# Thyroid hormones in pregnancy and preeclampsia

## *Gebelikte ve preeklampside tiroid hormonları*

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## *Abstract*

**Objective:** There is a state of hypothyroxinemia in normal pregnancy and in preeclampsia, when biochemically raised TSH occurs. Identification of changes in thyroid hormones in preeclampsia might be of help in preventing the occurrence of preeclampsia.

**Material and Methods:** The present study was carried out in a hundred women with preeclampsia, 100 age- and parity matched normotensive pregnant women and 50 age-matched healthy non-pregnant women. Thyroid hormones [total T3,T4 and TSH], serum albumin and uric acid were analyzed in these subjects.

**Results:** Women with preeclampsia had higher TT3, TT4 levels as compared to non pregnant women [$p<0.05$], but preeclamptic TT3,TT4 levels were lower compared to normotensive pregnant women [$p<0.05$, $p<0.01$]. TSH levels were higher in both preeclamptic & normotensive pregnant women compared to nonpregnant women [$p<0.001$] and levels were lower in normotensive pregnant women as compared to nonpregnant women [$p<0.001$]. A significant negative correlation was observed between birth weight and TSH levels [$r=-0.296$, $p<0.001$] serum albumin and TSH levels in preeclamptic women [$r=-0.781$, $p<0.01$]. Also, a significant positive correlation was observed between birth weight and albumin [$r=0.298$, $p<0.001$]; birth weight and serum uric acid levels [$r=-0.46$, $p<0.01$], and serum albumin and TT3 & TT4 levels [$r=0.409$ & $r=0.35$, $p<0.01$ respectively].

**Conclusion:** These findings indicate that there is state of hypothyroxinemia in normal pregnancy and in preeclampsia. Identification of changes in thyroid hormones in preeclampsia might be of help in preventing the occurrence of preeclampsia.

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**Key words:** Preeclampsia, thyroid, pregnancy, thyroxine, uric acid, albumin

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## *Özet*

**Amaç:** Gebelikte ve preeklampside TSH yükselmesi görüldüğünde ortaya çıkan bir hipotiroksinemi durumu vardır. Gebelikte tiroid hormonlarının değişiminin saptanması preeklampsi gelişiminin engellenmesine yardım edebilir.

**Gereç ve Yöntemler:** Bu çalışma preeklamptik 100 gebe ve yaş eşleştirmesi yapılmış tansiyonu normal 100 gebe ve 50 gebe olmayan kadın karşılaştırılarak yapıldı. Tiroid hormonlar [total $T_3$,$T_4$ and TSH], serum albumin and urik asid düzeyleri analiz edildi.

**Results:** Preeklamptik hastalar gebe olmayanlar ile karşılaştırıldığında daha yüksek $TT_3$, $TT_4$ düzeylerine sahiptiler [$p<0.05$], fakat preeklamptiklerin $TT_3$,$TT_4$ düzeyleri normotansif gebelerinkinden daha düşük idi [$p<0.05$, $p<0.01$]. TSH düzeyleri preeklamptiklerde ve normal gebelerde gebe olmayan gruba göre daha yüksek idi [$p<0.001$], fakat TSH düzeyleri normotansif gebelerde gebe olmayanlara göre daha düşük idi [$p<0.001$]. Preeklamptik gebelerde doğum kilosu ile TSH arasında [$r=-0.296$, $p<0.001$] ve serum albumini ile TSH arasında ($r=-0.781$, $p<0.01$] anlamlı bir negatif korelasyon saptandı. Ayrıca doğum kilosu ile serum albumini arasında [$r=0.298$, $p<0.001$]; doğum kilosu ile serum ürik asid düzeyleri arasında ($r=-0.46$, $p<0.01$], ve serum albumin ile $TT_3$ ve $TT_4$ arasında [$r=0.409$ & $r=0.35$, $p<0.01$) anlamlı bir pozitif korelasyon saptandı.

**Sonuç:** Bu bulgular normal gebelikte ve preeklampside bir hipotiroksineminin varlığını teyit eder. Gebelikte tiroid hormonlarındaki değişimlerin saptanması preeklampsi gelişiminin öngörüsünde fayda sağlayabilir. (J Turkish-German Gynecol Assoc 2009; 10: 168-71)

**Anahtar kelimeler:** Preeklampsi, tiroid, gebelik, tiroksin, ürik asid, albumin

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## Introduction

During normal pregnancy, changes in thyroid function are well-documented, but information about thyroid function in complicated pregnancy is scanty. During pregnancy, there is an increased thyroid demand and increased iodine uptake and synthesis of thyroid hormones. Estrogen induces a rise in serum TBG and the placenta releases several thyroid stimulatory factors in excess e.g. hCG. Alpha subunit of hCG is identical to that of TSH and has weak thyrotropic activity (1). Hypothyroidism has been listed as one of the causes of high blood pressure (2). In preeclampsia, there is failure of estrogen production due to placental dysfunction resulting in lowering of TBG, $TT_3$, $TT_4$ along with growth retardation of the fetus (3). Increasing evidence suggests that oxidative stress and altered endothelial cell function may have a role in preeclampsia (4-6). Also, oxidative stress has been proposed as another contributing source of the hyperuricemia noted in preeclampsia apart from renal dysfunction (8). In preeclampsia, an increase in the superoxide anion, which

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may inactivate NO, leading to reduced relaxation and increased vasoconstriction (6, 7). Experimental studies have indicated that release of NO is altered in hypothyroidism and the resulting endothelial cell dysfunction might be a pathogenetic mechanism for hypothyroidism in preeclampsia (9).
The present study was undertaken to evaluate thyroid hormones in preeclamptic women as compared to normotensive pregnant women and healthy non pregnant controls.

## Methods

The present study was carried out on 100 women with preeclampsia admitted to or attending the Outpatient Department of Obstetrics and Gynecology in Pt. BDS PGIMS, Rohtak, between August 2005 to October 2006. Hundred age & party-matched normotensive pregnant women and fifty age-matched, healthy non-pregnant women served as controls. Inclusion criteria of preeclampsia were blood pressure of ≥ 140/90 mmHg on at least two occasions, six hours apart and/or proteinuia. Exclusion criteria were: history of chronic hypertension, any renal disease, any metabolic disorder or medication known to affect thyroid function. The preeclampsia group was sub-divided into two groups namely, mild preeclampsia (n=50) and severe preeclampsia (n=50). Study samples were drawn before starting any treatment and serum was separated for assay for thyroid hormones ($T_3$,$T_4$,TSH) by radioimmunoassay (RIA) (10), albumin and uric acid (8). The data so obtained was analyzed statistically and student's t-test and regression analysis was carried out.

## Results

Table 1 shows clinical characteristics of women in the study and control groups. There was a significant difference in $TT_3$(total $T_3$)levels in normotensive pregnancy as compared to healthy non-pregnant women ($p < 0.001$, Table 2). Women with preeclampsia had higher $TT_3$ levels as compared to non pregnant women ($p<0.05$), but, the $TT_3$ levels were slightly lower in preeclamptic women as compared to normotensive pregnant women ($p>0.05$).
$TT_4$ (total $T_4$) levels were raised significantly in both preeclamptic and normotensive pregnant women as compared to non-pregnant women ($p<0.01$ and $p<0.001$ respectively). $TT_4$ levels were significantly higher in normotensive women as compared to preeclamptic women ($p<0.01$).
TSH levels were higher in preeclamptic women as compared to nonpregnant control ($p<0.001$)and they were lowered significantly in normotensive pregnant women as compared to non-pregnant women ($p<0.001$, Table 2). No significant influence of age and parity on thyroid hormonal levels could be observed in any of the three groups. A significantly higher number (78%) in the severe preeclampsia group had raised TSH levels than in the mild preeclampsia group (35%) ($p<0.001$). On the other

**Table 1. Clinical Characteristics (mean +SD)**

| | Preeclampsia | | Normotensive Non Pregnant | | |
|---|---|---|---|---|---|
| | Total | Mild | Severe | | |
| Age (years) | 23.07 + 2.75 | 23.08+ 3.01 | 23.01+2.28 | 23.04+ 2.17 | 23.50 + 2.01 |
| Gestational age (weeks) | 37.77 + 1.7 | 38.67+ 0.81 | 36.87 + 1.90 | 39.09 + 1.3 | - |
| Birth weight (kg) | 2.32 + 0.43 | 1.55 + 0.22 | 2.09 + 0.46 | 2.74 + 0.24 | - |
| Placental weight(g) | 438.25+56.90 | 472.5 + 34.71 | 404 + 54.24 | 502.50 + 50.81 | - |
| Serum albumin(g/l) | 3.38+0.2 | 3.52 + 0.19 | 3.24 + 0.22 | - | - |
| Serum uric acid (mg/dl) | 6.54+ 1.15 | 5.42 + 0.79 | 7.66 + 1.51 | 2.31+0.81 | 2.02 + 0.71 |

**Table 2. Thyroid hormone levels in various groups (mean + SD)**

| | Preeclampsia | | Normotensive Non Pregnant pregnant | | |
|---|---|---|---|---|---|
| | Total (n=100) | Mild (n=50) | Severe (n=50) | (n=100) | (n=50) |
| $TT_3$ (ng/dl) | 128.23$^{+}$±36.53 | 136.82±36.82 | 119.64±34.48$^{b}$ | 134±34.56* | 115.88±22.89 |
| $TT_4$ ($\mu$g/dl) | 10.12$^{++,a}$±2.64 | 10.84±2.53 | 9.39±2.57 | 12.14±2.49* | 7.9±1.40 |
| TSH ($\mu$lU/ml) | 4.52 $^{++,a}$±2.30 | 3.42±1.61 | 5.63±2.37 | 2±1.18 | *2.67±1.24 |

$^{+}$compared to non pregnant $p<0.05$
$^{++}$compared to non pregnant $p<0.001$
preeclampsia
i. compared with mild $p<0.05$
ii. compared with mild $p<0.01$
iii.compared with mild $p<0.001$
a compared to normotensive pregnant $p<0.01$
* compared to normotensive pregnant $p<0.001$

hand, the level of $TT_3$ and $TT_4$ was not statistically significant amongst these two subgroups.

Severe preeclamptic women had higher uric acid levels and low serum albumin levels as compared to mild preeclamptic ones ($p<0.001$ in both cases, Table 2). A significant negative correlation was observed between birth weight and TSH levels in preeclamptic women ($r=-0.296$, $p<0.001$), and significant positive correlation between birth weight and albumin levels ($r=0.298$, $p<0.001$). Also, a highly significant correlation of birth weight with serum uric acid levels ($r=0.46$, $p<0.01$) was noted in preeclampsia.

Serum uric acid levels showed a positive correlation with TSH levels ($r=0.507$, $p<0.01$) and a negative correlation with $TT_4$ levels ($r=-0.204$, $p<0.05$) in preeclampsia. No significant correlation could be observed between serum uric acid levels and $TT_3$ levels in preeclampsia.

A highly significant positive correlation was observed between serum albumin and $TT_3$ & $TT_4$ levels in preeclampsia ($r=0.409$ & $r=0.356$ respectively, $p<0.01$), while there was a significantly negative correlation between serum albumin levels and TSH levels ($r=-0.781$, $p<0.01$) in preeclampsia (fig 1). No significant correlation was observed between birth weight and thyroid hormone levels in normotensive controls.

## Conclusion

In the present study, $TT_3$ levels were significantly higher in normotensive pregnant women as compared to nonpregnant women ($p<0.001$). The $TT_3$ levels were slightly lower in preeclampsia as compared to normotensive pregnant patients ($p>0.05$, table 2). This fall was observed only in the severe form of preeclampsia and not in the mild form of preeclampsia. These findings are in agreement with those reported in the literature (11).

On the other hand, lower $TT_3$ levels in preeclampsia as compared to normotensive pregnant have been reported in the literature (12-14).

During preeclampsia, there is involvement of the liver and kidney that may lead to decreased peripheral conversion of $T_4$ to $T_3$, hence decreasing the $T_3$ levels. Also, "low $T_3$ syndrome" has been reported in preeclampsia (13-15). In addition to this, there is loss of proteins and protein-bound hormones in the urine in preeclampsia which may also contribute to low $TT_3$ levels in preeclampsia as compared to controls (12). Also, it may be a reflection of an inability to compensate for increased fetal demand, increased thyroid break-down by the placenta and transfer of maternal $T_4$ to fetus. $TT_4$ levels were significantly higher during preeclampsia and normotensive pregnant women as compared to non pregnant women ($p<0.001$, Table 2) and the levels were lower in preeclamptic women when compared with normotensive pregnant women ($p<0.01$). Conflicting reports are available in the literature regarding $TT_4$ levels (9-12). A few reports have observed lower $TT_4$ levels in preeclampsia (11, 12) while others have reported higher $TT_4$ levels (14) . This may again be due to high TSH (Table 2)and low free thyroxine index along with concurrent loss of proteins in preeclampsia.

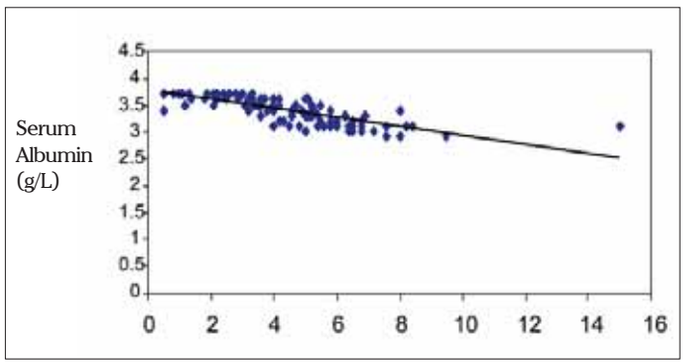


**Figure 1. Correlation between tsh and serum albumin in preeclampsia group**

In the present study, high TSH levels were observed in preeclamptic women as compared to controls (Table 2). Our findings lend support to earlier reports where preeclamptic women were observed to have a higher incidence of biochemical hypothyroidism compared with normotensive pregnant women (11, 12, 15, 17). In contrast, Qublan et al reported no significant difference in TSH levels between these two groups (18).

Pregnancy is generally associated with hypothyroxinemia and the degree of hypothyroxinemia might reflect the severity of preeclampsia. In the present study, a highly significant negative correlation between birth weight and TSH levels was observed in preeclampsia ($r=0.296$, $p<0.01$). However, no correlation between birth weight and thyroid hormones in normotensive pregnant women was observed. In the present study, preeclamptic women with lower birth-weight babies had a higher degree of hypothyroxinemia and higher TSH levels and this may be explained by placental dysfunction in preeclamptic patients. Placental dysfunction may cause failure in estrogen production, leading to a decrease in TBG, $TT_3$ and $TT_4$ levels with simultaneous growth failure of the fetus (12). TBG is reported to be lower in unsuccessful pregnancies indicating placental function deterioration in pregnancy (13). Also, low TBG, $TT_4$ and $TT_3$ levels have been reported in preeclampsia, which was attributed to placental dysfunction in preelamptic women (3).

In the present study, a significant inverse correlation of serum uric acid with $TT_4$ levels in preeclampsia ($r=-0.204$, $p<0.05$)and a positive correlation with TSH levels ($r=0.507$, $p<0.01$) was observed, suggesting that a state of biochemical hypothyroidism is related to preeclampsia. However, no correlation was observed between uric acid levels and $TT_3$ levels ($r=0.119$, $p>0.05$). Our findings are in agreement with those reported in the literature (11).

Albumin levels also showed a positive correlation with both $TT_3$ & $TT_4$ levels ($r=0.409$ & $r=0.356$ respectively, $p<0.01$) and a negative correlation with TSH levels ($r=0.781$, $p<0.01$) in preeclampsia. Our studies are in agreement with other reports (11, 15). Reduced serum albumin and hyperuricemia observed in preeclampsia along with their significant correlation reflects the severity of fetal involvement in preeclampsia with $TT_4$,$TT_3$ & TSH, while hyperuricemia reflects the severity of fetal involvement in preeclampsia, and serum albumin was reduced due to proteinuria occurring in preeclampsia. In the present study, a significant positive correlation of birth weight with albumin levels

(r=0.298), p<0.01)and negative correlation of birth weight with serum uric acid levels was observed in preeclampsia (r=-0.46, p< 0.01). Many workers have observed low $TT_4$, $TT_3$ levels in women with preeclampsia who had small -for -gestational age babies as compared to women with appropriate- for -gestational age infants, thus reflecting the severity of preeclampsia (11, 17).
Raised TSH levels in preeclampsia with a concomitant decrease in $TT_3$ & $TT_4$ levels have been correlated with the severity of preeclampsia and high levels of endothelin. Since endothelial dysfunction has been implicated in widespread vasospasm and poor perfusion of many organs, including the fetoplacental unit in preeclampsia, nitric oxide has been implicated in the pathophysiologic mechanisms of preeclampsia (18). Experimental studies have shown that release of nitric oxide is altered in hypothyroidism in animals (19). Altered release of nitric oxide in endothelial cell dysfunction might be a pathogenetic mechanism for hypothyroidism in preeclampsia (9, 18, 19).
There is a state of hyperthyroxinemia in normal pregnancy and in preeclampsia, a biochemical hypothyroidism (raised TSH) occurs. Thyroid hormonal levels correlated with the severity and outcome of preeclampsia. Thyroid hormones are known to regulate neurodevelopment, probably from early fetal life onwards and may be responsible for preterm birth in preeclampsia. Large scale multicentic studies may discover the association and mechanism of thyroid abnormality in preeclamptic women. Identification of thyroid hormones and thyroid screening during pregnancy might be of help in preventing the occurrence and instituting timely intervention and appropriate measures in terms of possible thyroid hormone administration in preterm infants in future. The changes in thyroid hormones in preeclampsia merit further studies in order to assess the severity of the conditions.

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