

Predictive Value of Obstetrical Doppler Parameters to Predict Oxidative Stress and Cord Blood PH in Newborn Infants

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OBJECTIVE: We sought to determine the clinical value of obstetrical Doppler performed at early stages of active labor in predicting oxidative stress and cord blood pH in neonates.

STUDY DESIGN: A total of 54 pregnant women with oligohydramnios who were in active labor were enrolled for the study. Active labor was confirmed for each woman according to uterine contraction frequency, cervical dilatation and effacement. Subjects with amniotic fluid index (AFI) lower than 80 mm were included in the study. Doppler assessment included uterine artery (UtA), umbilical artery (UmA) and middle cerebral artery (MCA) measurements. Umbilical cord lengths were measured after delivery. Cord blood gamma glutamyl transferase (GGT) levels and umbilical arterial blood pH were analyzed.

RESULTS: Umbilical artery PI significantly predicted cord blood GGT levels >101 iu/L (area under curve=0.690, P=0.018). Umbilical artery PI significantly predicted cord blood pH<7.21 (area under curve (AUC) =0.870, P=0.015). None of the MCA Doppler parameters were significantly correlated with cord blood pH or cord blood GGT (P>0.05). Also, MCA Doppler studies could not significantly predict cord blood pH<7.21 OR GGT>101(P>0.05).

CONCLUSION: This data led us to conclude that UmA Doppler parameters at early periods of active labor in high-risk population may be predictive for newborn well-being.

Keywords: Obstetric Doppler, Fetal acidemia, Oxidative stress

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Introduction

Amniotic fluid has an essential role in fetal health. It has bacteriostatic, anti-inflammatory and thermoregulatory effects. Stable and adequate fluid amounts lead to proper growth of the fetal lung and musculoskeletal system. Oligohydramnios is a risk factor for uteroplacental insufficiency and hypoxemia.¹ The stability of the fetal circulation ensures an uninterrupted exchange from maternal blood and enables the fetus to tolerate labor. The failure on this delicate circulation leads oxidative distress. Umbilical cord pH value is a sensitive marker for fetal asphyxia.² Gamma Glutamyl Transferase (GGT) is a sensitive marker for oxidative stress

and an early indicator for fetal distress.³ Obstetric Doppler ultrasonography (US) is a noninvasive assessment method in predicting of fetal condition in active labor. Doppler velocimetry of umbilical artery (UmA), uterine artery (UtA) and middle cerebral artery (MCA) is a useful technique to detect the alterations of circulation in fetal distress. The analysis of the obstetric Doppler velocimetry waveforms includes resistance index (RI), pulsatility index (PI) and peak systolic/end diastolic ratios (S/D).⁴ The aim of this study was to determine the clinical value of obstetrical Doppler performed at early stages of active labor in patients with oligohydramnios to predict oxidative stress and cord blood pH in neonates.

Material and Method

This prospective observational cohort study was performed after approval from the local institutional review board. All of the subjects provided written informed consent to participate enrolled in the study. The study was conducted among 54 pregnant women in active labor. Maternal age, gravidity, parity, body mass index, umbilical cord lengths, cord blood pH and GGT levels were recorded. The base criterions of active labor for each woman comprised regular uterine contractions accompanying cervical dilatation and effacement.

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The inclusion criteria were: Pregnancies without medical, obstetric or surgical events that complicate the pregnancy except for isolated oligohydramnios (amniotic fluid volume <80 mm); spontaneous active phase of labor with cervical dilatation up to 4 cm and uterine contractions occurring at least every 5 minutes; gestational age ≥ 37 weeks and vertex presentation. The participants included in the study were healthy and did not have previously diagnosed diabetes mellitus, chronic hypertension, renal or cardiovascular diseases. There was no chronic drug use and they did not have any bleeding disorder. Cases with obstetric complications such as pre-eclampsia, eclampsia, gestational hypertension, intrauterine growth restriction, placental abruption, intrauterine fetal death, preterm birth, chorioamnionitis or prolonged ruptured of membranes were excluded from the study. The amniotic fluid index (AFI) was measured with Logiq S6 ultrasound machine (General Electric, USA) in all cases. Gray scale and Doppler US studies were performed in 1-8 MHz bandwidth convex transabdominal probe with mean 3.5 MHz broadband (Esaote, MyLab60, Geneva, Italy) by an experienced radiologist and a gynecologist at the same session. The results were evaluated and final decisions were made, therefore interobserver divergence was prevented. Cases with AFI lower than 80 mm were diagnosed as oligohydramnios, and were included in the study. After the gray scale examination, we applied color flow mapping window and spectral analysis. The Doppler signal was optimized with adjustment of probe position, gain measurements and the angle of insonation for accurate determination. We obtained the proper signal after 5 similar consecutive waveforms. The peak systolic and end diastolic flow velocities were measured. We measured S/D, PI and RI ratios and also observed Umbilical Vein (UmV) traces in all subjects. All ratios observed from the bilateral UtA, UmA, UmV and MCA were recorded for each case. Cord length was measured to assess whether it has any impact on Doppler assessment. The cord blood measurements of GGT were also analyzed using a Beckman automatic analyzer (Abbott-USA).

Statistical analysis

The statistical analyses were performed using the Statistic Package for Social Sciences (ver. 12.0; SPSS Inc., Chicago, IL). Correlation analysis was used to show associations between variables. ROC analysis was used to determine cut off values and binary logistic regression test was used to calculate odds ratios. The p value 0.05 was accepted as statistically significant.

Results

Mean values of subject characteristics, Doppler parameters, serum GGT and cord blood pH were as follows; mean gravidity (2.6 ± 1.7), parity (1.2 ± 1.5), gestational age (38.6 ± 1.9 weeks), birth weight (3070.6 ± 421.9 gr), cord length

(50.1 ± 10.5 cm), amniotic fluid index (49.3 ± 21 mm), UmA systole/diastole ratio (s/d) (2.5 ± 2.6), UmA RI (0.5 ± 0.1), UmA PI (0.8 ± 0.4), MCA s/d (3.6 ± 1.2), MCA RI (0.7 ± 0.1), MCA PI (1.3 ± 5.4), right UtA (1.9 ± 0.5), left UtA s/d (1.9 ± 0.5), serum GGT (135.9 ± 93.7 iu/L), cord blood pH (7.3 ± 0.05).

Umbilical artery RI significantly correlated with cord blood pH ($r = -0.263$, $P = 0.03$). Umbilical artery PI significantly correlated with both cord blood pH ($r = -0.350$, $P = 0.009$) and GGT levels ($r = -0.294$, $P = 0.03$). UmA S/D > 2.8 was associated with low pH. Although cord length significantly correlated with umbilical artery PI ($r = 0.385$, $P = 0.004$), it was not correlated with cord blood pH or GGT levels. In addition, UmA PI significantly predicted cord blood Ph < 7.21 [area under curve (AUC) = 0.870, $P = 0.015$, Figure 1].

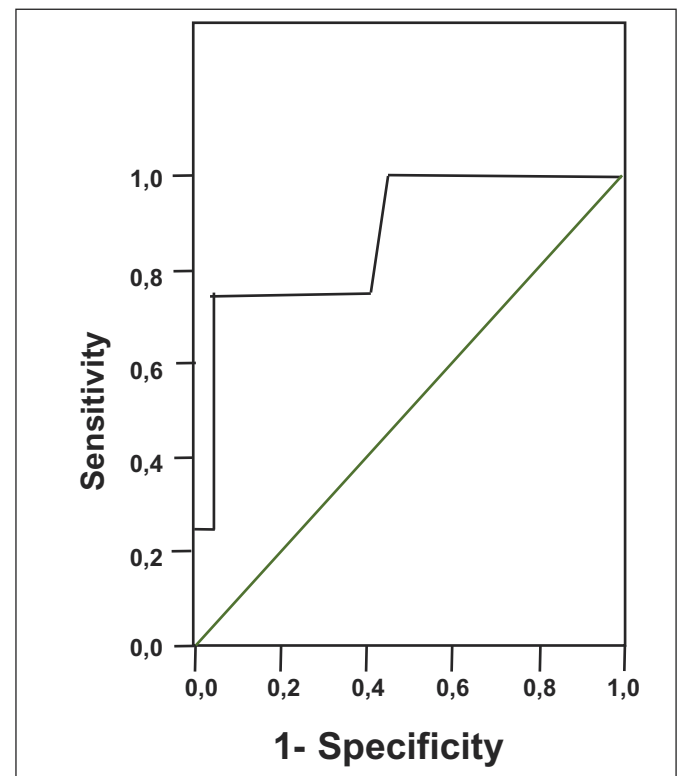


Figure 1: ROC curve for UmA PI to predict low pH

Lowest level of GGT was 101 iu/L in group with cord pH lower than 7.21. There were 4 newborns with cord pH lower than 7.21, while there were 33 newborns with cord blood GGT level higher than 101 iu/L. In all subjects, the UmV waveforms had non-pulsatile, continuous pattern. Umbilical artery PI significantly predicted newborns with cord blood GGT levels > 101 iu/L (AUC = 0.690, $P = 0.018$, Figure 2). Optimal cut off value was obtained at value of 1.08 with 75% sensitivity and 61% specificity to predict cord pH while optimal cut off to predict GGT > 101 iu/L was 0.73 with 69% sensitivity and 64% specificity. Umbilical artery RI was also a significant predictor for GGT > 101 iu/L (AUC = 0.672, $P = 0.03$). Cut off value was found to be 0.51 with 71% sensitivity and 60% specificity.

Cord blood pH again was significantly predicted by Uma S/D (area under curve =0.813, $P=0.03$). Cut off value was 2.85 with 75% sensitivity, 90% specificity. None of the MCA Doppler parameters were significantly correlated with cord blood pH or cord blood GGT ($P>0.05$). Also, MCA Doppler studies could not significantly predict cord blood $pH<7.21$ OR $GGT>101$ ($P>0.05$).

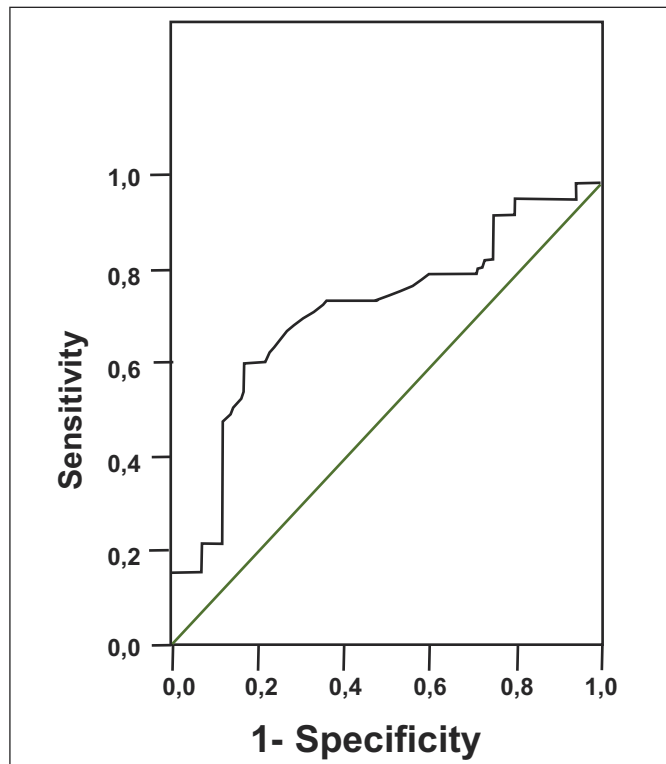


Figure 2: ROC curve for Uma PI to predict high serum GGT levels

In multivariate analysis Uma s/d (beta coefficient:-0.372, $P=0.021$) and Uma PI (beta coefficient:-0.425, $P=0.013$) values were significantly associated with cord pH while cord blood GGT was found to be significantly associated with only Uma PI values (beta coefficient:0.344, $P=0.005$).

Odds ratios

Uma PI>1.08 was associated with low pH (odds ratio=72(95%CI ,4.9-1038, $P<0.05$).

Uma S/D>2.8 was associated with low pH (odds ratio=18(95% CI, 1.4-235.7, $P<0.05$).

Uma PI>0.73 was associated with high GGT (odds ratio=4.9(95%CI, 1.3-18.4, $P<0.05$).

Uma RI>0.51 was associated with high GGT (odds ratio=3.7(95% CI 1.2-11.6, $P<0.05$).

Discussion

In this study, we primarily aimed to assess the value of various Doppler parameters in predicting oxidative stress and

umbilical cord pH in newborns. Doppler measurements were performed in 54 women with term pregnancies and isolated oligohydramnios, during early stage of active labor. As previous studies on midtrimester uteroplacental Doppler US revealed inefficiency of Doppler screening for anticipating the risk of pregnancy complications, we aimed to assess the value of Doppler analysis during active labor.⁵

Alterations in the fetoplacental circulation may reflect hemodynamic disturbance and subsequent fetal hypoxemia.^{4,6-9} During normal active labor, the fetus continues to have uninterrupted fetoplacental blood circulation. The degree of reduction in uteroplacental blood flow is dependent on the intensity and frequency of uterine contractions. Studies on simultaneous intrapartum pulse oximetry and Doppler US indicate that reduced arterial oxygenation is associated with profound changes in fetal hemodynamics, and could be tolerated for only a limited period in active labor.^{10,11}

Umbilical cord blood pH is a reliable marker for fetal acidemia. Prenatal prediction of umbilical cord pH value is important, because it has a direct effect on fetal neurological outcomes. Umbilical arterial pH values below 7 are strongly associated with acidemia and adverse perinatal outcomes. The metabolic component of acidemia is the most important variable in neonatal morbidity.^{12,13} A previous study by Bolz et al. assessed the value of Uma and Uta Doppler indices to predict perinatal outcomes in low-risk pregnancies, the authors analyzed Doppler waveforms and perinatal outcome parameters in 514 low-risk pregnant women. They found an Increased Uma PI and RI correlated significantly with low cord blood pH. However, the authors concluded that Doppler waveforms had low prognostic value in predicting neonatal acidosis or low APGAR scores. Doppler assessment in this study was performed in a low risk population not in active labor.¹⁴ Differently from this study, we assessed the value of Doppler parameters in prediction of cord blood pH levels in patients with oligohydramnios that were also in active labor. Umbilical artery RI and PI was significantly correlated with cord blood pH ($p<0.05$). Also, Uma s/d and Uta PI significantly predicted cord blood $pH<7.21$ ($p<0.05$). Increased Uma S/D, RI and PI values and increased Uta PI value were associated with fetal acidemia. These results suggest that Uma RI, Uma PI, Uma s/d and Uta PI are valuable in prediction of cord blood pH levels in patients with oligohydramnios in early stage of labor. Another study by Figueras et al. investigated the value of MCA Doppler waveforms to predict umbilical cord gases in prolonged pregnancies.¹⁵ They concluded that proximal MCA PI significantly predicted Uma pO_2 at delivery, but did not predict cord blood pH in post-term pregnancies.¹⁵ In our study, MCA Doppler parameters did not have a correlation with neither cord blood pH nor cord blood GGT ($P>0.05$). These data suggest that MCA Doppler studies have a limited role in eval-

uating fetuses for acidemia or oxidative stress. As UmV studies did not exhibit any abnormalities in our study we could not conclude on UmV Doppler value in fetal acidemia or oxidative stress prediction. Likewise, umbilical cord length did not have an association with cord blood pH value.

A previous experimental study demonstrated that Glutathione is a key component of antioxidant system, which defends cells against the toxic effects of oxygen.¹⁶ Gamma-glutamyl cycle is a pathway for the synthesis and degradation of glutathione, in which the enzyme GGT plays a key role.¹⁷ As previously mentioned, GGT is a sensitive marker for oxidative stress.³ A recent study investigated cord blood oxidative stress markers and Doppler parameters in intrauterine growth restricted fetuses. A correlation between oxidative stress markers and UmA PI was demonstrated. As umbilical cord pH values were ≥ 7.25 in all of the cases, this study could not evaluate the association between Doppler parameters and fetal acidemia.¹⁸ Our study suggested that UmA PI and RI values are valuable as markers for increased GGT levels in fetal circulation. Especially, UmA PI >0.73 and UmA RI >0.51 were associated with 4.9-fold and 3.7-fold risk of high GGT levels, respectively. Although umbilical cord length significantly correlated with UmA PI, it did not have an association with GGT levels. As mentioned earlier, MCA studies did not have an association with GGT levels.

A recent study demonstrated that, among high-risk pregnancies with suspected IUGR, the use of umbilical arterial Doppler assessment significantly decreased the likelihood of labor induction, cesarean delivery, and perinatal deaths (1.2% vs 1.7%; RR, 0.71; 95% CI, 0.52-0.98).¹⁹ In this study, it was concluded that Doppler studies of vessels other than the UmA, as part of assessment of fetal well-being in pregnancies complicated by growth restriction should be reserved for research protocols.¹⁹ According to our findings, we believe that performing UmA Doppler may also be useful in assessing isolated oligohydramniotic pregnancies for fetal acidemia and oxidative stress.

In summary, our study suggests that UmA and UtA Doppler studies during early stage of active labor in pregnancies with isolated oligohydramnios are valuable in predicting umbilical cord blood pH and neonatal oxidative stress status. Taking into account that this was a preliminary study with a limited sample size, future studies with larger sample sizes are indicated to reach a final conclusion.

Obstetrik Doppler Parametlerinin Yenidoğanda Oksidatif Stres ve Kord pH'sını Öngörmedeki Değeri

AMAÇ: Aktif doğum eyleminin erken döneminde obstetrik Dopplerin oksidatif stres ve yenidoğan kord kanı pH sınırını öngörmedeki değerini tanımlamayı amaçladık.

GEREÇ VE YÖNTEM: Çalışmaya aktif doğum eyleminde oligohidramniyonu olan 54 hasta dahil edildi. Aktif doğum eylemi her hasta için uterin kontraksiyon, servikal dilatasyon ve efasman ile doğrulandı. Amniotik sıvı indeksi (AFI) 80 mm altında olan hastalar dahil edildi. Doppler değerlendirmesi umbilikal arter, uterin arter ve orta serebral arter parametrelerini içeriyordu. Umbilikal kord uzunluğu doğumdan sonra ölçüldü. Kord kanı gama glutamil transferaz (GGT) düzeyi ve umbilikal arter PH düzeyi ölçüldü.

BULGULAR: Umbilikal arter PI değeri, kord kanı GGT >101 u/L düzeyini anlamlı olarak öngörmekteydi (AUC=0,690, p=0,018). Umbilikal arter PI değeri, kord kanı pH $<7,21$ değerini anlamlı olarak öngörmekteydi (AUC=0,870, p=0,015). MCA doppler parametrelerinden hiçbiri ne kord kanı ne de pH değeri ile anlamlı korele idi (p $>0,05$). Ayrıca MCA Doppler çalışmaları kord kanı pH $<7,21$ veya GGT >101 değerini öngörmüyordu (p $>0,05$).

SONUÇ: Bu veriler aktif doğum eyleminin erken dönemindeki yüksek riskli hastalarda umbilikal arter Doppler parametrelerinin yenidoğan iyilik halini değerlendirmede öngörücü olabileceğini göstermektedir.

Anahtar Kelimeler: Obstetrik doppler, Fetal asidemi, Oksidatif stres

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