

ELEVATED SERUM LEVELS OF HUMAN CHORIONIC GONADOTROPHIN AND ALFA-FETOPROTEIN PREDICTING FOR DEVELOPMENT OF SEVERE PRE-ECLAMPSIA

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HASTANE

SUMMARY

Objective: Our purpose was to study the correlation between maternal serum total chorionic gonadotrophin (MShCG) levels and maternal serum alpha fetoprotein (MSAFP) levels measured at 15-19 week's gestation and pre-eclampsia.

Methods: This retrospective study was conducted from May 2002 to October 2003 at Zeynep Kamil Gynecology and Obstetrics Hospital. Thirty two cases with mild pre-eclampsia and thirty two cases with severe pre-eclampsia were recruited as the study groups. 305 normotensive women were enrolled as controls. Measurement of MShCG and MSAFP were made from 15-19 week's gestation as part of antenatal serum screening for Down's Syndrome in the second trimester. Serum alpha fetoprotein was measured by radio-immunoassay and serum total human chorionic gonadotrophin was measured by immunoradiometric technique.

Result: MShCG levels and MSAFP levels were significantly higher in severely pre-eclamptic women ($p < 0.05$), but not in those with mild pre-eclampsia, compared with those in their matched controls.

Conclusion: Elevated mid trimester serum human chorionic gonadotrophin levels and alpha-fetoprotein levels may help in the prediction of severe pre-eclampsia. High MShCG levels in severely pre-eclamptic women might reflect a significantly pathologic change and secretory reaction of placenta.

Key words: human chorionic gonadotrophin, maternal serum alpha-fetoprotein, pre-eclampsia

ÖZET

Serum Total Koryonik Gonadotropin ve Alfa Feto-Protein Düzeyleri ile Pre-Eklampsi Gelişimi arasındaki ilişki

Amaç: Gebeliğin 15-19 haftaları arasında bakılan serum total koryonik gonadotropin düzeyleri ve serum alfa feto-protein düzeyleri ile ileride gelişebilecek olan pre-eklampsi arasında ilişki olup olmadığını araştırmak.

Materyal ve Method: Bu çalışma Mayıs 2002 ve Ekim 2003 tarihleri arasında Zeynep Kamil Kadın Hastalıkları ve Doğum Kliniğine başvuran 369 gebe üzerinde yapılmıştır. Gerekli tetkikler ve muayeneler sonucunda 32'si hafif pre-eklampsi ve 32'si ağır pre-eklampsili hasta çalışma grubuna alınmış, kontrol grubu olarak normotansif 305 gebe kadın alınmıştır. İkinci trimester Down sendrom tarama testinde bakılan serum total koryonik gonadotropin düzeyleri ve serum alfa fetoprotein düzeyleri baz olarak alınmıştır. MSAFP radio-immunoassay, MShCG immunoradiometrik teknikle ölçülmüştür.

Bulgular: İkinci trimester tarama testinde ölçülen serum total koryonik gonadotropin ve serum alfa fetoprotein düzeyleri ağır preeklampside belirgin olarak daha yüksek bulunurken kontrol grubu ile karşılaştırıldığında hafif preeklampsi için belirgin bir farklılık saptanmamıştır.

Sonuç: İkinci trimester tarama testinde artmış serum total koryonik gonadotropin ve artmış serum alfa fetoprotein düzeyleri ileri dönemlerde gelişebilecek ağır preeklampsi tahmininde yardımcı olabilir.

Anahtar kelimeler: preeklampsi, human koryonik gonadotropin, alfa feto-protein

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INTRODUCTION

Preeclampsia is a syndrome unique to human pregnancy and strongly associated with adverse pregnancy outcome. Although the exact nature of the primary event causing preeclampsia is not known, evidence accumulated over the past few years indicates that abnormal placentation may be one of the initial events in the disease process⁽¹⁻⁴⁾. Several tests have been proposed to identify pregnant women at risk for development of preeclampsia⁽⁵⁻¹⁵⁾. But none of these tests have been widely accepted because of low predictive value or, for some tests, their invasive and time consuming nature.

Most of the adverse maternal and perinatal outcome occurs among patients with severe preeclampsia⁽¹⁶⁻²¹⁾. Therefore, it would be useful to be able to discriminate those at highest risk for development of severe preeclampsia.

A variety of biochemical and biophysical markers have been proposed of predicting the development of preeclampsia later in pregnancy.

Several studies have demonstrated elevated second trimester levels of human chorionic gonadotropin (hCG) and maternal serum alpha-fetoprotein (MSAFP) in patients with preeclampsia⁽²¹⁻²⁵⁾. However, studies utilizing mid-trimester serum hCG levels alone as a predicting test for preeclampsia have been proved to be unsatisfactory⁽²⁷⁻²⁸⁾.

The purpose of our study was to investigate the association of elevated second-trimester hCG and AFP levels with the subsequent development of preeclampsia in pregnancy.

MATERIAL AND METHODS

We retrospectively surveyed the medical data of women who both underwent mid-trimester maternal serum screening for fetal Down syndrome and had singleton deliveries of greater than 24 weeks' gestation in the Zeynep Kamil Women and Children's Hospital between May 2002 and October 2003.

Antenatal screening based on two maternal serum markers (MSAFP and MShCG). In all cases serum screening was performed between 15-19 weeks' gestation. Serum screening results were corrected maternal age, maternal weight and diabetes and were

reported in multiple median (MoM). Multiple median were calculated from values of normal singleton pregnancies. Exclusion criteria included multiple pregnancy, fetus with structural or chromosomal defects, chronic hypertension, diabetes, or other chronic vascular diseases.

Dating was based on the last menstrual period or an early sonogram. If a discrepancy of >5 days was noted between the two, ultrasonographic dating was used. Women who both fulfilled the criteria above and had a final diagnosis of pre-eclampsia-eclampsia were extracted as the study subjects. The diagnostic criteria for mild pre-eclampsia were: 1) blood pressure $\geq 140/90$ mmHg on more than two occasions greater than 6 h apart; and 2) proteinuria (protein excretion $\geq 1+$ on a dipstick random sample). Severe preeclampsia was defined as combinations of following: 1) blood pressure ≥ 160 mmHg systolic or $140 \geq$ mmHg diastolic on two occasions greater than 6h apart; 2) significant proteinuria (protein excretion $\geq 3+$ on a dipstick random sample); and 3) oliguria (urinary output < 400 ml/24 h). Eclampsia was defined as the occurrences of convulsions, not caused by any coincidental neurologic disease, in a woman whose condition also met the criteria for preeclampsia. The study subjects were further divided into two groups. 1 cases with mild preeclampsia; 2 cases with severe preeclampsia-eclampsia. For matched comparison, normal controls were selected from normotensive women of the surveyed population. Sixty four pregnant women with preeclampsia were matched with 305 normotensive, healthy pregnant women with singleton pregnancies in the third trimester. Among 64 subjects 32 had mild preeclampsia, and 32 had severe preeclampsia. The MSAFP was measured by radio-immunoassay and the MShCG was measured by immunoradiometric technique. An elevated level was defined as a concentration of 2.0 MoM or higher.

Statistical analyses were performed with SPSS for windows 10.0. The differences of prenatal variables and pregnancy outcomes among the control, mild preeclampsia, severe preeclampsia groups were carried out with ANOVA, Kruskal Wallis, Student's t, Mann Whitney u and X². p-value less than < 0.05 was considered statistically significant.

RESULTS

A total of 64 cases with preeclampsia were included as the study population. Among them 34 had mild preeclampsia and 34 had severe preeclampsia. There were 305 normotensive cases enrolled as the controls. There were no significant differences in maternal age, parity and history of previous abortion between women with preeclampsia and normotensive controls. Statistically significant differences were reached for levels of MShCG and MSAFP between three groups. Pregnancy outcomes are also summarized in Table I. There were significant differences seen for baby birth weight, gestational age, and 1 min and 5 min Apgar scores. (all p-values <0.001).

Levels of MShCG in the second trimester among the three groups are presented in Table II. There was a significant positive association between MshCG levels and severity of preeclampsia. The increasing trend between severity of preeclampsia and women with elevated MshCG (MshCG ≥ 2.0 MoM) was noted. The OR increased proportionally from 1.66 for mild preeclampsia to 3.1 for severe group, with reference to the control group. However, there were no significant differences in serum levels of total hCG between patients with mild preeclampsia and severe preeclampsia ($P > 0.05$) and no significant difference

was found between the normotensive and mild preeclampsia. ($P > 0.05$) The AFP MoM values were significantly high in the severe preeclampsia group compared with any other group. ($P < 0.01$) No significant difference in AFP values were found between mild preeclampsia and severe preeclampsia and no significant difference between mild preeclampsia and control group. ($P > 0.05$)

DISCUSSION

In recent years, many studies have been conducted to determine the association between maternal serum hCG levels in the mid-trimester and subsequent development of preeclampsia. As early as 1950 the placental hormone hCG was reported to be elevated in toxemia-affected pregnancies⁽²⁹⁾. In 1968, Teoh and Sivasambo observed a third trimester rise in hCG levels in hypertensive patients⁽³⁰⁾. Most researchers indicated that an unexplained elevation of serum hCG significantly correlated with the occurrence of preeclampsia⁽²²⁻²⁷⁾. By contrast, Morssink et al⁽³¹⁾ and Pouta et al⁽³³⁾ demonstrated no association between them. Regarding the relation between levels of serum hCG and severity of preeclampsia, Hsu et al⁽³⁴⁾, Morssink et al⁽³²⁾ and Long-Chien Lee et al⁽³⁵⁾

Table I: Prenatal assessments and pregnancy outcome

	Severe PET(n=34)	Mild PET(n=34)	Control(n=369)	P
Prenatal Assessment				
Age	27.41 \pm 5.60	28.84 \pm 5.24	27.85 \pm 5.77	0.567
Gravidity	2.06 \pm 1.29	2.44 \pm 1.85	2.23 \pm 1.45	0.534
History of abortion	0.19 \pm 0.47	0.41 \pm 0.80	0.33 \pm 0.77	0.583
MShCG	1.86 \pm 1.56	1.53 \pm 0.76	1.33 \pm 0.74	0.050*
MSAFP	1.37 \pm 0.84	1.12 \pm 0.48	1.06 \pm 0.59	0.005***
Pregnancy Outcome				
Baby birth weight	1751.56 \pm 794.05	3192.66 \pm 671.74	3404.95 \pm 467.83	0.000***
1 min apgar	6.00 \pm 2.14	7.66 \pm 0.55	7.88 \pm 0.55	0.000***
5 min apgar	7.38 \pm 2.24	8.84 \pm 0.37	8.90 \pm 0.42	0.000***
Gestational age(w)	33.78 \pm 3.27	38.09 \pm 1.87	40.18 \pm 1.29	0.000***

Data are expressed as mean \pm standard deviation. PET=preeclampsia; MoM= multiples of the median; MShCG=maternal serum total hCG;

MSAFP= maternal serum alpha-fetoprotein

Table II: Levels of maternal serum hCG in the midtrimester

MshCG (MoM)	Severe PET (n=34)		Mild PET (n=34)		Control (n=305)		X-	p
	No.	(%)	No.	(%)	No.	(%)		
<0.5	2	6.3	2	6.3	26	8.5	8.96	0.061
0.5-2.0	19	59.4	23	71.9	235	77.0		
2.0<	11	34.4	7	21.9	44	14.4		
%95CI	3.10		1.66		1		-	-
	1.4	6.89	0.67	4.07	-	-		

PET= preeclampsia; CI=%95 confidence interval; MoM= multiples of median

evaluated cases with preeclampsia and demonstrated that significantly raised serum hCG was only associated with severe preeclampsia. Our data confirm previous reports that demonstrated an association between elevated second trimester maternal serum hCG and the subsequent development of preeclampsia. Our data support also a significant association between elevated MshCG and severity of preeclampsia. Women with mild preeclampsia had a 1.66-times greater chance, while women with severe preeclampsia had a 3.1-times greater chance of having MShCG exceeding 2.0 MoM than did women with a normal pregnancy. On the otherhand David M. Stamilio et al. found no association between severe preeclampsia and elevated second trimester hCG levels evaluated at multiple cutoff points(1.5,2.0,2.5, and 3.0)

In many studies unusually high AFP values have been associated with preeclampsia and or gestational hypertension⁽³⁷⁻⁴⁰⁾. On the otherhand, Tanaka et al⁽⁴¹⁾,Simpson⁽⁴²⁾ did not found an association with elevated MSAFP and preeclampsia. Schröcksnadel et al⁽⁴³⁾ reported significantly lower levels of MSAFP in hypertensive pregnancy. Nevertheless, from the reported studies it is suggested that the severity of the hypertensive disorder may be related to the strength of the association:Walters et al⁽³⁷⁾ found that proteinuric preeclampsia was associated with high MSAFP ($p<0.05$) but non proteinuric preeclampsia was not. Raija Rätty et all⁽⁴⁴⁾ also found the AFP values in the severe preeclampsia differed significantly from all other groups. We found significant association between high MsAFP and severe preeclampsia ($p<0.05$). The relationship between high hCG or AFP levels and preeclampsia is unclear.In preeclampsia examination of pathologic placentas reveals focal cellular necrosis in the syncytiotrophoblast and increased mitotic activity with cellular proliferation in the cytotrophoblast.In addition , the proliferating cytotrophoblast in severe preeclampsia is transformed into syncytiotrophoblast within 72 hours.Whether this abnormal trophoblastic secretory reactions in severe preeclampsia patients may reflect more severe pathologic changes of the placenta or a different disease entity from mild preeclampsia awaits further investigation. Being able to predict which patients are greatest risks for development of severe preeclampsia would be of great value in preventive and interventional studies because it would be possible discriminate a high risk population that

could benefit from more aggressive treatment and intense observation.

Our data support that high second trimester MShCG or MSAFP levels are risk factors for development of severe preeclampsia. We conclude that elevated second trimester hCG levels seem an imported predictor of placental dysfunction. These patients may require increased obstetric surveillance like assessment for the risk factors predicting preeclampsia and serial assessments of fetal growth. 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.

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