Clinical Research

Association Between Second Trimester Maternal Serum Markers and Birth Weight*

Buğra ÇOŞKUN[1,a], Demet KOKANALI[2], Coşkun ŞİMŞİR[1], Bora ÇOŞKUN[1], İrem Eda GÖKDEMİR[2], Eser ÇOLAK[3], Şevki ÇELEN[2]

[1]*Liv Hospital Ankara, Kadın Hastalıkları ve Doğum Kliniği, Ankara, Türkiye*
[2]*SBÜ Zekai Tahir Burak Sağlık Uygulama ve Araştırma Merkezi, Kadın Hastalıkları ve Doğum Kliniği, Ankara, Türkiye*
[3]*Başkent Üniversitesi Konya Uygulama ve Araştırma Merkezi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Konya, Türkiye*

ABSTRACT

Objective: We aimed to determine if any of the second trimester serum marker levels had a significant association with birth weight in uncomplicated pregnancies.

Material and Method: Five hundred and forty pregnant women whose second trimester (16-18 weeks) aneuploidy screening and delivery was performed at SBU Zekai Tahir Burak Health Application and Research Center Obstetrics and Gynecology Clinic, are included in this retrospective study. All women had their last menstrual period confirmed by their first trimester ultrasound. Levels of maternal serum alpha-fetoprotein (AFP), β-human chorionic gonadotropin (hCG), and unconjugated estriol (uE3) were calculated as coefficients of the median (MoM). Associations between the second trimester markers levels and infant birth weights were assessed using correlation analysis. The effects of various contributing factors on birth weight were investigated with linear regression analysis.

Results: There were significant negative correlations between maternal age at screening (r =-0.48; p =0.03), maternal serum AFP level (r =-0.45; p =0.03) and birth weight of the newborn. Besides, there were positive correlations between amount of weight gain during pregnancy (r =0.44; p =0.04), maternal serum uE_3 level (r =0.47; p =0.03) and birth weight of newborn. However, maternal weight and BMI at screening and maternal serum β hCG level did not have a significant correlation with birth weight of newborn. However, maternal serum uE3 level was the only factor that affected the birth weight on linear regression model.

Conclusion: Second trimester maternal serum uE3 level might be useful in predicting birth weight among uncomplicated pregnant women.

Keywords: *Alpha Feto Protein, Unconjugated Estriol, Birth Weight.*

ÖZET

İkinci Trimester Maternal Serum Belirteçleri ve Doğum Ağırlığı Arasındaki İlişki

Amaç: Komplike olmayan gebeliklerde, ikinci trimester prenatal tarama serum belirteç düzeylerinden herhangi birinin doğum ağırlığı ile anlamlı bir ilişkisi olup olmadığını belirlemeyi amaçladık.

Gereç ve Yöntem: Bu retrospektif çalışmaya SBÜ Zekai Tahir Burak Sağlık Uygulama ve Araştırma Merkezi Kadın Hastalıkları ve Doğum Kliniğinde doğum yapan ve ikinci trimesterda (16-18 hafta) anöploidi taraması yapılmış 540 gebe dahil edildi. Tüm kadınların son adet tarihi ilk trimester ultrasonu ile teyit edildi. Maternal serum alpha-fetoprotein (AFP), β-insan koryonik gonadotropin (hCG) ve konjuge olmayan estriol (uE3) değerleri medyanın (MoM) katları olarak hesaplandı. İkinci trimester serum belirteç düzeyleri ile bebek doğum ağırlıklarının arasındaki ilişkiler korelasyon analizi ile değerlendirildi. Katkıda bulunan çeşitli faktörlerin doğum kilosu üzerindeki etkileri lineer regresyon analizi ile araştırıldı.

Bulgular: Tarama sırasındaki maternal yaş (r =-0.48; p =0.03) ve maternal serum AFP düzeyi (r =-0.45; p =0.03) ile yenidoğan doğum ağırlığı arasında anlamlı negatif korelasyon vardı. Ayrıca, hamilelikte kilo alımı miktarı (r =0.44; p =0.04) ve maternal serum uE3 düzeyi (r =0.47; p =0.03) ile yenidoğan doğum ağırlığı arasında pozitif korelasyon vardı. Tarama sırasındaki maternal ağırlık, VKİ ve maternal serum β hCG düzeyi ile yenidoğanın doğum ağırlığı arasında anlamlı bir korelasyon görülmedi. Bununla birlikte maternal serum uE3 düzeyi, lineer regresyon modelinde doğum ağırlığını etkileyen tek faktör olarak izlendi.

Sonuç: İkinci trimester maternal serum uE3 düzeyi, komplike olmayan hamile kadınlarda doğum ağırlığını öngörmede faydalı olabilir.

Anahtar Sözcükler: *Alfa Feto Protein, Unkonjuge Estriol, Doğum Ağırlığı.*

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In the past, age of 35 years and older maternal age was used to identify women with the highest risk for a delivering a Down syndrome baby. In younger women, the use of serum biochemical screening for Down Syndrome has been identified in the 1980s and 1990s (1). Merkatz et al. (2) suggested the use of maternal serum AFP levels as a routine prenatal screening for the detection of significant anomalies in 1984. In the following years, maternal serum human hCG and uE3 levels were combined with AFP for the screening of fetal chromosomal abnormalities such as Down syndrome and Trisomy 18 (1). Nowadays, second trimes-

[a]Yazışma Adresi: Buğra ÇOŞKUN, Liv Hospital Ankara, Kadın Hastalıkları ve Doğum Kliniği, Ankara, Türkiye
Tel: 0532 350 1404 e-mail: drbugracoskun@gmail.com
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ter maternal serum AFP, hCG and uE3 levels, which are called as the triple test, are used for fetal aneuploidy screening frequently. Triple Test has become the preferred test in many centers for Down syndrome and open neural tube defect screening, between 15 and 19 gestational weeks (3). In the following years, abnormal triple screening results have been associated with other abnormal obstetrical results (4). Namely, the abnormal elevation in serum levels of both AFP and hCG has been reported to be associated with adverse pregnancy outcomes such as preeclampsia, intrauterine growth restriction, preterm labour (5-8). Also some studies suggest that fetal birth weight may be associated with second trimester maternal serum markers (9).

The infants with a birth weight below the 10 percentile for gestational age are defined as small for gestational age (SGA) (10). Children born as SGA have more perinatal problems such as cerebral palsy, respiratory distress or stillbirth; also SGA babies are at risk of developing neurological, cardiovascular and metabolic diseases in the future.(11-13). Lindqvist et al. (14) found that the risk of adverse outcomes decreased significantly in SGA infants with early diagnosis. Early identification can lead to prescription of preventional medication like low-dose aspirine and affected patients can be examined more frequently to guarantee the best possible maternity care(15).

In general, LGA is defined as a birth weight greater than the 90 percentile for age(16). Infants who are born large for gestational age (LGA), especially fullterm or postterm infants, are at risk for perinatal morbidity and potentially longterm metabolic complications such as birth injuries (brachial plexus injury, perinatal asphyxia, and clavicular injury) primarily due to shoulder dystocia. respiratory distress generally due to respiratory distress syndrome, transient tachypnea of the newborn, or meconium aspiraton, hypoglycemia, and polycythemia(16-18).

The increased risk of perinatal mortality and morbidity associated with birth weight of neonates can be reduced substantially in cases predicted prenatally, through close monitoring, timely delivery and prompt neonatal management. Several studies have reported on the association between low or high levels of several maternal serum biochemical markers and the birth weight of neonates. But the results are still controversial. Therefore, we aimed to determine if any of the second trimester serum markers levels had a significant association with birth weight in uncomplicated pregnancies.

MATERIAL AND METHOD

Five hundred and forty pregnant women whose second trimester (16-18 weeks) aneuploidy screening and delivery performed at SBU Zekai Tahir Burak Health Application and Research Center Obstetrics and Gynecology Clinic which is a government based hospital in the capital city Ankara, in Turkey, between 1st January 2013 and 31st December 2014 were conducted in this retrospective study. The Ethical Committee of the hospital approved the protocol of study. The data were collected from hospital records. Patient characteristics that were recorded included maternal age, weight and height, gestation age at screening, cigarette smoking during pregnancy, presence of any systemic diseases, weight gain during pregnancy, gestational age at birth and neonatal birth weight. Pregnancies with incomplete information, detected abnormal fetal karyotype, congenital malformations, multiple pregnancies, complications such as hypertension, preeclampsia, diabetes mellitus, fetal growth restriction and also smoking were excluded.

For all women, gestational age at delivery were confirmed by a first trimester ultrasound. Fetal birth weights for all newborns were recorded and converted in percentile for gestational age at delivery and gender according to Turkish population data (19). And newborns were classified as SGA (defined as below, birth weight of≤10th percentile), appropriate for gestational age (AGA; defined as newborn with a birth weight between 10th and 90th percentile), LGA (birth weight of ≥90th percentile).

The second trimester prenatal screening test was performed for each pregnant women between 16th to 18th weeks of gestation. Maternal serum AFP, β-hCG levels were measured by using ELISA method and uE3 levels were measured by using RIA method for each women. And all values were reported as multiples of the median (MoM). All women were followed until delivery at monthly intervals and delivered at our hospital. All neonates were normal and did not suffer from any complication.

SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL,USA) was used for statistical analysis of the study data. Kolmogorow Smirnow test was used to determine the data distributions. Numeric variables with normal distribution were presented as mean ± standard deviation. Median (minimum-maximum) value was used where normal distribution was absent. For the numeric variables with normal distribution, the difference between the groups was compared by one-way analysis of variance test. When the p value from the variance analysis was statistically significant, post-hoc Tukey test was used to determine which group differed from which others. Kruskal-Wallis test was used for numeric variables where normal distribution was absent. Pearson's correlation test was used to assess correlations. The effects of different factors on birth weight were assessed using a linear regression model. The sample size was determined according to the results of the central limit theorem (20). A p value <0.05 was considered statistically significant.

RESULTS

A total of 620 pregnant women who had undergone second trimester aneuploidy screening were included to this retrospective study. Eighty pregnant women were

withdrawn from study because of the exclusion criteria mentioned above. Finally, study population included 540 screened singleton pregnancies with their live newborns. Of these newborns, 44 (8.1%) were SGA, 61 (11.3%) were LGA and 435 (80.6%) were AGA.
The demographic and clinical characteristics of the groups were depicted in Table 1.

Table 1. *Clinical characteristics of the study groups.*

Characteristics	SGA group (n =44)	AGA group (n =435)	LGA group (n =61)	p
Maternal Age at Birth (years)	26.42±6.53	27.68±5.85	28.39±6.06	0.45
Maternal weight at screening (kg)	65.12±5.32	65.81±5.18	66.55±5.78	0.57
Maternal BMI at screening (kg/m^2)	21.44±3.28	22.79±3.89	22.61±3.31	0.22
Weight gain during pregnancy (kg)	11.18±0.43	12.14±0.46	12.44±0.35	0.37
Triple Test Time (week)	17.14±0.34	17.26±0.52	17.44±0.41	0.35
Maternal serum AFP level (MoM)	1.86±0.24	1.47±0.28	1.20±0.34	0.12
Maternal serum uE$_3$ level (MoM)	0.90±0.23	1.07±0.22	1.18±0.28	0.20
Maternal serum β hCG level (MoM)	1.17±0.33	1.13±0.25	1.15±0.22	0.73
Birth Time (week)	39.1 (35.8-40.8)	39.2 (35.6-41.5)	39.3 (36.3-41.5)	0.66
Fetal Birth Weight (gram)	2702.89±203.68	3290.21±324.05	3892.28±300.96	<0.01

Data are listed as mean ± standard deviation and median (minimum-maximum value).
SGA: Small for Gestational Age, AGA: Appropriate for Gestational Age, LGA: Large for Gestational Age,BMI: Body Mass Index; AFP: Alpha-fetoprotein; uE$_3$: Unkonjugated Estriol; hCG: human chorionic gonadotropin.
p <0.05 was considered statistically significant differences.

There were no statistically significant differences between groups in terms of demographic and clinical caharacteristics except for birth weight of newborn. As expected, LGA group has the biggest value (3892.28±300.96 g.) while SGA group has the smallest (2702.89±203.68) (p <0.001). Mean MoM values of AFP level among women with SGA, AGA and LGA newborns were 1.86±0.24, 1.47±0.28,1.20±0.34 MoM respectively (p =0.123). Mean MoM values of uE3 level among women with SGA, AGA and LGA newborns were 0.90±0.23, 1.07±0.22, 1.18±0.28 Mom, repectively (p =0.202). Mean MoM values of βhCG level among women with SGA, AGA and LGA were 1.17±0.33, 1.13±0.25, 1.15±0.22 MoM respectively (p =0.728).
There were significant negative correlations between maternal age at screening (r =-0.48; p =0.03), maternal serum AFP level (r =-0.45; p =0.03) and birth weight of newborn. Besides, there were positive correlations between amount of weight gain during pregnancy (r =0.44; p =0.04), maternal serum uE$_3$ level (r =0.47; p =0.03) and birth weight of newborn. However, maternal weight and BMI at screening and maternal serum β hCG level did not have a significant correlation with birth weight of newborn (Table 2).

Table 2. *Correlation analysis of factors with infant birth weight.*

	r	p
Maternal age at screening	-0.48	**0.03**
Maternal weight at screening (kg)	0.04	0.87
Maternal BMI at screening (kg/m^2)	0.12	0.45
Weight gain during pregnancy	0.44	**0.04**
Maternal serum AFP level	-0.45	**0.03**
Maternal serum uE$_3$ level	0.47	**0.03**
Maternal serum β hCG level	0.34	0.12

r: Pearson's correlation coefficient
BMI: Body Mass Index; AFP: Alpha-fetoprotein; uE$_3$: Unkonjugated Estriol; hCG: human chorionic gonadotropin
p < 0.05 was considered statistically significant.

On linear regression analysis, birth weight of newborn was not affected by maternal age at screening, amount of weight gain during pregnancy and maternal serum AFP level. On the other hand, maternal serum uE3 level (p =0.03) was found to be the only effective factor for birth weight of newborn (Table 3).

Table 3. *Linear regression model of confounding factors related to fetal birth weight.*

R2=0.644	β	SE	95% CI for β	p
Maternal age	-0.10	21.15	-55.00-34.25	0.63
Weight gain during pregnancy	0.07	57.81	-101.29-142.64	0.73
Maternal serum AFP level	0.39	412.85	-28.52-1713.55	0.06
Maternal serum uE3 level	0.45	303.27	86.88-1366.58	**0.03**

β standardized coefficient; SE Standard error; CI Confidence interval, AFP: Alpha-fetoprotein; uE$_3$: Unkonjugated Estriol
p < 0.05 was considered statistically significant.

DISCUSSION

Various studies have been conducted to investigate the effects of prenatal screening tests in the second trimester on the outcomes of pregnancy. These obstetric outcomes include preeclampsia, oligohydramnios, preterm delivery, gestational diabetes mellitus (GDM), SGA or LGA neonates. However, there is still no consensus on this issue. In our study, we found that serum AFP levels were inversely correlated with birth weight of neonates while there was a positive correlation between serum uE3 levels and birth weight. In addition, maternal serum uE3 level was the only significant factor that was found to be independently related for birth weight of newborn.
The basic and necessary condition for fetal growth is the good feeding of the fetus. For feeding the fetus, the fetoplacental unit should function well (20). Fitzgerald et al. suggested that increased second trimester hCG was related to placental immaturity or abnormal placentation. However, previous studies reported different

results. Namely, either high or low hCG levels in the 2nd trimester might be associated with fetal growth restriction (21). In our study, hCG levels were not significantly different between SGA, AGA and LGA groups. This suggests that hCG levels and birth weight are unrelated in uncomplicated pregnancies where placentation is normal.

Lee et al. (22) have reported a relationship between increased AFP and reduced birth weight. Acceptance of AFP as an indicator of placental damage confirms the existence of this relationship (23). However, some studies reported no such relationship (20). The possible cause of this discrepancy is that AFP may be an indicator of a complicated maternal condition such as preeclampsia and imply AFP may not be a specific indicator for fetal growth. The fact that the relationship between the AFP and birth weight in our study disappeared in the presence of other factors supported this condition.

In our study, uE was the only independent parameter associated with birth weight and this relationship was a positive one. Estriol is synthesized in fetal liver, adrenal cortex and placenta and is found in maternal serum as an indicator of fetoplacental status (24). Significant relationships between fetal and maternal well-being and distress have been reported with the levels measured in the second trimester (24). As such, increased levels are associated with fetomaternal well-being while decreased levels are associated with fetomaternal distress. Therefore, it is expected that estriol level will be related to fetal growth.

Nowadays it is well known that birth weight is related to maternal characteristics, such as age, body mass index and smoking status, and medical conditions, such as diabetes mellitus and hypertension. The similarity and exclusion of these parameters between the groups allows more reliable comparison of the investigated biochemical parameters. In addition, as far as we know, our study is the first study conducted in a relatively large Turkish population including SGA, AGA and LGA group. On the other hand, having a retrospective design may raise suspicion about the reliability of the data.

As a result, there is a positive relationship between fetal birth weight and maternal serum uE3 level measured for fetal aneuploidy screening in second trimester. This relationship is independent of other biochemical parameters. This biochemical parameter level may be useful in monitoring and management of pregnancies where birth weight is important. However, prospective studies with more participation are needed to find definite results.

REFERENCES

1. ACOG Committee on Practice Bulletins. ACOG Practice Bulletin No. 77. Clinical Management Guidelines for Obstetrician-Gynecologists. Obstet Gynecol 2007; 109: 217-27.
2. Merkatz IR, Nitowsky HM, Macri JN, Johnson WE. An association between low maternal serum alpha-fetoprotein and fetal chromosomal abnormalities. Am J Obstet Gynecol 1984; 148: 886-94.
3. Cunningham F, Leveno K, Bloom S, Hauth J, Rouse D, Spong C. Williams Obstetrics. New York, NY: McGraw-Hill 2005: 313-40.
4. Gagnon A, Wilson RD. Society of Obstetricians and Gynaecologists of Canada Genetics Committee. Obstetrical complications associated with abnormal maternal serum markers analytes. J Obstet Gynaecol Can 2008; 30: 918-32.
5. Huang T, Hoffman B, Meschino W, Kingdom J, Okun N. Prediction of adverse pregnancy outcomes by combinations of first and second trimester biochemistry markers used in the routine prenatal screening of Down syndrome. Prenat Diagn 2010; 30: 471-7.
6. Smith GC, Shah I, White IR, Pell JP, Crossley JA, Dobbie R. Maternal and biochemical predictors of antepartum stillbirth among nulliparous women in relation to gestational age of fetal death. BJOG 2007; 114: 705-14.
7. Wax JR, Lopes AM, Benn PA, Lerer T, Steinfeld JD, Ingardia CJ. Unexplained elevated midtrimester maternal serum levels of alpha fetoprotein, human chorionic gonadotropin, or low unconjugated estriol: recurrence risk and association with adverse perinatal outcome. J Matern Fetal Med 2000; 9: 161-4.

8. 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: 12-5.
9. Dane B, Batmaz G, Kılavuz K, Rüstemoğlu Y, Güler H, Dane C. Analysis of the relationship between maternal second trimester AFP, HCG, estriol levels and uterine artery Doppler findings in the prediction of pregnancy complications. Perinatal J 2012; 20: 24-9.
10. Battaglia FC, Lubchenco LO. A practical classification of newborn infants by weight and gestational age. J Pediatr 1967;71: 159-63.
11. Barker DJ, Gluckman PD, Godfrey KM, Harding JE, Owens JA, Robinson JS. Fetal nutrition and cardiovascular disease in adult life. Lancet 1993; 341: 938-41.
12. McIntire DD, Bloom SL, Casey BM, Leveno KJ. Birth weight in relation to morbidity and mortality among newborn infants. N Engl J Med 1999; 340: 1234-8.
13. Jacobsson B, Ahlin K, Francis A, Hagberg G, Hagberg H, Gardosi J. Cerebral palsy and restricted growth status at birth: population-based case-control study. BJOG 2008; 115: 1250-5.
14. Lindqvist PG, Molin J. Does antenatal identification of small-for-gestational age fetuses significantly improve their outcome? Ultrasound Obstet Gynecol 2005; 25: 258-64.
15. Bujold E, Morency AM, Roberge S, Lacasse Y, Forest JC, Giguère Y. Acetylsalicylic acid for the prevention of preeclampsia and intra-uterine growth restriction in women with abnormal uterine artery Doppler: a systematic review and meta-analysis. J Obstet Gynaecol Can 2009; 31: 818-26.
16. Mandy GT, Weisman LE, Kim MS. Large for gestational age newborn. Up To Date 2011.
17. Lackman F, Capewell V, Richardson B, daSilva O, Gagnon R. The risks of spontaneous preterm delivery and perinatal mortality in relation to size at birth according to fetal versus neonatal growth standards. Am J Obstet Gynecol 2001; 184: 946-53.
18. Ju H, Chadha Y, Donovan T, O'Rourke P. Fetal macrosomia and pregnancy outcomes. Aust N Z J Obstet Gynaecol 2009; 49: 504-9.
19. Salihoglu O, Karatekin G, Uslu S, Can E, Baksu B, Nuhoglu A. New intrauterine growth percentiles: a hospital-based study in Istanbul, Turkey. J Pak Med Assoc 2012; 62: 1070-4.
20. Kim SM, Yun HG, Kim RY, et al. Maternal serum placental growth factor combined with second trimester aneuploidy screening to predict small-for-gestation neonates without preeclampsia. Taiwan J Obstet Gynecol 2017; 56: 801-5.
21. Lee SE, Kim SC, Kim KH, et al. Detection of angiogenic factors in midtrimester amniotic fluid and the prediction of preterm birth. Taiwan J Obstet Gynecol 2016; 55: 539-44.
22. Beta J, Bredaki FE, Rodriguez Calvo J, Akolekar R, Nicolaides KH. Maternal serum α-fetoprotein at 11-13 weeks' gestation in spontaneous early preterm delivery. Fetal Diagn Ther 2011; 30: 88-93.
23. Settiyanan T, Wanapirak C, Sirichotiyakul S, et al. Association between isolated abnormal levels of maternal serum unconjugated estriol in the second trimester and adverse pregnancy outcomes. J Matern Fetal Neonatal Med 2016; 29: 2093-7.

Buğra ÇOŞKUN 0000-0003-1938-3833
Demet KOKANALI 0000-0001-6915-3257
Coşkun ŞİMŞİR 0000-0003-4919-6748
Bora ÇOŞKUN 0000-0002-2338-7186
İrem Eda GÖKDEMİR 0000-0002-4864-6818
Eser ÇOLAK 0000-0002-8184-7531
Şevki ÇELEN 0000-0001-7033-3474