Comparison of testosterone hormone in the sera of patients with preeclampsia and healthy pregnant women

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Abstract:
Objective: to determine the level of serum testosterone in preeclamptic (PET) groups and normotensive pregnant women in second and third trimester.
Methods: Fifty five pregnant women with preeclampsia (PET) (twenty five of them in the second trimester of pregnancy while the rest of them were in the third trimester of pregnancy and the same number for healthy pregnant women.
Results: serum testosterone was significantly higher in preeclamptic groups compared with normal pregnant women groups (p<0.001). Also serum testosterone was significantly higher in the third trimester compared with second trimester for preeclamptic groups (p<0.001), and also shows nonsignificant decrease in third trimester compared with second trimester for healthy pregnant women (p=0.36).

Introduction:
Hypertension in pregnancy is a significant problem, if it is associated with proteinuric (which indicates multisystemic disease, known as preeclampsia), it will be associated with increased morbidity and mortality for both mother and baby (Sheinam, 2007). Hypertension in 20 weeks of gestation (Sheinam, 2007). Major preexisting risk factors for PET include primigravida state, history of PET in previous pregnancy, large body size, a family history of PET, multiple pregnancy, preexisting maternal hypertension, pregestational diabetes, antiphospholipid antibody syndrome, vascular or connective tissue disease and advanced maternal age (> 35 to 40 years) (Chan, et al., 2006).

The aetiology of this disease is still in debate and many theories were introduced in this field by many investigators in different countries. One of these thewory which relates the disease to uteroplacental ischemia, suggests the following:-
1- Preeclampsia begins with uteroplacental ischemia, which is an increase intramural resistance in the myometrial vessels, leads to heightened myometrial tension produced by large fetus in a primipara, twins or hydramnios (Ficioglu, et al. 2003).
2- The uteroplacental ischemia leads to the production of vasoconstrictor substance, which enters the circulation and produces renal vasoconstriction leading to increased production of renin - angiotensin and aldosterone (Ficioglu, et al., 2003).

3- The renin-angiotensin system produces a generalized vasoconstriction and aggravates further the uteroplacental ischemia (Takeuchi, et al., 2004). It is followed by systemic of cytotoxic products that damage maternal vascular endothelium (Buhimschi, et al., 2006).

4- Aldosterone leads to water and electrolyte retention and generalized edema (John, 2008).

Androgen are responsible for the manifestation of primary and secondary sex characteristics and preservation of libido, sense of well being (Gronowski, et al., 1999), lean mass and bone density (Nini, et al., 2000). Androgens are involved in a negative biofeed back mechanism on the hypothalamic pituitary axis to inhibit gonadotropin secretion (Bagatell, et al., 1994). They are group of C19 steroid, androgen precursor by the adrenal cortex is dehydroepiandrosterone (DHEA) (Chape-DCA, Harvey-R, and Ferries-DR). Adrenal androgen themselves are weak, they are converted in peripheral tissue to testosterone (as strong androgen) and to estradiol (Chape, et al., 2003).

Testosterone is the major male hormone secreted from the leydig cells (interstitial cells), under the influence of luteinizing hormone (LH) (Ivanova, et al., 1994). In female, the follicular theca cells produce C19 androgens. These are converted to C18 estrogens by granulosa cells (Vasudevan and Sreekuman-S.). In human male the peripheral aromatization of testosterone to estradiol (E2) account for 80% of the production of the latter (Murray, et al., 2011). In female, adrenal androgens are important substrates, since as much as 50% of the estradiol E2 produced during pregnancy comes from the aromatization of androgens (Murray, et al., 2003). Aromatase activity is present in adipose cells and also in liver, skin and other tissues (Ojeda, et al., 2007). Increased activity of this enzyme may contribute to the estrogenization that characterizes such disease as cirrhosis of the liver, hyperthyroidism and obesity (Ojeda, et al., 2007).

Methods:

This study was conducted in Babylon Maternity and Pediatrics Teaching Hospital. Fifty five pregnant women with preeclampsia (twenty five of them in the second trimester of pregnancy (G1) while the rest of them were in the third trimester of pregnancy (G2)) and the same number for healthy pregnant women (twenty five of them in the second trimester of pregnancy (G3) and thirty of them were in the third trimester of pregnancy (G4)).

All the patients were nonsmokers, have no other diseases (ie, cardiac, hepatic, renal, endocrine and other disease) which may have effect on the measured parameters were excluded from the study. Pregnancy is divided into 1st trimester (1-12 week), 2nd trimester (13-28 week) and 3rd trimester more than 28 weeks. Depending on the gestational age.

Blood samples (5ml) were collected by venipuncture, and sera were separated by centrifugation at 1500 xg for 2 minutes. And sera were transferred into eppendorf tube and was used for measurement of testosterone by enzyme Linked immunosorbant assay (ELISA). The statistical analysis is based on ANOVA test to determine the differences between groups and within groups. Normal value for tesoterone level in female is (0.2 -0.8 ng/ml).
Result:

Serum testosterone was significantly higher \((p<0.001)\) in preeclamptic groups \((G1&G2)\) compared with normal pregnant women groups \((G3&G4)\) \(p=0.36\). Also serum testosterone was significantly higher in \(G2\) compared with \(G1\), and also shows nonsignificant decrease in \(G4\) compared with \(G3\), [Fig(1), Table(1), Table (2)] 

Table (1): Serum data of testosterone in preeclamptic and normal pregnant women \((2^{\text{nd}}\ and\ 3^{\text{rd}}\ trimester)\)

<table>
<thead>
<tr>
<th>Measured parameter</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>G4</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Testosterone(ng/ml) (\pm SD))</td>
<td>1.46±0.199</td>
<td>2.41±0.54</td>
<td>0.82±0.198</td>
<td>0.74±0.24</td>
</tr>
</tbody>
</table>

\(\text{mean} \pm \text{SD}\)*

Figure (1): Serum data of testosterone in preeclamptic and normal pregnant women \((2^{\text{nd}}\ and\ 3^{\text{rd}}\ trimester)\)
Discussion:

Many previous studies reported the changes in estrogen levels during normal and complicated pregnancy. Besides, there are numerous studies concerning the role of metabolic syndrome in the aetiology of preeclampsia (Iou, et al., 2005), (Reyes, et al., 2006), (Rebecca, et al., 2003). In our study, levels of serum testosterone were found to be significantly higher in women with preeclampsia than in normotensive women with similar gestational age. Such increase in hormone level in both 2nd and 3rd trimester can be attributed to:

1 - Low expression of the aromatase gene due to small or impaired for the conversion of testosterone to estrogen. The decrease of enzyme activity lead to a subsequent increase in testosterone level (Rebecca, et al., 2003).

2 - In the late pregnancy, when the fetal adrenal gland become mature it will result in further increment in the level of testosterone by conversion of DHEA to testosterone (Rebecca, et al., 2003).

3 - Human chorionic gonadotropin increase in PET and this will stimulates the ovarian thecal cell to synthesis androstenedione and testosterone (Steier, et al., 2007).

4 - The decrease in testosterone clearance in normal pregnancy is intensified in PET patients. This will lead to increase in serum testosterone levels (Bammann, et al., 1980).

5 - Insulin stimulate the production of testosterone by ovarian tissue which suggests that hyperinsulinemia could be primary change that triggered the increased release of testosterone (Ahmed-I, et al., 2009). However, hyperinsulinemia should also stimulate the production of adrenal androgen (Lemieux, et al., 2012).

Our results were in agreement with the results reported by Golmahamed, 2005 and Jasim, 2008.

The increase in serum testosterone levels in the second trimester of normal pregnancy in comparison with those values of the 3rd trimester can be attributed to the increase of aromatase activity with progressive course of pregnancy (Rebecca, et al., 2003).

<table>
<thead>
<tr>
<th>Groups</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 vs G2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>G1 vs G3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>G1 vs G4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>G2 vs G3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>G2 vs G4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>G3 vs G4</td>
<td>=0.36</td>
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References: