Obstetrics; *Maternal-Fetal Medicine and Perinatology*

Evaluation of Antenatal Maternal Serum Biomarkers in Pregnancies Over 41 Weeks

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OBJECTIVE: To examine association between maternal antenatal serum biomarkers and post-term pregnancies.

STUDY DESIGN: Singleton pregnant women (n=186) managed at the Zekai Tahir Burak Women's Health, Education and Research Hospital in Turkey from July 2010 to December 2010 were analyzed retrospectively. Maternal serum levels of PAPP-A, free β-hCG, AFP, HCG and unconjugated E3 were noted routinely in antenatal screening programs. We compared these biomarkers in pregnancies between 37 and 41 gestational weeks (n=73) and ≥41 (n=113) gestational weeks.

RESULTS: There was no statistically significant difference in maternal PAPP-A, free beta-hCG, AFP, total hCG and unconjugated E3 levels between the two groups. Although birth weights were higher in pregnant women ≥41 weeks, this difference was not considered significant (p=0.19). There were no SGA babies in the group of post-term pregnancies.

CONCLUSION: There were no statistically significant differences in maternal serum markers for pregnant women having their period of ≥41 gestational week.

Key Words: Post-term pregnancy, Maternal serum screening

Gynecol Obstet Reprod Med; 2011;17:72-75

Introduction

Screening markers are used to calculate a pregnant woman's risk of having a child with Down syndrome and variety of serum markers are used to screen for Down syndrome in the first and/or second trimester. Combined test is performed in the first trimester and it involves determination of nuchal translucency by sonography combined with measurement of the serum markers pregnancy-associated plasma protein-A (PAPP-A) and beta hCG from 11th to 14th weeks of gestation. It is estimated that the sensitivity of detecting trisomy 21 is about 90% for a false positive rate of 5%.[1] Triple tests consist of alpha-feto protein (AFP), unconjugated estriol (E3) and hCG, it is performed from 16th to 18th weeks. The predicted detection rate is 60% and the false-positive rate is 5.2%.[2]

Recently, there is some evidence that low levels of maternal serum PAPP-A and free beta-hCG in the first trimester and elevated levels of AFP and hCG in the second trimester may be associated with an increased risk of various obstetrical complications, such as miscarriage, preterm delivery, pregnancy induced hypertension, fetal growth restriction.[3-7]

We examined association between maternal antenatal serum biomarkers and post-term pregnancies.

Material and Method

Singleton pregnant women (n=186) managed at our hospital from July 2010 to December 2010 were analyzed retrospectively. Maternal serum levels of PAPP-A, free β-hCG, AFP, HCG and unconjugated E3 were noted routinely in antenatal screening programs. We compared these biomarkers in pregnancies between 37 and 41 gestational weeks and ≥41 gestational weeks.

Study selection criteria were pregnant women with first and early second-trimester ultrasound dating confirming menstrual dates; and who had both first and second-trimester screening tests. Pregnancies were excluded if they were complicated by[1] gestational hypertension or diabetes;[2] maternal systemic diseases;[3] oligohydramnios;[4] maternal drug use;[5] major fetal malformation and chromosomal anomalies;[6] multiple gestations.

The fetal database was searched to identify singleton preg-

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Submitted for Publication: *07. 06. 2011*
Accepted for Publication: *17. 09. 2011*

nancies resulting in live births and with complete data on maternal age, maternal weight, maternal height, background, family history, cigarette smoking status, obstetrical history, delivery history, birth weight. Small for gestational age (SGA) was defined as birth weight <10th percentile for gestational age, as determined from the tables constructed by Olcay for the Turkish population. Impaired glucose tolerance was defined when 2-hours value was between 140 mg/dl and 200 mg/dl.

All pregnant women were assessed by Bishop Score before labor induction on their admission. For labor induction, pregnant women having a score of ≥5 were applied intravenous oxytocin and the ones which had the score <5 were applied intravaginal dinoprostone.

All pregnant women who accepted the first-trimester screening test and second-trimester test had blood drawn at their general practitioner between gestational weeks of 11-14 and 16-19. The serum samples were analyzed for levels of PAPP-A, free beta-hCG, AFP, total hCG and unconjugated E3 were measured by the Kryptor analyzer (a random Access immunoassay analyzer) using time-resolved amplified cryptate emission technology. Serum concentrations were transformed to multiples of the median value (MoM) in normal pregnancies of the same length of gestation, and rates of detection of various combinations of the markers were estimated by multivariate analysis. MoM values were corrected for maternal weight, self-recorded smoking status and ethnicity.

We used SPSS 16.0 to compare levels of PAPP-A, free beta-hCG, AFP, total hCG and unconjugated E3 in the cases and controls. P<0.05 considered to be statistically significant.

Results

There are no statistical differences between two groups in terms of maternal age, maternal weight, maternal height, maternal hemoglobin, maternal white blood cell, maternal blood pressure, pulse, fever, gravida, parity, birth weight, history, family history, obstetric story, applied induction types, birth types, caesarean indications, meconium in amniotic fluid, smoking in maternal period, and impaired glucose tolerance.

Fifty-nine pregnant women examined were in their pregnancy period of ≥41 weeks, 14 of them are ≥42 weeks. For labor induction, 41 of 73 patients were given medication (intravaginal dinoprostone for 9 patients (12 %) and intravenous oxytocin for 32 patients (56%) (p=0.00)). We found statistically significant difference in delivery time (11.5 vs. 5.2 h) (p = 0.00) (Table 1).

There were no SGA babies in the group of post-term pregnancies. In the control group 7 SGA babies were observed (0.3 %). There was no statistically significant difference in maternal PAPP-A, free beta-hCG, AFP, total hCG and unconjugated E3 levels between the patients having SGA babies. PAPP-A levels were observed between the values of 0.63 MoM-3.36 MoM (Table 2). Although birth weights were higher in pregnant women ≥41 weeks, this difference was not considered significant (p=0.19). Thirteen pregnant women delivered babies over ≥ 4000 gram, 7 of them were beyond ≥41 weeks and other 6 pregnant women were in the control group. There was no significant difference between these patients.

In consideration of all pregnant women, impaired glucose tolerance was observed in 14% (26/186) of all patients. Comparison of patients by using 5 biomarkers according to impaired glucose tolerance, there was no statistical difference. We found no statistical difference in terms of PAPP-A, free hCG, AFP, HCG and uE3 between the two groups (Table 3).

Table 1: Demographic and pregnancy characteristics of the study groups

Parameters	**> 41 weeks (n=73)**	**37-41 weeks (n=113)**	**p**
Maternal age (years)	25.9 ± 5.1	27.3 ± 5.2	NS
Maternal weight (kg)	77.7 ± 9.2	74.1 ± 10.1	NS
Maternal height (cm)	160 ± 5.0	161 ± 7.8	NS
Gravida	1.7	1.7	NS
Parity	0.5	0.5	NS
Times of delivery (hours)	11.5 ± 6.6	5.2 ± 4.2	0.00
Need for induction (%)	56	12	0.00
Cesarean section (%)	35	33	NS
Smoker (%)	10	9	NS
Impaired glucose tolerance (%)	12	15	NS
Meconium status (%)	10	8.8	NS
Birth weight (kg)	3.5 ± 0.4	3.3 ± 0.3	NS

Values are either mean (SD) or percentage.

Table 2: Correlation between PAPP-A levels and gestational week in SGA (<10 centile) babies

Birth weight (g)	PAPP-A (MoM)	Gestational weeks
2570	3.36	37.6
2618	1.56	39.1
2630	1.54	37.5
2640	0.63	39.3
2700	1.51	40.2
2750	0.73	40.4
2780	0.70	40.3

Table 3: Multiples of median (MoM) levels of serum biomarkers

Variable (MoM)	>41 weeks	37-41 weeks	P
PAP-A	0.92	1.07	NS
Free beta-hCG	1.09	1.08	NS
AFP	0.96	0.98	NS
hCG	1.11	1.12	NS
uE3	1.50	1.51	NS

***PAPP-A**; Pregnancy-associated plasma protein-A, **AFP;** Alpha fetoprotein, **uE3**; Unconjugated estriol, **MoM**: A multiples of the median **NS**; Not significant*

Discussion

A pregnancy that is completed in 42 weeks is defined as post term pregnancy (PT). Although the fetal, maternal and neonatal risks increase beyond 41 weeks, there is no conclusive evidence that prolongation of pregnancy is the major risk factor. Other risk factors for adverse outcomes have been identified; the most important of which are restricted fetal growth and fetal malformations. The etiology of PT is mostly unknown, but both fetal and placental abnormality and placental sulphate deficiency can be associated with prolongation of pregnancy. We were interested in whether abnormal serum concentrations of PAPP-A and free beta-hCG in the first trimester and AFP, total hCG and uE3 in the second trimester are associated with post term pregnancy which is thought that it is an etiology placental dysfunctional.[8]

We found no correlation in birth weights and PAPP-A (p= 0.833). Although decrement in the PAPP-A levels was observed in pregnant with advanced gestational week, there was no statically significant difference (p=0.102).

In literature, maternal serum levels of these analytes have been shown to be associated with adverse outcome with low levels o PAP-A (<0.04 MoM) having been suggested as a marker for impaired placental function and placentation.[9] There are studies however reporting contrasting views[10] like our study. In contrast to reported data, the lowest PAPP-A level was 0.09 MoM and maternal PAPP-A levels in SGA babies, were as low as 0.63 MoM.

For fetuses without sonographically identified structurally defects, elevated levels of maternal serum AFP have been associated with variety of obstetrical complications.[11] Previous studies found that the level of AFP value increased in placenta abruption, intrauterine growth restriction, still-born baby, stomach wall detection, fetus edema, tumors of umbilical cord, pregnancy induced hypertension and amniocentesis. The fact indicates that part of adverse pregnancy outcomes related to pathological change. Perenc reported oligohydroamnios, fetal triploidy and vacuolization of the trophoblastic caused significant changes of AFP level, total beta-hCG and uE3 in maternal serum. Yang also reported that placenta chorine angiopathy is the pathologic basis of fetal distress in pregnancy with hepatitis B virus infection, and is long-term anoxia second respond of the placenta. Yan-ping suggested that placenta pathological changes causing chronic fetal distress are probably the reasons of positive triple screening.[12] In our study; there was no statistically difference in AFP values. The patient who had the highest AFP value (3.43 MoM) had delivery by a caesarean section because of 3100 gram cephalopelvic disproportion in the 37th week of gestational.

Smith et al. postulated that there is no relationship between the free beta-hCG levels in the first trimester and poor pregnancy outcomes and a there is a week relationship between total hCG in the second trimester and poor pregnancy outcomes. In our study; there is no statistically significant difference observed between the patients in the >41 weeks pregnancy and 37-41 weeks pregnancy in terms free beta-hCG values in first trimester and total hCG MoM values in second trimester.[13]

There is no statistically significant difference between the levels of unconjugated estriol MoM >41 week with gestational control group.

As a result of serum scanning in the second trimester for trizomi 21, the relation between the decrement in maternal hCG level and diabetes mellitus were determined. Another study showed that there is a decrement in the PAPP-A and free beta hCG levels of both the pregnant women who have pre-existing diabetes during their existing pregnancy period and the patients that will develop gestational diabetes at their ongoing pregnancy period during the first trimester.[14,15] In this study; there is no statistically significant difference observed by serum scanning markers in the pregnant women having impaired glucose tolerance and this requires further investigation.

The mechanism triggering the birth has not been determined definitely yet. Placental dysfunction is one the subjects investigated to find out the mechanism. For this purpose, in this study; serum markers released from the placenta used in

Down's syndrome scanning are investigated. Although no statistically differences were found out, a decrement in the serum PAPP-A levels were observed with advanced gestational age. Moreover, in this study, there is no statistically relationship observed in PAPP-A, free beta-hCG, AFP, HCG and uE3 levels in maternal serum markers for pregnant women having their period of ≥ 41gestationel week. Further studies are necessary for this purpose.

41 Hafta Üzerindeki Gebeliklerde Antenatal Serum Belirteçlerinin Değerlendirilmesi

AMAÇ: Postterm gebeliklerle maternal antenatal serum belirteçlerinin ilişkisini incelemektir.

GEREÇ VE YÖNTEM: Temmuz 2010 - Aralık 2010 arasında Zekai Tahir Burak Kadın Sağlığı Eğitim ve Araştırma Hastanesinde takip edilen 186 tekil gebeliği olan hasta retrospektif olarak çalışmaya dahil edildi. Antenatal tarama programında bakılan PAPP-A, free β-hCG, AFP, HCG ve E3 düzeyleri kaydedildi. Bu belirteçler 37-41.gebelik haftasında olan 73 hasta ile ≥ 41 hafta olan 113 hasta arasında karşılaştırıldı.

BULGULAR: İki grup arasında PAPP-A, serbest beta-hCG, AFP, total hCG ve E3 düzeyleri açısından anlamlı farklılık saptanmadı. Her ne kadar doğum ağırlığı ≥ 41 hafta olan gebelerde daha fazla ise de istatistiksel anlamlılık saptanmadı (p= 0,19). Postterm gebelik grubunda SGA bebek yoktu.

SONUÇ: ≥41 gebelik haftasında olan hastalarda antenatal maternal serum belirteçlerinde anlamlı farklılık bulunmamaktadır.

Anahtar Kelimeler: Postterm gebelik, Maternal serum tarama.

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