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Thyroid Stimulating Hormone As A Possible Predictor Of Preeclampsia

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Abstract
Background*- Thyroid disorders constitute one of the most common endocrine disorders in pregnancy.Thyroid undergoes profound modification in pregnancy but less study has been done on thyroid function changes in preeclampsia . Pregnancy is associated with increased total thyroxin (T4) and, in preeclampsia, biochemical hypothyroidism occurs (i.e. raised thyroid-stimulating hormone, TSH). Hypothyroidism has been listed as one of the causes of high blood pressure.****Material and Methods****-The present study was carried out on the pregnant women in their second and third trimesters attending outpatient department of obstetric and gynaecology from October2012 to September2014. 100 Preeclamptic women were included in the study group and 50 normotensive women were included in the control group. Both groups were screened for hypothyroidism and the data so collected entered into MS exel and data analysis done.****Result****- Incidence of hypothyroidism in normotensive pregnant women was 12% and the incidence of hypothyroidism in preeclamptic women was 42%. The mean (±SD) TSH of the study and control group was 2.407±0.171mIU/L and I.5±0.954mIU/L respectively. The mean (±SD) fT3 of the study group and control group were 1.422±0.621 pg/ml and 1.604±0.63 pg/ml respectively. The difference in the number of pregnant women of the two groups having high TSH titre was also significant. More number of preeclamptic women had increased serum TSH level at the time of diagnosis when compared with normotensive pregnant women.****Conclusion****- In the present study, serum TSH was significantly higher in preeclamptic women than in normotensive women and fT3 and fT4 were slightly lower in preeclamptic women. Since pregnancy is generally associated with hyperthyroxinemia, degree of hypothyroxinemia might reflect the severity of preeclampsia.*

Keywords*-Preeclampsia,thyroid stimulating hormone,pregnancy.*

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I Introduction

Preeclampsia is a multisystem disorder of unknown etiology and is a major cause of maternal and fetal morbidity and mortality. It complicates 2-8% of pregnancies and account for more than 50,000 maternal deaths worldwide.Preeclampsia was previously determined by EPH, an abbreviation for edema, proteinuria and hypertension. The term has been changed because of a very high incidence of generalized edema in healthy pregnant women. According to the new definition, the disease is now defined by high blood pressure and proteinuria.Diagnostic criteria for preeclampsia are hypertension(Blood Pressure of more than 140/90 mm Hg on atleast two occasions and at least 4-6 hours apart after the 20th week of gestation. It is severe if Blood Pressure is >160/110 mmHg) and proteinuria(Urinary protein excretion of >300mg per 24 hours. Excretion of protein >5g per day is considered severe). Dipstick proteinuria of >1+ correlates to a protein concentration of >300mg/l.

Tissue edema is no longer used as a diagnostic criteria as it occurs in about 80% of healthy pregnant women, but it is markedly increased in women with Preeclampsia compared to normal pregnancies. Quick increase of edema and weight gain of >1kg a week are considered dangerous.Risk factors that may cause preeclampsia are- age <20 and >35, previous preeclampsia,BMI>35,Gestational or pre-existing diabetes mellitus ,Family history of preeclampsia,Primigravida,Multiplegestation,Chronic hypertension, Nephropathy. Preeclampsia has been called the 'disease of theories'. Despite enormous efforts in research over the past decades, the etiology of PE still remains elusive. Some of the theories trying to explain the etiology and pathophysiology of preeclampsia are-impaired placentation,impaired angiogenesis,genetic, Loss or

dysregulation of maternal immune tolerance to paternally derived placental and fetal antigen, endothelial dysfunction.

Pregnancy is associated with profound modifications in the regulation of thyroid function. These changes are the result of various factors like an increase of thyroxin binding globulin (TBG) due to elevated estrogen and human chorionic gonadotrophin (HCG), increase renal losses of iodine due to increased glomerular filtration rate, modification in the peripheral metabolism of maternal thyroid hormones, and modification in iodine transfer to the placenta.During pregnancy, thyroid undergoes physiological changes, such as moderate enlargement of the gland and increasing of vascularization. Human chorionic gonadotropin (hCG) causes thyroid stimulation since the first trimester, due to structural analogy with thyroid-stimulating hormone (TSH). The thyrotropic activity of hCG also causes a decrease in serum TSH in the first trimester so that pregnant women have lower serum TSH concentrations than non-pregnant women.The circulating levels of thyroid-binding globulin (TBG) are also increased due to increased hepatic synthesis and estrogen mediated prolongation of TBG half-life from 15 minutes to 3 days, a few weeks after conception and reaches a plateau during mid-gestation.On the other hand the increased renal clearance of iodine, fetal intake and placental metabolism causes a relative decline in the availability of iodide.Hence, total concentrations of thyroxine (T4) and of triiodothyronine (T3) increase in early pregnancy and achieve a plateau early in the second trimester, reaching a concentrations value of 30–100% greater than prepregnancy state, primarily following the rise in TBG.

However some authors have reported a decrease of free T4 and T3 concentrations, whereas others have reported no change or even an increase; therefore changes in free-hormone during pregnancy are controversial, though pregnant women in general have lower free-hormone concentrations at term than non-pregnant women.

Serum TSH has been reported to be increased whereas free triiodothyronine (FT3) and FT4 decreased with gestational age by Ashoor et al. (2010 a). There is a transient rise in FT4 in the first trimester due to the relatively high circulating human chorionic gonadotropin concentration and a decrease of FT4 in the second and third trimester, although within the normal reference range. Changes in FT3 concentration are also seen parallel to the FT4, within the normal range. The decline in free thyroid hormones may be due to interaction of TSH, estrogen and thyroid-binding proteins.

Thyroglobulin frequently increases during pregnancy reflecting an enhanced activity of the thyroid gland. The fetal thyroid begins concentrating iodine and synthesizing thyroid hormones after 12 weeks of gestation; before this time thyroid hormone is supplied by maternal reserves, in order to promote the physiological fetal brain development.

Thyroid disorders constitute one of the most common endocrine disorders in pregnancy. Overt hypothyroidism complicating pregnancy has been reported to be 2%-3%. Women with thyroid dysfunction overt and subclinical are at increased risk of pregnancy related complications such as threatened abortion, preeclampsia ,preterm labour, placental abruption ,and postpartum hemorrhage. 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. Fetal complications include low birth weight babies, preterm deliveries, intrauterine growth restriction, fetal loss, still birth and neonatal death. There is also some evidence that subclinical hypothyroidism, defined by an increased serum concentration of TSH in the presence of normal levels of T4 and triiodothyronine (T3) is associated with adverse neuropsychological development of the child.

The mechanism of thyroid function alteration in preeclamptic women is not well understood. In preeclampsia, there is failure of estrogen production due to placental dysfunction, resulting in lowering of TBG, TT3 and TT4 that result into biochemical hypothyroidism. FT4 concentration is not related to plasma albumin. It also result in growth restriction of fetus. Mild alteration in the thyroid hormones might occur due to non-thyroidal illness acting as a stress factor as well as due to decreased plasma albumin concentrations in these patients. Serum total T3 (TT3) and TT4 decreases significantly and TSH increases significantly in preeclamptic women in their third trimester. The titers of fT3 are reported to be significantly related to the decreased plasma albumin concentration in preeclamptic women. Also it has been suggested that reduced serum concentrations of thyroid hormones in preeclampsia may be due to the loss of protein and protein-bound hormones in the urine.

In preeclampsia, an increase in superoxide anion due to oxidative stress, which may inactivate NO, leads to reduced relaxation and increased vasoconstriction. Also Nitric oxide, a vasodilator released from the endothelial cells, regulates secretion of thyroid hormones by modulating regional blood flow. Animal studies showed that the release of nitric oxide is altered in hypothyroidism . Hence this hampered release of nitric oxide in hypothyroidism causing endothelial cell dysfunction might play an important role in the pathogenesis of preeclampsia

The decrease in thyroid hormones with concomitant increase in TSH titers has been found to be correlated with the severity of preeclampsia.

Also it has also been observed that preeclamptic and eclamptic women with higher TSH levels along with lower thyroid hormones are more likely to have small for gestation newborns. TT4 and TT3 concentrations in preeclamptic and eclamptic women correlated positively with the birth weight of their infants.Lao et al (1990) observed a negative correlation between the birth weight of the infants and TSH levels in preeclamptic patients.

Another reason for reduced thyroid hormone in preeclampsia may be due to increased soluble fms-like tyrosine kinase (sFlt1). Soluble fms-like tyrosine kinase (sFlt1) is a protein that inhibits blood vessel growth. Blood concentrations of sFlt1 normally increase during the last two months of pregnancy, but concentrations are much higher in women with preeclampsia. sFlt1 known to inhibit the action of several different proteins, including vascular endothelial growth factor (VEGF). Certain drugs, called VEGF inhibitors, function similarly to sFlt1 and inhibit VEGF. These drugs, which are used to treat various illnesses and other conditions, including cancer, can cause side effects, such as increased blood pressure and reduced thyroid activity (hypothyroidism).

Because VEGF inhibitors can cause hypothyroidism, researchers studying the effects of increased sFlt1 in preeclampsia examined whether excess sFlt1 during preeclampsia is associated with hypothyroidism. The researchers in the NICHD's DESPR analyzed blood samples taken from 141 pregnant women at baseline (21 weeks of pregnancy) and again after the onset of preeclampsia. The women who developed preeclampsia had evidence of reduced thyroid function, which included increased blood levels of thyroid-stimulating hormone (TSH).

The researchers next measured TSH levels from a large group of women (7,121 women) who previously had preeclampsia to test whether preeclampsia was associated with hypothyroidism later in life. These women were from the Nord-Trondelag Health Study. Blood samples for TSH measurements were collected approximately 20 years after pregnancy. Blood samples from a group of women who did not have preeclampsia served as the controls. Similar to the earlier findings that TSH was increased during pregnancy in preeclamptic women, TSH was also increased 20 years after preeclamptic women had given birth, indicating long-lasting thyroid function effects.

These findings indicate that preeclampsia is associated with reduced thyroid function during and many years after pregnancy.

Thyroid disorders are relatively frequent in women of childbearing age. Moreover, overt and subclinical hypothyroidism and hyperthyroidism are associated with poor pregnancy outcome. Therefore, the correction of maternal thyroid dysfunction during all stages of pregnancy is very important for the health outcome for both mother and fetus.

Serum TSH provides the most sensitive test to reliably detect thyroid function abnormalities. During pregnancy the lower and upper reference limits for serum TSH are decreased by about 0.1-0.2 mIU/L and 1.0 mIU/L, respectively, compared to the TSH reference interval of 0.4–4.0 mIU/L ofnonpregnant women. The Endocrine Society and the most recent American Thyroid Association (ATA) guidelines recommend using a TSH upper limit value of 2.5 mIU/L for preconception and the first trimester and 3.0 mIU/L for the second and third trimesters. In accordance with the new ATA guidelines for women in pregnancy, trimester-specific reference intervals for TSH, as defined in populations with optimal iodine intake, should be applied, even though many commercial laboratories still do not provide these reference ranges.

TRIMESTER	TSH (mIU/L)
First trimester	0.1-2.5
Second trimester	0.2-3
Third trimester	0.3-3

Serum TSH has been known as most reliable indicator of thyroid function tests. Hence the present study has been planned to study thyroid hormones in preeclamptic women and in normotensive women.

II Methods

This study was conducted in the Obstetrics and Gynaecology department of PMCH, Patna from October 2012 to September 2014. The study was carried out on 100 women with preeclampsia admitted or attending the outpatient department of obstetric and gynaecology. 50 age and parity matched normotensive pregnant women served as control. Inclusion criteria of preeclampsia were blood pressure of>140/90mmHg on atleast two occasions , six hours apart and or proteinura. Exclusion criteria were: history of chronic hypertension, any renal disease, any metabolic disorder or medication that may affect thyroid function. Study samples for thyroid hormone assay were drawn before starting any treatment. The current third generation chemiluminescent immunoassays for detection and quantificaton of TSH is used. Following the most recent guideline recommended by Endocrine Society and American Thyroid Association (ATA), upper limit value of 2.5 mIU/L for the first trimester and 3.0 mIU/L Sr TSH for the second and third trimesters is used. Both groups

were screened for hypothyroidism. Data were entered and analysed in MS Excel. Ethical clearance was taken from ethical committee.

III Results

TABLE- 1SHOWING DISTRIBUTION OF CASES IN STUDY AND CONTROL GROUP

CASES	NUMBER	PERCENTAGE %
STUDY	100	66.66
CONTROL	50	33.33

Total number of cases in the study group were 100 and 50 in the control group.

TABLE- 2SHOWING AGE DISTRIBUTION OF CASES IN STUDY AND CONTROL GROUPS

AGE GROUPS	STUDY N=100	CONTROL N=50
< 20	15	9
20 - 24	45	19
25 - 30	23	18
> 30	17	4

Maximum number of cases were in the age group 20-30 years.

TABLE – 3PARITY DISTRIBUTION OF CASES AMONG STUDY AND CONTROL GROUPS

PARITY	CASE	CONTROL
PRIMI	76	33
MULTI	24	17

76% of cases were primigravidae in the study group and 66% were primigravidae in the control group

TABLE – 4SHOWING GESTATIONAL AGE DISTRIBUTION BETWEEN STUDY AND CONTROL GROUP

GESTATIONAL AGE(weeks)	STUDY GROUP n=100	CONTROL GROUP n=50
< 30	13	2
30 - 36	79	40
36 - 40	8	8

Most of the cases belonged to gestational age group between 30-36 weeks.

TABLE – 5SHOWING CORRELATION BETWEEN MEAN AGE OF CASES IN STUDY AND CONTROL GROUPS

PARAMETER	STUDY GROUP	CONTROL GROUP	p - VALUE
MEAN AGE Years±SD	32.95±3.66	33.98±2.76	0.08208

Mean age of study group and control group were 32.95±3.66 years and 33.98±2.76 years respectively. There was no statistically significant difference between the two groups. (p>0.05)

TABLE - 6SHOWING CORRELATION BETWEEN MEAN PARITY OF THE CASES IN STUDY GROUP AND CONTROL GROUP

GROUPS	MEAN PARITY ±SD	p - VALUE
STUDY GROUP	1.29±0.55	0.38906
CONTROL GROUP	1.375±0.56	

The mean (±SD) parity of the study group and control group were 1.29±0.55 and 1.375±0.56 respectively. There was no any statistically significant difference between the two groups. (p>0.05)

TABLE – 7SHOWING CORRELATION BETWEEN MEAN GESTATIONAL AGE OF THE CASES IN STUDY AND CONTROL GROUPS

GROUPS	MEAN GESTATIONAL AGE±SD	p = VALUE
STUDY	32.95±3.66	0.8208
CONTROL	33.98±2.76	

Mean gestational age (±SD) of the study and the control groups were 32.95±3.66 weeks and 33.98±2.76 weeks respectively.
There was no statistically significant difference between the study and the control groups.

TABLE – 8SHOWING INCIDENCE OF HYPOTHYROIDISM IN NORMOTENSIVE PREGNANT WOMEN

CONDITION	NUMBERS N=50	PERCENTAGE (%)
EUTHYROID	4 4	8 8
HYPOTHYROIDISM	6	1 2

This table shows that the percentage of normotensive women with hypothyroidism was 12%

TABLE – 9SHOWING INCIDENCE OF HYPOTHYROIDISM IN PREECLAMPTIC PREGNANT WOMEN

CONDITION	NUMBERS N=100	PERCENTAGE (%)
EUTHYROID	5 8	5 8
HYPOTHYROID	4 2	4 2

This table shows that the incidence of hypothyroidism in preeclamptic women was 42%.

TABLE – 10SHOWING THYROID FUNCTION TEST OF NORMOTENSIVE AND PREECLAMPTIC PREGNANT WOMEN

PARAMETERS	STUDY	CONTROL	p = value
TSH (mIU/L) Mean ±SD	2.407±1.71	1.5±0.9546	0.00066
fT3 (pg/ml) mean±SD	1.422±0.621	1.604±0.63	0.09654
fT4 (ng/dl) mean	0.933±0.404	1.08±0.393	0.031

In my study, mean sTSH of the study and the control groups were 2.407±1.71mIU/L and 1.5±0.9546mIU/L. There was statistically significant difference between the two groups. ($p<0.05$). fT3 and fT4 were slightly higher in control group but this was not statistically significant.

TABLE – 11SHOWING DISTRIBUTION OF NORMAL AND INCREASED SERUM TSH LEVEL IN BOTH THE STUDY AND CONTROL GROUPS

GROUPS	STSH <3mIU/L	STSH >3mIU/L	TOTAL	ODDS RATIO
CONTROL	4 4	6	5 0	
STUDY	5 8	4 2	1 0 0	
TOTAL	1 0 2	4 8	1 5 0	5.31

Out of 100 preeclamptic women in study group, 42 had sTSH >3mIU/L.
Out of 50 normotensive pregnant women in the control group, 6 had sTSH> 3mIU/L.
Hence, 42 out of 48 pregnant women with sTSH >3mIU/l had preeclampsia and 58 out of 102 pregnant women with normal sTSH level had preeclampsia. Odds ratio = 5.3
Hence this difference between the two groups is statistically significant. ($p<0.05$).

IV Discussion

This study was conducted in the Obstetrics and Gynaecology department of PMCH from October2012 to September2014 in Patna to determine the thyroid hormone levels in cases of 100 preeclamptic women and 50 matched controls in the second and third trimester. Number of cases studied were 100 in study group and 50 in control group (table 1) and maximum number of the cases belonged to 20-30 years (table 2). It was in correlation with a study by Sardana et al. (2009) who also studied 100 preeclamptic women and 50 normotensive women. Also in a study carried out in Bucharest University Emergency hospital by Rodiac Todusa (2010), patients studied were between 18-35 years.

Maximum number of cases were primigravidae which corresponded with the study carried out by Kumar A. et al. in Delhi in 2002, in which primigravidae women were in majority in both study and control groups. Also in a study by Roofi et al. (2014), majority of the pregnant women were primigravida. Maximum number of cases belonged to gestational age between 30-36 weeks (table 4) .Similar study was carried out by

Sardana et al.(2009) in PGIMS, Rohtas in which pregnant women were between 28-36 weeks. The mean (±SD)age of the study and control groups were 23.68±4.55 years and 24.72±4.72 years respectively and there was no statistically significant difference between the two groups (p>0.05). Lao TT et al (1990) also studied the mean age 28.40±5.20 years and 27.50±5.10 years of study and control groups and there was no statistically significant difference between the two groups. Kumar A et al. found (2005), the mean age of the study and control groups were 28.40±6.24 years and 27.50±5.91 years respectively. Mean parity of the study group and control group were 1.29±0.55 and 1.375±0.56 as shown in table 6. It was in correlation with the study carried out by Khadem et al (2012) in which mean parity of the study group was 1.28±0.90 years and mean parity of the control group was 1.30±0.88 years. Khanam et al. (2005) also found mean parity of 1.28±0.90 years in study group and 1.30±0.88 years in control group .Also, the mean gestational age at the time of taking blood sample for thyroid hormonal levels was 32.95±3.66 weeks in the study group and 33.98±2.76 weeks in the control group (table 7). The difference between the two groups was not statistically significant (p=0.8208).It was similar to other studies. Larijani et al (2004) found the mean (±SD) gestational age was 35.67±6.88 weeks. Khadem et al (2012) also studied mean gestational age of 34.30±2.92 weeks in study group and 35.10±2.82 weeks in control group.In this study, incidence of hypothyroidism in normotensive pregnant women was 12% (table 8) and the incidence of hypothyroidism in preeclamptic women was 42% (table 9). Lao TT et al (1990) in their study found that preeclamptic women had higher TSH while T4 and T3 were slightly low but not significantly lower in their third trimester of pregnancy. Sardana et al (2009) also found that women with preeclampsia had higher TSH than normotensive women. Ajmani et al (2013) in his study found hypothyroidism associated with preeclampsia in 22.3% vs 8% in euthyroid women.The mean (±SD) TSH of the study and control group was 2.407±0.171mIU/L and I.5±0.954mIU/L respectively and there was highly significant difference between the two groups (p<0.05).The mean (±SD) fT3 of the study group and control group were 1.422±0.621 pg/ml and 1.604±0.63 pg/ml respectively and there was no statistically significant difference between the two groups (p>0.05) as shown in table 10.

The mean (±SD) fT4 level was 0.933±0.404 ng/dl 1.08±0.393 ng/dl in the study group and in the control group. The difference between the two groups was not statistically significant (p<0.05). It was similar to the study carried out by khaliq et al (1998) in which he found that serum t3 and t4 were decreased and sTSH was significantly increased in cases of preeclampsia as compared to normal pregnancy. Kumar A et al. (2005) in the antenatal clinic of a public hospital of Delhi found the mean (±SD) TSH of the study group and control group were 4.6±3.64mIU/l and 2.5±2.01mIU/l respectively and there was highly significant difference between the two groups. (P<0.05)

It has been suggested that the reduced concentration of t3 and t4 levels might be explained by the loss of protein and protein bound hormones. Since t3 is mostly the product of peripheral conversion of t4, the involvement of organs such as liver and kidney contributes to low level of t3.

In this study, out of 100 pregnant women in the study group, 42 had higher TSH titre. Hence 42 out of 48 pregnant women with raised sTSH titre had diagnosis of preeclampsia and 58 out of 102 pregnant women with raised TSH titre had diagnosis of preeclampsia. This difference between the two groups was found statistically significant (p<0.05) (table 11).The difference in the number of pregnant women of the two groups having high TSH titre was also significant. Kumar et al. (2005) also observed statistically significant higher number of cases with preeclampsia (76.7%) in the pregnant women with abnormally high level of TSH.

V Conclusion

In the present study, serum TSH was significantly higher in preeclamptic women than in normotensive women and fT3 and fT4 were slightly lower in preeclamptic women. Since pregnancy is generally associated with hyperthyroxinemia, degree of hypothyroxinemia might reflect the severity of preeclampsia. Thyroid screening and identification of hypothyroidism during pregnancy can predict preeclampsia and help in preventing its occurrence by timely intervention in terms of thyroid hormone administration in appropriate measures.

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