Functional Status of Maternal Thyroid Gland in Eclampsia

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Abstract
Marked changes in maternal thyroid activity occur in pregnancy. During pregnancy bodily hormonal changes and metabolic demands result in complex alteration in the bio-chemical parameters of thyroid activities. Besides these, thyroid enlargement, increased thyroid capability for iodine uptake and increase in basal metabolic rate are evidential though these findings are not usually associated with symptoms of hyperthyroidism in pregnancy. Serum concentration of thyroid hormone thyroxine and triiodothyronine in complicated pregnancy like eclamptic toxemia is another field of controversy. To evaluate the changes in thyroid function in normal pregnancy and eclamptic toxemia, a study was undertaken in Rajshahi Medical College Hospital. We collected serum specimens from non pregnant but married women, normal 3rd trimester pregnant women and patients with eclampsia at 3rd trimester of pregnancy and measured serum concentrations of total and free thyroxine (TT4 & FT4) and total and free triiodothyronine (TT3 & FT3) by using RIA. Among the study subjects, 10 women were married but non pregnant, 12 women were in their 3rd trimester of normal pregnancy and 32 patients of eclamptic toxemia with 3rd trimester of pregnancy. In normal pregnancy, FT4 and FT3 levels remained normal while TT4 and TT3 levels were elevated. In patients with toxemia of pregnancy, the mean serum TT3 concentration was significantly lower than that of normal pregnancy and the serum FT3 concentrations were below the normal pregnancy range. The mean serum TT4 and FT4 concentrations in patients with eclampsia were however, significantly higher than those in normal pregnant women.

Introduction
In pregnancy maternal physiological adjustment of different organ systems occur which includes circulatory, metabolic and hormonal changes to supply adequate nutrition to the growing fetus.1 There is evidence for presence of other thyroid stimulators like human chorionic gonadotropin hormone (hCG) besides thyroid stimulating hormone (TSH) in pregnancy. There is also evidence for increase concentration of thyroxine binding globulin (TBG) which is induced by increased estrogen production in pregnancy.2,3,4 In normal pregnancy increased serum concentration of TBG results in increased serum concentration of total T4 and to a lesser extend of total T3. There is different opinion in different studies regarding alterations in serum free hormone levels in pregnancy.5

In normal pregnancy, FT4 and FT3 levels remained normal while total T4 and T3 levels were elevated. In patients with toxemia of pregnancy, the mean serum total T3 concentration was significantly lower than that of normal pregnancy and the serum FT3 concentrations were below the normal pregnancy range. The mean serum TT4 and FT4 concentrations in patients with eclampsia were however, significantly higher than those in normal pregnant women.

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were however, significantly higher than those in normal pregnant women.

In Bangladesh little works have been done in this regards where eclampsia is among major health problems. The present study has been designed to compare the total and free thyroxine and triiodothyronine in normal pregnancy, in eclampsia and in non pregnant (control) subjects.

**Materials and Methods**

The study was conducted in the department of physiology, Rajshahi Medical College with collaboration of department of Gynec and Obstetrics, Rajshahi Medical College Hospital. The total duration of the study was 12 months. The age of the subjects were ranged from 18 to 35 years. Those having present or past history of any kind of thyroid disease, diabetes mellitus or glycosuria were excluded from the study.

A total of 54 subjects were selected as study subject in this study. The study subjects were divided into 3 groups. The group I includes 10 apparently healthy non pregnant women without having hormonal contraceptives at least for 6 months. The group II includes 12 women in their normal 3rd trimester of pregnancy. The group III includes 32 women (patients) of 3rd trimester pregnancy with eclamptic toxemia. The objectives of the study were explained to the subjects and a written concept was taken from each of them. Detailed case history was obtained and bed-side examination of blood for random blood sugar (RBS) and urine for urine sugar were done carefully. Single sample of 10ml ante cubital venous blood was obtained with all aseptic measures. After let it be clotted, it was centrifuged for 30 minutes and the supernatant (serum) was taken in a separate test tube. Thus the serum was ready and used for hormone analysis in the laboratory of the Center for Nuclear Medicine and Ultrasound (CNMU), Rajshahi. TT₄ and TT₃ were measured by conventional RIA (Radioimmunoassay) method. FT₄ and FT₃ were measured by two-step magnetic FT₄-RIA and FT₃-RIA respectively. The kits used for the tests were manufactured by Beijing Atomic High Tech. Co. Ltd. China.

The obtained data was analyzed in computer using software SPSS for window version 11.5. Test of probability for significant difference was conducted by T-test (unpaired) for two independent means.

**Results:**

Serum TT₄ and TT₃ are expressed in nmol/L and serum FT₄ and FT₃ are expressed in pmol/L. The results are presented as mean ± SE (standard error of mean). The bio-chemical parameters of thyroid function of study subjects are given in Table 1

| Parameters          | Group I n=10 non pregnant | Group II n=12 3rd trimester | Group III n=32 eclampsia |
|---------------------|---------------------------|-----------------------------|--------------------------|
| TT₄ (nmol/L) mean ± SE | 105.5 ± 8.7               | 148.9 ± 3.6                 | 179.8 ± 9.5              |
| TT₃ (nmol/L) mean ± SE | 1.4 ± 0.1                 | 3.0 ± 0.2                   | 2.3 ± 0.1                |
| FT₄ (pmol/L) mean ± SE | 18.5 ± 1.6                | 20.4 ± 2.7                  | 26.6 ± 2.2               |
| FT₃ (pmol/L) mean ± SE | 4.8 ± 0.4                 | 4.6 ± 0.3                   | 3.8 ± 0.2                |
Serum total thyroxine (TT₄):
The mean serum TT₄ is significantly higher in normal pregnancy and in eclampsia than that of non pregnant women (Table 2 and 3). The mean serum TT₄, though higher in eclampsia than that of normal 3rd trimester pregnancy but the difference is not significant (Table 4). Out of 32 patients of eclampsia, serum concentrations of TT₄ in 3 patients in this study are higher than normal range. The mean serum TT₄ is 21% higher in eclampsia than that of normal pregnancy.

Table 2: Showing statistical comparison between non pregnant and normal 3rd trimester of pregnancy.

| Parameters        | Group I n =10 non pregnant | Group II n =12 normal 3rd trimester | Significance       |
|-------------------|-----------------------------|------------------------------------|--------------------|
| TT₄ (nmol/L)      | 105.5 ± 8.7                 | 148.9 ± 3.6                        | Significant (P = 0.011) |
|                   | mean ± SE                   |                                    |                    |
| TT₃ (nmol/L)      | 1.4 ± 0.1                   | 3.0 ± 0.2                          | Highly significant (P =0.000) |
|                   | mean ± SE                   |                                    |                    |
| FT₄ (pmol/L)      | 18.5 ± 1.6                  | 20.4 ± 2.7                         | Non-significant (P =0.001). |
|                   | mean ± SE                   |                                    |                    |
| FT₃ (pmol/L)      | 4.8 ± 0.4                   | 4.6 ± 0.3                          | Non-significant (P =0.001). |
|                   | mean ± SE                   |                                    |                    |

Serum total triiodothyronine (TT₃):
The mean serum TT₃ in this study is significantly higher both in normal pregnancy and in eclampsia than that of non pregnant women. In contrast to TT₄, the rise of TT₃ is pronounced in normal pregnancy than non pregnant women. The mean serum TT₃ is significantly lower in eclampsia than that of normal pregnancy.
**Table 3:** Showing statistical comparison between non pregnant and 3rd trimester of pregnancy with eclampsia.

| Parameters     | Group I n =10 non pregnant | Group III n =32 eclampsia | Significance                  |
|----------------|-----------------------------|---------------------------|-------------------------------|
| TT₄ (nmol/L)   | 105.5 ± 8.7                 | 179.8 ± 9.5               | Highly significant (P=0.000)  |
| mean ± SE      |                             |                           |                               |
| TT₃ (nmol/L)   | 1.4 ± 0.1                   | 2.3 ± 0.1                 | Highly significant (P =0.001) |
| mean ± SE      |                             |                           |                               |
| FT₄ (pmol/L)   | 18.5 ± 1.6                  | 26.6 ± 2.2                | significant (P =) 0.006       |
| mean ± SE      |                             |                           |                               |
| FT₃ (pmol/L)   | 4.8 ± 0.4                   | 3.8 ± 0.2                 | Non-significant (P =0.047).   |
| mean ± SE      |                             |                           |                               |

**Serum free thyroxine (FT₄):**
The mean serum FT₄ is higher in normal pregnancy than that of non pregnant women but the value is not significantly (Table 2). The mean serum FT₄ is significantly higher in eclampsia than that of non pregnant women (Table 3). The mean serum FT₄ is higher in eclampsia than that of normal pregnancy but the value is not significantly (Table 4).

**Table 4:** Showing statistical comparison between normal 3rd trimester of pregnancy and 3rd trimester of pregnancy with eclampsia.

| parameters     | Group II n =12 normal 3RD trimester | Group III n =32 eclampsia | Significance                  |
|----------------|-------------------------------------|---------------------------|-------------------------------|
| TT₄ (nmol/L)   | 148.9 ± 3.6                         | 179.8 ± 9.5               | Non significant (P =0.046)   |
| mean ± SE      |                                     |                           |                               |
| TT₃ (nmol/L)   | 3.0 ± 0.2                           | 2.3 ± 0.1                 | Significant (P =0.016)       |
| mean ± SE      |                                     |                           |                               |
| FT₄ (pmol/L)   | 20.4 ± 2.7                          | 26.6 ± 2.2                | Non-significant (P ≤ 0.05).  |
| mean ± SE      |                                     |                           |                               |
| FT₃ (pmol/L)   | 4.6 ± 0.3                           | 3.8 ± 0.2                 | Non-significant (P ≤ 0.05).  |
| mean ± SE      |                                     |                           |                               |

**Serum free triiodothyronine (FT₃):**
There were no significant differences in mean serum FT₃ between normal pregnancy, eclampsia and non pregnant women (Table 2, 3 & 4). In 12 of the 32 patients of eclampsia, the serum concentrations of FT₃ are slightly below normal range and 26 of them show their serum FT₃ concentrations lower than that of normal pregnancy.
Discussion
The present study represents an evaluation of thyroid hormones level in normal pregnancy and pregnancy with eclampsia without detectable thyroid abnormalities. The result of this study indicates an important modification in thyroid activity in pregnancy. We have focused our attention on both total and free $T_4$ and $T_3$ in 3rd trimester of normal pregnancy and 3rd trimester pregnancy with eclampsia and on comparing them with non pregnant control subjects. In normal pregnancy, mean serum concentration of both $TT_3$ and $TT_4$ are increased significantly and the elevations remain significant in eclampsia than that of control subjects. The mean serum $FT_4$ and $FT_3$ though elevated but are not significant in normal pregnancy than the control. In eclampsia, the mean serum $FT_4$ is significantly different than that of non pregnant women when difference is nonsignificant in case of $FT_3$. Similar results have been observed in the findings of previous investigators that is, in normal pregnancy, while the serum concentrations of total thyroxine and triiodothyronine are elevated, the absolute serum concentrations of free thyroxine and triiodothyronine remain within the range of non pregnant women.

The increase in serum binding forms of thyroid hormones may be due to the marked increase in circulating level of the major thyroxine binding protein (TBG), which is induced by high estrogen level in pregnancy. In addition, stimulatory effects of human chorionic gonadotropin hormones of placental origin, increased metabolic demand of the body and mental stress in pregnancy may have important role for over all thyroid activity and elevated thyroid hormone levels in pregnancy. During pregnancy increased estrogen level causes increase production of protein by the liver, consequently TBG production by hepatocytes is also increased. High estrogen level on the other hand reduces peripheral degradation due to oligosaccharide modification. As a result the TBG content in the plasma is elevated in pregnancy. As the binding capacity of the plasma is increased due to elevated TBG in the serum, more hormones bind to TBG and the total plasma content of thyroid hormones is increased but free hormone levels remain unchanged and hyperthyroidism does not likely.

The mean serum $FT_4$ difference is significant and $FT_3$ difference is nonsignificant between eclampsia and non pregnant women in this study. The mean serum $FT_3$ in eclampsia is even reduced than that of non pregnant and pregnant women. As the cause of this reduced $FT_3$ associated with significant rise of $TT_4$ in eclampsia, we held responsible the reduced extrathyroidal conversion (peripheral deiodination) of $T_4$ to $T_3$.

Eclampsia is a pregnancy induced autointoxication with multi system disorder when the most affected organs are brain, livers and kidneys. Functional disorder in these organ systems is evidential in eclampsia. On the other hand, liver, kidneys and muscles are the important organs of peripheral deiodination (conversion of $T_4$ to $T_3$) and in maintenance of normal serum level $T_4$ and $T_3$, that is why involvement of liver and kidneys is likely to change $T_4$ and $T_3$ levels in eclampsia.

There is controversy in different studies regarding free hormone levels in pregnancy. Different investigators showed free hormone levels remain unchanged, decreased or even increased in pregnancy compared to non pregnant control. The present study shows no significant change in free hormone levels between non pregnant and pregnant women and may be another addition of the ongoing controversy.

In some other studies, the investigators observed that in variety of systematic illness, protein-energy malnutrition (PEM), prolong starvation, anorexia nervosa, Cushing’s syndrome, excessive steroid therapy etc. when systemic disorder developed, the extra thyroidal deiodination of $T_4$ to $T_3$ had been reduced. Due to wide range of normal limits, these differences usually neither exceed normal limit nor produce significant change on metabolism.

Eclampsia is a major health problem in developing countries like Bangladesh. Poverty, low socioeconomic condition, poor nutritional status, early marriage and late pregnancy are common in Bangladeshi population. Illiteracy, ignorance and
fanaticism badly affect their life style. Lack of awareness, inadequate antenatal care and poor obstetrical facilities predispose to high rate of morbidity and mortality in eclampsia in this country.

Though the exact mechanism of change in thyroid function in pregnancy is difficult to explain, the present study may be helpful to resolve the debate. For further studies, the following may be helpful to explain the exact mechanism:-

1. Estimation of serum TSH, beta-hCG and estrogen level.
2. Estimation of plasma proteins including TBG.
3. Inclusion of subjects during pregnancy and eclampsia of all terms (1st, 2nd, and 3rd trimester of pregnancy).
4. Increase in number of sample size.

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