THE EFFECT OF SECOND TRİMESTER MATERNAL SERUM AFP, hCG, uE3 LEVELS ON ADVERSE PREGNANCY AND NEONATAL OUTCOMES

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SUMMARY

OBJECTIVE: Our purpose was to investigate the association between second trimester maternal serum screening markers and adverse pregnancy and neonatal outcomes.

METHODS: Pregnancy outcomes were evaluated in 226 women receiving routine prenatal care offered maternal serum screening. Adverse pregnancy outcomes such as preform delivery, small for gestational age, preeclampsia, perinatal death, macrosomia, oligohidroamnios, polihidroamnios and also adverse neonatal adverse outcomes such as neonatal intensive care unit admission , apgar score less than 7 at the 5 minutes, O2 requirement, jaudince, infections,meconium aspiration were evaluated. We compered the mean of MSAFP, MShCG, MSUE3 levels in each of these outcomes with controls. And also the patient were grouped according to AFP levels: elevated MSAFP (≥2,5 MOM), to hCG levels: elevated MShCG(≥2 MOM) .

RESULTS: The means of the MSAFP MoM values in the preterm delivery and the means of MSAFP and MShCG levels in the preeclampsia, small for gestational age, perinatal mortality and neonatal morbidity outcomes also was statistically significant compared with controls. Among 226 patients 8(%3,5) had unexplained elevated MSAFP and 12 (%5,3) had unexplained MShCG levels. Elevated MSAFP levels was significantly associated with only preterm delivery and perinatal mortality. No statistically significant association was found when subjects and controls were compared for SGA, preclampsia, oligohidroamnios, polihidroamnios, macrosomia and neonatal morbidite. The risk of neonatal morbidity with elevated MShCG levels was eleven times greater than that of control group. The risks of another adverse outcomes with elevated MShCG levels were not reach statistically significant levels.

CONCLUSIONS: A prospective multi-center study including a larger population is needed to recommend a closer follow up such as serial ultrasonographic evaluation, detection of early preterm labour signs, third trimester nonstress test, biophysical profiles and close monitoring labour for these patients. Current studies at our clinic involving larger populations are continuing.

Key Words: Maternal serum screening, adverse pregnancy outcome

İKİNCİ TRİMESTER MATERNAL SERUM AFP, hCG, uE3 SEVİYELERİNİN GEBELİK VE NEONATAL SONUÇLAR ÜZERİNDEKİ ETKİSİ

ÖZET

AMAÇ: Bu çalışmada ikinci trimester maternal serum AFP, hCG, uE3 değerleri ile olumsuz gebelik ve yenidoğan sonuçları arasında bir ilişkinin olup olmadığının araştırılmasıdır.

METOD: Antenatal takiplerinde maternal serum tarama testi uygulanan 226 hastanın gebelik sonuçları incelendi. Olumsuz gebelik sonuçları olarak erken doğum,gestasyonel yaşına göre küçük olma, preeklampsi, perinatal ölüm, makrozomi, oligohidroamnios, polihidroamnios kötü yenidoğan sonuçları olarak da yoğun bakıma kabul, 5. dakika apgar skorunun 7 nin altında olması, oksijen ihtiyacının olması, sarılık, infeksiyon, mekonyum aspirasyonu kabul edidi. Tüm bu sonuçlarda anne serumunda ölçülen AFP, hCG, uE3 MoM değerlerinin ortalamaları karşılaştırılırken; serum AFP seviyesi ≥2,5 MOM, hCG seviyesi ≥2 MOM olması araştırıldı.

BULGULAR: Erken doğumla sonuçlanan gebeliklerde serum AFP MoM ortalamasının gestasyonel yaşına göre küçük, preeklampsi ve perinatal ölümle sonuçlanan gebeliklerde ve olumsuz neonatal sonuçlarda serum AFP ve hCG MoM ortalamaları kontrollere göre daha yüksek bulundu. Açıklanamayan serum AFP yüksekliği 8(%3,5),hCG yüksekliği ise 12(%5,3) gebede bulunurken, yüksek AFP seviyelerinde sadece erken doğum ve perinatal mortalite riskinin fazla olduğunu, diğer olumsuz sonuçlar için risk oluşturmadığını, yüksek serum hCG seviyelerinde ise olumsuz neonatal sonuçların 11 kez daha fazla oluştuğu görüldü.

SONUÇ: Daha geniş populasyon içeren çalışmalar yapılırsa serum AFP, hCG seviyelerine göre seri ultrasonografi takipleri, erken doğum eylemi için tarama testleri, üçüncü trimester nonstress testleri, biyofizik profil ve yakın eylem takibi yapılacak gebe kadınların tesbitinin yapılabileceğini düşünüyoruz. Halen bu çalışma kliniğimizde devam etmektedir.

Anahtar kelimeler: Maternal serum belirteçleri, olumsuz gebelik sonuçları

Maternal serum screening for Down's syndrome using multiple biochemical markers has become a common practice. Previous reports showed a correlation between unexplained second trimester biochemical markers elevations and various pregnancy complication (1,2). By using these markers it may be possible to identify high-risk pregnancies as early as 16 weeks 'gestation. Both elevated maternal serum human chorionic gonadotropin and alpha-fetoprotein levels presumed to be early sign of placental dysfunction (3,4).

MATERIALS AND METHODS:

The study population was derived from 226 women who had received maternal serum screening tests including maternal serum alpha- fetoprotein (AFP) , human chorionic gonadotropin (hCG), unconjugated estriol (uUE3) at 16-20 gestational weeks as part of routine obstetrics care at Department of Obstetrics and Gynaecology, Fatih University Medical School between June 1998 and November 1998.AFP, hCG, uE3 were assayed by the Düzen Laboratories Group, Ankara-Turkey and median values were calculated for AFP, hCG uE3 with completed menstrual weeks. Gestational age was based on the first day of the last menstrual period and confirmed by using ultrasound dating. Maternal weight, diabetes, smoking, early trimester bleeding can effect the levels of MSAFP and hCG. After adjusted these factors incorrect gestational dating, multiple pregnancies, insulin dependent diabetes mellitus, detected fetal chromosomal and structural abnormalities were excluded. We evaluated the following results as a adverse pregnancy outcomes: preterm delivery (PD), defined as delivery before 37 completed weeks and; small for gestational age (SGA), defined as birth weight below the tenth percentile using the fetal growth curves of Brenner et al (5)

macrosomia, defined as birth weight over 4500g; preeclampsia, defined as persistent blood pressure levels >140/90 and proteinuria of 300 mg or more in a 24 hour collection, polyhydramnios, defined as amniotic fluid index (AFI) greater than 20 cm; oligohydroamnios, defined as an AFI less than 5 cm. Perinatal death was determined as a death between 20 weeks gestation and the first 7 days after birth. Adverse neonatal outcomes was defined as neonatal intensive care unit admission , apgar score <7 at 5 minutes, O2 requirement, jaudince, infections, meconium aspiration respiratory difficulties.

We compared the mean of MSAFP, MShCG, MSuUE3 levels in each of these outcomes with controls. Finally the patient were grouped according to AFP levels: elevated MSAFP (≥2,5 MOM), to hCG levels: elevated MShCG (≥2 MOM) . We did not evaluate patients with elevated MSAFP and hCG results together. The relative risks of adverse pregnancy outcomes with elevated MSAFP and MShCG levels was calculated with %95 confidence intervals. Statistical analysis was performed by Student t test, chi-square analysis and Mann- Whitney U test for compering means. P≤0.05 was considered significant.

RESULTS

The age range of the 226 women in this study extended from 18 to 40 and the mean screening gestational week is 17,6. Characteristics of women are summarized in Table 1.

The mean of the MSAFP MoM values in the preterm delivery was 1,25±0,42 and in the control groups have no preterm delivery was 1,04 ±0,43. Statistical significant difference was found (p<0,05). The means of MSAFP and MShCG levels in

the preeclampsia, SGA were significant compared with means of MSAFP and MShCG levels of control groups. The mean of MSAFP and MShCG levels in the perinatal mortality and neonatal morbidity outcomes also was statistically significant compared with controls. The mean of MSuE3 MoM levels in the pregnancy and neonatal complication group compered with controls was not significant. The mean of MSAFP, MShCG, MSuE3 MoM levels in the pregnancy and neonatal outcomes summarised in the Table 2.

Among 226 patients undergoing maternal serum screening during the study period 8 (%3,5) had unexplained elevated MSAFP and 12 (%5,3) had unexplained MShCG levels.

Women with elevated MSAFP levels were older than with normal serum levels. There were no statistically significant differences between study and controls subjects with respects to gestational weeks, body mass index. Some characteristics of study population summarized in Table 3. Elevated MSAFP levels was significantly associated with only preterm delivery and perinatal mortality. The relative risk of perinatal mortality was 6.08 (CI=1,3-59) and all fetal death occurred after 24 weeks and none of them because of preterm delivery. No statistically significant association was found when subjects and controls were compared for SGA, preclampsia, oligohidroamnios, polihidroamnios, macrosomia and neonatal morbidite. The association between elevated MSAFP levels and adverse pregnancy and neonatal outcomes presented in Table 4. The risk of neonatal morbidity with elevated MShCG levels was eleven times greater than that of control group (relative risk= 11, 95% confidence interval 3,6 to 37,8).The risks of another adverse outcomes with elevated MShCG levels were not reach statistically significant levels. Table 5 details the

association between elevated MShCG (≥2 MoM) levels with adverse pregnancy and neonatal outcomes.

CONCLUSION

AFP is an oncofetal glycoprotein produced from the second month of pregnancy by the yolksac and, from the third month, by the fetal liver and gastrointestinal tract (6). Maternal serum levels of AFP are influenced by a combination of fetal production, clearence of fetal kidney and placental surface between fetus and the mother.

An elevated MSAFP level is believed to reflect plasental dysfunction (3,4). Unexplained elevation of second trimester maternal serum AFP has been reported to be associated with adverse pregnancy outcomes, including SGA, preterm delivery, and preeclampsia (7,8). Waller et al. has reported that an unexplained elevated second trimester MSAFP level associated prediction of adverse pregnancy outcome (9). As many as %36 of pregnancies with unexplained MSAFP levels has been reported to have at least one adverse outcomes such as preeclampsia, fetal death, fetal growth restriction, abruption, preterm delivery (10). Committee of the American Society of Human Genetics stated that women who have increased concentrations of MSAFP and whose fetuses does not have a demonstrable abnormality by ultrasound and karyotyping have an increased risk for poor pregnancy outcomes, such as perinatal death and low birthweight (11). However some authors suggested that unexplained elevation of MSAFP levels did not a predictor of adverse outcomes (12).

In our study we found the means of MSAFP MoM values in pregnancies with complicated preterm delivery, preeclampsia, SGA and perinatal death and also neonatal complication groups were higher than controls.

hCG is produced by the placental cytotrophoblast and excreted directly into the maternal circulation and it is possible that abnormal levels are early sign of placental dysfunction. The reduced oxygen supply may result proliferation of cytotrophoblastic cells and increasing hCG production (13).

There were many reports of a link between unexplained MShCG levels and adverse pregnancy outcome such as preterm labour, low birth weight, especially preeclampsia and LBW (14,15,16,17). The fact that raised levels of both MSAFP and MShCG are associated with a higher incidence of placenta -related pregnancy complication suggests that there is a common pathophysiological mechanism (18).

This seems to suggest that in our population unexplained levels of MSAFP and hCG levels identify patient at high risk for preterm delivery, perinatal death, and neonatal morbidity. We realise that the number of subjects in this study is relatively small, limiting the power. However our findings suggest that the subjects with unexplained elevated MSAFP and MShCG levels need to be reconsidered for increased risk of premature delivery, neonatal morbidity and perinatal death. İn our study elevated MSAFP and MShCG levels did not appear to have additional predictive value for some adverse pregnancy outcomes such SGA; preeclampsia, oligohidroamnios, polihidroamnios.

We believe that most women with unexplained elevated MSAFP and hCG levels will go on to have uncomplicated pregnancy outcomes. However prospective multi-center study including a larger population is needed to recommend a closer follow up such as serial ultrasonograpy, detection of preterm labour signs, third trimester nonstress test, biophysical profiles and close monitoring labour for these patients. Current studies at our clinic involving larger populations are continuing.

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Table 1. Characteristic of women in the study

Characteristic	Mean
Maternal age(years)	27,10± 5,1
Gravid	1,99± 0,39
Parity	0,75± 1,29
Gestational weeks of screening	17,6± 1,84

Table 2. Pregnancy outcomes according to the MSAFP, MShCG, MSuE3 MoM levels comparing with controls.

	MSAFP	MShCG	MSuE3
Preterm delivery (n=37)	1,25±0,42*	1,14±0,60	1,11±0,39
Controls(n=189)	1,04±0,43	1,05±0,56	1,11±0,36
Preclampsia (n=7)	1,22±0,32*	1,25±0,54*	1,26±0,45
Controls (n=219)	1,03±0,42	1,03±0,57	1,10±0,36
SGA (n=13)	1,23±0,42*	1,20±0,56*	1,18±0,33
Controls (n=213)	1,02±0,43	1,03±0,57	1,10±0,37
Polihidroamnios (n=19)	1,02±0,40	1,00±0,49	1,20±0,36
Controls(n=207)	1,04±0,43	1,04±0,57	1,10±0,36
Olgihidroamnios (n=54)	1,09±0,49	1,01±0,62	1,07±0,31
Controls (n=172)	1,02±0,41	1,05±0,55	1,12±0,38
Makrosomia (n=11)	1,32±0,36*	1,01±0,60	1,05±0,34
Controls(n=214)	1,02±0,43	1,04±0,57	1,11±0,37
Perinatal mortality (n=6)	1,38±0,59*	1,60±0,75*	1,19±0,42
Controls (n=220)	1,02±0,42	1,03±0,55	1,10±0,36
Neonatal morbidity (n=37)	1,25±0,51**	1,33±0,79**	1,07±0,32
Controls (n=189)	0,99±0,40	0,99±0,49	1,11±0,37

*p<0.05 **p=0.001

Table 3. Characteristics of women with elevated MSAFP and hCG levels and controls

Characteristic	hCG≥2 MoM	hCG<2 MoM	AFP≥2 MoM	AFP<2 MoM
	n=12	n=214	n=8	n=218
Age	25,9±4,1	27,1±5,1	23,6±3,8*	27,2±5,0
GW	17,2±1,9	17,6±1,8	16,9±1,4	17,6±1,8
BMI	25,1±3,6	25,0±3,1	25,1±3,6	25,0±3,1

GW: gestational weeks of test were performed

BMI: Body mass index (weight/height ^{2})

*P<00.5

Table 4. Incidence and relative risk for adverse outcomes associated with elevated MSAFP.

Outcome	MSAFP≥2 MoM		MSAFP <2 MoM		RR(95% CI)	
SGA	0%	(0/8)	5,1%	(13/218)	0,96	(0,90-0,97)
Preeclampsia	0%	(0/8)	3,2%	(7/218)	0,96	(0,94-0,99)
Macrosomia	0%	(0/8)	5,0%	(11/218)	0,94	(0,92-0,97)
Oligohidroamnios	37,5%	(3/8)	23%	(51/218)	1,96	(0,45-8,5)
Polihidroamnios	0%	(0/8)	8,7%	(19/218)	0,91	(0,87-0,95)
Preterm delivery*	50%	(4/8)	15,1%	(33/218)	4,07	(1,02-17,9)
Perinatal Mortalite*	12,5%	(1/8)	2,2%	(5/218)	6,08	(1,30-59)
Neonatal morbidite	25%	(2/8)	16%	(35/218)	1,74	(0,33-8,91)

MSAFP=maternal serum alpha-fetoprotein; MoM=multiples of the median; RR=relative risk;CI=confidence interval; SGA=small for gestational age

*P<0.05

Table 5. Incidence and relative risk for adverse outcomes associated with elevated MShCG.

Outcome	MShCG≥2MoM		MShCG<2MoM		RR(95% CI)	
SGA	7,1%	(1/14)	5,6%	(12/212)	1,2	(0,1-10)
Preeclampsia	0%	(0/14)	3,3%	(7/212)	0,9	(0,94-0,96)
Macrosomia	7,1%	(1/14)	5%	(10/212)	1,5	(0,1-13)
Oligohidroamnios	35,7%	(5/14	23,1%	(49/212)	1,2	(0,8-3,2)
Polihidroamnios	0%	(0/14)	8,9%	(19/212)	0,93	(0,87-0,95)
Preterm delivery	21,4%	(3/14)	16,0%	(34/212)	1,5	(0,4-6)
Perinatal mortality	7,1%	(1/14)	2,3%	(5/212)	3,1	(0,3-29,2)
Neonatal morbidity*	64,2%	(9/14)	10,3%	(22/212)	11	(3,6-37,8)

MSAFP=maternal serum alpha–fetoprotein; MoM=multiples of the median; RR=relative risk; CI=confidence interval; SGA=small for gestational age

**p<0.000