Perinatal and neonatal outcomes of growth restricted fetuses with positive end diastolic and absent or reversed umbilical artery doppler waveforms

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ABSTRACT

الأهداف: من أجل تقييم نتائج النمو المحصورة للأجنة داخل الرحم مع الغياب أو الانتهاء المعكوس– للتيار الانبساطي في الشريان السري.

الطريقة: أجريت هذه الدراسة بقسم طب النساء والولادة بمستشفى باكيروكي التعليمي للنساء والأطفال في الفترة ما بين عام 2002م وعام 2006م. تمت متابعة حالة نمو الأجنة المحصور ل110 امرأة حاملة بواسطة الأشعة بالموجات فوق الصوتية وبدراسات أشعة دوبلر للشريان السري. تم تقسيمهم الى مجموعتين. المجموعة الأولى ، النمو المقيد داخل الرحم مع نماذج موجات تيار ايجابي وانبساطي (n=137) والمجموعة الثانية النمو المقيد داخل الرحم مع غياب أو الانتهاء المعكوس للتيار الانبساطي (n=163) تم تسجيل النتائج قبل وبعد الولادة لكلتا المجموعتين.

النتائج: صاحب المجموعة الأولى معدل أعلى من الوفيات قبل الولادة والإصابة بالأمراض من المجموعة الثانية
p=0.02, odds ratio [OR]: 1.09, 95% confidence interval [CI] 1-3.5), (*p*=0.03, OR: 2, 95% CI 1.2-3.2
في المجموعة الأولى كان هنالك نسبة ملحوظة أكثر من إدخال الأجنة وحدة العناية المركزة. ازداد تكرار الإصابة بمتلازمة ضيق التنفس وإنتان الدم والنكرزة في المجموعة الأولى. لم يكن هنالك فرقاً ذو دلالة إحصائية في الحاجة إلى التنفس الاصطناعي لمتلازمة ضيق التنفس.

خاتمة: تقترح بياناتنا أن لدى الحمل مع غياب أو الانتهاء المعكوس– للتيار الانبساطي في الشرايين السرية نسبة أعلى من الوفيات قبل الولادة والإصابة بالأمراض.

Objective: To evaluate the outcome of intrauterine growth restriction fetuses with absent or reversed end-diastolic flow in the umbilical artery.

Methods: This was a retrospective study conducted at the Department of Maternal Fetal Medicine of the Bakirkoy Women and Children's Teaching Hospital, Istanbul, Turkey between 2002 and 2006. Three hundred and ten pregnant women with growth-restricted fetuses confirmed by ultrasound were followed up with Doppler studies of the umbilical artery. The population was subdivided into 2 groups. Group 1, intrauterine growth restriction with positive end diastolic flow velocity waveforms, (n=137) and group 2, intrauterine growth restriction with absent or reversed end diastolic velocities, (n=163). Perinatal and neonatal outcomes of the 2 groups were recorded.

Results: Group 1 was associated with a higher perinatal mortality and morbidity rate than group 2 (*p*=0.02, odds ratio [OR]: 1.09, 95% confidence interval [CI] 1-3.5), (*p*=0.03, OR: 2, 95% CI 1.2-3.2). In group 1, significantly more neonates were admitted to the neonatal intensive care unit, but no difference was seen in neonatal intensive care unit stay. The frequency of respiratory distress syndrome, septicemia, and necrotizing enterocolitis increased in group 1. There was no significant difference in need for ventilation of respiratory distress syndrome.

Conclusion: Our data suggest that pregnancies with absent or reversed end-diastolic flow in the umbilical arteries have high perinatal mortality and morbidity.

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Intrauterine growth restriction (IUGR) characterizes the fetus that fails to reach its intrinsic growth potential and is at increased risk of perinatal morbidity and mortality. Historically, the management of IUGR has been dependent on antenatal biophysical profile and umbilical artery Doppler studies. Abnormal Doppler flow velocity with absent or reversed end-diastolic (ARED) flow in the umbilical artery (UA) is strongly associated with IUGR. Fetuses affected by this condition are at increased risk for academia and hypoxemia and significant mortality and morbidity, probably also during adult life.[1-4] The optimal timing of delivery in pregnancies complicated by IUGR is an issue of controversial debate. The use of Doppler ultrasound has helped in better management of these patients. We studied 2 different groups by IUGR: positive end-diastolic flow velocity waveforms (group 1) and absent or reversed end-diastolic velocities (group 2). The aim of this retrospective observational study was to compare perinatal and neonatal outcomes in patients with a positive end-diastolic flow, as compared to those with absent or reversed diastolic flow in the umbilical artery.

Methods. The Ethics Committee of our teaching hospital approved the study. Between 2002 and 2006, IUGR fetuses with ARED and positive end-diastolic flow velocity waveforms in the UA were examined retrospectively. Inclusion criteria were: normal fetal anatomy, estimated weight below the 10th percentile and availability of neonatal follow-up.[5] Those presenting with fetal or chromosomal abnormalities as well as multiple pregnancies were excluded. Gestational age was determined by last menstrual period and/or sonographic examination prior to 20 weeks of gestation. A 5 MHz sector–ultrasound transducer was used for ultrasound examinations (Voluson 730 Expert, General Electric Medical Systems). We assessed Doppler measurements transabdominally in a free-floating loop of the umbilical cord when the patient was in a semi-recumbent position. We used the lowest possible wall filter during measurement. All recordings were obtained in the absence of fetal breathing and fetal movements. An average of 5 consecutive Doppler velocimetry waveforms were recorded for the analysis. Oligohydramnios was defined as amniotic fluid index less than 5 cm. Doppler measurements were carried out in the umbilical artery once every 2 weeks until delivery. Fetal heart rate (FHR) patterns were obtained on a daily basis. Fetal lung maturation was accelerated by maternal application prior to time delivery (intramuscular betamethasone 12 mg, 2 doses, 24 hours apart). Doppler measurement alone was not considered an indication for delivery. Decision to deliver was taken in situations such as abnormal fetal heart rate patterns and poor biophysical profile. The FHR was considered as abnormal in case of fewer than 80 beats for more than 3 minutes, or late decelerations. Neonatal outcomes were recorded until 3 months after birth. They included diagnosis to delivery interval, gestational age at birth, and admission to neonatal intensive care unit (NICU), duration of NICU stay, neonatal morbidity, duration of hospital stay, and perinatal and neonatal mortality. Perinatal mortality was defined as intrauterine fetal death ± early neonatal death < postnatal 7th day. Neonatal mortality was defined as postnatal death 0-28 days. Neonatal morbidity was defined as the presence of a cerebral hemorrhage (stage I-IV), respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), septicemia, RDS requiring intubation, pulmonary hemorrhage, and pneumothorax.

Statistical analysis was performed using MedCalc 9.3 (www.medcalc.be, Belgium). Variation of data was evaluated visually by normal plots and statistically by Kolmogorov-Smirnov tests and analyzed according to the results by Pearson's Chi-square test, Fisher's exact test and Mann-Whitney U-test. We applied enter logistic regression to assess the relative risk for (adverse perinatal and neonatal outcomes) perinatal mortality, neonatal mortality and morbidity, and admission to NICU. Statistical significance was assumed to be $p<0.05$.

Results. We had a total of 322 patients, and 310 patients met inclusion criteria. We found ARED flow in 163 cases (absent end-diastolic flow [AED] = 117, reversed end-diastolic flow (RED) = 46). There were no differences in maternal age, gravidity, and parity between the 2 groups. The frequencies of smoking were significantly different in ARED groups. The overall incidence of severe preeclampsia was 50.3% (n=167). **Table 1** shows the clinical characteristics of mothers. **Table 2** shows perinatal and neonatal outcomes. There were no differences in gestational age at diagnosis of ARED flow or positive end-diastolic flow, but ARED flow was associated with lower gestational age at birth, 5-minute Apgar scores, birth weight, and diagnosis to delivery interval between the 2 groups. An amniotic fluid index <5 was observed significantly more often in the ARED groups (p=0.02). A significantly higher number of cesarean sections was performed in the ARED groups (p=0.005). The mean indication for cesarean delivery was severe preeclampsia and non-reassuring fetal status as determined by the FHR tracing. The overall mortality was 24.2% (75/310). The ARED flow was associated with a higher perinatal mortality rate than positive end-diastolic flow (p=0.02; odds ratio [OR]: 1.09 95% confidence interval [CI] 1-3.5). There was no difference in the frequency of neonatal and >28 days mortality. The overall neonatal

Table 1 - Maternal Characteristics.

Parameter	Group 1	Group 2	*P*-value
Maternal age (year)	28.1 (95% CI 27.2-29.1)	28.4 (95% CI 27.6-29.3)	0.66
Gravidity	2.07 (95% CI 1.8-2.2)	2.07 (95% CI 1.8-2.3)	0.45
Parity	0.8 (95% CI 0.6-1.04)	0.6 (95% CI 0.5-0.7)	0.14
Tobacco abuse, n (%)	13 (8.5)	31 (17.3)	0.01
Maternal Risk Factors, n (%)			0.0001
Gestational HT	8 (5.2)	16 (8.9)	
Mild preeclampsia	8 (11.8)	32 (17.9)	
Severe preeclampsia	72 (47.1)	45 (25.1)	
HELLP syndrome	4 (2.6)	23 (12.8)	
Chronic HT	2 (1.3)	2 (1.1)	

HT - hypertension, HELLP - hemolysis elevated liver enzymes and low platelets, 95% CI - 95% confidence interval

Table 2 - Fetal and neonatal characteristics.

Parameter	Group 1	Group 2	*P*-value
Gestational age at diagnosis (weeks)	30.8 (95% CI 30.3-31.3)	30.1 (95% CI 29.6-30.6)	0.57
Gestational age at delivery (weeks)	32.8 (95% CI 32.3-33.3)	31.3 (95% CI 30.84-31.7)	0.000*
Diagnosis to delivery internal (days)	14.1 (95% CI 11.2-17.06)	7.5 (95% CI 5.8-9.2)	0.000*
Oligohydramnios, n (%)	50 (33.3)	87 (55)	0,02
Mode of delivery, n (%)			
Cesarean section	109 (71.2)	148 (84.1)	0.005
Vaginal delivery	44 (28.8)	28 (15.9)	
Fetal weight (g)	1390.2 (95% CI 1307.9-1472.6)	1071.3 (95% CI 1011.01-1131.71)	0.000*
5 minute apgar	7.3 (95% CI 6.9-7.7)	6.5 (95% CI 6.07-7.09)	0.02
5 minute apgar <7, n (%)	25 (17.2)	38 (24.1)	0.14
Neonatal morbidity, n (%)	42 (28.2)	75 (44.1)	0.03
Mortality, n (%)	24 (16.3)	51 (31.3)	0.02
Perinatal	20 (13.6)	38 (23.3)	0.02
Neonatal	9 (6.1)	20 (12.3)	0.06
Postnatal (0-3 month)	11 (7.5)	26 (16)	0.02
>28 days	3 (2.0)	6 (3.4)	0.42
Admission to NICU, n (%)	21 (14.1)	51 (30.5)	0.01
NICU stay (days)	9.6 (95% CI 5.2-13.9)	12.3 (95% CI 8.3-16.4)	0.42
Hospital stay (days)	14.9 (95% CI 21.2-28.7)	25 (95% CI 21.2-28.7)	0.000*

NICU - neonatal intensive care unit, *-p<0.001

Table 3 - Follow-up neonates in neonatal intensive care unit.

Parameter	Group 1	Group 2	OR	95% CI	*P*-value
Respiratory distress syndrome (RDS)	27 (18.1)	54 (32)	2.1	1.2-3.2	0.005
Intubation	15 (10.2)	26 (15.9)	1.6	0.8-3.2	0.14
Duration of intubation (days)	6.4 (95% CI 2.5 10.3)	4.6 (95% CI 2.8 - 6.3)			0.30
Septicemia	21 (14.3)	39 (23.8)	1.8	1.04-3.3	0.03
Necrotizing enterocolitis (NEC)	7 (4.7)	21 (12.7)	2.9	1.2-7.1	0.01
Intraventricular hemorrhage (stage I – IV)	6 (4.1)	9 (5.5)	1.3	0.4-3.9	0.60
Bronchopulmonary dysplasia (BPD)	4 (2.7)	5 (3.1)	1.1	0.2-4.2	0.85
Pulmonary hemorrhage	1 (0.7)	5 (3.1)	4.6	0.5-40	0.21
Pneumothorax	3 (2)	2 (1.2)	0.5	0.09-3.6	0.67

OR- odds ratio, 95% CI - 95% confidence interval

morbidity was 36.7%. The risk of neonatal morbidity was increased in pregnancy complicated by ARED flow (p=0.03; OR: 2, 95% CI 1.2-3.2). In the ARED group, significantly more neonates were admitted to the NICU, but no difference was seen in NICU stay. The frequency of RDS, septicemia, and NEC increased in the ARED flow group. There was no difference in need for ventilation of RDS. **Table 3** shows neonatal outcomes. Logistic regression analysis confirmed that birth weight showed the strongest association with perinatal death (p=0.013), whereas birth weight was significantly related to neonatal mortality and morbidity (p=0.018; p<0.0001). Abnormal UA Doppler waveforms (p=0.03), birth weight (p=0.008), and oligohydramnios (p=0.03) were strongly associated with admission to NICU. Birth weight was associated with adverse neonatal outcomes (including RDS, NEC, and IVH), whereas oligohydramnios was related to RDS (p=0.003).

Discussion. Intrauterine growth restriction is a frequent clinical problem and a major cause of perinatal and/or neonatal mortality and morbidity. Optimal management of the pregnancy complicated by IUGR remains unclear. Umbilical artery Doppler velocimetry has been clearly shown to reduce perinatal mortality when used as an adjunct to other means of prenatal testing.[6] The use of Doppler ultrasound in high risk pregnancies to assess UA waveforms studies was associated with a 29% reduction in perinatal mortality and resulted in a reduction of antenatal admissions, induction of labor, and cesarean sections for fetal distress.[7,8] In this study, fetuses with ARED flow in the UA had an adverse fetal outcome more often than positive end-diastolic flow. Fetuses with ARED flow in the UA had at an extremely high-risk of perinatal mortality, as compare to fetuses with positive end-diastolic flow. The perinatal mortality rate of 23.3% in the ARED flow is similar to Gerber et al.[9] We found that from ARED flow pregnancies had a higher risk of developing RDS (OR 2.1), septicemia (OR 1.8), and/or NEC (OR 2.9). The severity of perinatal and neonatal complications related to gestational age at delivery and birth weight. In the ARED groups, gestational age at birth and birth weight were lower than the positive end-diastolic flow groups (**Table 2**). The earlier detection of abnormal flow and FHR patterns, as well as the development of maternal preeclampsia, was the indication for delivery. The Growth Restriction Intervention Trial (GRIT)[10] studied the topic of optimal timing of delivery in IUGR fetuses monitored by FHR patterns and UA Doppler analysis. There was no significant difference between infants who had been delivered immediate delivery group and those with delayed delivery with regard to the short-term outcome. In our study, those fetuses with positive end-diastolic flow in the UA were managed expectantly by monitoring UA flow and FHR as main parameters for clinical decision-making. As expected, a high correlation was found between abnormal flow velocimetry in the UA Doppler and birth weight (p<0.0001). Birth weight was significantly related to adverse perinatal and neonatal outcomes. The presence of abnormal UA Doppler studies was associated with earlier delivery (p<0.0001). Several studies have found that small for gestational age babies with abnormal UA Doppler studies are smaller and their mothers were delivered earlier than those with normal UA Doppler studies.[11,12] Cosmi et al[13] reported that neonatal death was increased in the fetuses with ARED flow. They also concluded that fetuses with IUGR, low birth weight and ARED, had increased perinatal morbidity and mortality. Our study found a significantly higher frequency of neonatal morbidity in the ARED group, including RDS, NEC, and septicemia, but no difference was found in the incidence of RDS needed in ventilation. Logistic regression analysis showed that the frequency of RDS and NEC was not influenced by ARED flow. The higher frequency of RDS in the ARED flow group may be explained by the lower gestational age at delivery in the group. We found an association between ARED flow in IUGR and NEC. These results confirm observations of other matched control studies.[14,15] During abnormal placental perfusion a redistribution of fetal cardiac output is needed to maintain an adequate supply of oxygen and nutrients to vital organs, resulting in increased blood flow to the heart and brain at the cost of less vital organs, such as kidneys and bowels.[16] Owing to this reduction we expected an increase in frequency of NEC.[17,18] There have been reports about an association between abnormal Doppler flow and neonatal hemorrhage.[19,20] In fetuses with a comprised UA diastolic flow, an extremely low cerebral artery vascular resistance exists and sudden cerebral hyperperfusion may occasionally occur, leading to cerebral hemorrhage.[21] We did not detect a significantly different incidence of neonatal cerebral hemorrhage between ARED flow and positive end-diastolic flow groups.

Our study has several limitations. We could not observe the ductus venosus flow velocity waveform in this study. However, Müller et al[22] and Schwarze et al[23] reported that growth-restricted fetuses with umbilical absent or reverse end-diastolic flow velocities, determination of blood flow velocities in the ductus venosus is a useful additional parameter for prediction of fetal outcome and for timing delivery. Long-term follow-up of IUGR infants suggests that they continue to be at a disadvantage regarding cognitive delays and behavioral problems, which are reflected in decreased academic achievement throughout childhood.[24,25] However, in this study we could not mention to long-term neurologic outcomes.

In conclusion, we showed that IUGR fetuses with ARED flow were admitted more frequently to the neonatal intensive care unit than those IUGR fetuses who have normal Doppler velocimetry in the UA. Doppler blood flow velocity studies can help us in timing the delivery of an IUGR fetus. In the presence of normal UA Doppler velocimetry, the examinations should be repeated weekly, as the women with normal Doppler findings had low perinatal and neonatal outcomes. When there is absent or reversed flow of the umbilical artery, it is safer to deliver the fetus for a better perinatal outcome, as perinatal mortality was higher in the ARED flow groups.

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