Original Article

Correlation of Thyroid Functions with Severity and Outcome of Pregnancy

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Abstract

Background: During normal pregnancy, changes in thyroid function are well documented; however, information regarding thyroid function in preeclampsia is scanty. **Aim:** 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. **Subject and Methods:** Thyroid hormones were analyzed in mild ($n = 50$) and severe ($n = 50$) cases of preeclamptic women and normotensive women ($n = 100$). **Results:** Thyroid-stimulating hormone (TSH) and TT4 levels were higher in mild preeclampsia as compared with severe preeclampsia ($P < 0.001$ and $P < 0.01$, respectively). TT3 levels were lower in preeclampsia (more so in severe preeclamptics as compared with normotensive pregnant and non-pregnant women). Preeclamptic with raised TSH levels had significantly higher mean arterial blood pressure and low birth weight (BW). A negative correlation was observed between BW and TSH levels ($r = 0.296$, $P < 0.001$) and BW and TT4 levels. A positive correlation was observed between BW and TT3 levels. **Conclusion:** These findings indicate that there is a state of biochemical hypothyroidism that correlates with severity of preeclampsia and influences obstetric outcome in these women. Identification of thyroid hormone in pregnancy might be of help in predicting occurrence of preeclampsia.

Keywords: Birth weight, Preeclampsia, Thyroid function

Introduction

During normal pregnancy, changes in thyroid function are well documented; however, information regarding thyroid function in preeclampsia is scanty. Pregnancy is associated with increased total thyroxine (T_4) and, in preeclampsia, biochemical hypothyroidism (raised thyroid-stimulating hormone [TSH]) occurs.[1] Hypothyroidism has been listed as one of the causes of high blood pressure.[2] In preeclampsia, there is failure of estrogen production due to placental dysfunction, resulting in lowering of TBG, TT_3 and TT_4 along with growth retardation of fetus. Casey, *et al.* (2005) did not observe any increased incidence of preeclampsia in sub-clinically hypothyroid women.[3] There are conflicting reports in the literature regarding relationship between BW and thyroid hormonal status. Few workers have found a significant correlation between BW and thyroid function in preeclampsia,[4] while others have found no correlation.[1]

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A correct interpretation of the modifications in serum TSH concentrations is crucial to correctly assess the alterations in pregnancy-associated thyroid function parameters. Some authors found no change in serum TSH in pregnancy, while others observed significant increases in TSH throughout gestation. Earlier, a transient fall in serum TSH during the second and third months of pregnancy in normal women has been reported. The patterns of modifications in serum TSH levels in the second part of gestation have been the subject of longstanding controversy.

Clinical thyroid dysfunction has been associated with pregnancy complications such as hypertension, pre-term birth, low BW, placental abruption and fetal death.[3] It has been reported that pregnant women with subclinical hypothyroidism were three-times more likely to be complicated by placental abruption. Pre-term birth was almost two-fold higher in women with subclinical hypothyroidism.[4]

It has been reported that women with subclinical hypothyroidism

identified during pregnancy have an increased risk for severe preeclampsia when compared with euthyroid women.[4]

There is also some evidence that subclinical hypothyroidism, defined by an increased serum concentration of TSH in the presence of normal levels of T_4 and triiodothyronine (T_3) is associated with an increased risk for pregnancy complications and adverse neuropsychological development of the child.[3-5] Serum TSH have been reported to be increased whereas free triiodothyronine (FT_3) and FT_4 decreased with gestational age by Ashoor *et al*.[5] There is a transient rise in FT_4 in the first trimester due to the relatively high circulating human chorionic gonadotropin concentration and a decrease of FT_4 in the second and third trimester, although within the normal reference range. Changes in FT_3 concentration are also seen, in which they broadly parallel the FT_4, again within the normal range. The precise reason for the decline in free thyroid hormones is not clear but the interaction of TSH, estrogen and thyroid-binding proteins is of importance.

The relationship between subclinical hypothyroidism and pregnancy outcomes has not been well studied. Hence, 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.

Subject 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 Gynecology in Pt. B.D. Sharma, PGIMS, Rohtak, in the third trimester of pregnancy (between 28 and 36 weeks), between August 2005 and October 2006. 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 (TT_4, TT_3, TSH).[7] IRMA kits were used for TSH, T_4 and T_3 analysis. Immunoradiometric assay kit for the *in vitro* quantitative measurement of human TSH, TT_4 and TT_3 in serum and plasma was supplied by BRIT, Mumbai, India. 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. For TSH, inter-assay coefficient of variation (CV) was 22% and intraassay CV was 3.8%. For T_4, interassay CV was 4.7% and intraassay CV was 4.5%. For T_3, the interassay CV was 3.6% and the intraassay CV was 2.3%. 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

In the present study, preeclamptic women had raised TSH and TT_4 levels, as compared with normotensive pregnant and non-pregnant women [Table 1]. TSH and TT_4 levels were higher in mild preeclampsia as compared with severe preeclampsia ($P < 0.001$ and $P < 0.01$, respectively). TT_3 levels were lower in preeclampsia (more so in severe preeclamptics) as compared with normotensive pregnant and non-pregnant women [Table 1]. TSH, TT_4 and TT_3 levels were lower in normotensive pregnant women as compared with non-pregnant women ($P < 0.001$, $P < 0.001$ and $P < 0.05$, respectively).

Preeclamptic women delivered at earlier gestation (37.77 (1.7) vs. 39.03 (1.30) weeks) and had lower infant BWs (2.32 (0.43) vs 2.74 (0.24) kg) as compared with normotensive controls [Table 1a]. In the present study, highly significant negative correlation was observed between BW and TSH levels in preeclampsia, while no such correlation could be observed in normotensive controls [Table 2]. A negative correlation was observed between BW and TT_4 in preeclampsia, but it was not statistically significant. Also, positive correlation was observed between BW and TT_3 levels, although it was not statistically significant.

Preeclamptic women were grouped into three groups according to the levels of mean arterial pressure (MAP). TSH levels increased significantly while T_3 and TT_4 levels decreased significantly with increase in MAP [Table 3].

To correlate severity of disease in preeclamptic women with thyroid function studies, 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). Preeclamptics with raised TSH levels had significantly higher MAP as compared with those with normal TSH levels [$P < 0.001$, Table 4]. Also, BW 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 BW and TSH levels in preeclampsia [$r = -2.296$, $P < 0.001$, Table 2].

Discussion

In the present study, TT_3 levels were significantly lower in preeclamptic women, more so in several preeclamptic as compared with normotensive pregnant and non-pregnant women [Table 1]. Our findings are in agreement with those

Table 1: Thyroid function tests in various groups (mean (SD))

Parameters	Non-pregnant (*n*=50)	Normotensive pregnant (*n*=100)	Mild preeclampsia (*n*=50)	Severe preeclampsia (*n*=50)	Preeclampsia (*n*=100)
TT_3 (ng/dL)	115.88 (22.89)	134.00 (34.56)	136.82 (36.82)	119.64 (34.48)[a,*]	128.23 (36.53)***
TT_4 (μg/dL)	7.9 (14.0)	12.14 (2.49)	10.84 (2.53)***	9.39 (2.57)[b,**]	10.12 (2.64)***
TSH (μIU/mL)	2.67 (1.24)	2.00 (1.18)	3.42 (1.61)**	5.63 (2.37)[c,**]	4.52 (2.30)***

[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

Table 1a: Clinical characteristics (mean (SD))

Parameters	Preeclampsia			Normotensive	Non-pregnant
	Total	Mild	Severe		
Age (years)	23.07 (2.75)	23.08 (3.01)	23.01 (2.28)	23.04 (2.17)	23.50 (2.01)
Gestational age (weeks)	37.77 (1.7)	38.67 (0.81)	36.87 (1.90)	39.09 (1.3)	-
Birth weight (kg)	2.32 (0.43)	1.55 (0.22)	2.09 (0.46)	2.74 (0.24)	-
Placental weight (g)	438.25 (56.90)	472.5 (34.71)	404 (54.24)	502.50 (50.81)	-

Table 2: Correlation of (r-value) of birth weight and maternal thyroid function tests

Parameters	Preeclampsia	Normotensive pregnant
BW-TT_3	0.171	0.080
BW-TT_4	0.193	–0.011
BW-TSH	–0.296*	–0.030

**P*<0.01 as compared with normotensive pregnant, in rest, *P* not significant

Table 3: Thyroid hormone levels according to three levels of mean arterial pressure (mean (SD))

Parameters	A	B	C
MAP (mmHg)	MAP<105 (*n*=4)	MAP=105–115 (*n*=45)	MAP>115 (*n*=51)
TT_3 (ng/dL)	154.50 (23.96)	137.04 (35.85)	118.39 (35.39)[+,a]
TT_4 (μg/dL)	13.02 (1.09)	10.83 (2.44)*	9.26 (2.57)[+,b]
TSH (μIU/mL)	3.10 (1.78)	3.46 (1.74)	5.57 (2.32)[c]

**P*<0.05 as compared with A, [+]*P*<0.05 as compared with A, [a]*P*<0.05 as compared with B, [b]*P*<0.01 as compared with B, [c]*P*<0.001 as compared with B, MAP=Mean arterial pressure, TSH: Thyroid-stimulating hormone

reported in the literature.[8] During preeclampsia, involvement of liver and kidney may lead on to decreased peripheral conversion of T_4 to T_3; hence, decreasing T_3 levels.[9] Also, "low T_3 syndrome" has been reported in preeclampsia.[10] Loss of proteins and protein-bound hormones in the urine of preeclamptics may also contribute to low TT_3 levels.

TT_4 and TSH levels were significantly higher in preeclamptics and normotensive pregnant women [Table 1]. These levels were higher in mild preeclamptics as compared with severe ones. Conflicting reports are available regarding TT_4 status in preeclampsia.[11,12] Both low and high TT_4 levels have been reported in preeclampsia.[12] Finding of high TSH level in preeclamptics lends support to earlier reports of high incidence of biochemical hypothyroidism in preeclamptics.[12,13] In contrast, Qublan, *et al*. have reported no significant differences in TSH levels between these two groups.[14]

Because pregnancy is associated with hyperthyroxinemia, the degree of hypothyroxinemia might reflect the severity of preeclampsia. In the present study, a significant negative correlation was observed between BW and TSH levels, and a positive correlation was observed between BW and TT_3 and TT_4 levels, although it was not statistically significant. Our findings are in agreement with those reported in the literature.[12,14] In contrast, Kaya *et al*. observed no correlation between thyroid hormone levels with BW of babies, which they attributed to protein loss, causing low infant BW. In the present study, preeclamptic women with lower BW babies had a greater degree of hypothyroxinemia and high TSH levels. This may be explained by placental dysfunction in preeclamptic patients causing growth failure of fetus.

In the present study, with increase in MAP, TSH levels increased significantly in preeclamptics, while TT_3 and TT_4 levels decreased significantly. Our findings are in agreement with those of Kalif *et al*.[15]

In the present study, TT_3 and TT_4 levels were significantly lower in severe preeclamptics as compared with mild ones ($P < 0.05$ and $P < 0.01$, respectively). Severe preeclamptics have significantly higher TSH levels as compared with mild counterparts ($P = 0.001$). Seventy-eight percent of severely preeclamptic women had raised TSH levels as compared with only 32% of women with mild preeclampsia. Preeclamptics with raised TSH levels had significantly higher MAP as compared with those with normal TSH levels [Table 4]. Also, BW was lower in preeclamptic women having high TSH levels as compared with those with normal TSH levels. A significant negative correlation was observed between BW and TSH levels in preeclampsia [r = –0.296, $P < 0.001$, Table 2]. Many workers have observed low TT_4 and TT_3 levels in preeclamptics who had small for gestational age (SGA) babies as compared with women with appropriate for gestational age infants thus reflecting severity of preeclampsia.[12,15] A study has reported that changes in

Table 4: Correlation of mean arterial blood pressure birth weight in preeclamptic women with different thyroid-stimulating hormone levels

Parameters	Normal TSH levels (*n*=45) (0.17–4.05 μIU/mL)	Raised TSH levels (*n*=55) (>4.05 μIU/mL)
MAP (mmHg)	112.27 (6.21)	127.36 (14.25)*
Birth weight (kg)	2.47 (0.26)	2.19 (0.49)*

*P<0.001 as compared with those with normal TSH levels, MAP: Mean arterial pressure

thyroid hormonal levels might be correlated with occurrence and severity of morbidity and mortality of preeclampsia, and TSH levels 5 μIU/mL carry a higher risk of development of preeclampsia.[13]

The mechanism of thyroid hormone changes in preeclampsia is not well understood. Placental dysfunction along with faulty estrogen production and reduced peripheral conversion of T_4 to T_3, and endothelial dysfunction in preeclampsia, play a significant role in the pathogenesis. Altered release of nitric oxide in endothelial dysfunction might be a pathogenetic mechanism in preeclampsia.[11] Impaired placental function deprives the fetus from sufficient oxygen and nutrient supplies. This may lead to a compromised fetal condition and a low T_4 syndrome may develop.

It has been shown that in SGA fetuses, the fetal pituitary gland can be stimulated to produce TSH after maternal administration of TSH,[13] suggesting an intact fetal hypothalamic–pituitary axis. There is a state of subclinical biochemical hypothyroidism that correlates with the severity of preeclampsia and influences the obstetric outcome in these women. There is hypothyroidism (raised TSH, low TT_3 and TT_4) in preeclampsia, and it correlates with the severity of preeclampsia.

Identification of thyroid hormones and thyroid screening during pregnancy in the future might be helpful in predicting the occurrence, and timely interventions and appropriate measures 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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