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Research Article

THYROID HORMONAL STATUS IN PREGNANCY AND PRE-ECLAMPSIA AND ITS CORRELATION WITH MATERNAL AGE AND PARITY

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ABSTRACT
Pre-eclampsia is defined as a triad of hypertension, edema and proteinuria. It usually occurs after 20 weeks of gestation producing cardiovascular, hematological, endocrinological and biochemical changes. It is a well recognized cause of maternal & fetal morbidity & mortality. A state of hypothyroxinemia exists in normal pregnancy, which is more pronounced in pre-eclampsia. The mechanism of hypothyroidism in pre-eclamptic women has not yet been clearly identified, but the changes in thyroid function during pregnancy are accounted for by high circulating estrogen levels. Aims and Objectives of the study was 1) to evaluate the thyroid hormonal status in normotensive pregnant females and in patients with pre-eclampsia. 2) to evaluate the influence of maternal age and parity on thyroid functions. 3) to find the correlation of thyroid hormones with albumin. A case control study was conducted on 40 diagnosed patients of preeclampsia and 40 age and parity matched normotensive pregnant subjects in the age group 20-40 years with singleton pregnancy, venous blood samples from both the groups were collected and assayed for thyroxine (T4), Tri-iodothyronine (T3), Thyroid Stimulating Hormone (TSH) and serum albumin. Serum TSH was increased significantly while T4 and T3 were decreased in pre-eclampsia as compared to normal pregnancy. No influence of parity and maternal age was observed on thyroid functions. A significant positive correlation was observed between serum albumin and T3 & T4 levels in preeclampsia, while there was a negative correlation between serum albumin levels and TSH. In the present study the result shows that T4 and T3 are significantly lower and TSH is significantly increased in pre-eclamptic patients compared to normotensive pregnant females. There is no effect of maternal age on thyroid functions in the patients, neither there is any difference in the two parity groups. Thyroid disorder may thus be one of the predisposing causes for pre-eclampsia. Hence, thyroid hormonal assay may be considered as a screening test for early diagnosis and treatment of pre-eclampsia and prevention of its complications.

Keywords: *Preeclampsia, Hypothyroid, Pregnancy, Maternal Age, Parity, Albumin*

INTRODUCTION
Pre-eclampsia is a fairly common complication of pregnancy affecting about 5% of all pregnancies. Preeclampsia was classically defined as a triad of hypertension, edema and proteinurea. Preeclampsia adversely affects the maternal and fetal outcome due to its widespread multi organ involvement thus, showing its effect on the endocrinological, hematological and biochemical parameters. The incidence in primigravida is about 10% and in multigravida 5%. Due to its widespread multi organ involvement, preeclampsia is regarded as one of the most common causes of perinatal morbidity and mortality resulting in an estimated 35 ~ 300 deaths per 1000 births depending on neonatal support.
Preeclampsia is more prevalent in developing countries like Bangladesh where poverty, malnutrition, micronutrient deficiencies, early marriage, early child birth and lack of antenatal care are more common. Numerous theories of potential causes exist including genetic, dietary, vascular and auto immune factors. The causes of preeclampsia remains unknown however, placental dysfunction may initiate the systematic vasospasm, ischemia and thrombosis that eventually damages maternal organs. Preeclampsia has been shown to have pronounced effect on thyroid gland.
However, during normal pregnancy, changes in thyroid function are well documented, but information about thyroid function in complicated pregnancy is scanty. It has long been recognized that maternal

thyroid hormone excess or deficiency can influence maternal & fetal outcome at all stages of pregnancy and can interfere with ovulation and fertility. Normal pregnancy entails substantial changes in thyroid function and major alterations in the thyroid system during pregnancy can be seen.

Firstly, there is an increased blood concentration of T4-binding globulin. Thyroid Binding Globulin (TBG) is one of several proteins that transport thyroid hormones in blood, and has the highest affinity for T4 (Thyroxine) of the group. Estrogen stimulates expression of TBG in liver, and the normal rise in estrogen during pregnancy induces roughly a doubling in serum TBG concentrations.

Increased levels of TBG, leads to an increase in the extra thyroidal pool of thyroid hormones, consequently, enhanced production and secretion of thyroid hormones. The net effect of elevated TBG synthesis is to force a new equilibrium between free and bound thyroid hormones and thus, a significant increase in total T4 and T3 levels.

The increased demand for thyroid hormones is reached by about 20 weeks of gestation and persists until term. Secondly, there is an increased demand for iodine. This results from a significant pregnancy-associated increase in iodide clearance by the kidney (due to increased GFR), and siphoning of maternal iodide by the fetus.

The WHO recommends increasing Iodine intake from the standard 100 TO 150 µG/day to atleast 200 µG/day during pregnancy. Thirdly, thyroid stimulation by human chorionic gonadotropin (HCG) is seen. The human placentae secrets huge amounts of a hormone called HCG. The subunit of HCG is identical to that of TSH and has a weak thyrotropic effect. TSH and HCG are similar enough in that HCG can bind and transduce signaling from the TSH Receptor on thyroid epithelial cells. Toward the end of the first trimester of pregnancy in humans, when HCG levels are highest, a significant fraction of the thyroid-stimulating activity is from HCG. During this time, blood levels of TSH often are suppressed. The thyroid-stimulating activity of HCG actually causes some women to develop transient hyperthyroidism. The net effect of pregnancy thus, is an increased demand on the thyroid gland.

In contrast to normal pregnancy, in preeclampsia there is a failure of estrogen production due to placental dysfunction resulting in lowering of TBG, TT3, TT4 along with growth retardation of the fetus.

Oxidative stress and altered endothelial cell activation have also been postulated to play a role in the pathogenesis of preeclampsia. In preeclampsia, there is an increase in superoxide anion which inactivates nitric oxide (no). This in turn leads to decrease relaxation and increase vasoconstriction pathognomic of preeclampsia.

Increasing evidences have gathered to substantiate that hypothyroidism alters the release of no thus leading to endothelial cell dysfunction, which might be a pathogenic mechanism for hypothyroidism in preeclampsia.

As in normal pregnancy, there are different views about the mechanism and clinical significance of low concentrations of thyroid hormones in preeclampsia, which are attributed to decrease plasma protein concentrations and high levels of endothelin.

High levels of certain molecules in the blood like soluble FMS-like tyrosine kinase 1 (SFLT-1) may cause symptoms of preeclampsia. This molecule acts by blocking a protein called vascular endothelial growth factor (VEGF). Previous studies have found that some cancer patients receiving treatments that block VEGF have developed hypothyroidism.

Thus, the presence of SFLT-1 in blood in patients of preeclampsia may predispose them to hypothyroidism. Studies conducted at various levels have found that the increase in the level of TSH is strongly associated with increasing levels of SFLT-1, hinting a correlation between the severity of blood pressure and the levels of thyroid hormones

Also, certain studies conducted by national institutes of health have documented that women who had preeclampsia during their pregnancies were more likely to have reduced thyroid functioning more than 20 years after they had given birth, when compared to women who had not had preeclampsia during pregnancy.

Thus, even though there is a state of hypothyroxinaemia during normal pregnancy, it is more pronounced in preeclampsia.

During preeclampsia, there is involvement of the liver and kidney. It has been suggested that that the reduced serum concentration of thyroid hormones in preeclampsia may be in part explained by the loss of protein and protein bound hormones in urine.

11] Previous research states that preeclampsia among nulliparous women is associated with a greater subsequent risk of SCH in pregnancy. And women with a H/0 preeclampsia are at a greater risk of hypothyroid functions many years after preeclampsia. The findings of this study have important implications for the subsequent care of the women with PE. Women with PE should be followed closely for the development of CVD and renal disease thus, warranting the measurement of thyroid hormones in preeclampsia.

Few studies have been done in the recent past to demonstrate the difference in the thyroid status in normotensive pregnant females and preeclamptic females. A study done by Manjunathan *et al.*, (2014) showed that there was a significant increase in TSH levels in preeclampsia than in normal pregnancy [Hyperlink \L "THY14" 11].

A study conducted by Asmehan (2010) suggested that preeclampsia among nulliparous women is associated with a greater subsequent risk of subclinical hypothyroidism in pregnancy and women with a history of preeclampsia are at greater risk of hypothyroid function many years after preeclampsia. Further, they even found that the mean TSH levels were significantly increased in mild and severe preeclamptic women compared with healthy normotensive pregnant ones.

Aims and Objectives

1) The study was conducted to evaluate the functioning of thyroid gland in normotensive pregnant females and in patients with pre-eclampsia.
2) To evaluate the influence of maternal age and parity on thyroid functions.
3) To find the correlation of thyroid hormones with albumin.

MATERIALS AND METHODS

A case control study was conducted from June 2014 to July 2015 at the Department of Biochemistry, GMCH on 40 diagnosed patients of preeclampsia and 40 age and parity matched normotensive pregnant subjects in the age group 20-40 years with singleton pregnancy.

- Venous Blood samples from both the groups were collected. All samples were sent to the laboratory with different code numbers. Sera was separated and stored at -20° C until assayed. Assays for Thyroxine (T4), Tri- iodothyronine (T3), Thyroid stimulating hormone (TSH) and serum Albumin were performed.
- Written informed consent was taken from both the case and the control group.
- Inclusion criteria - 40 diagnosed patients of preeclampsia (BP > 140/90mmHg & proteinuria >300mg/l in 24 hour) after 20 weeks of gestation were included in the case group and controls were 40 matched normotensive pregnant subjects.
- Both groups had no history of thyroid disease before pregnancy.
- Exclusion criteria:

Patients with:

1. History of hypertension, renal disorders, cardiovascular diseases
2. Any metabolic disorders before or during the pregnancy and
3. History or intake of any medication such as levothyroxine that may have an effect on thyroid function.

RESULTS AND DISCUSSION

In the present study, the results shows that TT_3 and TT_4 are significantly lower and TSH is significantly increased in pre-eclamptic patients compared to the value in control group. There is no effect of maternal age in the patients neither there is any difference in the two parity groups.

Kumar *et al.*, (2005) observed similar findings in pre-eclamptic and eclamptic women with high TSH level and low thyroid hormones. Their finding suggested that preeclamptic women had higher incidence of biochemical hypothyroidism compared with normotensive pregnant women. It has been suggested that

reduced concentration of thyroid hormones in preeclampsia may be due to the loss of protein-bound hormones in the urine.

Similar findings were put forward by Sardana *et al.,* (2009) who observed that TSH levels in pre-elampsia were higher than that of normotensive pregnant females but higher than that in non-pregnant females ($p<0.001$).

There is an increase in TBG in pregnancy due to estrogen and as approximately as 99.97% of TT4 is bound to TBG. So, assessment of the Total T4 value is difficult. Also, it was suggested that reduced concentration of thyroid hormones in pregnancy may be due to loss of protein and protein bound hormones in the urine. Since T3 is mostly the peripheral conversion of T4, the decrease in T3 level is associated with the T4 level and is a normal consequence besides involvement of liver and kidneys in pre-eclampsia.

Satyanarayan *et al.,* (2015) in their study showed that thyroxine (T4) and tri-iodothyronine (T3) levels showed no difference between the normal pregnancy (9.03 ± 1.18, 1.21 ± 0.3) and pre-eclampsia patients (10.16 ± 1.13, 1.25 ± 0.11), but TSH levels in pre-eclampsia patients were increased (7.22 ± 1.3) when compared to normal pregnancy ($p = 0.0001$).

Tolino *et al.,* (1985) have reported low T3 levels in the presence of normal or raised T4. This is known as low-T3 syndrome and has been observed by some authors in pre-eclampsia. But in the present study we did not find any such finding.

Osanthanondh *et al.,* (2009) in their study showed that in patients with pre-eclampsia, the mean serum T_3 concentration was significantly lower than that of normal pregnancy and the serum FT_3 concentrations in three out of nine patients were below the normal pregnancy range. The mean serum T_4 and FT_4 concentrations in patients with preeclampsia were, however, significantly higher than those in normal pregnant women.

In the present study, the correlation between TT3 and albumin is significant and direct, as most of the T3 is bound to plasma proteins.

So, proteinurea accounts for its increased loss. While the concentration of albumin with TT4 is not significant as is found in studies by Lao *et al.,* (1990) as the values of TT4 depends on the different degree of saturation with TBG of TT3 and TT4.

The correlation between TSH and albumin is significant and inverse because the preeclamptic patients are in a state of hypothyroidism.

Women who experience preeclampsia, a serious complication of pregnancy, may have an increased risk for reduced thyroid functioning later in life, report a team of researchers from the National Institute of Health Sciences, USA.

Also, the low T3 and T4 levels reflect the severity of preeclampsia and these patients tend to have LBW babies.

The findings of this study have important implications for the subsequent care of the women with preeclampsia and routine screening of thyroid hormone levels during pregnancy.

Table 1: Mean Values in Normal Pregnancy and in Pre-Eclampsia

Mean ±SD	Control (Normal Pregnancy)	Case (Pre-eclampsia)	P Value
Age(Years)	26.19±2	26.15±4	
Parity	1.30±0.88	1.28±0.90	
TT3(ng/dl)	195.6±7.41	150.62±10.32	<0.05*
TT4(µg/dl)	14.36±1.11	11.31±0.94	<0.05*
TSH(µIU/ml)	4.65±1.34	8.64±0.34	<0.05*
Albumin(g/dl)	4.95±0.49	2.86±0.34	<0.05*

*p<0.05 is significant

The comparison of thyroid functions between normal pregnancy and pre-eclampsia is shown in Table 1. Serum TSH increased significantly while TT_4 and TT_3 decreased significantly in pre-eclampsia as compared to normal pregnancy.

Table 2: Thyroid Hormone Levels According to Maternal Age in both the Groups

		Age<30 Yrs	Age>30 Yrs	P Value
TT3	Normal	193.5±8.30	198.75±4.20	0.4
	PEP	153.54±12.61	149.09±8.84	0.11
TT4	Normal	14.11±1.05	14.72±1.09	0.07
	PEP	11.43±1.09	11.20±0.88	0.09
TSH	Normal	2.37±0.6	2.29±0.20	0.1
	PEP	3.63±0.70	3.84±0.40	0.6

$p<0.05$ is significant.

The thyroid functions in the two age groups (< 30 years and >30 years) in normal and preeclamptic pregnancy is shown in Table 2. There was no significant change in the levels of TSH, TT3 and TT4 in the two groups.

Table 3: Comparison of Thyroid Functions in Primipara and Multiparous Woman

		Primiparous	Multiparous	P Value
TT3	Normal	197.66±6.94	192.5±7.01	0.3
	PEP	3.57±0.66	3.94±0.28	0.9
TT4	Normal	14.81±0.81	13.67±1.15	0.06
	PEP	11.64±1.10	10.96±0.69	0.08
TSH	Normal	2.25±0.27	2.47±0.09	0.07
	PEP	3.57±0.66	3.94±0.28	0.5

$p<0.05$ is significant.

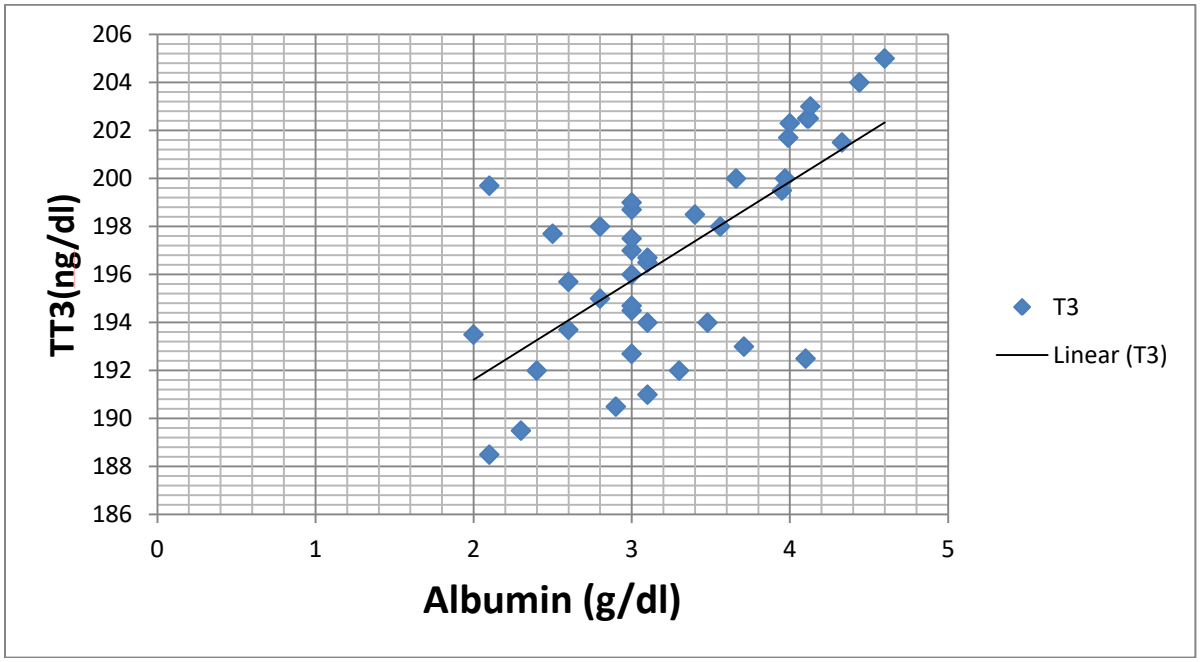
The thyroid functions were compared for both the groups in the multiparous and primiparous women and the values are shown in Table 3. There was no significant change in TSH, T_3 and T_4 in the two parity groups.

Table 4: Correlation between Thyroid Hormones and Maternal Age, Parity, Albumin in Preeclampsia

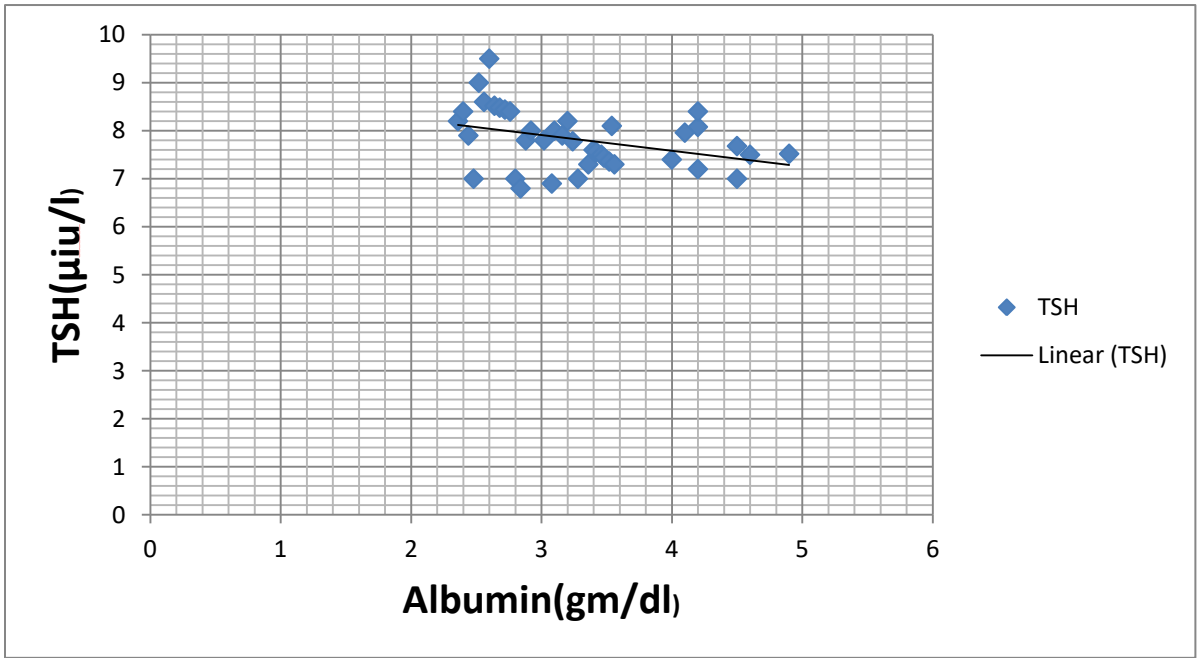
	TSH		TT3		TT4	
	R	P Value	R	P Value	R	P Value
Maternal age	0207	0.09	0.190	0.140	0.156	0.150
Parity	0.143	0.105	0.212	0.099	0.243	0.109
Albumin	-0.531	<0.05*	0.672	<0.001*	0.180	0.190

*$p<0.05$ is significant.

Serum Albumin decreased significantly from 4.95± 0.49gm/dl in normal pregnancy to 2.86± 0.34 in pre-eclampsia ($p< 0.05$). The correlation of serum Albumin with TT_3 was significant and direct ($r=-0.531; p<0.001$) while with TSH was significant and inverse ($r=0.672; p<0.05$). There was no correlation between serum Albumin and TT_3 (Table 4).



Graph 1: Correlation of TT3 with Albumin (r=0.62)



Graph 2: Correlation of TSH with Albumin (r=-0.531)

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