSH	3.04 ± 1.13	1.98 ± 1.02	3.38 ± 2.01 [###]	5.11 ± 1.78 [###]	4.21 ± 2.65 [#]

[a]P<0.05 as compared with mild preeclampsia, [b]P<0.01 as compared with mild preeclampsia, [c]P<0.001 as compared with mild preeclampsia, [##]P<0.001 as compared with Normotensive pregnant, [###]P<0.01 as compared with Normotensive pregnant, [#]P<0.05 as compared with Normotensive pregnant. TSH – Thyroid Stimulating Hormone

Preeclamptic women delivered at earlier gestation (34.54 ± 1.28 vs. 37.43 ± 1.03 weeks) and had lower infant BWs (1.98 ± 0.46 vs 1.42 ± 0.32 kg) as compared with normotensive controls [Table 2]. In the present study, highly significant negative correlation was observed between birth weight and TSH levels in preeclampsia, while no such correlation could be observed in normotensive controls [Table 3]. A negative correlation was observed between birth weight and T_4 in preeclampsia, but it was not statistically significant. Also, positive correlation was observed between birth weight and T_3 levels, although it was not statistically significant.

Table 2: Clinical characteristics (mean ± S. D.)

Parameters	Preeclampsia (n=50)			Normotensive	Non - Pregnant
	Mild	Severe	Total		
Age (years)	22 ± 2.87	22.13 ± 1.78	22..02 ± 2.16	22.11 ± 2.37	22.21 ± 2.22
Gestational age (weeks)	37.43 ± 1.03	35.19 ± 2.15	34.54 ± 1.28	36.13 ± 1.04	-
Birth weight (Kg)	1.42 ± 0.32	2.18 ± 0.38	1.98 ± 0.46	2.04 ± 0.42	-

Table 3: Correlation of (r-value) of birth weight and maternal thyroid function tests

Parameters	Preeclampsia	Normotensive pregnant
Birth wt. - T_3	0.172	0.078
Birth wt. - T_4	0.189	-0.012
Birth wt. – TSH	-0.292[#]	-0.027

[#]P<0.01 as compared with normotensive pregnant., in rest, P-value was not significant

Based on the levels of mean arterial pressure (MAP), the preeclamptic women were grouped into three groups. Significant decrease in the level of T_3 and T_4 was observed along with a significant increase in the serum level of TSH [Table 4].

Table 4: Thyroid hormone levels according to three levels of mean arterial pressure (mean ± SD)

Parameters	A	B	C
MAP (mmHg)	<105 (n = 7)	= 105 – 115 (n = 40)	> 115 (n = 53)
T_3 (ng/dL)	150 ± 22.78	133.35 ± 33.63	114.39 ± 33.23 [a,#]
T_4 (µg/dL)	12.67 ± 1.23	9.87 ± 2.27 [#]	8.78 ± 2.13 [b,#]
TSH (µIU/mL)	3.87 ± 1.23	2.98 ± 1.06	4.63 ± 1.89 [c]

To study the correlation of severity of disease in preeclamptic women with thyroid function, preeclamptics were divided into two groups: those with normal TSH levels (0.17-4.05 µIU/mL) and those with raised TSH levels (above 4.05 µIU/mL). Higher MAP was observed in preeclamptics with raised TSH levels as compared with those with normal TSH levels [*P*<0.001, Table 5]. Also, birth weight was lower in preeclamptic women having high TSH levels, and it was significantly lower as compared with normal counterparts (*P*<0.001). A significant negative correlation was deserved between birth weight and TSH levels in preeclampsia [r = -2.292, *P*<0.001, Table 3].

Table 5: Correlation of mean arterial blood pressure birth weight in preeclamptic women with different thyroid-stimulating hormone levels

Parameters	Normal TSH levels (n = 40) (0.17 – 4.05 µIU/mL)	Raised TSH levels (n = 60) (>4.05 µIU/mL)
MAP (mmHg)	110.17 ± 5.17	124.48 ± 13.29
Birth weight (Kg)	2.13 ± 0.34	1.98 ± 0.46

P<0.001

Discussion

As per present study observations, T_3 levels were significantly lower in preeclamptic women as compared with normotensive pregnant and non-pregnant women [Table 1]. The present study findings are in agreement with those previously reported [6-8]. The decreased T_3 serum levels can be attributed to the reduced peripheral conversion of T_4 to T_3 due to involvement of liver and kidney in preeclampsia [9].

T_4 and TSH levels were observed to be significantly higher in preeclamptics and normotensive pregnant women [Table 1]. Osathanondh *et al* have reported both low and high T_4 levels in preeclampsia1. Finding of high TSH level in preeclamptics is supported by the earlier reports of Tolino *et al*. The present study reports a non – significant positive correlation was observed between low birth weight and T_3 and T_4 levels and a significant negative correlation was observed between low birth weight and TSH levels. These findings are supported by previous literature from Osathanondh *et al*. and Qublan *et al*, but Kaya *et al* reported no correlation between thyroid hormone levels with BW of babies, which they attributed to protein loss, causing low infant birth weight [1, 8, 10].

The TSH levels in preeclamptics of present study population increased significantly with increase in MAP, as was also reported by Kaliq *et al* [11]. The pathogenesis of preeclampsia in thyroid dysfunctional cases lacks a complete explanation. Factors, such as placental dysfunction associated with decreased estrogen production and reduced peripheral conversion of T_4 to T_3 play a significant role. Placental dysfunction may deprive the fetus from sufficient oxygen and nutrient supplies, as per Kumar *et al*. [12].

Hence, it is important to study the variation in serum levels of thyroid hormones and perform thyroid screening during pregnancy to be able to predict the occurrence, and provide timely interventions in terms of possible thyroid hormone administration in pre-term infants might affect the severity of morbidity and mortality associated with preeclampsia.

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