Human chorionic gonadotropin and Testosterone in Normal and Preeclamptic Pregnancies in Relation to Fetal sex


Abstract

Background: The gender related difference may be the result of pregnandiol excretion in the latter half of pregnancy.

Aim: This study is to evaluate the effects of fetal gender on serum human chorionic gonadotropin [HCG] and testosterone in normotensive and preeclamptic pregnancies

Methods: The study consisted of fifty women with singleton pregnancy in their third trimester. Twenty five pregnancies were uncomplicated Among those there were thirteen male, and twelve female fetuses Twenty five pregnancies were complicated by preeclampsia. Among those thirteen were with male, and twelve were with female fetuses. Human chorionic gonadotropin and total testosterone were measured in maternal peripheral blood.

Results: In male bearing pregnancies, maternal HCG and testosterone serum levels were significantly higher in preeclamptic than in normotensive mothers. In female bearing pregnancies, testosterone levels were significantly higher in preeclamptic than normotensive mothers, whereas the HCG levels were not significantly different.Male Bearing preeclamptic women had significantly higher testosterone levels than female Bearing preeclamptic women, whereas the HCG levels were not significantly different. In uncomplicated pregnancies the HCG levels significantly higher in female bearing than in male bearing mothers.

Conclusion: In preeclamptic pregnancies with male fetuses; the maternal serum HCG levels were significantly higher than in uncomplicated pregnancies. Total testosterone level were significantly higher in pregnancies whether with male or female fetuses. It was also significantly higher in male bearing than female bearing pregnancies. This may indicate an androgen influence on the pathophysiology of preeclampsia

Key words: human chorionic gonadotrophin; fetal sex; testosterone.

Introduction

The endocrinologic and physiologic changes that accompany human pregnancy have been defined in appreciable details. The implanted blastocyst forms the trophoblast which is subsequently organized into placenta. The placenta provides the nutritional connection between the embryo and the maternal circulation and produces a number of hormones1. The concentration of the hormones measured in serum from maternal blood changes dramatically during pregnancy one of them is the HCG (2) HCG is a glycoprotein produced by syncytiotrophoblast (3). It is a heterodimer of >and B subunits linked by disulfide bonds (4, 5) Testosterone is principal hormone of the testes, it is a C19 steroid with an- OH group in the 17 position, synthesized from cholesterol in the androsterone and adrenalecortex. Its secretion is under the control of LH. Testosterone is secreted from the testes. Small amount of testosterone is also secreted in female from the ovary as well. (6) Sex is determined by two chromosomes called the sex chromosomes X and Y. The Y chromosome is necessary and sufficient for the prediction of testes and the testis-determining gene product is called SYR [sex determining region of the Y chromosome]. (6, 7) The differentiation of the primitive gonads into testes or ovaries in utero is genetically determined in human but the formation of male genitalia depends upon the presence of functional secreting testis. In the absence of the testicular tissue development, female genitalia will occur (6)
Preeclampsia is diagnosed as blood pressure of equal or greater than 130/90 mmHg but less than 160/110 mmHg with proteinuria of 1+ or 2+ on dipstick in two samples 6 hours apart or greater than 0.3 gram in a 24 hours urine collection. Preeclampsia is often referred as the disease of theories with many mechanisms proposed to account for clinical picture, whilst vascular dysfunction is important in the pathophysiology of preeclampsia. The aetiology appears to be due to abnormal trophoblast invasion. Amounts of testosterone are also secreted in females probably from the ovary but possibly from the adrenal as well. Gender effect on HCG and testosterone levels during pregnancy. Fetal gender has been shown to have a significant influence on maternal serum levels of HCG (MSHCG) and testosterone. During the first trimester of normal pregnancies, there is a gender difference in maternal HCG and significantly higher level in the late first trimester (10-14 weeks gestation) in women carrying female fetuses. The same gender related difference was demonstrated in the second trimester (35 weeks), the HCG levels in maternal blood were significantly higher in pregnancies with female fetuses. Also the HCG level at 35 weeks of gestation is higher than 16 weeks of gestation in maternal blood.

Alternatively, it has been proposed that the gender-related difference in MSHCG is mediated by the sex chromosomes of the trophoblast whereby some genes on the X-chromosome that escape inactivation may be over-expressed by the placenta in the presence of a female fetus.

In male fetus, development of Leydig cells leads to an increase in fetal testosterone production between gestational weeks 10 and 20. Continuous exposure of the Leydig cells to HCG would not desensitize the fetal testes and would allow the maintenance of augmented testosterone production during development. During pregnancy the maternal serum levels of FSH and LH and of bioactive FSH at 17 to 24 weeks of gestation were higher in female than in male fetuses and in both sexes decreased between 25 and 41 weeks of gestation. The mean FSH value was higher in female fetuses between 26 and 36 weeks and the mean LH secretion level was higher in males.

The study sample consisted of 50 women, all of them were attending Al-Elwy Maternity Hospital, who were between 18 and 40 years of age with singleton pregnancy, 25 of them had uncomplicated pregnancies and 25 had pregnancies complicated by preeclampsia. In the group of uncomplicated pregnancies 13 were bearing male fetuses and 12 were bearing female fetuses. In the group of women with preeclampsia 13 had male and 12 had female fetuses. Gestational age was calculated from the first day of the last menstrual period, unless ultrasonography results found a discrepancy of 14 days or more. They were examined physically, with blood pressure measured, urine specimens were collected and analyzed, and detailed ultrasonographic. Structural examinations of the fetuses were performed simultaneously. Pregnancies with maternal diabetes, fetal malformations, chromosomal abnormalities, and/or multiple pregnancies were excluded. Sera for Lab diagnosis were collected from preeclampsia and normotensive pregnancies on admission for labour. HCG, and testosterone levels were measured with VIDAS which is automated quantities test for use on the VIDAS instruments for the quantitative measurement of human chorionic Gonadotropin and testosterone in human plasma [Lithium heparinate or EDTA] using the ELFA technique [Enzyme Linked Fluorescent Assay].

Methods

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Results

The results of this study showed the following:

In the group of preeclamptic woman:

1. Diastolic Blood pressure ranged from 90 to 110 mmHg and no differences were seen between male and female-bearing pregnancies.
2. Proteinuria was measured to 1+ and 2+ and no difference was found between male and female-bearing pregnant women.
3. There were no significant differences in serum HCG levels in preeclamptic with female fetuses and those of normotensive women.
4. In preeclamptic pregnancies with male fetuses, there is significantly higher levels of serum HCG than in normotensive women pregnant with male fetuses [p<.001].
5. Serum total testosterone levels were significantly lower than in normotensive pregnancies with male as well as with female fetuses [p<.001].

6. Maternal serum testosterone levels in male-bearing preeclamptic pregnancies were significantly higher than female bearing preeclamptic pregnancies [p<.02].

In the group of uncomplicated pregnancies:

1. Maternal serum HCG levels were significantly higher in pregnancies with female fetuses than in those with male fetuses [p<.005].
2. Maternal serum testosterone value shows no significant gender differences.

There was no statistical correlation between HCG and total testosterone in maternal blood either in male or female bearing pregnancies.

Table 1 HCG and testosterone levels of Uncomplicated 12 female and 13 male bearing Pregnancy cases used in this study

<table>
<thead>
<tr>
<th>n</th>
<th>Testosterone[ng/mL]</th>
<th>n</th>
<th>HCG [mlu/mL]</th>
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<tbody>
<tr>
<td></td>
<td>Female</td>
<td>male</td>
<td>Female</td>
</tr>
<tr>
<td>1</td>
<td>0.98</td>
<td>2.21</td>
<td>12630.72</td>
</tr>
<tr>
<td>2</td>
<td>2.22</td>
<td>2.40</td>
<td>14401.75</td>
</tr>
<tr>
<td>3</td>
<td>1.05</td>
<td>1.10</td>
<td>13838.36</td>
</tr>
<tr>
<td>4</td>
<td>0.96</td>
<td>2.32</td>
<td>17885.44</td>
</tr>
<tr>
<td>5</td>
<td>1.06</td>
<td>2.21</td>
<td>20227.20</td>
</tr>
<tr>
<td>6</td>
<td>1.04</td>
<td>2.23</td>
<td>12876.00</td>
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<td>7</td>
<td>2.36</td>
<td>0.79</td>
<td>19916.48</td>
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<tr>
<td>8</td>
<td>1.24</td>
<td>1.21</td>
<td>18164.00</td>
</tr>
<tr>
<td>9</td>
<td>1.02</td>
<td>1.03</td>
<td>15120.20</td>
</tr>
<tr>
<td>10</td>
<td>2.83</td>
<td>1.41</td>
<td>12320.30</td>
</tr>
<tr>
<td>11</td>
<td>0.68</td>
<td>0.69</td>
<td>13200.36</td>
</tr>
<tr>
<td>12</td>
<td>0.94</td>
<td>0.96</td>
<td>14408.00</td>
</tr>
<tr>
<td>13</td>
<td>1.34</td>
<td>13</td>
<td>13070.35</td>
</tr>
</tbody>
</table>

3.1
Table 2 Testosterone levels of uncomplicated 12 female and 13 male bearing pregnancy cases used in this study

<table>
<thead>
<tr>
<th>N</th>
<th>Testosterone [ng/mL]</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.93</td>
<td>2.21</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.71</td>
<td>2.42</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1.18</td>
<td>2.76</td>
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</tr>
<tr>
<td>4</td>
<td>2.95</td>
<td>2.67</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2.17</td>
<td>3.01</td>
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</tr>
<tr>
<td>6</td>
<td>1.09</td>
<td>2.25</td>
<td></td>
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<tr>
<td>7</td>
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<tr>
<td>13</td>
<td>3.0</td>
<td>33.3</td>
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</table>

Table 3 Serum testosterone in uncomplicated and preeclamptic Third-Trimester Pregnancies With Male or Female Fetuses

<table>
<thead>
<tr>
<th>Fetal sex</th>
<th>n</th>
<th>Mean ± SEM</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>13</td>
<td>1.54 ± 0.19</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>13</td>
<td>2.95 ± 0.21</td>
<td>&lt;.001</td>
</tr>
<tr>
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<td>12</td>
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<td></td>
</tr>
<tr>
<td>n</td>
<td>12</td>
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<td>&lt;.001</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>&lt;.02</td>
<td></td>
</tr>
<tr>
<td>hCG= human chorionic gonadotropin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NS=not significant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=number of cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEM=standard error of mean</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.5
Table 4 Serum testosterone in uncomplicated and preeclamptic Third-Trimester Pregnancies With Male or Female Fetuses

<table>
<thead>
<tr>
<th>Fetal sex</th>
<th>Uncomplicated n</th>
<th>Mean ± SEM</th>
<th>P</th>
<th>preeclamptic n</th>
<th>Mean ± SEM</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>13</td>
<td>1.54 ± 0.19</td>
<td></td>
<td>13</td>
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<td></td>
<td>12</td>
<td>2.23 ± 0.19</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td></td>
<td>NS</td>
<td></td>
<td></td>
<td>&lt;.02</td>
</tr>
</tbody>
</table>

hCG= human chorionic gonadotropin
NS=not significant
n=number of cases
SEM=standard error of mean

3.5

Table 5 HCG in uncomplicated and preeclamptic Third-Trimester pregnancies With Male or Female Fetuses

<table>
<thead>
<tr>
<th>Fetal sex</th>
<th>Uncomplicated n</th>
<th>Mean ± SEM</th>
<th>P</th>
<th>preeclamptic n</th>
<th>Mean ± SEM</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>13</td>
<td>11750 ± 679</td>
<td></td>
<td>13</td>
<td>16148 ± 1022</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female</td>
<td>12</td>
<td>16249 ± 978</td>
<td></td>
<td>12</td>
<td>12717 ± 1164</td>
<td>NS</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td></td>
<td>&lt;.005</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
</tbody>
</table>

hCG= human chorionic gonadotropin
NS=not significant
n=number of cases
SEM=standard error of mean

3.4

Discussion

The study shows that maternal serum hCG levels in the third trimester was significantly elevated in uncomplicated female bearing than uncomplicated male bearing pregnancies [p<.005] (10, 11, 12).

It goes with the previous studies that were done by steier JA, Myking OL, Bergsdo PB P<0.004, while Gol M, Altunyurt S, Cimrin D, Gulcu S Bagi M, and Demir N found that such results were significant at p=0.001.

The difference between our P value and the P value in the previous studies is due to sample size difference and the sample population is not representative of all population.

The gender related difference may be the result of pregandiol excretion in the latter half of pregnancy. It was suggested that this gender related difference is may be due to differential rate of inactivation or utilization of hCG by the fetus or the mother, or the male and the female gonads differentially regulate placental gonadotropin production (13,14,15).

This sex difference has a specific relation to the development of the fetal pituitary-gonadal-system and the difference may be mediated at a more fundamental level by the sex chromosomes of the trophoblast (16,17,18). In our study the testosterone level in uncomplicated pregnancies shows no significant gender differences while
In a study carried out by Nagamani M, MC Donough PG, Ellegood Jo, and Mahesh VB there was a sex difference in the level of testosterone in the maternal peripheral blood before 20 weeks of pregnancy while our study that was carried the third trimester shows no sex difference, and this may be attributed to pituitary gonadotrophin effect on the testosterone level in the third trimester.

The serum hCG level is especially significant in sever preeclampsia and superimposed preeclampsia than in normotensive cases. Several studies have found elevated hCG concentrations in maternal blood in preeclamptic pregnancies but without regard to fetal gender [19,20].

In the present study the hCG level in maternal blood in male bearing preeclamptic pregnancies were significantly higher compared with male bearing uncomplicated pregnancies [P<0.001], whereas in preeclampsia with female fetuses no significant increase in the maternal hCG level was observed.

Nougura Sanchez MF, Agala Barahonat, Arredondo Soberon F, and Morgan MA have found elevated hCG maternal serum levels in preeclampsia. And they attribute these findings to the placental changes during preeclampsia [21].

The preeclampsia-eclampsia Syndrome is a vasospastic disorder and probably has placental origin. The placental theories for the etiology of preeclampsia are focused on the hypoxic effect in the trophoblast tissue of second trimester [21].

The placental ischemic changes are evident and seen in uteroplacental bed. Examination of the placenta in pregnancies complicated by preeclampsia have revealed focal cellular necrosis with increased mitotic activity in the syncytiotrophoblast and cellular proliferation in cytotrophoblast interrelated with the stages of Trophoblastic invasion of the spiral arteries during the 14 and 20 weeks, when trophoblastic invasion is over the spiral arteries become a high resistance system.

The defect observed in preeclampsia is the lack of invasion of the trophoblast to the maternal arteries the diminished placental perfusion creates endothelial damage. These changes might explain the elevated maternal serum hCG level in male bearing pregnancies complicated by preeclampsia [21,22,23].

In our study we agree with this explanation since the placenta seems to play a fundamental role in preeclampsia as the condition improves rapidly after its removal, but there is still no explanation for the no increase in maternal serum hCG levels in female bearing pregnancies with preeclampsia.

In our study the testosterone levels in preeclamptic women were found to be significantly higher in the third trimester compared to the levels found normotensive women [P<.001], and this finding goes with the previous study of androgen levels of preeclamptic patients in the third trimester.

The study found that testosterone levels were found to be significantly higher [P<.05] in preeclamptic women in the third trimester compared to the levels of normotensive control.

In our study the levels of maternal serum testosterone in male bearing preeclamptic pregnancies are significantly higher than these in female bearing preeclamptic pregnancies [P<.02].

The stimulating effect of the hCG fetal testes, the testosterone levels in male fetuses are significantly higher than in female fetuses. The fetal ovaries are regarded as hormonally inactive in the first part of pregnancy but later they might have steroidogenic capacity [25,26,27,28]. The serum levels of total testosterone increase throughout normal pregnancy and are primarily a result of progressive estrogen-induced increase in the concentration in sex hormone-binding globulin concentration [29,30].

All the oestrogens are secreted from the placenta into the maternal circulation principally in the unconjugated form, conjugated in the maternal liver excreted in urine. Low expression of the aromatize gene or small or impaired placenta as found in preeclampsia will increase the release of androgens from the placenta late in pregnancy [31]. Other studies showed a reduced conversion of androgens to oestrogens in placental tissue from preeclamptic pregnancies leading to elevated androstenedione and testosterone [32].

So the level of testosterone found to be significantly higher in preeclamptic women in the third trimester compared to the value of normotensive women [34].

The elevated plasma levels of testosterone could be contributed to the
HCG and Testosterone in......

derothesis of preeclampsia

References

10- Danzer H, Braunstein CD, Raso J, Forsythe A. Maternal serum.
20- Rijhsinghani A, Yankowitz J, Strauss
HCG and Testosterone in…….

RA, Kuller JA Patil S,william- son RA-
Risk of preeclampsia in second-trimester
triploid pregnancies Obstet Gynecol

21- Noguera Sanchez MF, Ayala Barahonat
Arredondo Soberon F, Norgan MA
Observations on pre-eclampsia-eclampsua
and the advances in the evolution of some
laboratory tests. Gynecol obstet Mex 1997

22- Jones CJP, Fox H. An ultrastructural and
ultrahistochemical study of the human
placenta in maternal pre-eclampsia Placenta

23- leels, chung Dy cole LA, copel JA,
loszakit, CD elevated Serum nicked and
urinary beta-core fragment hCG in

24- Serin IS, Kulam, Basbug M,
Unluhizarcik, Guer S, Tayyar M.
Androgen levels of preeclamptic Gynaecol

25- HuHeniemi IT, Korenbrot CC, Jaffe
RB. HCG binding and stimulation of
testosterone biosynthesis in human fetal
testis. J Clin Endocrinol Metab

26- Wilson, foster, Kronenberg Larsen:
william Textbook of endocrinology, 9th
edition Ch.27.P1259, 1263-1264.Ch.
29.P1322: Ch. 31P1534-1536.

27- Jaffe RB. Neuroendocrine-metabolic
regulation of pregnancy In: Yan SSC,
Jaffe RB, Barbieri RL, eds Reproductive
endocrinology. Physiology,
pathophysiology, and clinical management
Philadelphia: WB Saunders Company,

28- Rodeck CH, Gill D, Rosenberg DA,
Collins WP,. Testosterone levels in
midtrimester maternal and fetal plasma and
amniotic fluid. Prenat Diasm 1985:5:175-
80.

29- Bammann BL Coulam CB, Yang NS
Total and free testosterone during
pregnancy. [Am J ObstetGynecol 1980:
137:293-8.

30- Rivarola MA,Forest MG,Migeon
CJ.Testosterone androstendione and
dehydroepiandrosterone in plasma during
pregnancy and delivery: Concentration and
protein binding J Clin Endocrinol Metab

31- Guumbach MM. The role of estrogen
in the male and female: evidence from
mutations in synthesis and action. Horm
Res 2000: 53:23-24.[CrossRef] [ISI]
[Medline.]

32- Rebecca Troisi Nancy Potischman
James M Roberts, Roberta Ness William
Crombleholme, David Lykms, Pentti
Siiteri, and Robert N Hoover International
Journal of Epidemiology 2003:43:455-
460@ International Epjdemiological
Association .

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