

Aysel KABUKÇU¹
S. Lütfü ÖNDEROĞLU¹
Yahya LALELİ²
Tekin DURUKAN¹

Women with Elevated Second Trimester Human Chorionic Gonadotropin Level Are at Increased Risk for Preeclampsia*

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Abstract: Objective: Our purpose was to determine whether unexplained elevations in maternal serum human chorionic gonadotropin (hCG) in the second trimester is associated with an increased risk of preeclampsia.

Methods: Between April 1992 to April 1995, 610 pregnant women undergoing second trimester triple marker screening for Down's syndrome who were delivered at our institution were included to the study. 81 women with an hCG level greater than 2.0 multiples of median (MOM) served as the study group and 481 women with hCG levels <2.0 MOM served as controls. Pregnancies with fetal chromosomal and structural anomalies and maternal serum alpha-fetoprotein level greater than 2.0 MOM were excluded

from the study. Statistical analyses were performed using Student's t test. Whenever statistical significance was detected, odds ratios and 95% confidence intervals were also calculated.

Results: Women with elevated hCG levels were at increased risk for preeclampsia (Odds ratio 5.93, 95% confidence interval 1.97 to 15.88).

Conclusion: Pregnancies with unexplained elevated hCG levels should be regarded as having a higher risk of preeclampsia.

Key Words: Human chorionic gonadotropin, second trimester, Preeclampsia.

Departments of ¹Obstetrics and Gynecology,
²Düzen Laboratuvarlar Grubu, Faculty of
Medicine, Hacettepe University,
Ankara-Turkey

Introduction

In current screening test for Down's syndrome (namely maternal serum alpha-fetoprotein-AFP- human chorionic gonadotropin- hCG-, unconjugated estriol plus maternal age) an elevated level of hCG is an important predictor of fetal aneuploidy (1). The positive predictive value of the multiple marker screening test is approximately 4.3% (2). Besides Down's syndrome, triploidy, trophoblastic diseases, and multiple gestations have been associated with elevated hCG levels (3). In the majority of cases the cause of the elevated maternal hCG levels is not known. hCG is produced by placental trophoblasts and excreted directly into the maternal circulation, and its is possible that abnormal levels are an early sign of placental dysfunction.

The association between elevated maternal serum hCG in the second trimester with adverse pregnancy outcome such as preterm labour, pregnancy-induced hypertension, and low birth weight has been documented in a few clinical report (4,5).

Pregnancy-induced hypertension is a systemic disease characterised by endothelial injury (6). The disease begins early in pregnancy but overt disease usually appears after the second trimester. Twin and molar pregnancies which are associated with elevated hCG levels also carry an increased risk of preeclampsia. As early as 1950, hCG was reported to be elevated in toxemia of pregnancy (7). Some new clinical reports hypothesized a relation between elevated second trimester hCG levels and hypertensive pregnancy disorders (8,9).

In view of these findings we undertook this study to determine whether women with unexplained elevated serum hCG levels are at increased risk for pregnancy-induced hypertension and for preeclampsia in our population.

Materials and Methods

From April 1992 to April 1995, 610 maternal

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serum samples were collected for multiple marker screening test (maternal serum AFP, hCG, unconjugated estriol). In the Hacettepe University Obstetrics and Gynecology Department tests were performed for only nondiabetic and singleton pregnancies, and samples collected between 15th and 20th gestational weeks. Gestational age was estimated by ultrasonographic dating of the pregnancy. Women whose maternal serum Down's syndrome screen risk was greater than 1/250 were assigned to the increased-risk group and genetic counselling and amniocentesis were performed.

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

AFP, hCG, and unconjugated estriol were assayed by the Düzen Laboratories Group, Kavaklıdere, Ankara using commercially available kits (Kodak). Results were converted into multiples of the median for each of the three analytes by using APF Prenatal Interpretive Software from Robert Maciel Associated Inc (Robert Maciel Associates, Inc. 870 Massachusetts Avenue Post office box 212).

We obtained the patients' obstetrics history, biochemical results, and pregnancy outcomes from hospital delivery records.

Pregnancy-induced hypertension was defined as 15 point diastolic or 30 point systolic rise over first trimester blood pressure values; if the first trimester blood pressure was unknown, it was defined as persistent blood pressure levels > 140/90. The same blood pressure criteria were used for preeclampsia and including the criteria of proteinuria of at least 0,5 gr/L for urine samples collected over 24 hours. Intrauterine growth retardation was defined as birth weight lower than the 10th percentile for gestational age.

Statistical analyses were performed using Student's t test. Whenever statistical significance was detected, odds ratios and 95% confidence intervals were also calculated.

Results

Unexplained hCG elevation was observed in 81 patients (13%). Elevations of hCG caused by fetal

anomalies (n=5) were excluded from the study. Patients with unexplained elevated AFP levels (n=33) and both elevated AFP and hCG levels (n=5) were also excluded from the study, because, 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 (10,11).

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

Elevated maternal serum hCG levels in the second trimester of pregnancy were associated with a shortening of the mean gestation by 1.6 weeks. Elevated hCG levels were also associated with birth weight

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 (grams)	2881±952	3292±498	<0.01

NS= not significant

reduction of 411 grams compared to controls.

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 (PIH), preeclampsia, intrauterine growth retardation, and abruptio placenta.

The risk of preeclampsia in women with elevated maternal serum hCG levels in the second trimester was five times greater than that of the control group (odds ratio 5.93, 95% confidence interval 1.97 to 15.88).

As a consequence of preeclampsia, the incidence of

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
PIH	3 (4.0%)	12 (2.0%)	1.50 (0.42 to 5.45)
Preeclampsia	7 (8.6%)	8 (1.7%)	5.93 (1.97 to 15.88)
Growth retardation	9 (11%)	11 (2.2%)	5.34 (2.14 to 13.34)
Abruption placenta	2 (2.5%)	3 (0.6%)	4.03(0.66 to 24.53)

intrauterine growth retardation was 11% among patients with elevated hCG levels and 2.2% in patients with normal hCG levels (odds ratio 5.34, 95% confidence interval 2.14 to 13.34).

Although the frequency of PIH among women with elevated hCG levels was approximately 1.5 times that of the controls (odds ratio 1.50, 95% confidence interval 0.42 to 5.45) and odds ratio of abruptio placentae 4.03, 95% confidence interval 0.66 to 24.53 these findings were not statistically significant because lower limits of confidence intervals included one.

Discussion

New studies suggest a link between increased hCG and adverse pregnancy outcomes. Gonen et al reported that in 284 women with unexplained second trimester hCG level elevations, they found that these unexplained elevations increased the relative risk of hypertension, preterm delivery and fetal growth retardation (4). A few clinical reports document a relation between elevated second trimester hCG levels and hypertensive pregnancy disorders (8,9). They suggest that elevated serum hCG level reflects early placental dysfunction.

PIH rarely appears until the third trimester but the disease process begins early in pregnancy. The placenta is typically the tissue affected in pregnancies

complicated by hypertension (13). It may be considered that early placental vascular damage in the preeclamptic pregnancies leading to decreased oxygen supply may result in increased hCG production by hyperplastic cytotrophoblastic cells (8). Indeed, hCG production has been shown to increase when normal placental villi in organ cultures were maintained under hypoxic condition (12). It may be hypothesized that placental health can be predicted by second trimester maternal serum hCG levels.

Our findings show that women with unexplained second trimester hCG levels have an increased risk of preeclampsia, and fetal growth retardation. A higher incidence of intrauterine growth retardation and preterm delivery with the presence of preeclampsia may be expected.

We conclude that unexplained elevations of hCG in the second trimester has a predictive value for subsequent preeclampsia. These pregnancies may require careful obstetric management to achieve a more favorable outcome.

Correspondence author

Aysel KABUKÇU

AGE Blokları, 4. Sokak, No. 38/8

Eryaman, Ankara-Turkey

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