Tri-iodothyronine (T3), Thyroxine (T4), and Thyroid- Stimulating Hormone (TSH) in preeclampsia and normal pregnancy

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Abstract

Background: In most developing countries like Bangladesh, the incidence of preeclampsia is much higher in comparison to the developed nations. More than 70% of the preeclamtic pregnant mothers have high thyroid-stimulating hormone (TSH) concentration than that of the normal pregnant mothers. **Objective:** To compare free triiodothyronine (FT_3), free thyroxine (FT_4) and thyroid-stimulating hormone (TSH) status of preeclamptic as compared to normal pregnant mothers. **Methods:** This was a cross-sectional comparative study conducted at Department of Obstetrics and Gynecology, Rajshahi Medical College Hospital, Rajshahi, Bangladesh. A total number of 134 pregnant women consisting of 66 preeclamptic (cases) and 68 normal pregnant women (control) were enrolled in the study on the basis of some inclusion and exclusion criteria. Data on back ground characteristics and biochemical parameters of the cases and control were collected by a preformed data collection sheet. **Result:** The mean ages of the cases and control group were 27.45±3.88 years (range 19-35 years) and 26.45±4.16 years (range 19-35 years) respectively. The mean free triiodothyronine (FT_3) and free thyroxine (FT_4) of the control group were 2.89±0.20 pg/ml and 1.39±0.09 ng/d respectively. These mean thyroid hormones were slightly higher in preeclamtic group but within the normal range and not statistically significant. The mean Thyroid Stimulating Hormone (TSH) in control group was 1.80±0.08 μIU/ml. It was 6.16±0.85 μIU/ml in preeclamtic group, significantly($p<0.001$) higher than that of control group. **Conclusion:** A significantly higher serum TSH level was observed in preeclamptic as compared to normal pregnant mothers. But there was no significant difference in serum FT_3 and FT_4 between them and were within normal limits. This study findings suggested that subclinical hypothyroidism may be associated with preeclamsia and may reflect the severity of preeclampsia.

Key words: free triiodothyronine (FT_3), free thyroxine (FT_4), TSH, hypothyroidism, preeclampsia.

Introduction

In most developing countries like Bangladesh, due to the lack of proper antenatal checkup, poverty, ignorance and poor education, the incidence of preeclampsia is much higher in comparison to the developed nations.

Preeclampsia is a leading cause of maternal and feotal morbidity and mortality throughout the world and still is one of the most complex problems in Obstetrics.[1] Preeclampsia is a multi-system disorder in pregnancy of unknown etiology characterized by development of hypertension to the extent of 140/90 mm Hg or more with proteinuria (greater than 0.3 gm/l in 24-hour urine collection or greater than 1 gm/l in a random sample) after the 20th week in a previously normotensive and non-proteinuric woman. [2,3] Edema has been abandoned as a diagnostic criterion because it occurs in more than 80% of normal pregnant women.[4]

During pregnancy women with preeclampsia are more likely to develop subclinical hypothyroidism.[5] Those who had preeclampsia in their first pregnancy were 70% more likely to have high thyroid-stimulating hormone (TSH) concentrations years later than were women who had not had preeclampsia. Those who had preeclampsia in two pregnancies had a nearly six fold increased risk of high TSH levels.[6]

Subclinical hypothyroidism is a laboratory definition: a raised concentration of thyroid stimulating hormone (TSH) yet a normal concentration of free thyroid hormone (FT_3, FT_4) without specific symptoms of thyroid dysfunction. Patients with subclinical hypothyroidism have an increased risk of progressing to overt hypothyroidism.[7] Measurement of serum TSH is generally considered the best screening test for thyroid disease; increased values usually indicate hypothyroidism, and decreased values usually indicate hyperthyroidism. This test has proved to be both sensitive and specific. Some patients who have elevated serum TSH levels, suggesting hypothyroidism, but have normal levels of thyroid hormone, whether measured as free T_4 or free T_3 index.[8] Elevated maternal thyroid-stimulating hormone (TSH) has been associated with adverse maternal and fetal effects, which may justify screening for thyroid function during pregnancy.[9]

Untreated or inadequately treated hypothyroidism in

preeclampsia has been associated with adverse health outcomes for both mother and child like maternal anaemia, congestive heart failure, abruption placenta, preterm delivery, post-partum haemorrhage, maternal death, pre mature birth, low birth weight, fetal death and impaired neuropsychological development in children. Thyroxin replacement therapy substantially reduces the associated morbidity and improves the quality of life. Identification of hypothyroidism in preeclampsia might be of help in preventing the occurrence of preeclampsia.[3]

This study will be carried out to facilitate a better understanding to evaluate an association between preeclampsia and hypothyroidism. So, assessment of thyroid function in preeclamptic women will help to prevent maternal and perinatal morbidity and mortality.

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Methods

This cross-sectional comparative study was conducted at Department of Obstetrics and Gynecology, Rajshahi Medical College Hospital, Rajshahi, Bangladesh. A total number of 134 pregnant women consisting of 66 preeclamptic (cases) and 68 normal pregnant women (control) were enrolled in the study. The inclusion criteria of the cases (preeclamptic women) were all consecutively diagnosed cases of preeclampsia (blood pressure ≥140/90mmHg taken on two occasions at 6 hours apart and urinary protein of 0.3 gm/l or more) with gestational age 20 -40 weeks, singleton pregnancy and no history of thyroid disease before and through pregnancy. The inclusion criteria of the controls were healthy pregnant mother (normotensive and urinary protein nil/ trace) with gestational age 20 -40 weeks, singleton pregnancy and no history of thyroid disease before and through pregnancy. The patients with the history of hypertension, renal disorders, cardio vascular diseases, any metabolic disorder before or during the pregnancy, and history of intake of any medication such as levothyroxine that may affect on thyroid function were excluded from the study. Written informed consent was obtained from all patients participating in the study and they were assured about the privacy of the data. The study was approved by the Ethical Review Committee of Rajshahi Medical College, Rajshahi.

Preeclampsia was defined as mild when blood pressure (BP) >140/90 mmHg but <160/110 mmHg on two more occasions at least 6-h apart with proteinuria of 1^+ on dipstick reagent strip, and as severe when BP ≥160/110 mmHg with proteinuria of 2^+ or more on reagent strip. BP was measured with the patient in lying position keeping cuff of sphygmomanometer at the level of heart. When DBP was found to be more than 90 mmHg, it was confirmed on two occasions at least 6 hours apart.

After hospitalization, under full aseptic precaution 5 ml of venous blood was drawn from each women (cases and controls), after the diagnosis was made before the initiation of the antihypertensive treatment. The collected blood was then allowed to stand for about 30 minutes to clot. After 30 minutes the clot was separated from the test tube by a wooden stick and was centrifuged at 2000 rpm for 5 minutes. The separated serum was carefully drawn by micropipette and should be stored in micro-centrifuged tube at -35°C until the analysis was done. Serum free triiodothyronine (FT_3), free thyroxine (FT_4) and Thyroid Stimulating Hormone (TSH) were estimated by FT_3 ELISA (Tietz 1976), FT_4 ELISA (Tietz 1976) and TSH ELISA (Engall 198O) method. Random urine sample was collected in a clean test tube and assayed for presence of protein by dipstick reagent strip (Hallak 1999).

The statistical analysis was performed using SPSS, version 16. For evaluating two groups, chi-square and Independent sample 't-test' were used. $p \leq 0.05$ was considered statistically significant.

Results

A total of 134 pregnant women participated in the study. Among them 66 were preeclamtic (cases) and 68 were healthy pregnant women(controls). The mean ages of the cases and control group were 27.45±3.88 years (range 19-35 years) and 26.45±4.16 years (range 19-35 years) respectively. The mean gestational ages of the cases and controls were 30.60±2.89 weeks and 30.69±3.41 week rerspectively. In cases, 42 (63 .6 %) women were nullipara and 24 (36.4%) were multipara. On the contrary in control group, 43 (63.2%) women were nullipara and 25 (36.8%) were multipara. There was no significant association of parity between the groups. There was no significant difference between both the groups in regards to their age, parity and gestational age (Table 1).

Table 1. Background characteristics of case and control groups.

Characteristics	Cases (n=66) Mean ±SD/ N (%)	Controls (n=68) Mean ±SD / N(%)	$U\chi^2$ value	P vlue
Age (years)	27.45±5.88	26.45±4.16	0.56	ns
Gestational age (wks)	30.60±2.89	30.69±3.41	0.88	ns
Parity				
Nullipara	42 (63 .6 %)	43 (63.2%)	.0023	ns
Multipara	24 (36.4%)	25 (36.8%)		

The mean free triiodothyronine (FT3) and free thyroxine (FT4) of the control group were 2.89±0.20 pg/ml and 1.39±0.09 ng/d respectively. These mean thyroid hormones were slightly higher in preeclamtic group but within the normal range and not statistically significant. The mean Thyroid Stimulating Hormone (TSH) in control group was 1.80±0.08 µIU/ml. it was 6.16±0.85 µIU/ml in preeclamtic group, significantly($p<0.001$) higher than that of control group (Table 2).

Table 2. Serum FT_3, FT_4 and TSH of the study subjects

Hormones	Cases (n=66) Mean ±SD/ N (%)	Controls (n=68) Mean ±SD / N(%)	t	p
FT_3 (pg/ml)	3.22±0.38	2.89±0.20	1.09	ns
FT_4 (ng/dl)	1.51±0.20	1.39±0.09	1.95	ns
TSH (µIU/ml)	6.16±0.85	1.80±0.08	6.77	<0.001

Results are expressed as mean ±SD; ns= not significant; Statistical difference was calculated using Student's unpaired 't' test.

The mean FT3 and FT4 in mild PE group were 3.55±0.21 pg/ml and 1.86±0.12 ng/dl respectively, which were significantly lower in severe PE. The mean TSH in mild PE group was 5.43±0.55 µIU/ml. It was slightly higher in severe PE but was not statistically significant (Table 3).

3. Serum FT3, FT4 and TSH in PE group on the basis of blood pressure.

Hormones	Mild PE (Sample group) (n=34)	Severe PE (Sample group) (n=32)	t	p
FT_3 (pg/ml)	3.55±0.21	2.86±0.07	5.32	<0.05
FT_4 (ng/dl)	1.86±0.12	1.34±0.08	2.39	<0.05
TSH (µIU/ml)	5.43±o.55	6.94±0.07	1.28	ns

Severe PE (DBP >110 mmHg); Results are expressed as mean ± SD; n=number of subjects; ns not significant; Statistical difference was calculated using Student's unpaired 't' test.

Discussion

The physiological changes in the thyroid gland during pregnancy are well understood but only a few reports provide information about thyroid function in complicated pregnancies. Preeclampsia is a serious complication of pregnancy with unknown etiology that may occur at any stage of second or third trimester.[10,11] Data on the level of thyroid hormones in Preeclampsia are still scanty and controversial.[12]

A prospective study was conducted by Qublan et al. (2003)[13] to determine the thyroid function in 27 severe preeclampsia and 26 healthy normotensive controls. Both the groups were matched according to gestational age. They found a statistically significant increase in terms of systolic blood pressure, diastolic blood pressure but there were no significant changes in the levels of free triiodothyronine (FT_3), free thyroxine (FT_4) and thyroid stimulating hormone (TSH) between the two study groups. They concluded that the thyroid function is not altered in preeclampsia. Their finding was in accordance with the current study by Khadem et al.(2012).[1]

Basbug et al. (1999)[14] conducted the study on 37 proteinuric preeclamptic and 20 normotensive pregnant women to measure thyroid hormones, TSH and endothelin. A significant decrease in concentrations of total thyroxine (TT_4), total triiodothyronine (TT_3), free thyroxine (FT_4) and free triiodothyronine (FT_3) and a significant increase ($p<0.01$) in thyroid stimulating hormone (TSH) were observed in preeclamptic group as compared with the normotensive group. The authors believed that changes in thyroid function during pregnancy are accounted for by high levels of circulating estrogen but the mechanism of hypothyroidism in preeclamptic women has not been identified. Lao et al. (1990)[15] measured plasma concentrations of total thyroxine (TT_4) and free thyroxine (FT_4), total triiodothyronine (TT_3) and free triiodothyronine (FT_3), thyroid stimulating hormone (TSH), plasma albumin and urate in 39 proteinuric preeclamptic patients presenting before labor. Preeclamptic patients had significantly lower FT_4 and higher TSH concentrations compared with values in third trimester normotensive pregnancies. The results suggested that mild biochemical hypothyroidism may be found in preeclampsia and the concentrations of TT_3, TT_4, FT_3 and TSH may reflect the severity of preeclampsia.

In this study, the mean TSH value was found to be significantly raised in preeclamptic patients as compared to comparison group. Mean serum Free Triiodothyronine (FT_3) and free Thyroxine (FT_4) in preeclamtic group were remain within normal limit and were not significantly differ than the control

group. It suggests that the subclinical hypothyroidism of the pregnant mother may be associated with the development of preeclampsia. In a study, Kumar et al. (2005)[16] observed that mean serum TSH levels were significantly increased without concomitant changes in free T3 and T4 in preeclampsia, Free thyroxine (FT_4) and free triiodothyronine (FT_3) were within normal limits in preeclamptic and normotensive groups. They also suggested that the abnormal TSH titers might be associated with the risk for manifestation of preeclampsia. However, it needs a further study to investigate the causal relationship of subclinical hypothyroidism to develop preeclampsia.

Several studies showed a relation between the level of thyroid hormones and development and severity of preeclampsia. Although pregnancy is usually associated with mild hyperthyroxinemia, preeclamptic women have high incidence of hypothyroidism that may correlate with the severity of Preeclamsia .[12,14,17] Moderate decrease in thyroid hormones with concomitant increases in TSH levels in maternal serum correlated with severity of preeclampsia. Patients with severe preeclampsia showed significantly lower levels of free T_4 and freeT_3 with higher levels of TSH levels in comparison with the mild cases. Changes in results of thyroid function tests induced by preeclampsia might be consequences of the dysfunction in the hypothalamic-pituitary-thyroid axis, secondary to the disease itself.[12,14] The findings of the present study was in accordance with these studies.

The results of this study have certain implication in clinical practice. Routine estimation of thyroid hormones and TSH in antenatal care of a pregnant mother might be the basis of risk assessment and as well as the hormones replacement therapy to prevent the preeclampsia as well as to prevent maternal and perinatal morbidity and mortality due to preeclampsia.

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