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

*** Maad S. Al-Adami** *M.B.Ch.B., F.I.C.O.G.*** **Wasan Wajdi** *M.B.Ch.B., F.I.C.O.G.*
***** Rawneq A. Abbas** *M.B.Ch.B.*

Abstract

Back ground: The gender related difference may be the result of pregandiol 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 pergnancy 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 uncomplucated 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 pathophysiologic of preeclampsia

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

Al – Kindy Col Med J 2011; Vol. 7 No. 2 P: 1-8

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 hetrodimer 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 leydig cells and also formed from anderostendione secreted by adrenal cortex. Its secretion is under the control of LH. Testosterone is secreted from the testes. Small amount of testosterone is also secreted in female probably from the ovary but possibly from the adrenal 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 collection8 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. [9]

Amounts of testosterone are also secreted in female probably from the ovary but possibly from the adrenal as well. [6] 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. [22]

During the first trimester of normal pregnancies, there is a gender difference in maternal HCG is and significantly higher level in the late first trimester [10-14 weeks gestation] in women carrying female fetuses [11]. The same gender elated difference was demonstrated in the second trimester (35 weeks), the HCG levels in maternal blood were significantly higher in pregnancies with female fetuses [22].

Also the HCG level at 35 weeks of gestation is higher than 16 weeks of gestation in maternal blood [10].

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 [11, 15].

In male fetus, development of Lydig cells leads to an increase in fetal testosterone production between gestational weeks 10 and 20. Continuous exposure of the Lydig cells to HCG would not desensitize the fetal testes and would allow the maintenance of augmented testosterone production during development [12].

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 mean FSH and LH content of fetal pituitary glands and the level of fetal serum FSH are greater in female than in male fetuses at mid gestation. This difference has been ascribed to the higher concentration of plasma testosterone between 11 and 24 weeks in the male fetuses [the only major difference in circulating gonadal steroids between the male and the female fetuses and higher levels of fetal testicular inhibin]. [26]

This study aim to evaluate the effects of fetal gender on serum HCG and testosterone in normotensive and preeclamptic pregnancies

Methods

The study sample consisted of 50 women, all of them were attending Al- Elwya 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 colleced and analyzed, and detailed ultrasonsgraphic. Structural exam-inations 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, andvtestosterone 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].

Results

The results of this study showed the following :
In the group of preeclamptic woman:-

1. Diastolic Blood presure ranged from 90 to 110 mmHg and no differences were seen between male and female -bearing pregnancies.
2. Proteinuria was measured to1+ and 2+ and no difference was found between male and female-bearing pregnant women.
3. There were on 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 highr levels of serum HCG than in normotensive women pregnant with male fetuses [p<.001].
5. Serum total testosterone levels were significantly higher than in normotensive pregnancies with male as well as with female fetuses [p<.001]
6. Maternal serum testosterone levels in male-bearing preeclamptic pregnancies 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

n.	Testosterone[ng/mL] Female	male	n.	HCG [mlu/mL] Female	male
1	0.98	2.21	1	22630.72	11056.34
2	2.22	2.40	2	14401.75	12006.59
3	1.05	1.10	3	13838.36	11076.00
4	0.96	2.32	4	17885.44	9972.00
5	1.06	2.21	5	20227.20	11170.14
6	1.04	2.23	6	12876.00	12748.30
7	2.36	0.79	7	19916.48	11056.80
8	1.24	1.21	8	18164.00	9988.00
9	1.02	1.03	9	15120.20	19009.30
10	2.83	1.41	10	12320.30	9200.30
11	0.68	0.69	11	13200.36	12016.00
12	0.94	0.96	12	14408.00	10380.00
13	.	1.34	13	.	13070.35
3.1					

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

N.	Testosterone [ng/mL] Female	male
1	1.93	2.21
2	2.71	2.42
3	1.18	2.76
4	2.95	2.67
5	2.17	3.01
6	1.09	2.25
7	2.93	2.46
8	2.97	3.50
9	1.96	3.37
10	2.92	3.26
11	1.98	4.92
12	2.01	2.65
13	3.0	33.3

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

		uncomplicated		preeclamptic	
Fetal sex	n	Mean ± SEM	n	Mean ± SEM	P
Male	13	1.54 ± 0.19	13	2.95 ± 0.21	<.001
Female	12	1.36 ± 0.20	12	2.23 ± 0.19	<.001
P		NS		<.02	

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

3.5

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

			Uncomplicated	preeclamptic	
Fetal sex	n	Mean + SEM	n	Mean ± SEM	P
Male	13	1.54 ± 0.19	13	2.95 ± 0.21	<.001
Female	12	1.36 ± 0.20	12	2.23 ± 0.19	<.001
P		NS		<.02	

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

			Uncomplicated	preeclamptic	
Fetal sex	n	Mean ± SEM	n	Mean ± SEM	P
Male	13	11750 ± 679	13	16148 ± 1022	<.001
Female	12	16249 ± 978	12	12717 ± 1164	NS
P		<.005		NS	

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 etiologt 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 damege. These changes might explain the elevated maternal serum hCG level in male bearing pregnancies complicated by preeclmpsia [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 [24].

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 incease 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 and erostendione 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 [24].The elevated plasma levels of testosterone could be contributed to the

endothelial dysfunction involved in the pathogenesis of preeclampsia [25]

References

1- Robet K. Murray, Daryl K. Granner, Peter A Mayes, Victor W.1 Rodwell Harpers Biochemistry, 24th Edition.

2- Oleary P. Bovne P flett P Beilbv J. James I. Longitudinal assessment of changes in reproductive hormones during normal pregnancy. 1991 May 37[5]:667-72.

3- Bagshave KD, searle E, Wass MB. Human gonadotropin. In: 3 Gray CH, James VTH, eds. Hormones in blood. 3rd ed Vol 1. London: Academic Press 1979:363-408.

4- Juan De leon, M.D., George sifuentes, M.D., Cullen Hopkins, M.D.4, Vivian Noble, R.N., Terry Gimpel, B.S., Thomas Myles, M.D., and Joaquin Santolaya-Forgas, M.D., Ph.D. Maternal serum Free P-hCG Levels in Uncomplicated pregnancies at the 10th-15th Week of Gestation and the Development of Obstetic Complications The Journal of Reproductive Medicin 2004, 49[2]:89-29.

5- Charib SD, Wierman ME, Shuqnik MA, et al: Molecular biology of the pituitary gonadotropins. Endocrinol Rev. 1990:11:177-199.

6- William F. Ganong, Review of medical physioloy 20th edition 2001 chapter 23, the Gonads: Development and function of the reproduction system p:398-399, p:434-435.

7- Placental Peptide Hormones: Pituitary-like-hormones, placental human choionic Gonadotropin, fetal compartement & fetal Gonads, Endotext internet website [Female Reproductive Endocrinology.

8- Emmanuelle Baulon, William Dfraser, Bruno piedboeuf, pierre8. Bue Kens and Xuxiong pregnancy-induced hypertension and infant growth at 28 and 42 days postpartun. BMC pregnancy and childbirth 2005, 5:10.

9- Obstetrics by Ten Teachers 17th adition 2000 chapter 2 disorders of placentation P: 161.

10- Danzer H, Braunstein CD, Rasor J, Forsythe AW. Maternal serum.

11- Brudy, S. and Carlstrom, G. [1962] Human choionic gonadotropin concentrations and fetal sex prediction. Fertil Steril 1984:34:336-40.

12- Johan Ami Steier, Per B. Bergsj, Thorsen, and Ole L Myking. Human chorionic gonadotropin in maternal serum in relation to fetal gender and utero-placental blood flow. Acta Obstetricia et. Gynecologica Scandinavica Volume 83 Page 170 -February 2004.

13- Nora R. Miller, M, D., David Garry, D,O,. Hillel W. cohen, Dr. PH- and Relnaldo Figueraa, N.D., Serum Androgen Markers in preeclampsia. Volume 48, Number 4/April 2003.

14- Rawlings, WJ. and Krieger, V.I. [1964] Fertil. Sleril., 15, 173. Reyes, F.I., Boroditsky, R. R., Winter J.S and Faiman, C [1974]. Studies on human sexual development. II. Fetal and maternal serum gonadotropin and sex steroid concentrations. J. din. Endocrinol Metab.. 38,612-617.

15- Hobson, B. and Wide, L. [1974] Chorionic gonadotrophin in the human placenta in relation to the sex of the foetus at term./. Endocr- inol., 60,75-80.

16- obiekwe, B.C and chard [1982] Human choionic gonadotropin levels in maternal blood in late pregnancy: relationto birth weight, sex and condition of the infant at birth Br. J.Obster. Gynaecol, 89 543-546.

17- Leporrier, N-, Herrou, M. and Leymarie, P. [1992] Shift of the fetal sex ratio in hCG selected pregnancies at risk for Down syndrome. Prenat Diagn., 12,703-704.

18- Steier JA, Myking OL, Ulstein M.Human chorionic gonadotropin in cord blood and peripheral maternal blood insingleton and twin pregnancies at delivery. Acta Obstet Gynecol Scand 1989, 68:689-92.

19- Sorensen TK, williams MA, Zingheim RW, Clement SJ, Hickok DE, Elevated second-trimester human chorionic gonadotropin and subsequent pregnancy-induced hypertension Am J Obstet Gynecol , 1993:169:834-8.

20- Rijhsinghani A, Yankowitz J, Strauss

RA, Kuller JA Patil S,william- son RA-Risk of preeclampsia in second-trimester triploid pregnancies Obstet Gynecol 1997:90:884-8.

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 Jul:65:300-4.

22- Jones CJP, Fox H. An ultastructural and ultrahistochemical study of the human placenta in maternal pre-eclampsia Placenta 1980-1:61-78.

23- leels, chung Dy cole LA, copel JA, Ioszakit, CD elevated Serum nicked and urinary beta-core fragment hCG in preeclamptic pregnancies. Obstet Gynecol. 1997 Des: 90[6]:889-92.

24- Serin IS, Kulam, Basbug M, Unluhizarcik, Gucer S, Tayyar M. Androgen levels of preeclamptic Gynaecol Scand 2001 Nov:80[11] 1009-13.

25- HuHteniemi IT, Korenbrot CC, Jaffe RB. HCG binding and stimulation of testosterone biosynthesis in human fetal testis. J Clin Endocrinol Metab 1977:44:963-7.

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, 1999:751-811.

28- Rodeck CH, Gill D, Rosenberg DA, Collins WP,. Testosterone levels in midtrimester maternal and fetal placma 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 1968:28:34:40.

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 Crombleholrne, David Lykms, Pentti Siiteri, and Robert N Hoover International Journal of Epidemiology 2003:32:455-460@ Intemational Epjdemiological Association .

****From the Department of Iraqi Medical Collage /Baghdad University***
Corespondence Address to :Dr. Maad S. Al-Adami
Recived at : 5h Oct 2009 Accepted at : 4th Jan 2010

Al – Kindy Col Med J 2011; Vol. 7 No. 2 P: 8