

The Effect of Cord Blood Bile Acid Levels on the Meconium Passage in Utero in Normal Pregnancies

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ABSTRACT

OBJECTIVE: To investigate the effect of bile acids on meconium passage in utero in normal pregnancies.

STUDY DESIGN: This prospective case control study was performed at Zekai Tahir Burak Women's Health and Teaching Hospital between September 1, 2010 and January 1, 2011. Inclusion criteria were: singleton viable pregnancy, gestational age ≥ 37 weeks. Exclusion criteria were: presence of any maternal disease, obstetric cholestasis, hepatic infections and multiple pregnancies. Sixty one pregnant women were recruited for the study: 31 women with meconium stained amnion liquid and 30 women with normal amnion liquid. Demographic data and clinical data were collected. Each patient's cord blood gases, cord blood bile acids levels, maternal serum liver function tests and bilirubin levels were investigated.

RESULTS: There were no significant differences in maternal age, gestational age, parity and body mass index. We found no differences in the serum bilirubin levels and liver function tests. And there were also no differences in the cord blood gas values between the two groups. The mode of delivery was significantly different between the two groups. We didn't find a statistically significant difference in cord blood bile acid levels between the two groups.

CONCLUSION: Cord blood bile acid levels appeared to have no significant effect of meconium passage in normal pregnancies.

Keywords: Cord blood, Meconium, Bile acids

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Introduction

Meconium-stained amniotic fluid (MSAF) occurs as a result of the passage of fetal colonic contents into the amniotic cavity and encountered in approximately 12% of all deliveries.¹ Although the presence of meconium was considered as the signs of fetal maturity, recent studies claimed that it was released as response to hypoxia. Major component of meconium is water and other components are mucopolysaccharides, bilirubin, intestinal enzymes, hair and squamous cells.² However its content and composition may vary with advanc-

ing gestation and underlying antenatal problems of both fetus and mother. Intrahepatic cholestasis is one of those medical conditions encountered upto 0.4 to 15% of incidence in different populations and associated with MSAF.³ Intrahepatic cholestasis is generally diagnosed in second and third trimester of pregnancy with typical elevations of bile acids and transaminases in the maternal serum. Recent studies also supported the findings of increased rates of meconium staining of the amniotic fluid in women with intrahepatic cholestasis of pregnancy.⁴⁻⁸ MSAF in women with intrahepatic cholestasis was explained with stimulatory effect of bile acids on fetal colonic motility rather than with fetal hypoxia.⁹ Although the increased colonic activity with bile acids were claimed in the intrahepatic cholestasis of pregnancy, the underlying mechanism of meconium passage in other pregnancies with no signs of liver disease were not clearly understood. In order to prevent the associated fetal risks with meconium passage in low-risk pregnant populations, the probable predisposing factors and complex mechanism were required to be resolved. To our knowledge, there are no reports about the effect of bile acids on the meconium passage in normal pregnancies. Therefore we aimed to investigate the role of umbilical cord bile acids on meconium passage in normal term pregnancies in this study.

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Material and Method

This prospective case control study was conducted at the Zekai Tahir Burak Women's Health Training and Research Hospital between September 1, 2010 and January 1, 2011. Local Ethical Committee approved this study and all participants gave written informed consent. This study was consistent with the ethical standards for human research established by the Declaration of Helsinki. A total of 61 pregnant women with singleton term pregnancy (gestational age ≥ 37 weeks) who gave birth within this study period were recruited for the study: 31 women with meconium stained amniotic fluid included the "study group" and 30 women with normal amniotic fluid included the "control group". Exclusion criteria were as follows; presence of systemic disease, obstetric cholestasis, hepatic infections, multiple pregnancy and fetal congenital abnormalities. The patients' demographic data and clinical data including umbilical cord blood PH and bile acids levels, maternal serum liver function tests and bilirubin levels of each patient were reviewed. Serum transaminases, direct and total bilirubin levels were measured before the labor. Umbilical cord blood was collected soon after birth of fetus and the serums were prepared immediately by centrifugation at 4000 rpm for 10 minutes. Aliquots were stored at -80°C until further analysis. Bile acids (cholic acids and chenodeoxycholic acids) levels were assayed with spectrophotometer (Cobas mira plus- Roche). Serum AST and ALT were determined by IFCC with/without pyridoxal phosphate. Blood chemistry was determined by a Roche automated Clinical Chemistry analyzer.

Statistical analysis was performed using SPSS version 16.0 (SPSS Inc, Chicago, IL). A probability value of 0.05 was considered significant.

Results

In this study period, cases included the 31 women with meconium stained fluid and controls included the women with clear amniotic fluid. Both the mean maternal age and BMI of the women were similar in both cases and controls (27.2 vs 26.6 years $p=0.39$; 29.2 vs 28.5 kg/m^2 ; $p=0.30$). Mean gestational age was 39.3 weeks in both groups. Demographic characteristics of all participants were shown in Table 1. All women gave birth a live baby in this study period and only one in the cases had less than 7 points in 5 minutes APGAR scores. None of the baby required neonatal care in Neonatal Intensive Care Unit (NICU). In the umbilical cord

blood gas analysis, PHs were not different between two groups (7.36 vs 7.27; $p=0.097$). The major mode of delivery was vaginal delivery in both groups; 17 women (54.8%) in the study group and 25 women (83.3%) of cases. As expected, the rate of cesarean delivery statistically more common in the women with meconium stained amniotic fluid compared to those with clear amniotic fluid (45.2% vs 16.7%; $p=0.01$).

All maternal blood tests were done before the labor. The maternal serum transaminases (ALT and AST) were not different between cases and controls; ($p=0.33$ and $p=0.14$). Serum total bilirubin level were similar in both women with meconium stained and clear amniotic fluid (0.36 vs 0.37 mg/dL ; $p=0.41$). Serum conjugated bilirubin levels were also not different between study and control group (0.09 vs 0.15 mg/dL ; $p=0.066$). In concordance with the maternal test results, umbilical cord fetal bile acids were also similar in both fetuses with meconium stained and clear amniotic fluid (7.28 vs 8.70 $\mu\text{mol}/\text{L}$). The details of the maternal and fetal parameters were shown in Table 2.

Table 1: Demographic characteristics of participants

	Cases (n=31)	Controls (n=30)	p
Age (yr) (mean \pm SD)	27,2 \pm 5,1	26,6 \pm 4,9	0,385
^a BMI (kg/m^2)	29,2 (23,3-39,4)	28,5 (23,3-35,5)	0,300
Gestational Age (weeks) (mean \pm SD)	39,3 (0,79)	39,3 \pm 1,09	0,365
Gravidity [median(range)]	2 (1-8)	2 (1-8)	0,231
Parity [median(range)]	1 (0-7)	1 (0-2)	0,245
^a BMI: Body mass index			

Table 2: Fetal and maternal parameters of the participants

	Cases (n=31)	Controls (n=30)	p
AST (IU/L) (mean \pm SD)	19,4 \pm 5,1	20,3 \pm 5,6	0,325
ALT (IU/L) (mean \pm SD)	12,7 \pm 3,8	15,5 \pm 5,6	0,143
Total Bilirubin (mg/dL) (mean \pm SD)	0,36 \pm 0,07	0,37 \pm 0,2	0,413
Direct Bilirubin (mg/dL) (mean \pm SD)	0,09 \pm 0,03	0,15 \pm 0,16	0,066
Hemoglobin (g/dL) (mean \pm SD)	12,3 \pm 1,03	12,4 \pm 1,07	0,215
Mode of delivery (n,%)			0,01
Vaginal	17 (54,8)	25 (83,3)	
Cesarean section	14 (45,2)	5 (16,7)	
Apgar scores (n,%)			0,121
1-Min<5	2 (6,4)	1 (3,3)	
5-Min<7	1 (3,2)	0	
Birth Weight (g) (mean \pm SD)	3378 \pm 410	3339 \pm 439	0,754
Umbilical cord pH (mean \pm SD)	7,26 \pm ,07	7,27 \pm 0,06	0,097
Umbilical cord bile acid $\mu\text{mol}/\text{L}$ (mean \pm SD)	7,28 \pm 2,9	8,7 \pm 1,9	0,099
NICU admission (n %)	0	0	

Discussion

Because the meconium-stained amniotic fluid was associated with higher perinatal mortality than those with normal amniotic fluid, it is an important problem that obstetrician face during the labor follow-up. The mechanism of more higher rate of meconium paasege in pregnancies complicated with gestational cholestasis was explained with colonic activity stimulation of increased serum bile acid levels.¹⁰ However, there is no data about relationship between meconium passage and serum bile acid levels in normal pregnancies. In the present study we compared umbilical cord blood bile acid levels of term pregnant women with meconium-stained amniotic fluid to those with clear amniotic fluid.

The relationship between meconium passage in utero, as evidenced by meconium-stained amniotic fluid, and fetal acidosis at birth is controversial. In theory, fetal hypoxemia leads to anal sphincter relaxation and increased gastrointestinal motility that leads to meconium passage. However, there is insufficient data to support this pathophysiology. In fact in animal models, Ciftci et al.¹¹ and Kizlican et al.¹² have shown that meconium passage in utero is a normal, physiologic process that occurs independent of fetal oxygenation and acid-base status. In these experiments the rate of intestinal peristalsis and meconium release was not affected by fetal hypoxia-asphyxia, whereas some authors¹³⁻¹⁵ have found a relationship between meconium-stained amniotic fluid and lower fetal blood gas values. In this study we did not find any difference between two groups according to umbilical cord blood PH suggesting that there is no correlation between fetal acidosis and meconium passage in utero.

It is kown that meconium passage is more prevalent in pregnancies complicated with gestational cholestasis. To date it was known that the meconium passage in utero is independently correlated with the maternal serum bile acid level in patients with obstetric cholestasis.¹⁰ Studies in animal models have shown that high maternal serum bile acid levels stimulate fetal colonic motility, causing passage of meconium.^{16,17} Campos et al.⁹ found that the appearance of meconium in amniotic fluid by the third day of experiments in the fetuses infused with cholic acid, in the absence of detectable changes in fetal blood gases and heart rate, suggests that bile acid causes meconium passage in the fetus through a mechanism different from that postulated for hypoxic fetuses. On the other hand until now there was no study about correlation between meconium passage and serum bile acid levels in the patients with no liver diseases of pregnancy. In the present study we investigated the effect of bile acids on the meconium passage in normal pregnancies. But we did not find any differences between two group's bile acids serum levels.

Some authors found that the incidence of meconium-stained amniotic fluid increased with gestational age, lending support to the hypothesis that meconium passage is a physio-

logic event that is in large part due to developmental maturation of the fetal autonomic nervous system.¹⁸⁻²¹ In this study we could not conclude this theory because our study population was consisted of only term pregnancies.

In conclusion cord blood bile acid levels appeared to have no significant effect on meconium passage in normal pregnancies. Further investigations with large number of patients in different populations are required to explain the meconium passage mechanism in normal term pregnancies.

Normal Gebeliklerde Kordon Kanı Safra Asit Seviyesinin İntrauterin Mekonyum Pasajı Üzerine Etkisi

ÖZET

AMAÇ: Normal gebeliklerde umbilikal kord safra asitlerinin intrauterin mekonyum pasajı üzerine olan etkisini araştırmak.

GEREÇ VE YÖNTEM: Bu prospektif vaka kontrol çalışması, 1 Eylül 2010 ile 1 Ocak 2011 tarihleri arasında Zekai Tahir Burak Kadın Sağlığı Eğitim ve Araştırma Hastanesi'nde doğum yapan tekil canlı, 37 hafta üstü gebeler üzerinde yapıldı. Gebeliği 37 haftadan küçük olan, herhangi bir sistemik hastalığı olan, obstetrik kolestazi, hepatik enfeksiyonu veya çoğul gebeliği olan kadınlar çalışma dışında tutuldu. Doğumda amnion mayisi mekonyumlu olan 31 gebe vakaları, amnion mayisi normal olan 30 gebe ise kontrol grubunu oluşturdu. Her iki grupta kordon kanı gazı değerleri, kordon kanı safra asit seviyeleri, maternal serum karaciğer fonksiyon testleri ve bilirubin seviyeleri karşılaştırıldı.

BULGULAR: Gruplar arasında maternal yaş, gestasyonel yaş, parite ve vücut kitle indeksi açısından fark yoktu. Vakalar ve kontroller arasında serum bilirubin seviyeleri ve karaciğer fonksiyon testleri açısından herhangi bir fark tespit edilmedi. Umbilikal kordon kanı gaz değerleri açısından da iki grup arasında fark yoktu. Beklendiği gibi mekonyumlu amniyon mayisi olan grupta normal amniyonu olan gruba göre istatistiksel olarak anlamlı olacak şekilde sezaryan oranı fazlaydı (%45,2 vs %16,7; p=0,01). Kordon kanı safra asit seviyesi ve pH'sı için de her iki grup arasında anlamlı fark saptanmadı.

SONUÇ: Normal gebeliklerde kordon kanı safra asit seviyelerinin mekonyum pasajı üzerine herhangi bir etkisi olmadığı görülmektedir.

Anahtar kelimeler: Umbilikal kordon kanı, Mekonyumlu amnion mayii, Safra asitleri

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