Research Article

Thyroid Function Tests in Preeclampsia

Sumaira Chowdhary¹, Shaugfta aara², Masarat Nazeer³, Musadiq Allaqband, ⁴
¹²³Senior Resident Department Of PHYSIOLOGY GMC Srinagar
⁴Senior Resident Department Of Paediatrics GMC Srinagar
Corresponding Author: Sumaira Chowdhary

Abstract:
Background: The thyroid hormones are protein-bound in the serum, and only 0.02% of T₄ and 0.2% of T₃ are free, biologically active hormones. 45–70% of thyroid hormones are bound to thyroxine-binding globulin (TBG), and the rest to transthyretin and albumin. Familial conditions, estrogen treatment and pregnancy may have effects on the concentrations of the binding proteins, leading to changes in thyroid hormone fractions until a new equilibrium is reached. Materials and Methods: Thyroid function tests were performed by chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of thyroid hormones (Total T₃, Total T₄ and TSH) in human serum and plasma values were presented as mean ± standard deviation. Student t’ test was used to compare hormonal levels. The corresponding value of 'p' was obtained from the standard table of critical 't' values at the appropriate degree of freedom. Statistical significance was considered as p<0.05.
Conclusion. The findings of present study indicate that as the severity of preeclampsia increases the level of TSH increases with corresponding decrease in T₃, T₄.

Keyword: Thyroid, PREECLAMPSIA, CHEMILUMINESCENT MICROPARTICLE IMMUNOASSAY (CMIA)

Introduction.

The thyroid is a small endocrine gland located in front of the trachea. It utilizes iodine to produce thyroid hormones, which are essential for normal growth, development, maturation and regulation of metabolism (Ganong, 2005).

The thyroid gland, in response to stimulation by TSH, produces 3,5,3',5'-tetraiodothyronine (T₄), 3,3',5'-triiodothyronine (T₃) and 3,3',5'-reverse triiodothyronine (rT₃). The synthesis of these hormones requires the amino acid tyrosine and the trace mineral iodine. Within the cells of the thyroid gland, iodide is oxidized to iodine by hydrogen peroxide; a reaction termed the "organification" of iodide. Iodine then binds to the number 3 position in the tyrosyl ring in a reaction catalyzed by thyroid peroxidase enzyme, a reaction yielding 3-monoiodotyrosine (MIT). A subsequent addition of another iodine to the number 5 position of the tyrosyl residue on MIT creates 3,5-diiodotyrosine (DIT). T₄ is created by Preeclamptic women having high incidence of hypothyroidism, that might correlate with the severity of preeclampsia (Lao et al., 1990).

Women with preeclampsia, were significantly more likely than control specimens, to have high concentration of TSH (Mustafa et al., 1999).

Comapcted thyroid hormones consist of two benzene rings. An inner tyrosyl ring, often also called the alpha ring, and an outer phenolic or beta ring. After the thyroid hormones are formed, lysosomal proteases sever T₄ (as well as any T₃ or rT₃) formed from the thyroglobulin molecule, and the hormones are released into the circulation. At the cellular level, the activity of thyroid hormones is mediated by interactions with nuclear T₃ receptors. Metabolic effects of thyroid hormones result when the hormones occupy specific receptors, evoking subsequent effects on intracellular gene expression. It is estimated a cell needs 5-7 times more T₃ to bind to the nuclear receptors to have a physiological effect, comparable to T₃ (Kohrle, 1996).

Thyroxine is produced in greater quantity than T₃ (at a ratio of 10:1), but T₃ is the major biologically active thyroid hormone and is mostly derived from T₄ in the peripheral tissues (Ganong, 2005; Hadley and Levine, 2007).

Thyroid hormone production is regulated by the pituitary through the action of thyrotropin (thyroid-stimulating hormone, TSH). TSH comprises of two subunits and it has one alpha-subunit in common with luteinizing hormone, follicle stimulating hormone and human chorionic gonadotropin (hCG), and one specific beta-subunit. TSH shows circadian and pulsatile secretion – its secretion peaks at around midnight and declines during the day. The function of the pituitary is controlled by the hypothalamus, which secretes thyrotropin-releasing hormone (TRH). It accelerates the production of TSH, whereas dopamine and somatostatin hinder it (Ganong, 2005).
The thyroid hormones are protein-bound in the serum, and only 0.02% of $T_4$ and 0.2% of $T_3$ are free, biologically active hormones. 45–70% of thyroid hormones are bound to thyroxine-binding globulin (TBG), and the rest to transthyretin and albumin. Familial conditions, estrogen treatment and pregnancy may have effects on the concentrations of the binding proteins, leading to changes in thyroid hormone fractions until a new equilibrium is reached (Ganong, 2005).

The thyroid hormones stimulate oxygen consumption and increase the metabolic rate. They have an effect on the heart and connective tissues and affect growth and development. Thyroid hormones have a marked effect on the brain development, especially on the cerebral cortex and the basal ganglia (Hadley and Levine, 2007).

During normal pregnancy, the maternal thyroid produces up to 50% more thyroid hormones. The rise in thyroid hormones results from physiological changes in pregnancy. Firstly, there is increased synthesis of TBG from the liver and increased binding of $T_4$ to TBG (Robbins and Nelson, 1958) as well as increased synthesis of $T_3$ (Lindberg et al., 1974). TBG is also more sialylated during pregnancy and has a reduced clearance rate (Ain et al., 1987).

During normal pregnancy, changes in thyroid function are well documented (Smith and Bold, 1983), but information about thyroid function in complicated pregnancy is scant. Human animal studies suggest, the cause of preeclampsia to be excess release of anti-angiogenic factors, such as soluble fms like tyrosine kinase-1 (sFlt-1 / sVEGFR-1), from placenta to maternal blood. The levels of these sFlt-1 increase during the last two months of normal pregnancy. These levels are very much increased in women with preeclampsia. In normal pregnancy there is increased Thyroid stimulating hormone (TSH) due to raised human chorionic gonadotropin (hCG) concentration (Larijani et al., 2004). But in preeclampsia the raised TSH is not due to change in hCG but the raised TSH is directly related to the circulating levels of sFlt-1 concentrations. This suggests that the effect of preeclampsia on thyroid function is mediated by sFlt-1 (Levine et al., 2009).

The renal podocytes require constitutive expression of VEGF for health and function. The reduced level of VEGF makes the endothelium of glomerular capillaries to become fenestrated (Risau, 1998) and may lead to proteinuria of preeclampsia.

Thyroid capillaries also have a fenestrated epithelium (Kamba and McDonald, 2007) which in turn increases the secretion of TSH. Thus, high levels of exposure to sFlt-1, as in preeclampsia, may be associated with increased risk of reduced thyroid function during and after pregnancy.

**Materials and Methods**

The present study was undertaken in the Postgraduate Department of Physiology, Government Medical College Jammu in collaboration with Department of Obstetrics and Gynaecology SMGS Hospital, and Department of Biochemistry, Government Medical College Jammu on 100 pregnant women in second and third trimester of pregnancy. Of the 100 subjects, 50 were preeclamptic women as cases and 50 normal pregnant women who were taken as controls, w.e.f. November, 2014 to October, 2015.

**Selection procedure of the subjects**

Subjects were selected from outpatient Department of Obstetrics and Gynecology, SMGS Hospital, Government Medical College, Jammu. After detailing the purpose and methodology of the study, all eligible subjects were requested to participate in the study.

Subjects willing to participate were allocated into two groups

- Group I (Disease Group): comprised of 50 preeclamptic women.
- Group II (Control Group): comprised of 50 normal pregnant women.

**EXCLUSION CRITERIA**

- Associated renal, hepatic, cardiac disease, metabolic disorder like diabetes mellitus, known thyroid disorder and past history of hypertension.

All the eligible subjects were examined by the investigator herself.

**THYROID FUNCTION TESTS**

Thyroid function tests were performed by chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of thyroid hormones (Total $T_4$, Total $T_3$ and TSH) in human serum and plasma (Patel et al., 1972; Sterling and Lazarus, 1977).

**Sample collection and handling:** (Serum $T_3$, Serum $T_4$, Serum TSH): 4ml of venous blood sample was collected in a glass tube (without anti-coagulant) and allowed to clot at room temperature. Human serum (including serum collected in serum separator tubes) or plasma collected in sodium heparin, lithium heparin or potassium EDTA anticoagulant tubes were used in the ARCHITECT thyroid hormonal assay.

The serum samples collected after centrifugation were stored at 2-8°C.

**Table 1:** Comparison of Age Group Distribution between Disease Group and Control Group.

<table>
<thead>
<tr>
<th>Age Groups (in years)</th>
<th>Disease Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 – 25</td>
<td>12</td>
<td>23</td>
</tr>
<tr>
<td>26 - 30</td>
<td>24</td>
<td>15</td>
</tr>
<tr>
<td>31 - 35</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>36 – 40</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>28.72 ± 4.26 years</td>
<td>26.88 ± 4.66 years</td>
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Thyroid functions were estimated in preeclamptic patients

In our study it was found that TSH levels mean (±SD) are significantly higher in preeclamptic group 6.19 ± 2.32 as compared to control group 2.22 ± 0.84 (p<0.001). T₃ and T₄ levels were significantly lower in preeclamptic group 0.92 ± 0.38, 5.29 ± 2.16 as compared to control group i.e. normal pregnant women 1.41 ± 0.29, 9.46 ± 1.96 respectively (p<0.05).

Similar results were seen in study conducted by Farah et al., (1999) who found that there was significant decrease in T₃ and T₄ levels and significant increase in TSH levels in preeclamptic women.

Kumar et al., (2005) observed the similar findings in preeclamptic women with high TSH levels and low thyroid hormones. Their findings suggested that preeclamptic women had higher incidence of biochemical hypothyroidism compared with normotensive pregnant women

Larjani et al., (2004) reported increased TSH levels and decreased free and total levels of T₃ and T₄ in a study of 39 preeclamptic patients as compared to 42 healthy controls. These findings are in agreement with others in the literature (Kaye et al., 1994; Tolino et al., 1985).

Conclusion: The findings of present study indicate that as the severity of preeclampsia increases the level of TSH increases with corresponding decrease in T₃, T₄.

BIBLIOGRAPHY.


Table 1 (Fig.1) depicts Age Group Distribution of normal pregnant women and women with preeclampsia. Age distribution among disease group shows a mean of 28.72 (SD ± 4.26) and a mean of 26.88 (SD ± 4.66) in control group. 48% of women among preeclampsia are in between ages 26-30 years and 46% of control group are in between ages 20-25 years.

Table 2: Comparison of Gestational Age Distribution between Disease Group and Control Group.

| Table 2: Comparison of Gestational Age Distribution between Disease Group and Control Group. |
|---|---|---|
| | Disease Group | Control Group |
| | Frequency | % | Frequency | % |
| 28 – 30 | 8 | 16.0 | 17 | 34.0 |
| 31 – 35 | 22 | 44.0 | 27 | 54.0 |
| 36 – 40 | 20 | 40.0 | 6 | 12.0 |
| Total | 50 | 100 | 50 | 100 |
| Mean ± SD | 34.24 ± 2.88 wks | 31.70 ± 2.81 wks |

Table 2 (Fig.2) shows the Gestational Age comparison between preeclamptic women and normal pregnant women with a mean of 34.24 (SD ± 2.88) in disease group and a mean of 31.70 (SD ± 2.81) in control group. It can be seen that 44% of the preeclamptic women are in between 31-35 weeks of gestation. In the control group 54% of the women are in between 31-35 weeks.

Table 3: T₃, T₄, and TSH values in Disease Group and Control Group.

| Table 3: T₃, T₄, and TSH values in Disease Group and Control Group. |
|---|---|---|---|---|
| | Disease Group | Control Group |
| | Mean ± SD | Range | Mean ± SD | Range |
| T₃ | 0.92±0.38 | 0.13-1.79 | 1.41±0.29 | 0.37-1.98 |
| T₄ | 5.29±2.16 | 2.10-12.66 | 9.46±1.96 | 5.30-14.07 |
| TSH | 6.19±2.32 | 2.34-13.10 | 2.22±0.84 | 0.16-3.70 |

Table 5 (Fig.5) shows the values of thyroid functions in preeclamptic women and normal pregnant women. Serum TSH is increased significantly while T₃ and T₄ are decreased significantly in preeclampsia as compared to normal pregnancy.

DISCUSSION

Pregnancy is associated with significant, but reversible changes in thyroid function, which are among the most profound seen as a result of a normal physiological state (Glinoer et al., 1990). Furthermore, human chorionic gonadotropin (hCG) can stimulate the thyroid gland because of its structural similarity to thyrotrophin (TSH) (Brent, 1997). Thyroid hormones have important role in embryogenesis and fetal development during pregnancy. Therefore, thyroid status is frequently assessed during pregnancy, both to evaluate suspected thyroid abnormalities, and to monitor the status of pre-existing thyroid disease (Haddow et al., 1999). Thyroid functions were estimated in preeclamptic patients.


