Human Chorionic Gonadotropin and Testosterone in Normal and Preeclamptic Pregnancies in Relation to Fetal Gender

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Abstract

Background: Preeclampsia-eclampsia is still one of the leading causes of maternal and fetal morbidity and mortality. Despite active research for many years, the etiology of this disorder exclusive to human pregnancy is an enigma.

Objective: To evaluate the effect of fetal gender on serum human chorionic gonadotropin and testosterone in normotensive and preeclamptic pregnancies.

Patients and Methods: A-case control study was conducted in AL-Kadhymia Teaching Hospital from May 2008 through March 2009. The sample consists of eighty women with singleton pregnancies. Forty pregnancies were complicated by mild preeclampsia; twenty male and twenty female fetuses. Forty pregnancies were uncomplicated; twenty male and twenty female fetuses. Maternal serum human chorionic gonadotropin and total testosterone were measured.

Results: In preeclamptic pregnancies with genders, maternal human gonadotropin and testosterone serum levels were significantly higher than normotensive mothers. In uncomplicated pregnancies with female fetuses, the maternal serum human chorionic gonadotropin was significantly higher than those with male fetuses (P value = 0.0008) whereas no significant gender difference was found in preeclamptic group. Male-bearing preeclamptic pregnancies had significantly higher maternal serum testosterone levels than female-bearing pregnancies complicated by preeclampsia (P value = 0.00226).

Conclusion: In preeclamptic pregnancies with either gender, both the maternal serum human chorionic gonadotropin and testosterone levels were significantly higher than in uncomplicated pregnancies.

Keywords: Human chorionic gonadotropin, testosterone, preeclampsia, fetal gender.

Introduction

Preeclampsia (PE) defined as hypertension of at least 140/90 mmHg recorded on two separate occasion, at least four hours apart and in the presence of at least 300mg protein in a 24-hour collection of urine arising de novo after the 20th week of gestation in a previously normotensive women and resolving completely by the sixth postpartum week.[1]

It is obvious that a single mechanism responsible for the syndrome pre-eclampsia does not exist instead; several mechanisms can act together and even multiply each other.

The search for the underlying cause of this disorder and for clinical marker to predict which women will develop pre-eclampsia is ongoing with its prevention being the ultimate goal. [2]

During normal pregnancy the hCG levels increase rapidly until a peak is reached at 60-80 days gestation thereafter the levels decrease, reaching a nadir at 16-18 weeks gestation. hCG Signals the ovary to maintain the corpus luteum and continue progesterone production, regulates fetal testicular testosterone production which is critical in the development of male external genitalia and possesses some Thyrotopin Stimulating Hormone (T.S.H.) like properties and can cause hyperthyroidism when present in high levels (as in trophoblastic neoplasms).[3], In women androgens are mainly produced by the adrenal glands, the ovary, and peripheral transformation. [4] Testosterone is the most potent androgen.

Blood testosterone levels are function of blood production rates and metabolic clearance rates; thus, these levels may not represent the actual state of androgenicity. Total testosterone levels in women are usually less than 70 ng /dL (ovarian 25% in stroma & follicles, adrenal origin 25% peripheral transformation of androstendione to testosterone 50%). [3]

Male neonate weight approximately 200 gm more than female at term so they are more prone to shoulder dystocia than female. Also male fetus are more prone to be post-term than female so induction of labour is more with male fetuses. [5]

The risk of pre-term labour, PE and placental abruption are increased in male fetuses. Hyperemesis gravidarum, hypertension related growth restriction and placenta accreta are more common in female fetuses. Fetal gender has a significant effect on maternal and cord blood hCG levels, particularly during the last trimester of the pregnancy. In the first & second trimesters no gender differences in the hCG levels were observed.

From the second to third trimester the hCG levels increased significantly in pregnancy with female fetus, while in pregnancies with male fetuses the hCG levels tended to decline, However the reason for this difference is obscure. [6],

In female bearing pregnancies maternal and cord blood hCG level, were significantly higher than in male bearing pregnancies.[7] A study shows that maternal serum hCG levels were significantly higher in both sexes between 8-12 weeks than the other three measurement periods.

At 8-18 weeks measurements, there were no sex related differences in maternal serum hCG levels. At 24-36 weeks, maternal serum hCG levels were significantly higher in pregnancies bearing female fetuses than those bearing male fetuses. [8] , Other

research shows that in women carrying a male fetus testosterone levels gradually increase during pregnancy, in women carrying a female fetus the level decreased after the first trimester.

A statistically significant difference existed in maternal testosterone concentration between both groups during the second half of pregnancy. Testosterone in pregnancy (of both sexes) at the end of gestation was significantly higher compared to non – pregnant values. [9]

Patients and Methods

This prospective case control study was carried out in the obstetrics and gynaecology department in AL-Kadhymia teaching hospital during a period from May 2008 through March 2009, Eighty pregnant women with singleton pregnancy were included in this study , their age ranged between 17-40 **Mean ± SD** (**24.98 ± 7.08**) years, their parity averaged between 0-8 **Mean ± SD** (**3.82±1.19)** children & their gestational age 34 completed weeks or more ,who were admitted to the delivery unit.

Forty pregnant women with mild PE and forty apparently healthy pregnant women were included in this study. The diagnosis of PE was based on clinical criteria that were hypertension (BP of 140/90 mmHg twice over 4 hours without prior comparison) and proteinuria OR the patient was already diagnosed as a case of PE during her current pregnancy and on treatment.

Forty apparently healthy pregnant women were comparable preeclamptic groups regarding the age, gestational age, parity and fetal sex. Pregnancies with maternal diabetes, fetal malformation, chromosomal abnormalities, any history of medical diseases and intrauterine death were excluded from the study.

Women included in the study were subdivided into four groups:

20 pregnant women in labour, bearing male fetuses and complicated by mild PE designated as Group A., 20 pregnant women in labour, bearing female fetuses and complicated by mild PE designated as Group B., 20 pregnant women in labour, bearing **male** fetuses with **uncomplicated** pregnancies as **control group** designated as Group C., 20 pregnant women in labour bearing **female** fetuses with **uncomplicated** pregnancies as **control group** designated as Group D.

A full general medical, surgical, drug and obstetrical history was taken from all women, accurate estimation of gestational age was done by available and reliable LMP with or without first trimester ultrasound scan. They were subjected to full general, physical and obstetrical examination.

Urine specimens were collected and semi quantitative dipstick tests were used for measurement of proteinuria (1+& 2+ corresponded to 300mg \24 hr & 1gm\24 hr respectively.

They were followed during their labour and postnatal period. Neonatal outcome was assessed by a pediatrician for estimation of Apgar score at one and 5 minutes; gestational age at birth & birth weight, In addition to the routine laboratory tests maternal venous blood samples were withdrawn for assessment of hCG and total testosterone as follows, five milliliters of venous blood were drawn from each patient and control and were transferred into clean new plane tube, left at room temperature for 15 minutes for clotting, centrifuged then serum was separated and divided into two parts: 1st part: for estimation of total testosterone by enzyme linked fluorescent Assay (ELFA) method using the VIDAS instrument and 2nd part: for estimation of serum hCG by radioimmunoassay technique using Gamma counter instrument.

Analysis of data was carried out using the statistical program Epi-info (version 6). Data were presented in simple measures of mean, standard deviation, and range (minimum-maximum values). The significance of difference of different means (quantitative data from different groups) was tested using independent student-t-test for difference between two groups. Statistical significance was considered whenever the P value was less than 0.05. For correlations, Pearson and spearman rank correlation tests were used.

Results

Table-1 shows the characteristic of women in the study. There were no significant difference between group A & group B in term of maternal age (P-value 0.779), parity (P- value 0.433) & gestational age. Significant difference was found between the two groups regarding blood pressure measurements (P- value 0.0001).

Table 1: Characteristics of women in the study

	Group 1 Preeclampsia Group (n=40) Mean ± SD	**Group 2 Control group (n=40) Mean ±SD**	**P-Value**
Maternal age (year)	24.98 ± 7.08	25.40±7.83	0.779
Parity	3.82±1.19	2.02±1.35	0.433
Gestational age (week)	37.40±1.29	38.28±1.11	0.244
Systolic BP	135.7±18.27	118.90±9.55	0.0001*

Diastolic BP	99.50±11.53	73.00±7.14	0.0001*

Data expressed as mean ± SD. ***P-value <0.05 considered significant.**

Table-2 shows comparison of the maternal serum levels of hCG in PE & uncomplicated pregnancies with male & female fetuses.

In uncomplicated pregnancies with female fetuses, the mean maternal serum hCG levels was 26100±3162 U/L which is significantly higher (t=13.83, P= 0.0008) than in those with male fetuses (18300±1250 U/L) whereas no significant gender difference was found in preeclamptic group (t=2.72, P=0.10665), 32690±2400 U/L and 34150±3150 U/L for preeclamptic male group and preeclamptic female group respectively.

In preeclamptic pregnancies with male fetuses, the mean maternal serum hCG levels (32690±2400 U/L) was significantly higher than in the normotensive male group (18300±1250 U/L) (t=23.78, P=0.00003).

This difference was also found between preeclamptic and uncomplicated pregnancies with female fetuses (t=65.06, P=00001).

Table 2: Serum hCG level in uncomplicated and preeclamptic third trimester Pregnancies with male and female fetuses.

Fetal sex	Uncomplicated N	Uncomplicated Mean ± SD (U/L)	Preeclamptic N	Preeclamptic Mean ± SD (U/L)	P-value
Male	20	18300±1250	20	32690±2400	0.00003
Female	20	26100±3162	20	34150±3150	0.00000
P-Value		0.0008		NS	

NS= not significant

Table- 3 shows comparison of the maternal serum levels of total testosterone in PE & uncomplicated pregnancies with male & female fetuses. Concerning the maternal serum levels of total testosterone, the mean maternal serum levels of total testosterone was significantly higher (t=269.43, P= 0.00000) in preeclamptic than in normotensive pregnancies with male (6.9±0.66 ng/ml *vs.* 3.5±0.65 ng/ml) as well as with female fetuses (6.1±0.88 ng/ml *vs.* 2.9± 0.25 ng/ml; t=15.64, P= 0.00067).

Male-bearing preeclamptic pregnancies had significantly (t=10.58, P= 0.00226) higher mean maternal serum testosterone levels (6.9±0.66 ng/ml) than female-bearing pregnancies complicated by PE (6.1±0.88 ng/ml).

Although, male-bearing normotensive pregnancies had higher mean maternal serum testosterone levels (3.5±0.65 ng/ml) than female-bearing normotensive pregnancies (2.9±0.25 ng/ml) but it was not significant (t=3.85, P= 0.06134)

Table 3: Serum testosterone in uncomplicated and preeclamptic third trimester Pregnancies with male or female fetuses.

Fetal sex	Uncomplicated N	Uncomplicated Mean±SD (ng/ml)	Preeclamptic N	Preeclamptic Mean±SD (ng/ml)	P-value
Male	20	3.5±0.65	20	6.9±0.66	0.00000
Female	20	2.9± 0.25	20	6.1±0.88	0.00067
P-Value		NS		0.00226	

NS= not significant

Discussion

The present study confirmed the previously reported finding of significantly higher hCG levels in maternal serum in third – trimester uncomplicated female – bearing pregnancies than in uncomplicated male – bearing pregnancies. [10]

Sorensen T K et al [11] Levine RJ et al [12] Said ME et al [13] Witlin AG et al [14] Feinberg RF et al [15] Rijhsinghani A et al [16] have found elevated hCG concentration in maternal blood in preeclamptic pregnancies but without regard to fetal gender.

In a study done by Basirat Z et al he concluded that PE is trophoblastic disorder since hCG which is secreted by trophoblast show elevated level in comparison with normal uncomplicated pregnancy, he also found that the level of beta- hCG in severe form of PE is higher compared to the milder ones .[17]

Gurbuz A et al revealed that the maternal serum hCG level is a useful laboratory tool when managing and treating hypertensive disorders that complicate pregnancy since serum hCG level is especially significant in severe PE and superimposed PE. Therefore, a high serum hCG level can be a helpful marker in the diagnosis and clinical management by preventing possible complications resulting from severe and superimposed PE. [18].

Jones CJP et al concluded that the placenta seems to play a 4fundamental role in PE, as the condition improves rapidly after its removal. Examination of the placenta in pregnancies complicated by PE have revealed focal cellular necrosis with increased mitotic activity in the syncytiotrophoblast and cellular proliferation in the cytotrophoblast A transformation of the cytrophoblast into the syncytiotrophoblast also has been reported. These changes might explain the elevated maternal serum hCG levels in PE pregnancies. [19]

Bammann BL et al found that the serum levels of total testosterone increase throughout normal pregnancy and are primarily as a result of progressive estrogen – induced increase in the, concentration of sex hormone–binding globulin concentration.[20],

MacGillivary I found lower maternal serum levels of estrogen in PE pregnancies than in normal pregnancies, so it is likely that other mechanism mediate the maternal serum testosterone levels. [21],

Jaffe RB suggested that the sources for the increased testosterone levels in maternal serum are not known but could be the ovarian theca – interstitial cells and the maternal adrenal cortex, which might be stimulated by hCG through out pregnancy.

The fetal serum levels of testosterone are much lower than the maternal levels, because of the stimulating effect of hCG on the fetal testis, the testosterone levels in male fetuses are significantly higher than in female fetuses, and this fact was in agreement with our study. [22]

In this study, levels of the potent androgen (testosterone) were found to be significantly higher in women with PE than in healthy controls, these finding were in agreement with that of Salamlekis-E et al who found the level of total & free testosterone appear to be higher in patients with PE compared to normotensive pregnant women during the third trimester of pregnancy. He explained this difference could indicate an involvement of testosterone in the pathophysiology of PE. [23],

Serin IS et al concluded that the higher blood androgen levels measured in PE pregnant patients in the third trimester compared to the values of normotensive controls may be implicated in the pathogenesis of PE. [24].

Acromite MT et al showed that androgen could cause physiologic changes similar to those seen in PE. High circulating androgen concentrations (in the male range) and exogenously administered androgen has both been linked to hypertension in vivo and in vitro. [25].

Seachrist D et al found that Testosterone administration increases the blood pressure and coronary collagen deposition in rats. [26] It appears that the action of testosterone on B.P. is mediated via a mechanism involving the renin-angiotensin system and the androgen receptor; and does not require conversion of testosterone to dihydrotestosterone. [27]

Diamant TZ et al found that the presence of polycystic ovarian syndrome, which is characterized by elevated levels circulating androgens, has been associated with significantly increased risk of pregnancy – induced hypertension. [28]

At 2000 Schellenberg concluded that the fetal gender probably plays no OR a very small role in the pathogenesis of this (disease of theories), but recent study done by Elsmen E et al revealed that male fetal gender is associated with an overall increased risk of PE . However, it was shown that the male: female birth ratio was decreased in PE associated with preterm delivery. The reason for this discrepancy is not known. [29]

The significantly increased maternal testosterone levels in PE pregnancies with male fetuses as well as with female fetuses, and the higher total testosterone maternal serum levels in male – than in female – bearing PE pregnancies , were not related to maternal HCG levels only. PE is a complex disease of unknown origin. A placental involvement in the pathophysiologic mechanism of the disease is likely our observation could indicate an androgenic mediated effect on PE.

Conclusion

From this study, we concluded that elevated maternal serum hCG levels and elevated maternal serum testosterone levels are found in pregnancies complicated by PE (of both gender) than normotensive pregnancies and may be used in prediction of the disease (PE) process.

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