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Research Article

Association of Maternal Hypothyroidism with Preeclampsia in Bangladeshi population

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Abstract

Preeclampsia (PE) is a leading cause of perinatal morbidity and mortality. Our aim of the study was to evaluate the association of hypothyroidism with preeclampsia during pregnancy and after delivery. The study comprises a total of 52 subjects including PE women (n=27) and uncomplicated pregnant women (n=25) matched by age. The serum hormone levels were estimated by ELISA methods. The demographic data and hormone levels were analyzed using unpaired t test and pearson two tailed analysis was used for correlation. Over all, significantly decreased concentrations of total triiodothyronine (T3) and thyroxine (T4) were observed in the preeclamptic group ($p<0.001$; $p<0.01$, respectively) compared with the normal pregnant group while the thyroid stimulating hormone (TSH) level was significantly ($p<0.001$) high. On the other hand, significant differences in T3 ($p<0.05$) and T4 ($p<0.001$) levels were found during pregnancy and after delivery among PE patients while TSH level non-significantly ($p>0.05$) increased. There were negative correlations of TSH with T3 ($r=-0.16$; $p>0.05$) and T4 ($r=-0.11$; $p>0.05$) observed though these were not statistically significant. Our findings suggested that hypothyroidism is associated with preeclampsia, and after delivery thyroid function become more deteriorated. Therefore, identification of thyroid abnormalities and appropriate measures might affect the occurrence and severity of the morbidity and mortality associated with preeclampsia.

Keywords: Hypothyroidism, Preeclampsia, Perinatal morbidity, Pregnancy.

INTRODUCTION

A life threatening disorder during pregnancy and postpartum period is preeclampsia (PE). It is a triad of oedema, hypertension and proteinuria occurring primarily after the 20th gestational week and most frequently near term (Marbie et al., 1994). Intrauterine growth retardation (IUGR), pre-term delivery, low birth weight, fetal death and neo-natal death due to complications of pre-term delivery are common perinatal outcomes associated with preeclampsia (Ware-Jauregui et al., 1999). Preeclampsia affects between 0.4% and 2.8% of all pregnancies in developed countries and many more in developing countries, leading to as many as 8,370,000 cases worldwide per year (Villar et al., 2003). In developing nations, the incidence of the disease is reported to be 4-18%, (Villar, 2006). Though PE is a serious problem its etiology is still poorly understood. Currently, there is no reliable, valid and economic screening test available for predicting

this pregnancy related disease (Cunnigham et al., 2010). Maternal hypothyroidism is considered to be a key intermediary step in the pathogenesis of preeclampsia. 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 (Kumar et al., 2005).

Hypothyroidism is defined by the increased level of thyroid stimulating hormone (TSH) and decreased levels of triiodothyronine (T3) as well as thyroxine (T4) (Kharb et al., 2013). It's an endocrine disorder with varied but often subtle clinical manifestations. Some of these include cold intolerance, weight gain, sluggishness, and slow mentation (Ipadeola et al., 2014). The study of thyroid disease in pregnancy is important due to the fact that, common thyroid diseases have a strong female predominance and autoimmune and neoplastic thyroid diseases often occur in young adults (Niswander et al., 1972). Although pregnancy is usually associated with very mild hyperthyroxinemia, preeclamptic women have high incidence of hypothyroidism that might correlate with the severity of preeclampsia (Lao et al., 1988 & 1990; Kaya et al., 1994). On the other hand, preeclampsia has also been observed in 16.7% of sub-clinical cases and 43.7% of overt cases of hypothyroidism during pregnancy (Davis et al., 1988).

Many studies showed a relation between the level of thyroid hormones and development and severity of preeclampsia (Raoofi et al., 2013). Kumar et al. (2005) showed that mean serum TSH levels were significantly increased without concomitant changes in free T3 and T4 in preeclampsia and abnormal TSH titers might be associated with the risk for manifestation of preeclampsia. Recently several investigators showed that the level of TSH increased whereas the levels of T3 and T4 decreased in preeclamptic mothers compared to normal pregnant mothers (Mostagel et al., 2008; Kharb et al., 2013; Raofi et al., 2013). Though the effects of preeclampsia in thyroid function have been reported by several investigators the effects after delivery are not clear at all. One study (Levine et al., 2009) reported that women who experienced preeclampsia may have an increased risk for reduced thyroid functioning later in life.

Preeclampsia is also a common problem in Bangladesh. Though we showed the association of oxidative stress with preeclampsia in our previous study (Hawlader et al., 2007) the relation of hypothyroidism in preeclamptic women has not yet been studied in Bangladeshi women. Therefore, the objective of this study was to investigate the association between maternal thyroid function and peeclampsia during and after pregnancy.

MATERIALS AND METHODS

Study Subjects

The study was conducted on 52 subjects (27 preeclamptic pregnant women denoted as patients and 25 healthy pregnant women as control) matched by age. Preeclamptic pregnant women were recruited from Dhaka Medical College Hospital and uncomplicated pregnant women were recruited from Azimpur Maternity Hospital, Dhaka, Bangladesh.

Subjects were selected based on following criteria:

1. Systolic blood pressure greater than 140 mmHg or a raise of at least 30 mmHg.
2. Diastolic blood pressure greater than 90 mmHg or a raise of at least 15 mmHg.
3. Proteinurea of 300 mg in a 24 hours urine collection.
4. Antepartum and postpartum Preeclampsia.

Subjects with uncomplicated pregnancies were

normotensive throughout gestation and had no proteinurea.

Sample Collection

Blood samples were obtained during February 2012 to June 2012. Blood samples were taken two times from each subject; during pregnancy (1 to 3 days before delivery) and after delivery (1 to 3 days after parturition). About 5.0 mL of peripheral blood was drawn from each subject and transferred into a sterile glass tube. Samples were kept in an ice chamber following collection and during transportation to the laboratory. After centrifugation, serum samples were collected in microcentrifuge tubes and store at -20°C until estimation of T3, T4 and TSH.

Assay of Triiodothyronine, Thyroxine and Thyroid Stimulating Hormone

The thyroid gland related hormones T3, T4 and TSH were estimated by ELISA based method (Bandarkar and Pillai, 1974) using ELISA kits (Abcam, USA).

The T3 and T4 assay was based on the competition between thyroid hormones (T3 or T4) and a constant amount of T3 or T4 respectively conjugated with horseradish peroxidase enzyme. Antibody to T3 or T4 was coated on ELISA plate. A measured amount of serum and a constant amount of T3 or T4 labeled with horseradish peroxidase were added. After incubation at room temperature for 60 minutes, the wells are washed 5 times by water to remove unbound T3 or T4 conjugate. Then a solution of tetramethylbenzidine (TMB) reagent was added and incubated for 20 minutes, resulting in the development of a blue color. Finally the reading was taken at 450 nm by an ELISA reader. The concentration of hormone was inversely proportional to the color intensity. The determined value for T3 or T4 was expressed as nmol/L.

The TSH was estimated using two monoclonal anti-TSH antibody. A mouse monoclonal antibody against TSH was used to coat the ELISA plate. The serum sample was added to the plate. Then a goat monoclonal anti-TSH antibody conjugated with horseradish peroxidase was added into the plate. After incubation at room temperature for 2 hours, the unbound labeled antibodies were removed by repeated washing with water. Then a solution of tetramethylbenzidine (TMB) reagent was added and incubated for 20 minutes, resulting in the development of a blue color. The color development was stopped with the addition of Stop Solution changing the color to yellow. Finally the reading was taken at 450 nm by ELISA reader. The concentration of TSH was directly proportional to the color intensity of the test sample. The determined value for TSH was expressed as mIU/L.

Statistical Analysis

All the results were expressed as mean ± SEM. The statistical analysis of the data was carried out with Statistical Package of Social Science (SPSS), version 17 and Graph pad Prism version 5. The comparisons between two groups were tested by unpaired t-test. A 95% confidence interval was used. *P* values less than 0.05 were considered as statistically significant. Correlations of TSH with T3 and T4 among the patients were evaluated using Pearson correlation coefficient.

RESULTS

Statistically significant differences among complicated and uncomplicated pregnancy are indicated in Table 1 to 2 and in Figure 1 to 2 along with their significant values.

Table 1: Baseline characteristics of the study subjects.

Parameters	Mean ± SEM		*p value*
	Control (n=25)	PE Patient (n=27)	
Maternal ages (years)	26±0.1	25.04±0.1	ns
Gest. ages (weeks)	38.36±0.7	34.11±0.5	< 0.001
Birth weight (kg)	2.9±0.1	2.2±0.1	< 0.001

Unpaired t-test was done as the test of significant. P<0.05 was taken as level of significance. PE; Preeclampsia.

Clinical and laboratory data

These clinical and laboratory data are shown in Table 1 and in Figure 1. The maternal age of study subjects was not significantly different. On the other hand, the

gestational age was significantly decreased in preeclampsia as compared with normal pregnancy (p<0.001) (Table 1). The fetal weight was also significantly lower in preeclampsia as compared with normal pregnancy (p<0.001) (Table 1). As shown in Figure 1 the systolic and diastolic blood pressure (BP) levels were significantly lower in normal pregnancy as compared with preeclampsia (p<0.001, respectively).

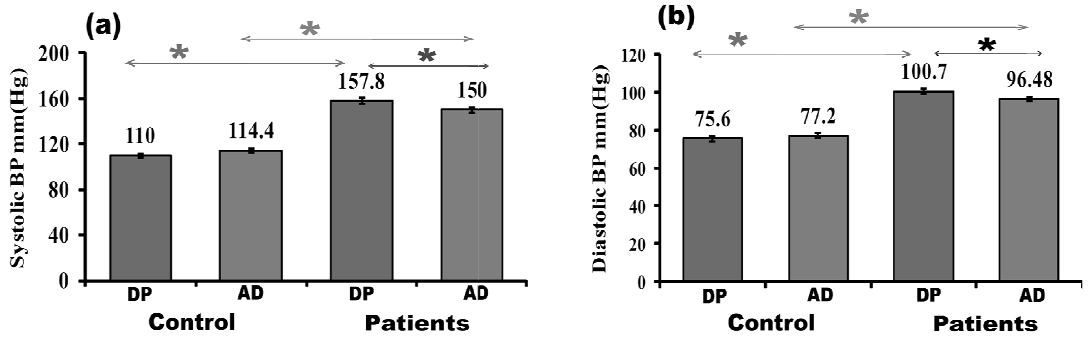

Figure 1: (a) Systolic and (b) Diastolic blood pressure of study subjects at different period. Unpaired t-test was done as the test of significant. P<0.05 was taken as level of significance. DP; During pregnancy, AD; After delivery. Control; Normal pregnancy, Patients; PE: Preeclampsia patients.

Analysis of thyroid hormones

As shown in Table 2 the serum level of total T3 was significantly lower in PE patients both during pregnancy and after delivery compared (p<0.001for both) to healthy control. The total T3 level was also significantly lower (p<0.05) in the patients after delivery (Table 2). The values of T4 in serum were significantly higher in control women compared (p<0.01, p<0.001 respectively) to PE patients both during pregnancy and after delivery. When we compared the results of patients during pregnancy and after delivery we found significant (p<0.001) decreased in values of T4 after delivery. We also found significantly increased level of TSH in serum of PE patients both during pregnancy and after delivery when compared (p<0.001 for both) to the control. On the other hand, the total TSH level increased in patients after delivery which was non-significant (table 2).

Table 2: Levels of thyroid hormones in study subjects.

Parameters	During pregnancy			After delivery		
	Control (n=25)	Patients (n=27)	p value	Control (n=25)	Patients (n=27)	p value
T3 (nmol/L)	1.86 ± 0.16	1.43 ± 0.09	<0.001	1.80 ± 0.08	1.19 ± 0.05*	<0.001
T4 (nmol/L)	150.7 ± 4.5	131.9 ± 4	<0.01	159.2 ± 3.5	107.9 ± 2.7‡	<0.001
TSH (mIU/L)	2.00 ± 0.17	5.09 ± 0.46	<0.001	2.99 ± 0.15	5.17 ± 0.38†	<0.001

Results are expressed as Mean±SEM. Unpaired t-test was done as the test of statistical significant. p<0.05 was taken as level of statistically significant. (; p<0.05, ‡; p<0.001 †; p>0.05, comparison among patients during pregnancy and after delivery).*

Correlation of T3 and T4 with TSH

Correlation of TSH with T3 and T4 among the patients during pregnancy were estimated and showed in figure 2 along with their significant values. There were negative correlations between TSH with T3 and T4 levels but that was not statistically significant (Figure 2a and 2b respectively).

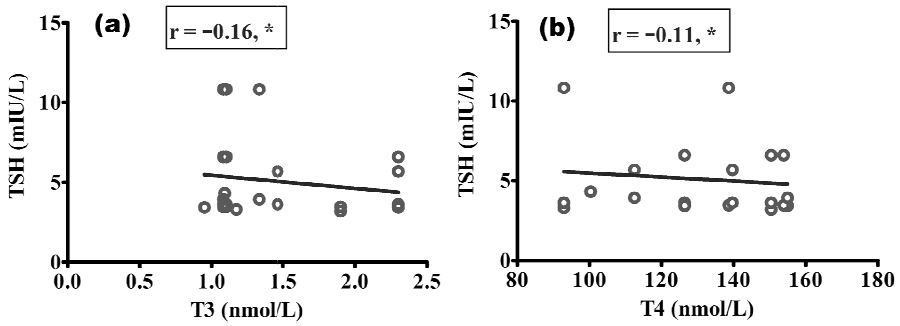

Figure 2: Correlation of TSH level with (a) T3 and (b) T4 level among the patients.*; $p>0.05$

DISCUSSION

Although there are no reliable, valid and economic screening tests available for predicting this pregnancy related disease (Cunnigham et al., 2010) but some studies showed an association between the levels of thyroid hormones and development of preeclampsia. In this study, we studied the effects of thyroid hormones in preeclampsia during pregnancy and after parturition.

We found significantly increased level of total TSH and decreased levels of T3 and T4 in preeclamptic mothers compared to normal mothers (Table 2) which is in accordance with the study of Kumar et al. (2005). Recently several research investigators also reported the significant association of thyroid hormones with the development and severity of preeclampsia (Mostaghel et al., 2008, Raoofi et al., 2013; Kharb et al., 2013; Ipadeola et al., 2014). The levels of thyroid hormones were also measured after parturition. The thyroid hormones levels were also significantly different among the study subjects. On the other hands T3 and T4 levels were significantly lower after delivery among preeclampsia patients while TSH non-significantly increased (Table 2). This result suggested that the thyroid function become more deteriorated after delivery in preeclampsia patients. Levine et al., (2009) reported that women who experienced preeclampsia might have an increased risk for reduced thyroid functions later in life.

In our study correlations analysis of TSH with T3 and T4 showed negative correlation though these were not statistically significant. There were several other studies that reported the negative correlation between thyroid hormones (Kharb et al., 2013; Qublan et al., 2003).

There are controversies about the mechanism and clinical significance of low concentrations of thyroid hormones in preeclampsia, which are attributed to decreased plasma protein concentrations (Lao et al., 1988) and high levels of endothelin, (Basbug et al., 1999) a potent vasoconstrictor produced by vascular endothelium after a vascular injury. On the other hand, 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 (Alfadda and Talima, 2004; Negro and Mestman, 2011). The mechanism of hypothyroidism in preeclamptic women has not been identified but the changes in thyroid function during pregnancy are accounted for by high circulating estrogens (Brent et al., 1999). So reduced serum concentration of T3 and T4 may be explained by faulty production of estrogen due to placental dysfunction in preeclamptic women.

In conclusion, women who develop preeclampsia are more likely to have lower normal limits of thyroid function during the final weeks of their pregnancies. Therefore, identification of thyroid abnormalities and appropriate measures might affect the occurrence and

severity of the morbidity and mortality associated with preeclampsia. The association between thyroid function and preeclampsia needs further investigation among Bangladeshi population because of the small number of subjects in this study.

CONFLICTS OF INTEREST

No competing financial interests exist.

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