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IS AMNIOTIC FLUID ANALYSIS DURING THE SECOND TRIMESTER A PREDICTOR FOR THE DETECTION OF PRETERM LABOR?

İKİNCİ TRİMESTERDE BAKILAN AMNİYOTİK SIVI ANALİZİ PRETERM DOĞUM ÖNGÖRÜSÜNDE BİR PREDİKTÖR MÜDÜR?

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ABSTRACT

Objective: Premature activation of the hypothalamic-pituitary-adrenal axis due to stress can initiate preterm labor. Many mechanisms have been proposed to explain etiopathogenesis. The most important one is clinical and subclinical chorioamnionitis. We aimed to assess the possibility of early detection and prevention of preterm labor based on second trimester amniotic fluid analysis.

Material and Method: One hundred and twenty-five pregnant women with singleton pregnancies who underwent amniocentesis were included. The first 2 cm^3 of the amniotic fluid obtained during the amniocentesis was used for glucose, interleukin-1, interleukin-6, high sensitivity C-reactive protein, electrolytes, progesterone/estrogen analysis, and cell counts.

Results: Sixteen women (13.8%) went into labor prior to 37 weeks of gestation. The mean age of the study population was 33.2±6.25 years. Ages were similar between the preterm and term groups (36.06±3.91 vs 32.77±6.43). Furthermore, the analysis of all parameters in the amniotic fluid did not show any statistical significant difference between the groups.

Conclusion: The possible effects of subclinical infection and steroid hormonal changes that are implied in the etiology of preterm labor were investigated in our study, and no evidence was found to support that these factors played a role in the etiology of preterm labor.

Keywords: Amniocentesis, preterm labor, glucose, interleukin, high sensitivity C-reactive protein, leukocyte count

ÖZET

Amaç: Strese bağlı hipotalamik-pitüiter-adrenal aksın prematür aktivasyonu preterm doğumu başlatır. Etiyopatogenezi açıklamak üzere pek çok mekanizma ileri sürülmüştür. En önemlisi klinik ve subklinik koryoamniyonittir. Preterm eylem riski taşıyan hastaların daha erken dönemde belirlenmesi, önlenmesi ve hastaların yanlış tanı nedeni ile gereksiz yere tokoliz tedavisi almasının önlenmesini amaçladık.

Gereç ve Yöntem: Çalışmamızda 16-26 gebelik haftalarında 125 tekiz gebe, onamı alınarak çalışmaya dahil edildi. Hastalardan 3'ünde karyotip anomalisi (Trizomi 21) saptandı, 1 hastanın gebeliği şiddetli preeklampsi nedeni ile 32. haftada sonlandırıldı, 5 hastaya da ulaşılamadı. Yüz on altı hasta ile çalışmaya devam edildi. Amniyosentez işlemi alınan ilk 2 cc'lik amniyon mayisi kullanılarak glukoz, IL-1, IL-6, HsCRP, hücre sayımı, elektrolit ve progesteron/estrojen oranı çalışıldı.

Bulgular: Gebelerin 16'sı 37. haftasını doldurmadan doğum yaptı (%13,8). Çalışma popülasyonun ortalama yaşı 33,2±6,25 idi. Çalışmamızda preterm doğum yapan grup ile miyadında doğum yapan grubun yaş ortalaması istatistiksel olarak benzer bulundu (36,06±3,91 vs 32,77±6,43). Ayrıca her iki grupta hastaların amniyon mayisindeki glukoz, IL-1, IL-6, HsCRP, hücre sayımı, elektrolit ve progesteron/estrojen oranı istatiksel olarak anlamlı bulunmadı.

Sonuç: Çalışmamızda preterm eylemin etiyolojisinde suçlanan subklinik enfeksiyon ve steroid hormon değişimleri incelenmiş ve bu hipotezleri destekleyen kanıt bulunamamıştır.

Anahtar Kelimeler: Amniyosentez, preterm doğum, glukoz, interlökin, yüksek sensitiviteli C-reaktif protein, lökosit sayımı

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INTRODUCTION

Preterm birth is one of the leading causes of neonatal morbidity and mortality. When congenital fatal anomalies are set aside, 75% of neonatal deaths are due to preterm birth (1, 2). The preterm birth rates in developed countries are between 7% and 12% of all births with a higher prevalence in developing countries (1, 3, 4). Worldwide, the prevalence of preterm birth rate is calculated approximately as 11%, and approximately 15 million children are born prior to 37 weeks of gestation each year (5).

Among surviving neonates, preterm birth may cause long-term morbidities such as cerebral palsy of prematurity and neurologic dysfunction (6). One of the primary objectives of obstetrics is to prevent preterm labor in order to avoid morbidities related to prematurity, as well as perinatal and neonatal deaths. Therefore, it is of utmost importance to detect high-risk patients for preterm birth at the early stages of pregnancy, before premature uterine contractions begin. The most convenient solution for preterm labor is to detect high-risk patients and to make a diagnosis at the right point in time and prevent preterm labor.

Many methods have been proposed for the early diagnosis of preterm labor. A role for biochemical markers in the early diagnosis of preterm labor is being discussed with increasing frequency. With potentially effective markers, it may be possible to detect high-risk patients and to provide close monitoring and early intervention (7-9). Some studies even compared the level of these markers in amniotic fluid with serum in order to understand their efficacy (10-12). Moreover, for patients who are determined to be at a low risk with such tests, aggressive tocolysis, lengthy hospital stays, and close patient follow-up can be avoided. Also, asymptomatic patients with high risk of preterm labor may be determined with these biochemical markers and timely interventions can be made to accelerate fetal maturation (13).

In our study, we sought to investigate the infection markers and steroid hormone levels in amniotic fluid in order to determine the risk of preterm labor before the symptoms appeared.

MATERIAL AND METHOD

Data source

One hundred and twenty-five pregnant women aged above 18 years with singleton pregnancies who underwent amniocentesis between 16 and 26 weeks of pregnancy for various reasons between March 2011 and September 2011 were included in the study.

The gestational ages of the patients who fulfilled the criteria were calculated according to their last menstruation dates and confirmed with ultrasonographic measurements. All participating women routinely gave informed consent for the use of their data for research purposes. The Medical Faculty Ethics Committee approved this study (18.04.2011/116) and the ethics standards of the 1975 Declaration of Helsinki as revised in 2000 were complied with. Patients whose amniotic fluid analysis revealed a chromosomal anomaly, and patients whose pregnancy ended prematurely due to fetal or maternal reasons other than preterm labor were excluded from the study.

Women with multiple gestation, being outside of 16-26 weeks of gestation, known intrauterine or vaginal infection, complications during current pregnancy, detected congenital malformation in fetus or history of preterm labor, late abortus or late pregnancy loss were excluded.

Technique

Amniocentesis was performed transabdominally with a 22-gauge injector under ultrasonographic guidance with a free hand technique. The first 2 cm^3 of the fluid samples were drawn into a sterile injector, sent to the laboratory and analyzed for glucose, interleukin-1 (IL-1), interleukin-6 (IL-6), high sensitivity C-reactive protein (HsCRP), electrolytes, progesterone/estrogen analysis, and cell counts. The patients were followed up for a healthy pregnancy and for the determination of the week of birth.

Statistical analysis

Statistical analysis was performed with SPSS software (Statistics Package for Social Sciences) version 24 for Mac. Independent samples t test, chi-square test and Mann-Whitney U test were analyzed to detect difference in mean values and characteristics between groups. Standard deviation (SD) was used to present the mean values. $p<0.05$ was considered statistically significant.

RESULTS

During the seven-month research period, 125 patients who had planned amniocentesis for genetic counselling were included in our study. They had no ultrasonographic anomalies and no intrauterine infections. Trisomy 21 was detected in 3 cases; one pregnancy was terminated at the 32nd week due to severe pre-eclampsia. Five patients could not be contacted. 9 patients with missing data were excluded from the study and the study was completed with 116 patients. The mean age of the study population was 33.2±6.25 years.

Sixteen patients (13.8%) gave birth before completing the 37th week of gestation. The remaining 100 patients (86.2%) had term pregnancies. When the patients with preterm and term birth were compared, the mean age of the preterm birth group was found to be higher. However, the difference was not statistically significant (p=0.069).

Table 1: Comparison of the patients in the study and control groups

	Preterm group (n=16, mean±SD or number (%) or min-max values)	Term group (n=100, mean±SD or number (%) or min-max values)	*p value*[a]
Mean maternal age	36.06±3.91	32.77±6.43	0.069
HsCRP<0.02 mg/dL	13 (81.2)	90 (90)	0.386
HsCRP≥0.02 mg/dL	3 (18.8)	10 (10)	0.386
Glucose level (mg/dL)	42.37±12.01	43.25±10.32	0.654
Estrogen level (pg/mL)	219.66±75.92	219.30±99.62	0.743
Progesterone level (ng/mL)	50.17±26.22	47.62±25.00	0.994
Progesterone/Estrogen ratio	0.25±0.12	0.23±0.11	0.660
IL-1 level (pg/mL)	37.63±15.50	40.40±50.79	0.211
IL-6 level (pg/mL)	814.79±663.94	744.58±721.56	0.278
Na level (mEq/L)	127.18±11.95	129.59±10.24	0.580
K level (mEq/L)	3.55±0.29	3.64±0.29	0.270
Cl level (mEq/L)	95.37±11.11	97.83±9.53	0.613
Leukocyte count ($x10^6/mm^3$)	0.13 (0.06-1.25)	0.16 (0.03-0.66)	0.990

SD: Standard deviation, hsCRP: High sensitivity C-reactive protein, IL-1: Interleukin-1, IL-6: Interleukin-6, Na: Sodium, K: Potassium, Cl: Chlorine
[a]Independent samples t test and chi-square test were applied.

Investigation of HsCRP level in amniotic fluid revealed that 13 patients had a HsCRP level of 0.02 mg/dL or above. Three of these patients were in the preterm group and 10 were in the term group. Statistical analysis showed no significant difference regarding HsCRP levels of the preterm and the term groups (p=0.654). When estrogen and progesterone levels and progesterone/estrogen ratio were analyzed, no statistically significant difference was observed. When the IL-1 and IL-6 levels were examined, there was no significant increase in the mean IL-1 level in the preterm group and there was minimal increment in the mean IL-6 level in the preterm group; however, the difference was not statistically significant. When the electrolyte levels (sodium (Na), potassium (K), and chlorine (Cl)) and leukocyte count in the amniotic fluid of the preterm and term groups were compared, no statistically significant difference was detected (Table 1).

DISCUSSION

Preterm birth is the leading cause of infant morbidity and mortality all over the world. For this reason, the pathogenic processes leading to preterm birth, development of preventive interventions and markers for the early prediction are major targets of obstetric research. The possible effects of subclinical infection and steroid hormonal changes that are implied in the etiology of preterm labor were investigated in our study. No significant evidence was found to support that these factors played a role in the etiology of preterm labor.

The theory claiming that the fetus is connected by an intrauterine inflammatory process during the very early stages of pregnancy by increasing the subclinical inflammatory response has been developed. A study that investigated amniotic fluid for genetic counselling purposes (between 16-20 weeks) found that the median CRP level in amniotic fluid was 183 ng/mL in women who gave birth prior to 34 gestational weeks, 113 ng/mL in those who gave birth between 34 and 37 gestational weeks, and 57 ng/mL in women who gave birth after 37 gestational weeks. A correlation was found between amniotic fluid CRP levels and preterm birth, and when a CRP cut-off level was set to 110 ng/mL, the probability of birth before 34 weeks of gestation could be predicted with 80.8% sensitivity and 69.5% specificity (14). Similarly, it was reported that when the CRP cut-off level in amniotic fluid was set at 0.65 mg/L, the probability of birth before 37 weeks could be estimated with 92.9% sensitivity and 78.7% specificity (15).

Another study published in the same year investigated a larger sample of patients and found that the probability of preterm labor was 9.3%. They obtained amniotic fluid between 15 and 18 weeks of gestation, and measured CRP, glucose, and leukocyte levels, and determined that there was no statistically significant difference between the preterm and term groups regarding the CRP levels and leukocyte counts. The glucose level, however, was found to be significantly lower in the preterm group. When glucose cut-off level was set at 46 mg/dL, the test was 100% sensitive and had a 100% negative predictive

value (16). Another prospective cohort series including 39 patients also found that all amniotic fluid biomarkers such as CRP, glucose, and IL-6 did not differ significantly between the pre-term and the term groups (17).

In this study, even though the CRP levels in the preterm group were found to be higher, there was no statistically significant difference between groups. There are, however, several studies demonstrating statistically significant results. A recent meta-analysis evaluating 14 prospective, retrospective, cohorts, and case-controlled studies concluded that higher amniotic fluid IL-6 and MMP-8 levels, and lower glucose level could be used as predictors for preterm delivery due to significant results (18, 19). Although these markers have been found to be predictors of preterm delivery, more evidence is needed to determine whether they should be used as screening tests in clinical practice (20).

Nevertheless, it is currently unknown whether or not a certain CRP level can trigger preterm birth. This raises the issue and difficulty of achieving a strong negative predictive value based on CRP levels alone. In addition, since CRP is the first acute phase reactant protein to appear in blood, there might be other cytokines responsible for the cascade of events leading to preterm delivery. Another issue is that although amniocentesis procedures typically last less than one minute, the needle may cause a slight CRP increase, and influence the contents of the sampled fluid.

Our study showed that glucose levels of the preterm and term groups were found to be at similar levels. A study that performed amniocentesis in 40 patients who were diagnosed as having preterm labor between weeks 28 to 36 gestation measured glucose levels and made cultures of the fluid samples to detect aerobic and anaerobic bacteria and mycoplasma. In culture-positive patients, glucose levels were significantly lower. When the cut-off was set at 16 mg/dL, the amniotic fluid glucose level could predict the infection with 77% sensitivity and 87% specificity. This study showed that for the diagnosis of intrauterine infection, the measurement of glucose level might prove to be a cheaper and easier method, as an alternative to culture. This method, however, can only be more widely used if the correlation between preterm labor and subclinical intraamniotic infection is determined (21).

Regarding the investigation of the role of subclinical intrauterine infections in preterm birth, a previously conducted study measured IL-6 and tumor necrosis factor (TNF)-α levels in amniotic fluid and examined the predictability of preterm labor. They found that IL-6 had 89.6% sensitivity and 80.3% specificity, whereas TNF-α had 81.3% sensitivity and 79.2% specificity for the detection of preterm labor. In the analysis made for positive intraamniotic culture, levels of IL-6 had 91.9% sensitivity and 73.8% specificity, and TNF-α had 78.4% sensitivity and 70.1% specificity (22). Similarly, an inverse correlation was also detected between amniotic fluid IL-6 levels and the gestational week of birth in other studies (23, 24).

Alvarez de Rosa et al investigated the relationship of preterm delivery and IL-1, 2, 6, 8, and IL-2 receptor levels in 103 pregnant women. The preterm delivery group was found to have significantly elevated IL-2 receptor levels and IL-6 levels were found to be significantly lower in the preterm delivery group among those who responded to tocolytics compared with non-responders. This study suggested that maternal serum IL-6 and IL-2 receptor levels might be of benefit in determining preterm labor and a possible response to tocolytics (25).

No statistically significant difference was observed between the groups in terms of amniotic fluid levels of IL-1 and IL-6 in our study. This result may be due to the low number of cases, or it may also be caused by the variation in cytokine expression due to the influence of environmental and genetic factors, such as race, which was shown to have such an effect (26).

In many animals, a change in systemic or local levels of steroid hormones is the factor that starts the delivery process. A decrease of progesterone levels has been shown in many animals (e.g. sheep, monkeys) to be the principal effector that starts delivery (27, 28). In humans, the events concerning steroid changes are not identical to those in sheep and take more time. The steroid changes in sheep occur in mere days, whereas the changes in humans start between weeks 34 and 36 of pregnancy and take longer than 5 weeks. The beginning of the estrogen increase begins between weeks 34 and 36 in-utero; however, there is no late increase before delivery (29). It is probable that instead of a triggering an increase, there is a certain concentration build-up in humans, or the changes are local and are not reflected in the mother's systemic circulation (30). Although the exact mechanism of the relationship between the decrease in progesterone and the start of labor is unknown, it is known that delivery can be delayed by administration of progesterone or synthetic progestin (31-33).

Furthermore, Romeo et al. investigated the local changes in progesterone and estrogen levels in term human deliveries, comparing the levels of estradiol, estriol, and progesterone by performing amniocentesis in 40 women at term pregnancy (20 pregnant women in active delivery and 20 pregnant women not in active delivery) (34). The study showed that progesterone/estrogen ratios were significantly lower in women in active delivery at term. It was emphasized that there were local changes in term delivery and that the progesterone/estrogen ratio was more related to the subject than the individual concentrations of estrogen and progesterone. However, another study investigated the relationship between estrogen/

progesterone ratio and term delivery and found no significant difference in plasma estrogen or progesterone concentrations of patients at term and patients at 37 to 42 weeks of gestation in whom labor hadn't started (35). In our study, no changes in the estrogen and progesterone levels, and the progesterone/estrogen ratio were detected in relation with preterm delivery. Although the hypothesis that estrogen and progesterone level changes are important in the etiology of preterm delivery is tempting, strong clues indicating no such connection exists have been reported.

Recent studies have attempted to detect intraamniotic changes through non-invasive techniques. This is promising as it may mean that in the future, detection of preterm delivery can be done as a routine detection test in gestational patients (36).

There are conflicting results in the literature regarding the parameters compared in this study. Data on the subclinical inflammation hypothesis and the steroid hormones hypothesis in the etiology of preterm delivery is not consistent and various studies point to different conclusions; therefore, there is a need for more studies in this subject, preferably conducted with non-invasive methods.

The strict inclusion criteria, the prospective and monocentric design are the strengths of our study. The size of study population is also acceptable. Nowadays, the more widespread use of non-invasive methods, rather than amniocentesis, can be considered as a limitation of our study. However, the definitive diagnosis of several conditions is still only possible by the performance of amniocentesis.

As a conclusion, although this study has found no significant differences between the subclinical infection markers and steroid hormonal changes in the second trimester amniotic fluid of preterm and term patients, a better understanding of the exact mechanisms of preterm labor in the future may uncover other potential ways for early detection of preterm delivery.

Ethics Committee Approval: Acibadem Mehmet Ali Aydinlar University, Medical Faculty Ethics Committee approved this study (18.04.2011/116) and the ethics standards of the 1975 Declaration of Helsinki as revised in 2000 were complied with.

Informed Consent: Written consent was obtained from the participants.

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