Maternal Serum Mid-Trimester Human Chorionic Gonadotrophin, Alfa-Fetoprotein and Unconjugated Estriol in Predicting Preeclampsia

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Abstract

Objective. *To evaluate the role of mid-trimester total human chorionic gonadotropin (hCG), alfa-fetoprotein (AFP) and unconjugated estriol (uE3) in the prediction of pre-eclampsia.*
Method. *We carried out a retrospective analysis of hCG, AFP, uE3 levels taken between 16-18 weeks of gestation from 278 women. None of these women had abnormal karyotype fetuses or malformations. The levels of maternal serum hCG, AFP, uE3 were compared between 20 severe pre-eclampsia, 96 mild pre-eclampsia and 112 controls.*
Results. *Levels of hCG in the second trimester triple test result from women who later developed severe pre-eclampsia were significantly elevated than control group (p=0.001, p<0.01). The mean gestational age at birth and mean birth weight of patients whose hCG were higher than 2 MoM (n=32) in triple test were significantly lower than patients with hCG equal or lower than 2 MoM (p<0.01).*
Conclusion. *Increased hCG was found to be significantly associated with severe pre-eclampsia developing later in pregnancy.*
Keywords: *Second trimester serum screening, hCG, pre-eclampsia*

Introduction

Pre-eclampsia and eclampsia are important causes of maternal and fetal morbidity and mortality[1]. Reliable and specific tests for prediction of pre-eclampsia before the onset of disease are not possible so far[2].

Human chorionic gonadotropin (hCG), alpha-fetoprotein (AFP) and uE3 levels in maternal serum have been used for Down syndrome screening for a long time and are commonly known as "the triple marker test". Fifty-six percent of fetal aneuploidy can be detected by a combination of abnormal serum levels of hCG and AFP[3]. In 1992, the relationship between elevated hCG and non-genetic pregnancy complications was studied for the first time[4]. After this report, many authors described that second trimester serum levels of hCG, AFP and uE3 may predict the development of pre-eclampsia later in pregnancy [5,6,7,8,9,10,11,12,13]. However, there is still not an agreement yet about which biochemical marker and with true cut-off can predict the development of

pre-eclampsia or adverse pregnancy outcomes.

The aim of the present study was to compare the relationship between second trimester hCG, AFP and uE3 levels in women with normal pregnancy outcome and with subsequently develop pre-eclampsia.

Material Methods

The pregnant women who developed pre-eclampsia were investigated retrospectively between January 2006 and December 2008 at the Obstetrics Departments of Ondokuz Mayis University and Erbaa- Tokat State Hospital. The list of women who had second trimester screening tests and who delivered at the Obstetrics Departments of Ondokuz Mayis University and Erbaa- Tokat State Hospital was obtained from hospital records. Obstetric histories, pregnancy complications, delivery details were also recorded from individual patient files in the file records department of Ondokuz Mayis University and Erbaa-Tokat State Hospital. Pre-eclamptic patients with antenatal Down syndrome screening test results, delivered at the Obstetrics Departments of Ondokuz Mayis University and Erbaa- Tokat State Hospital, were included in the study group. The control group consisted of women who spontaneously conceived normal pregnancies and healthy newborns. Study group was divided into two subgroups according to the severity of pre-eclampsia.

Women with pre-eclampsia were matched for gestational age with normotensive women who had a normal pregnancy outcome. The cases of pre-eclampsia that were identified and matched controls were investigated about the value of maternal serum hCG, AFP and uE3 in the prediction of pre-eclampsia.

Pre-eclampsia was defined as if the blood pressure diagnosed after 20 weeks of pregnancy was 140/90 mmHg or greater 6 hours apart with proteinuria of 300 mg/day or one dipstick measurement of ≥+1 according to the Committee of Terminology of American College of Obstetricians and Gynecologists definition. Pre-eclampsia was categorized as severe if the systemic blood pressure was 160/110 mmHg or more on two occasion 6 hours apart with severe daily proteinuria (5g/day) or the presence of severity evidences like visual disturbances, upper abdominal pain, convulsion, oliguria, headache, elevated serum liver enzyme or serum creatinine, thrombocytopenia.

Maternal serum screening testing, which measures hCG, AFP and estriol (uE3) levels were performed at 16-18 weeks of gestation. Tests were performed for only non-diabetic and singleton pregnancies. Gestational ages were estimated by ultrasonographic dating of the pregnancies. The maternal serum AFP was measured by radioimmunoassay and the maternal serum hCG was measured by immunoradiometric technique. The serum hCG, AFP, uE3 MoM values were available in all cases. Serum marker values were reported as multiples of median (MoM) to prevent potential bias from different assay methods. Both hCG and AFP MoM values were maternal weight and gestational age adjusted. Down syndrome screening risk greater than 1/250 was defined as an increased risk and amniocentesis was offered to those women.

Pregnancies with chronic hypertension, diabetes, abnormal fetal karyotype, fetal chromosomal or structural abnormalities, and multiple pregnancies were excluded from the study.

The Ethics Committee of Ondokuz Mayis University and Erbaa State Hospital approved the collection of triple test results and clinical information of the patients.

Statistical analyses were done with NCSS 2007& PASS 2008 Statistical Software (Utah, USA). Comparisons of the biochemical data in the pre-eclampsia groups with the normal group was calculated by Student's t-test. The comparisons of the markers between different diagnostic groups were made with the Kruskall-Wallis test. Mann-Whitney U tests were used for comparison of continuous variables. $P<0.05$ was considered statistical significance.

Results

One hundred sixty-six pre-eclamptic pregnant women who delivered at Ondokuz Mayis Universtiy and Erbaa-Tokat State Hospital were included to the study. Among them, ninety-six patients had mild pre-eclampsia and twenty patients had severe pre-eclampsia. The control group consisted of one hundred sixty-two women with uneventful pregnancies. The clinical characteristics of the study population are shown in table 1. The age of patient was between 16 to39 with the mean age was 26.02 ± 4.72 in the control group and 27.27 ± 4.8 and 30.35 ± 4.95 in mild pre-eclampsia and severe pre-eclampsia groups respectively. The mean age of severe pre-eclamptic patients was significantly higher than mild pre-eclampsia and control groups ($p<0.01$). Although gravidity, parity, the gestational age that triple test performed didn't differ between three groups; there were also significant differences between groups in regard to blood pressure of patients, gestational age at delivery and birth weight of their babies.

The mean hCG in severe pre-eclampsia and mild pre-eclampsia groups was 3.38 ± 1.80 MoM and 1.40 ± 0.73 MoM respectively whereas in the control group the mean level was 0.78 ± 0.33 MoM. Levels of hCG in the second trimester triple test result from women who later developed severe pre-eclampsia were significantly elevated than control group ($p<0.01$). There were also significant differences between severe and mild pre-eclampsia and mild and control group in respect to serum levels of hCG ($p<0.01$) (Table 1).

The mean value of AFP in the severe pre-eclampsia and the mild pre-eclampsia groups were 1.09 ± 0.42 and 0.99 ± 0.38 respectively. The AFP MoM values were not statistically significant between study and control groups ($p >0.05$) (Table 1). Similarly uE3 MoM values did not differ between groups ($p >0.05$) (Table 1).

The mean birth weights were 2211.5g ± 689.5g and 3421.3g ± 504g in the severe pre-eclampsia and mild preeclampsia groups and 3516.5g ± 462g in control group. Similarly, the mean gestational age at birth was significantly lower in severe pre-eclampsia group than mild pre-eclampsia ($p<0.01$) and control groups ($p<0.01$).

Among the 278 women in the present study population, 32 women had serum hCG higher than 2 MoM. Of thirty two patients, fifteen patients (75%) were in severe pre-eclampsia group, seventeen patients (17.7%) in mild pre-eclampsia group. Increased hCG was found to be

Table 1

Clinical characteristics and maternal mean serum AFP and HCG levels for the study population

	Control (n=162)	Mild Pre-eclampsia (n=96)	Severe Pre-eclampsia (n=20)
Age(year)	26.02±4.72**	27.27±4.80**	30.35±4.95**
•Gestational Age(week)	17.83±1.35	17.80±1.27	17.50±1.00
Birth Weight(gram)	3516.54±462,85**	3421.35±504,05**	2211.50±689.50**
Time of Delivery (week)	38.06±1.07**	38.12±1.13**	34.70±2.53**
Gravidity	1.54±0,90 (1)	1.77±1.17 (1)	1.80±1.10 (1)
Parity	0.54±0.86 (0)	0.75±1.01 (0)	0.75±1.02 (0)
HCG(MoM)	0,78±0,33**	1,40±0,73**	3,38±1,80**
AFP(MoM)	1,00±0,42	0,99±0,38	1,09±0,42
Esradiol(MoM)	1,16±0,42	1,20±0,45	1,18±0,83

*• Gestational Age That Triple Test Performed; ** statistically significant, p<0.01*

Table 2

Clinical and biochemical characteristics of study population according to HCG groups

	HCG>2.0 (n=32)	HCG≤2.0 (n=246)
Age (year)	28.12±5.39	26.59±4.80
•Gestational Age(week)	17.91±1.20	17.78±1.31
Birth Weight(gram)	2713.43±784.62**	3477.76±505.08**
Timeof Delivery(week)	36.47±2.77**	38.02±1.17**
Gravidity	1.81±1.30 (1)	1.62±0.97 (1)
Parity	0.75±1.13 (0)	0.61±0.92 (0)
AFP(MoM)	1,09±0,45	0,99±0,40
Esradiol(MoM)	1,27±0,70	1,14±0,45

*• Gestational Age That Triple Test Performed; ** statistically significant, p<0.01*

significantly associated with severe pre-eclampsia developing later in pregnancy.

The mean gestational age at birth and mean birth weight of patients whose hCG were higher than 2 MoM (n=32) in triple test were significantly lower than patients with hCG equal or lower than 2 MoM (p<0.01) (Table 2).

Discussion

The present study demonstrated that women with severe pre-eclampsia exhibit higher serum hCG MoM values than healthy controls in the mid-trimester triple test screening.

The role of maternal mid-trimester serum hCG in prediction of pre-eclampsia has been reported in many studies with different results. Most studies have found a relationship between severe pre-eclampsia and elevated serum hCG. Several studies concluded that hCG was predictive of pre-eclampsia [3,14,15,16]. In a few studies, there was no relationship between hCG in the second trimester and development of pre-eclampsia [3,17]. In the present study, the second trimester maternal serum hCG levels in patients who subsequently developed severe pre-eclampsia were significantly higher than those in controls. This study confirmed that increased hCG was significantly associated with severe pre-eclampsia later in pregnancy.

In pre-eclampsia, there is an inadequate trophoblastic invasion of the spiral arteries. It was speculated that the reactive hyperplasia of cytotrophoblastic cells to reduced oxygen supply causes increased production in hCG in pre-eclamptic patients[18]. It was shown that hypoxia increases hCG overproduction in trophoblastic cells cultured in vitro[19]. The failure of trophoblastic invasion causes ischemic damage to the syncytiotrophoblast. So changing the superficial layer of the syncytiotrophoblast causes an increased leakage of placental proteins like hCG into the maternal circulation. Both increased production and leakage into the maternal circulation explain the elevated maternal hCG levels in pre-eclamptic patients[20].

Several investigations have studied serum hCG threshold levels that predict complications of pregnancy including pre-eclampsia. In many studies, different hCG thresholds were used for prediction of pre-eclampsia or poor pregnancy outcome. The commonest hCG thresholds used in studies were hCG above 2.0, 2.5, 3.0 MoM[6,7,8,18]. The most accurate predictor was hCG>2.0 MoM[21]. So in present study, we also used hCG>2.0 MoM as threshold level for prediction of pre-eclampsia.

In several studies, it was shown that elevated maternal serum hCG in the second trimester predicted not only development of pre-eclampsia later in pregnancy, but also some other pregnancy complications like stillbirth, intrauterine growth restriction, preterm delivery[22, 23, 24]

In many reports, AFP was also studied for prediction of pre-eclampsia[25,26]. In the present study, the second trimester AFP and uE3 levels did not predict the third trimester pre-eclampsia development. In literature results are quite conflicting. Lambert G. M. et al[2] found that second trimester AFP and uE3 were uninformative for predicting pre-eclampsia. François Audibert et al[27] reported that hCG and AFP levels were significantly higher in women with pre-eclampsia than those control groups. In addition, AFP level was found significantly higher in fetal demise and severe intrauterine growth retardation without pre-eclampsia.

Stamilo et al[27] reported that AFP was not a good marker for prediction of pre-eclampsia. Our result confirms this suggestion. In a recent study, it was concluded that positive predictive value and sensitivity of second trimester serum tests using in combination were relatively low, but superior to individual markers[28].

In summary, the second trimester maternal serum hCG level in pregnant women who subsequently developed pre-eclampsia were significantly higher than those in normal pregnant women. The present finding suggests that second trimester maternal HCG level can predict the subsequent development of pre-eclampsia. ■

References

1. Wald NJ, Morris JK. Multiple marker second trimester serum screening for pre-eclampsia. J Med Screen 2001; 8: 65-68.
2. Lambert-Messerlian GM, Silver HM, Petraglia F, Luisi S, Pezzani I, Maybruck WM et al. Second-Trimester Levels of Maternal Serum Human Chorionic Gonadotropin and Inhibin A as Predictors of Preeclampsia in the Third Trimester of Pregnancy. J Soc Gynecol Investig 2000; 7: 3.
3. Wald NJ, Kennard A, Hackshaw A, McGuire A. Prenatal screening for Down's Syndrome. J Med Screen 1997; 4: 181-246.
4. Gravett CP, Buckmaster JG, Watson PT, Gravett MG. Elevated second trimester maternal serum hCG concentrations and subsequent adverse pregnancy outcome. Am J Med Genet 1992; 44: 485-486.
5. Waller DK, Lustig LS, Cunningham GC. Feuchtbaum LB. Hook EB. The association between maternal serum alpha-fetoprotem and preterm birch, small for gestational age infants, preeclampsia, and placental complications. Obstet Gynecol 1996;8S:S16-22.
6. Benn PA, Home D, Brigand S, Rodis JF. Clive JM. Elevated second-trimester maternal serum hCG alone or in combination with elevated alpha-fetoprotein. Obstet Gvneeol 1996:87:2 17-22.
7. Muller F. Savev L, LeFiblec B, Bussieres, L. Ndayizamba G. Colau JO et al. Maternal serum human chononic gonadotropm level at fifteen weeks is a predictor for preeclampsia. Am J Obstet Gvneeol 1996:175:37- 40.
8. Liu DF. Dickerman LH. Redline RW. Pathologic findings in pregnancies with unexplained increases in midtnmester maternal serum human chononic gonadotropin levels. Anat Pathol 1999; 1 11:209-15.
9. Spencer K. Second-trimester prenatal screening for Down syndrome and the relationship of maternal serum biochemical markers to pregnancy complications with adverse outcome. Prenat Diagn 2000; 20: 652–6.
10. Heikkila A, Makkonen N, Heinonen S, Kirkinen P. Elevated maternal serum hCG in the second trimester increases prematurity rate and need for neonatal intensive care in primiparous preeclamptic pregnancies. Hypertens Pregnancy 2001; 20: 99–106.
11. Hershkovitz R, Erez O, Sheiner E, Landau D, Mankuta D, Mazor M. Elevated maternal mid-trimester chorionic gonadotropin > or =4 MoM is associated with fetal cerebral blood fow redistribution. Acta Obstet Gynecol Scand 2003; 82: 22–7.
12. Brajenovic-Milic B, Tislaric D, Zuvic-Butorac M, et al. Elevated second trimester free beta hCG as an isolated fnding and pregnancy outcomes. Fetal Diagn Ther 2004; 19: 483–7.
13. Celentano C, Guanciali-Franchi PE, Liberati M, et al. Lack of correlation between elevated maternal serum hCG during second-trimester biochemical screening and fetal congenital anomaly. Prenat Diagn 2005; 25: 220–4.
14. Barker DJ: The developmental origins of chromic adult disease. Acta Paediatr Suppl 2004, 93(446):26-33
15. Aquilina J, Maplethorpe R, Ellis P, Harrington K: Correlation between second trimester maternal serum inhibin-A and human chorionic gonadotrophin for the prediction of pre-eclampsia. Placenta 2000, 21(5–6):487-492.
16. Ong CY, Liao AW, Spencer K, Munim S, Nicolaides KH: First trimester maternal serum free beta human chorionic gonado-trophin and pregnancy associated plasma protein A as predictors of pregnancy complications. BJOG 2000, 107(10):1265-1270.
17. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM: The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertens Pregnancy 2001; 20(1): 9- 14.
18. Gonen R, Perez R and David M. The association between unexplained second-trimester serum hCG elevation and pregnancy complications. Obstet Gynecol 1992; 80: 83-85.
19. Fox H. Effect of hypoxia on trophoblast in organ culture. A morphologic and autoradiographic study. Am J Obstet Gynecol 1970; 107: 1058-1064.
20. Redman CWG. Current topic: pre-eclampsia and the placenta. 1991; 12: 301-308.
21. Morris RK, Cnossen JS, Langejans M, Robson SC, Kleijnen J, Riet G et al. Serum screening with Down's syndrome markers to predict pre-eclampsia and small for gestational age: Systematic review and meta-analysis. BMC Pregnancy and Childbirth 2008; 8: 33 doi:10.1186/1471-2393-8-33.
22. Shenhav S, Gemer O, Volodarsky M, Zohav E, Segal S. Midtrimester triple test levels in women with severe preeclampsia and HELLP syndrome. Acta Obstet Gynecol Scand 2003; 82: 912-915.
23. Sayin NC, Canda MT, Ahmet N, Sezer A, Süt N, Varol FG. The association of triple test results with adverse pregnancy outcomes in low risk pregnancies with healthy newborns. Arch Gynecol Obstet 2008; 277: 47-53.
24. Duric K, Skrablin S, Lesin J, Kalafatic D, Kuvacic I, Suchanek E. Second trimester total human chorionic gonadotropin, alpha-fetoprotein and unconjugated estriol in predicting pregnancy complications other than fetal aneuploidy. Eur J Obstet Gynecol Reprod Biol 2003; 110: 12-15.
25. Raty R, Koskinen P, Alanen A. Prediction of pre-eclampsia with maternal mid-trimester total renin, inhibin A, AFP, and free ß-hCG levels. Prenat Diagn1999; 19: 122-127.
26. Stamilio DM, Sehdev HM, Morgan MA, et al. Can antenatal clinical and biochemical markers predict the development of severe pre-eclampsia? Am J Obstet Gynecol 2000; 182: 589-94.
27. Audibert F, Benchimol Y, Benattar C, Champagne C, Frydman R: Prediction of preeclampsia or intrauterine growth restriction by second trimester serum screening and uterine Doppler velocimetry. Fetal Diagn Ther 2005; 20(1): 48-53.
28. Dugoff L, Hobbins JC, Malone FD, et al. FASTER Trial Research Consortium. Quad screen as a predictor of adverse pregnancy outcome. Obstet Gynecol 2005; 106(2): 260–267.