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Original Article *Özgün Araştırma*

THE COMPARISON OF PAPP-A RESULTS AND BIRTH PARAMETERS IN NORMAL PREGNANCIES WITHOUT COMPLICATIONS AND IN PREGNANCIES WITH MECONIUM

Normal Komplikasyonsuz Gebeliklerde ve Mekonyumlu Gebeliklerde PAPP-A Sonuçlarının ve Doğum Parametrelerinin Karşılaştırılması

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ABSTRACT

Objective: In the present study, we compare first and second trimester screening test parameters in uncomplicated pregnancies with those in pregnancies complicated by meconium to assess their impact on birth outcomes. This analysis may uncover the potential of maternal serum pregnancy-associated plasma protein-A and alpha-fetoprotein levels as useful markers for meconium-stained amniotic fluid, thereby enhancing clinical strategies and monitoring approaches.

Material and Methods: The current study had a retrospective case-control design. In the study, a total of 1238 pregnant women were screened, and 528 who had both double and triple screening results were included.

Results: Pregnant women with meconium-stained amniotic fluid exhibited significantly different biomarker levels compared to those without. Specifically, the pregnancy-associated plasma protein A MoM levels were 0.9±0.1 versus 1.2±0.2 (p=0.012), and the alpha-fetoprotein MoM levels were 1.3±0.5 versus 0.9±0.0 (p=0.009), respectively. Fetal distress rates differed significantly between pregnant women with and without meconium-stained amniotic fluid, with 11 cases (10%) compared to 10 cases (2.4%) respectively (p=0.001). The requirement for neonatal intensive care was statistically significantly higher in pregnancies with meconium-stained amniotic fluid (n=30 (27.3%) vs. n=61 (14.6%), p=0.02).

Conclusion: Our study demonstrates that decreased maternal serum pregnancy-associated plasma-protein-A MoM levels, coupled with increased maternal serum alpha fetoprotein MoM levels are associated with meconium-stained amniotic fluid.

Keywords: *Meconium-stained amniotic fluid, PAPP-A, AFP, fetal distress, maternal serum screening tests*

ÖZ

Amaç: Bu çalışmada, birinci ve ikinci trimester tarama testi parametreleri, normal komplikasyonsuz gebelikler ile mekonyumla komplike olmuş gebeliklerde karşılaştırılarak bu parametrelerin doğum parametreleri üzerindeki etkilerini değerlendirmek amaçlanmıştır. Bu analiz, maternal serum gebelikle ilişkili plazma proteini A ve alfa-fetoprotein düzeylerinin mekonyumla boyanmış amniyotik sıvı için faydalı belirteçler olma potansiyelini ortaya koyarak klinik stratejilerin ve izlem yaklaşımlarının geliştirilmesine katkı sağlayabilecektir.

Gereç ve Yöntemler: Bu çalışma retrospektif olgu-kontrol çalışmasıdır. Çalışma kapsamında 1238 gebe taranmış, ikili ve üçlü tarama testi sonuçları birlikte bulunan 528 gebe çalışmaya dahil edilmiştir.

Bulgular: Mekonyumla boyanmış amniyotik sıvıya sahip gebelerde, bu durumu olmayanlara kıyasla biyobelirteç düzeyleri anlamlı olarak farklıydı; gebelikle ilişkili plazma proteini A MoM düzeyleri sırasıyla 0,9±0,1 ve 1,2±0,2 idi (p=0,012), alfa-fetoprotein MoM düzeyleri ise sırasıyla 1,3±0,5 ve 0,9±0,0 idi (p=0,009). Mekonyumla boyanmış amniyotik sıvıya sahip olan ve olmayan gebeler arasında fetal distres oranları anlamlı farklılık göstermekteydi; sırasıyla 11 vaka (%10) ve 10 vaka (%2,4) (p=0,001). Yenidoğan yoğun bakım ihtiyacı ise mekonyumla boyanmış amniyotik sıvı görülen gebeliklerde istatistiksel olarak anlamlı şekilde daha yüksekti (n=30 (27.3%) vs. n=61(14.6%), p=0,02).

Sonuç: Çalışmamız, azalmış maternal serum gebelikle ilişkili plazma proteini A MoM düzeylerinin ve artmış maternal serum alfa-fetoprotein MoM düzeylerinin mekonyumla boyanmış amniyotik sıvı ile ilişkili olduğunu göstermektedir.

Anahtar Kelimeler: *Mekonyumla boyanmış amniyotik sıvı, PAPP-A, AFP, fetal distres, maternal serum tarama testleri*

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INTRODUCTION

Pregnancy-associated plasma-protein-A (PAPP-A) is a glycoprotein produced by syncytiotrophoblasts in the placenta, and is found in maternal serum just after the implantation. PAPP-A, regulates the concentration of insulin-like growth factor (IGF) through the proteolysis of insulin-like growth factor binding protein (IGFBP).[1,2] IGF functions locally to stimulate mitosis and cellular differentiation, playing a role in both embryonic development and the regulation of fetal and placental growth. Therefore, PAPP-A regulates proliferation and cell growth.[3]

Serum PAPP-A levels of pregnant women increase during pregnancy. In the literature, there are numerous publications describing the relationship between changes in PAPP-A levels and fetal complications. There are studies explaining that an increase in PAPP-A levels is associated with hypertension and hypertension related conditions that develop in pregnant women, as well as studies on the relationship of low or excessively low PAPP-A levels with other conditions including abortion, gestational diabetes mellitus (GDM), and intrauterine growth restriction (IUGR).[4,5] Maternal serum alpha-fetoprotein (AFP) is a component of the triple screen performed in the second trimester. Studies have shown that elevated maternal serum AFP levels can effectively predict adverse pregnancy outcomes, including preeclampsia, preterm premature rupture of membranes (PPROM), IUGR, and preterm birth.[6,7]

In prolonged pregnancies, the fetal oxygen and nutrient needs may exceed the capacity of the placenta, and this relative impairment in placental function may lead to perinatal complications such as meconium aspiration syndrome, low Apgar scores and fetal distress.[8] The relationship between these perinatal complications and low serum PAPP-A levels has not yet been investigated. One of these perinatal complications is meconium-stained amniotic fluid, which occurs in approximately 12.5% of all pregnancies, with reported rates ranging from 8% to 22%.[9] This study aims to compare PAPP-A levels in normal, uncomplicated pregnancies and those with meconium-stained amniotic fluid, as well as to evaluate its effect on birth parameters. This analysis may help determine whether early maternal serum PAPP-A levels are associated with meconium-stained amniotic fluid, thereby improving clinical approaches and monitoring strategies.

MATERIALS AND METHODS

This study was structured as a retrospective case-control study. According to the rules of Helsinki Decleration. The protocol was approved by the Ethics Committee of Ankara Bilkent City Hospital (#TABED 1-24-416).

Study population

At the beginning of the current study, a total of 1238 pregnant women were screened. The flow diagram of the study is presented in Figure 1.

The final analysis comprised 528 pregnant women who had both double and triple screening results. The study compared two independent groups:

- Group 1: Term pregnancies with meconium-stained amniotic fluid (n=110).
- Group 2: Term pregnancies with normal, uncomplicated deliveries (n=418).

Exclusion criteria for the study were defined as follows:

- Presence of maternal diseases (e.g. diabetes mellitus, vascular malformations, hypertension, rheumatologic diseases, obesity, renal failure, cardiac disease, congenital hematological disorders, thyroid disease).
- Use of anticoagulant medications.
- Pregnancy-related complications like preeclampsia, gestational diabetes, and PPROM.
- Acute conditions characterized by inflammation, such as pancreatitis and appendicitis.

In addition, pregnancies in which fetal anomalies were detected at birth were excluded from the study.

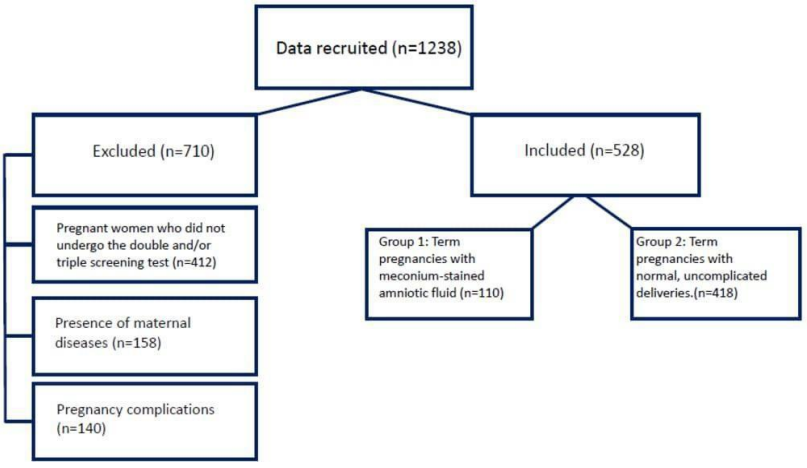

Figure 1: Flow diagram of the study

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Data collection

In this study, term pregnancies with normal, uncomplicated deliveries and pregnancies at term with meconium-stained amniotic fluid, who delivered at the Obstetrics and Gynecology Clinic of Ankara Bilkent City Hospital between 01.04.2022 and 01.04.2024 were included. The maternal serum MoM levels of free beta-human chorionic gonadotropin (fβ-hCG), beta-human chorionic gonadotropin (β-hCG), estriol (E3), AFP, and PAPP-A in these pregnancies were compared. The sociodemographic characteristics, fetal sonography findings including crown-rump length (CRL), and nuchal translucency (NT), presence of fetal distress, neonatal outcomes including neonatal intensive care requirement (NICR), and neonatal umbilical artery blood gas pH values were recorded.

Statistical Analysis

The data were analyzed using the SPSS v20 software program. The Shapiro–Wilk test was used to determine whether the data were normally distributed, and the homogeneity of variances was assessed with the Levene test. Comparison of normally distributed numerical variables was made with the student t test, comparison of non-normally distributed numerical variables was made with the Mann Whitney U test, and comparison of categorical variables was made with the chi-Square test. The hypothesis was established in two directions, and a p-value below 0.05 was accepted as statistically significant. The calculate.net web site was used to calculate the sample size of the study. Based on the 95% confidence interval of the study, α=5%, and the probability of meconium occurrence as 10%, the total sample size was calculated as 278 participants, 139 in the normal-uncomplicated term pregnancy group and 139 in the term pregnancy group who gave birth with meconium-stained amniotic fluid.

RESULTS

The pregnant women in groups 1 and 2 differed in terms of PAPP-A and AFP MoM levels (0.9±0.1 MoM vs. 1.2±0.2 MoM, p=0.012, and 1.3±0.5 MoM vs. 0.9±0.0 MoM, p=0.009, respectively). No statistically significant differences were observed between groups 1 and 2.

In terms of age, gravidity, body mass index (BMI) of the participants (28.9±4.8 vs. 28.1±4.4 years, p=0.554; 1 (1–5) vs. 1 (1–7), p=0.412; 28.3±4.9 vs. 29.2±4.0 kg/m^2, p=0.327, respectively). The birth weights of the fetuses did not differ significantly between groups 1 and 2 (3300±150 vs. 3310±210 gr, p=0.523). There was also no significant difference in gestational age at delivery between groups 1 and 2 (39.2±1.2 weeks vs. 39.3±1.3 weeks, p=0.653). In terms of fetal distress rates, there was a statistically significant difference between groups 1 and 2 (n=11 (10%) vs. n=10 (2.4%), p=0.001) (Table 1).

Table 1: Maternal demographics, obstetric and neonatal characteristics of the participants

Variables	Group 1 (n=110)	Group 2 (n=418)	p value
Age, years*	28.9±4.8	28.1±4.4	0.554
Gravida**	1 (1-5)	1 (1-7)	0.412
BMI***, kg/m^2*	28.3±4.9	29.2±4.0	0.327
Gestational age at delivery, weeks*	39.2±1.2	39.3±1.3	0.654
Birth weight (grams)*	3300±150	3310±210	0.523
Fetal Distress, n (%)	11 (10)	10 (2.4)	**0.001**

BMI: Body mass index; *Mean±Standard deviation,
** Median (Min-Max), *** BMI at the time of delivery

The NICR was observed to be statistically significantly higher in group 1 (n=30 (27.3%), p=0.02). NICR parameters and neonatal umbilical artery blood gas pH values are presented in Table 2.

There were no statistically significant differences in fetal sonography findings, including CRL and NT, between groups 1 and 2 (58.7±8.2 vs. 58.5±8.1 MoM, p=0.528; and 0.8±0.2 vs. 0.8±0.4 MoM, p=0.785, respectively). Table 3 presents the maternal serum levels of fβ-hCG, β-hCG, E3, AFP, and PAPP-A, as well as the fetal sonography findings.

Table 2: NICR parameters and neonatal arterial blood gas pH and lactate levels

Variables	Group 1 (n=110)	Group 2 (n=418)	P value
NICR, n (%)	30 (27.3)	61 (14.6)	**0.02**
Neonatal umblical artery blood gas pH*	7.26±0.2	7.30±0.4	0.337

* Mean±Standard deviation, NICR: Neonatal intensive care requirement

Table 3: The maternal serum fβ-hCG, β-hCG, E3, AFP, PAPP-A levels, and the fetal sonography findings

Variables	Group 1 (n=110)	Group 2 (n=418)	P value
fβ-hCG (MoM)*	1.0±0.5	1.1±0.6	0.254
β-hCG (MoM)*	0.9±0.4	1.0±0.4	0.845
E3 (MoM)*	0.9±0.3	1.0±0.4	0.448
AFP (MoM)*	1.3±0.5	0.9±0.4	**0.009**
PAPP-A (MoM)*	0.9±0.1	1.2±0.2	**0.012**
NT (MoM)*	0.8±0.2	0.8±0.4	0.785
CRL (mm)*	58.7±8.2	58.5±8.1	0.528

* Mean±Standard deviation, fβ-hCG: Free beta human chorionic gonadotropin, β-hCG: Beta human chorionic gonadotropin, E3: Estriol, AFP: Alfa-fetoprotein, PAPP-A: Pregnancy associated plasma protein-A, NT: Nuchal translucency, CRL: Crown-rump lenght.

DISCUSSION

First-trimester low maternal serum PAPP-A levels are linked to a higher risk of preterm birth, preeclampsia, stillbirth, admission to the neonatal intensive care unit, and small for gestational age (SGA) infants.[4,5,10] Reduced PAPP-A levels during the first trimester are

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associated with inadequate placentation during pregnancy and may consequently reflect reduced placental capacity, potentially leading to meconium aspiration.[8,11,12] In the current study, decreased serum levels of PAPP-A were statistically significant in term pregnancies with meconium-stained amniotic fluid. This suggests that, consistent with the existing literature, low maternal serum PAPP-A levels may indicate reduced placental capacitation and could indirectly contribute to meconium-stained amniotic fluid. These findings can also be interpreted as suggesting that a decrease in early pregnancy maternal serum PAPP-A concentrations may be associated with future meconium-stained amniotic fluid formation. In addition, the statistically significantly higher NICR rate in our participants with meconium-stained amniotic fluid is consistent with the literature. From a literature perspective, two opposing views emerge when evaluating the arterial blood gas of newborns delivered with meconium-stained amniotic fluid. One view suggests that meconium causes fetal acidemia in arterial blood gas, while the other argues that it has no significant effect.[13-15] This study found no statistically significant difference in arterial blood gas pH levels. Meconium is believed to induce vasoconstriction of the umbilical cord vessels and contribute to cord vessel necrosis, potentially leading to fetal distress or even death.[13,16] In this study, the rate of fetal distress was significantly higher in pregnancies with meconium-stained amniotic fluid compared to those without, consistent with the literature.

In the literature, low PAPP-A levels have been emphasized as a potential cause of various fetal complications, particularly low birth weight.[10] However, no significant difference was observed in fetal birth weights among the participants in the current study. Advanced maternal age, preterm gestational age at birth, primigravidity, and lower maternal BMI are risk factors for low birth weight.[17-19] However, our study also showed no statistically significant differences regarding these factors. This may also be considered an indicator of the well-matched characteristics of the study participants.

Reducing maternal and perinatal morbidity and mortality is the main objective of prenatal screening tests. Therefore, accurately predicting fetal distress or adverse pregnancy outcomes is vital for ensuring both maternal and fetal well-being. Currently, various studies explore different markers to enhance the prediction of fetal distress and pregnancy complications. Previous studies have demonstrated that low serum levels of PAPP-A and fβ-hCG may be associated with adverse clinical and biochemical outcomes in neonates postnatally. A decrease in serum PAPP-A levels in early pregnancy may predict fetal growth restriction (FGR). Furthermore, combining maternal serum fβ-hCG PAPP-A can enhance the diagnostic sensitivity for FGR.[20,21] The literature indicates that pregnant women with unexplained low maternal serum E3 levels in the second trimester have a higher incidence of gestational hypertension, gestational diabetes, preterm birth, and PPROM, particularly when maternal serum AFP or hCG levels are abnormally high or low. However, the clinical significance of elevated E3 levels has not been determined.[22] Therefore, studies suggest that high AFP levels may serve as a marker for pregnancies at high risk of complications, including early fetal death, fetal growth restriction, preeclampsia, IUGR, PPROM, and the threat of preterm birth.[6,7] AFP is associated with placental function.[19] Elevated AFP levels have been associated with diminished uteroplacental blood flow.[23] This may be related to fetal distress, which can lead to the passage of meconium.[8] In our study, maternal serum AFP levels were statistically significantly higher in participants with meconium-stained amniotic fluid. However, no statistically significant difference was found between the two groups regarding maternal serum β-hCG and E3 levels. In our study, the exclusion of complications such as PPROM and preeclampsia, which may influence β-hCG and E3 levels, not only enhanced reliability but also contributed to the standardization of the study group.

For spontaneous conceptions, CRL measurement before 14 weeks is routinely recommended to determine the onset of pregnancy and accurately calculate gestational age. To standardize practices, if the CRL is accurately measured, ultrasound dating should be used as the official reference for determining the pregnancy's start date, regardless of any discrepancies with the patient's assumption or the estimation based on the last menstrual period. The patient should be informed that this measurement offers the most accurate determination of the ultrasound-based pregnancy start date, which will serve as the reference for monitoring the pregnancy. However, extending the pregnancy beyond 42+0 weeks appears to increase fetal risk and should be discussed with the patient, weighing the potential risks against the disadvantages of induction.[24]

For the double test, CRL and NT are measured via ultrasound between 11 and 13+6 weeks of gestation. Increased NT (≥ 3.0 mm) has been associated with a 20–30% chromosomal abnormality detection rate in previous studies, and this rate rises to 40% for NT≥4.5 mm. In the current study, there was no statistically significant difference in CRL or NT measurements between the two groups. The similarity of ultrasound findings among participants is one of the strengths of our study, as it contributes to the standardization of the groups.

In conclusion, this study has shown that decreased maternal serum PAPP-A MoM levels and increased

maternal serum AFP MoM levels are both associated with meconium-stained amniotic fluid formation, although the MoM values are in normal ranges for those markers. To the best of our knowledge, our study is the first to assess early pregnancy PAPP-A MoM levels in pregnancies with meconium-stained amniotic fluid. Such combined or integrated markers may provide the accurate prediction of adverse obstetric outcomes. Further studies, particularly those prospective ones, will make significant contributions to the literature.

Conflict of Interest: The authors have no conflicts of interest to declare.

*Researchers' Contribution Rate Statement***:** Concept/Design: MDET, EMEK, NH; Analysis/Interpretation: EMEK, AT; Data Collection: MDET, NH; Writer: MDET, AT, NH; Critical Review: MDET, EMEK, NH, AT; Approver: MDET, AT.

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*Ethics Committee Approval***:** The protocol was approved by the Ethics Committee of Ankara Bilkent City Hospital (#TABED 1-24-416).

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