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Article

Elevated second trimester human chorionic gonadotropin level associated withadverse pregnancy outcome

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Abstract

Objective: Our purpose was to determine whether unexplained elevations in maternal serum human chorionic gonadotropin in the second trimester may be associated with adverse pregnancy outcome. *Method:* Between April 1992 and April 1995, 610 pregnant women undergoing second trimester triple marker screening for Down syndrome who delivered at our institution were evaluated. Eighty-one women with a hCG level greater than 2.0 multiples of the median (MoM) were included in the study group while 481 women with hCG levels < 2.0 MoM served as controls. Pregnancies with fetal chromosomal and structural anomalies and maternal serum alpha-fetoprotein levels greater than 2.0 MoM were excluded from the study. Pregnancy outcomes were obtained from hospital delivery records. Statistical analysis were performed by Student's *t*-test; odds ratios and 95% confidence intervals were also calculated. *Results:* Women with elevated human chorionic gonadotropin levels showed an increased risk for preeclampsia (odds ratio (OR): 5.93, 95% confidence interval (CI): 1.97–15.88), intrauterine growth retardation (OR: 5.34, 95% CI: 2.14–13.34), preterm delivery (OR: 5.66, 95% CI: 3.22–9.98), and preterm premature rupture of membranes (OR: 3.15, 95% CI: 1.23–8.07). *Conclusion:* Unexplained elevation of human chorionic gonadotropin in the second trimester appears to be associated with adverse pregnancy outcome. © 1997 International Federation of Gynecology and Obstetrics

Keywords: Human chorionic gonadotropin; Second trimester; Pregnancy outcome

1. Introduction

In current screening tests for Down syndrome, an elevated level of human chorionic gonadotropin (hCG) is an important predictor of fetal aneuploidy [1]. The positive predictive value of the multiple marker screening test is 4.3% [2]. Besides Down syndrome, triploidy, trophoblastic diseases, and multiple gestations have been associated with elevated hCG levels [3]. In the majority of cases the cause of the maternal hCG elevation is not known.

The association between elevated maternal

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serum hCG in the second trimester with adverse pregnancy outcome such as preterm labor, pregnancy-induced hypertension, and low birth weight has been documented in some clinical reports [4–7].

hCG was reported to be elevated in toxemia of pregnancy [8]. Twin and molar pregnancies associated with elevated hCG levels also carry an increased risk of preeclampsia. Also a relationship was reported between elevated hCG levels and hypertensive pregnancy disorders [9–11].

In view of these findings we undertook this study to determine whether women with unexplained elevated serum hCG levels are at increased risk for adverse pregnancy outcome.

2. Materials and methods

From April 1992 to April 1995, in the Hacettepe University Obstetrics and Gynecology Department, 610 maternal serum samples were collected for multiple marker screening test (maternal serum AFP, hCG, unconjugated estriol). Tests were performed for only non-diabetic and singleton pregnancies, and samples collected between 15–20 gestational weeks. Gestational ages were estimated by ultrasonographic dating of the pregnancies. Down syndrome screening risk greater than 1/250 was assigned as an increased-risk and genetic counseling and amniocentesis were offered to those women.

Pregnancies with fetal chromosomal and structural abnormalities and maternal serum AFP levels greater than 2.0 multiples of the median (MoM) were excluded from the study population. A group of 481 patients who met all the inclusion or exclusion criteria but with second trimester hCG levels < 2.0 MoM were considered as the control group.

AFP, hCG, and unconjugated estriol were assayed by the Düzen Laboratories Group, Kavaklidere, Ankara using commercially available kits (Kodak). Results were converted into multiples of the median for each of the three analytes by using AFP Prenatal Interpretive Software from Robert Maciel Associates Inc. (MA, USA).

Obstetric histories, biochemical results, and pregnancy outcomes were obtained from delivery records.

Preterm delivery was defined as delivery before 37 completed weeks, and preterm premature ruptures of membranes (PPROM) as rupture of membranes before 37 weeks of gestation. Pregnancy-induced hypertension (PIH) was defined as 15 mmHg diastolic or 30 mmHg systolic rise over first trimester blood pressure values; if the first trimester blood pressure was unknown, it was defined as persistent blood pressure levels $\geq$ 140/90 mmHg. The same blood pressure criteria were used for preeclampsia and including the criteria of proteinuria at least 0.5 g/l for urine samples collected over 24 h. Intrauterine growth retardation (IUGR) was defined as birth weight lower than 10th percentile for the gestational age.

Statistical analyses were performed using Student's t-test. Odds ratios and 95% confidence intervals were also calculated.

3. Results

Unexplained hCG elevation was observed in 81 patients (13%). Elevated hCG level associated with fetal anomalies ($n = 5$) were excluded from this study. Patients with unexplained elevated AFP level ($n = 33$) and both elevated AFP and hCG levels ($n = 5$) were also excluded from the study. It is known that unexplained AFP elevation in the second trimester of pregnancy could be associated with adverse pregnancy outcomes such as low birth weight, fetal death, and preterm delivery [12,13].

Table 1
Characteristics of study population

Characteristic	hCG > 2.0 MOM ($n = 81$)	Control ($n = 481$)	P
Maternal age (years)	30.2 ± 6.0	30.1 ± 5.1	NS
Gravida	2.2 ± 1.3	2.3 ± 1.3	NS
Parity	0.6 ± 0.8	0.8 ± 0.8	NS
Delivery week	37.0 ± 4.4	38.6 ± 1.6	< 0.01
Birth weight (g)	2881 ± 952	3292 ± 498	< 0.01

NS, not significant.

Table 2
Pregnancy outcomes in women with elevated serum hCG levels and in controls

Outcome*	hCG > 2.0 MOM ($n = 81$)	Control ($n = 481$)	Odds ratio and 95% confidence interval
Preterm delivery	27 (33%)	39 (8.1%)	5.66 (3.22–9.98)
PPROM	7 (8.6%)	14 (3%)	3.15 (1.23–8.07)
PIH	3 (4%)	12 (2%)	1.50 (0.42–5.45)
Preeclampsia	7 (8.6%)	8 (1.7%)	5.93 (1.97–15.88)
Growth retardation	9 (11%)	11 (2.2%)	5.34 (2.14–13.34)
Ablatio placenta	2 (2.5%)	3 (0.6%)	4.03 (0.66–24.53)

* Outcomes were not mutually exclusive.

Some characteristics of the study population are given in Table 1. There were no significant differences between study and control subjects with respect to maternal age (mean ± standard deviation) and mean gravida and mean parity.

Table 2 shows that the pregnancies of women with elevated maternal serum hCG levels in the second trimester were more frequently complicated by pregnancy-induced hypertension, preeclampsia, intrauterine growth retardation, abruptio placenta, preterm delivery, and preterm premature ruptures of membranes. The outcomes were not mutually exclusive. The positive and negative predictive values for abnormal outcomes when an unexplained hCG value > 2.0 MoM had been detected are given in Table 3.

Elevated maternal serum hCG levels in the second trimester of pregnancy were associated with shortening of the mean gestation by 1.6 weeks. The risk of preterm delivery for a woman with an elevated hCG level was 5 times that of the controls (OR: 5.66, 95% CI: 3.22–9.98). The risk of PPROM was 3 times higher among women with elevated hCG than those with normal levels.

The frequency of PIH among women with elevated hCG level was 1.5 times that of the controls (OR: 1.50, 95% CI: 0.42–5.45). But this finding was statistically insignificant, because the lower limit of confidence interval included one.

The risk of preeclampsia in women with elevated maternal serum hCG level in the second trimester was 5 times that of the control group (OR: 5.93, 95% CI: 1.97–15.88).

Two of the 81 patients (2.5%) with unexplained elevated hCG level had abruptio placenta, compared to 0.6% among the controls, (OR: 4.03, 95% CI: 0.66–24.53. This was also statistically insignificant.

As a consequence of preeclampsia, the incidence of intrauterine growth retardation was 11% among patients with elevated hCG level and 2.2% in patients with normal hCG level (OR: 5.34, 95% CI: 2.14–13.34). Elevated hCG level was associated with birth weight reduction of 411 g compared with controls ($P < 0.01$).

Table 3
Positive and negative predictive values for the adverse outcomes

Outcome	Positive predictive value (PPV)	Negative predictive value (NPV)
Preterm delivery	0.41	0.89
PPROM	0.33	0.86
Preeclampsia	0.47	0.86
Growth retardation	0.45	0.87
Ablatio placenta	0.40	0.86

4. Discussion

In the current Down syndrome screening tests elevated hCG level is an important predictor of fetal aneuploidy. The majority of cases with elevated maternal serum hCG are associated with structurally normal fetus. Recent studies suggest a relation between unexplained second trimester

hCG level elevations and hypertensive complications of pregnancy, preterm delivery, and fetal growth retardation [4–7].

Findings of earlier reports suggest a relation between preeclampsia and high third trimester hCG levels. It was reported that hCG was elevated in toxemia of pregnancy [8]. Recent reports document an association between elevated second trimester hCG levels and hypertensive pregnancy disorders [10,11]. In a clinical study hCG levels were assayed in 62 patients with toxemia; 28 of 62 patients with toxemia had serum hCG levels above the normal range speculating that early placental vascular damage leading to decreased oxygen supply might result in increased hCG production by hyperplastic cytotrophoblastic cells [13]. Indeed, hCG production has been shown to increase when normal placental villi in organ cultures were maintained under hypoxic conditions [14]. The pregnancies at risk for small for gestational age and hypertension may have early uteroplacental hypoperfusion and hence, the reduced oxygen supply to the cytotrophoblasts may result in increased production of hCG. PIH rarely appears until the third trimester but the disease process begins early in pregnancy. Typically, the placenta is the affected tissue in pregnancies complicated by hypertension [15]. It may be considered that these changes begin early in pregnancy, resulting in hypoperfusion of placental villi, proliferation of cytotrophoblast, and increased hCG production. The placentas of Down syndrome fetuses are about 2 weeks developmentally delayed compared to normal fetuses [16]. However, placental immaturity may be related to fetal growth restriction and prematurity because of poor delivery of substrate to the fetus resulting in suboptimal growth. It seems relatively easy to explain that pregnancies with elevated hCG could have a higher risk to end with preeclampsia, IUGR, abruptio placenta, and preterm delivery than PPROM.

Pregnancies complicated with hypertension are more frequently terminated earlier because of ominous fetal surveillance testing and causing more preterm deliveries; also it is not surprising to see a higher percentage of abruptio placenta and fetal growth restriction in this group of pregnancies. As we excluded the pregnancies with high AFP levels, our study group do not overlap to IUGR risk in that kind of pregnancy as stated previously [12,17–19]. It is difficult to bring a clear-cut explanation for the higher risk of PPROM in the studied group. There is increasing evidence that the cervical, decidual, and fetal membrane cells act together to promote parturition [20]. The release of proteases capable of degrading the extracellular matrix of the cervix and fetal membranes could be the result of some pathological events activating cervical, decidual and amniochorionic cells. The activation of cytokine network enhances fetal membrane and extracellular matrix degrading protease activity [21,22]. It can be speculated that abnormal obstetrical events related to placental insufficiency or dysfunction together with tissue hypoxia and early vascular damage of placental villi evidenced by high maternal serum hCG in midpregnancy could trigger the chain reactions leading to PPROM.

The results of this study show that women with unexplained elevated second trimester hCG levels have an increased risk for preterm delivery, PPROM, preeclampsia, and fetal growth retardation. We conclude that elevated second trimester hCG levels seem an important predictor of placental dysfunction. These pregnancies may require increased obstetric surveillance like serial assessment of fetal growth and assessment for the risk factors predicting preterm birth. Frequent antenatal visits during the late second and early third trimester may assist in early recognition of hypertensive complications of pregnancy and this may help to achieve a favorable outcome.

References

[1] Bogart MH, Pandian MR, Jones OW. Abnormal maternal serum chorionic gonadotropin levels in pregnancies with fetal chromosome abnormalities. Prenat Diagn 1987; 7: 623–630.

[2] Cheng EY, Luthy DA, Zebelman AM, Williams MA, Liepman RE, Hickok DE. A prospective evaluation of a second trimester screening test for fetal Down syndrome using maternal serum alpha-fetoprotein, hCG, and unconjugated estriol. Obstet Gynecol 1993; 81: 72–77.

[3] Kainer F, Wessel J, Struck E, Jiminez E. Sonographic

diagnosis of a partial mole with increased hCG in triploidy syndrome. Gynaecol Rundsch 1989; 29: 460–461.

[4] Gonen R, Perez R, David M, Dar H, Merksamer R, Sharf M. The association between unexplained second trimester maternal serum hCG elevation and pregnancy complications. Obstet Gynecol 1992; 80: 83–86.

[5] Wenstrom KD, Owen J, Boots LR, DuBard MB. Elevated second-trimester human chorionic gonadotropin levels in association with poor pregnancy outcome. Am J Obstet Gynecol 1994; 171: 1038–1041.

[6] Morssink LP, Kornman LH, Beekhuis JR, De Wolf BTHM, Mantingh A. Abnormal levels of maternal serum human chorionic gonadotropin and alpha-fetoprotein in the second trimester: relation to fetal weight and preterm delivery. Prenat Diagn 1995; 15: 1041–1046.

[7] Clark F, Dickinson JE, Walters BNJ, Marshall LR, O'Leary PC. Elevated mid-trimester hCG and maternal lupus anticoagulant. Prenat Diagn 1995; 15: 1035–1040.

[8] Loraine JA, Matthew GD. Chorionic gonadotropin in toxemias of pregnancy. J Obstet Gynaecol Br Empire 1950; 57: 542–551.

[9] Roberts JM, Taylor RN, Musci TJ, Rodgers GM, Hubel CA, McLaughlin MK. Preeclampsia: an endothelial cell disorder. Am J Obstet Gynecol 1989; 161: 1200–1204.

[10] 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: 834–838.

[11] Teoh ES, Sivasamboo MB. Immunological chorionic gonadotrophin titers in severe toxemia of pregnancy. J Obstet Gynaecol Br Commonw 1968; 75: 724–727.

[12] Milunsky A, Jick SS, Bruell CL, MacLaughlin DS, Tsung YK, Jick H et al. Predictive values, relative risks and overall benefits of high and low maternal serum α-fetoprotein screening in singleton pregnancies: new epidemiological data. Am J Obstet Gynecol 1989; 161: 291–297.

[13] Crosignani PG. Correlation of human chorionic somatomammotropin (hCS) with fetal nutrition. In: Josimovich JB, editor, Lactogenic Hormones, Fetal Nutrition and Lactation. New York: John Wiley and Sons, 1973: 203–220.

[14] Fox H. Effect of hypoxia on trophoblast in organ culture: a morphologic and autoradiographic study. Am J Obstet Gynecol 1970; 107: 1058–1064.

[15] Frusca T, Morassi L, Pecorelli S, Grigolato P, Gostaldi A. Histological factors of uteroplacental vessels in normal and hypertensive patients in relation to birth weight. Br J Obstet Gynaecol 1989; 96: 838–839.

[16] Bogart MH, Golbus MS, Sorg ND. hCG levels in pregnancies with aneuploid fetuses. Prenat Diagn 1989; 9: 379–384.

[17] Williams MA, Hickok DE, Zingheim RW, Luthy DA, Kimelman J, Nyberg DA et al. Elevated maternal serum α-fetoprotein levels and midtrimester placental abnormalities in relation to subsequent adverse pregnancy outcomes. Am J Obstet Gynecol 1992; 167: 1032–1037.

[18] Burton BK. Outcome of pregnancies in patients with unexplained elevated or low levels of maternal serum alpha-fetoprotein. Obstet Gynecol 1988; 72: 709–713.

[19] Nelson LM, Benson J, Burton BK. Outcome in patients with unusually high maternal serum alpha-fetoprotein levels. Am J Obstet Gynecol 1987; 157: 572–576.

[20] Lockwood CJ. Recent advances in elucidating the pathogenesis of preterm delivery, the detection of patients at risk, and preventive therapies. Curr Opin Obstet Gynecol 1994; 6: 7–18.

[21] Rechberger T, Woessner JF. Collagenase, its inhibitors and decorin in the lower uterine segment in pregnant women. Am J Obstet Gynecol 1993; 168: 1598–1603.

[22] Ito A, Sato T, Ojima Y, Chen LC, Nagase H, Mori Y. Calmodulin differentially modulates the interleukin-1-induced biosynthesis of tissue inhibitor of metalloproteinases and matrix metalloproteinases in human uterine cervical fibroblasts. J Biol Chem 1991; 266: 13598–13601.