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Comparing Fetal Arteries' Doppler Ultrasound Pulsatility Indexes Premature Preterm Rupture of Membrane in Admission and Pregnancy Termination

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ABSTRACT

Background & Objective: Premature preterm rupture of membrane (PPROM) is a cause of preterm birth. This study investigated the effectiveness of Doppler ultrasound in predicting fetal complications and neonatal outcomes of pregnant women with PPROM.

Materials & Methods: In this cross-sectional study, a total of 23 pregnant women with PPROM were chosen in their 24 to 34 weeks of gestational age. The fetuses' blood flow indices were evaluated by Doppler ultrasound pulsatility index (PI) in the middle cerebral, main pulmonary, right kidney, and fetal umbilical arteries and descendingaorta at admission (because of PPROM) and 24 hours before delivery, respectively. Neonatal outcomes were assessed within the first week of birth.

Results: The kidney artery PI increased (P=0.047) and pulmonary artery PI decreased (P=0.024) at pregnancy termination time. There was a negative correlation between the 5-minute Apgar score and fetal umbilical artery PI at admission (P=0.003) and pregnancy termination times (P=0.031). The fetal umbilical artery PI of neonates with abnormal brain ultrasound imaging results significantly decreased at admission (P=0.002) and pregnancy termination times (P=0.004).

Conclusion: Fetal artery Doppler ultrasound PI may be a valid tool for predicting neonatal outcomes of women with PPROM.

Keywords: Preterm premature rupture of membranes, Doppler indices, Neonatal outcomes



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Introduction

Preterm birth is a major cause of perinatal morbidity and mortality worldwide (1). Microbial infections of the amniotic cavity occur in pregnancies with preterm premature rupture of membranes (PPROM), 30% during hospital stay and 75% at preterm labor time (2-4). Intrauterine infections, either symptomatic or asymptomatic, induce inflammatory responses, releasing cytokines and chemokines that are known as fetal inflammatory response syndrome (FIRS). This syndrome has multiorgan involvement, causing histological chorioamnionitis, uterus contraction, and membrane rupture (2, 5-7).

The PPROM is associated with the risk of neonatal pulmonary hypoplasia, extremity abnormalities,

perinatal morbidity and mortality, and maternal morbidity (8). Also, studies have shown that most preterm infants who die from hypoxic failure after PPROM have significantly lower lung weights and impaired morphologic maturation of the lung. In addition, these infants have reduced airspaces and elastin (9).

Terminating pregnancy (abortion) before 34 weeks of gestational age is suggested in cases of intrauterine infection and possibility of adverse maternal and neonatal outcomes (2, 8); however, the infection cannot be diagnosed with the conventional and non-invasive methods. Hence, 27.3% of PPROM cases include septic infants who are born after 34 weeks of

gestational age due to the lack of early detection and treatment (10-12). Since there is evidence of abnormality in the arterial tone regulation under pathological conditions (13-15), intrauterine infections may have adverse effects on cardiac, cerebral, pulmonary, and kidney functions in at-risk fetuses (16).

Almost 50% of PPROM cases develop FIRS (2). Several studies have examined the effect of this syndrome on organ function to identify alarming changes and predict intrauterine inflammation and infection complications (14-21). A noninvasive and prenatal diagnosis of FIRS can be valuable in clinical management of the PPROM adverse outcomes (8, 22, 23). Therefore, this study investigated the effectiveness of Doppler ultrasound in predicting fetal complications and neonatal outcomes of pregnant women with PPROM as a noninvasive diagnosis approach.

Materials and methods

A total of 23 pregnant women with PPROM were chosen for this cross-sectional study at their 24 to 34 weeks of gestational age. All subjects were admitted to a university hospital in Tehran, Iran between January 2016 and January 2017. This study was approved by the ethics committee of Tehran University of Medical Sciences. Amniotic membrane rupture was defined as pooling on the speculum examination or a positive AmniSure test (in the absence of significant bleeding that may cause false positive results) in patients with a history of membrane rupture.

There were four exclusion criteria as follows: a) infants with intrauterine growth restriction (defined as estimated fetal weight below the 10th percentile); b) presence of major central nervous system, kidney, abdominal visceral, and pulmonary anomalies; c) clinical evidence of chorioamnionitis at PPROM diagnosis time; and d) being in the labor phase starting from the first 48 hours of hospital stay.

Patients with PPROM received corticosteroid therapy including two dosages of 12 mg betamethasone on two consecutive days. Antibiotic treatment was continued for a period of 48 hours with intravenous ampicillin (2 gr stat then 2 gr four times a day) followed by oral amoxicillin (500 mg three times a day) and erythromycin (400 mg four times a day) for seven days. Magnesium sulfate was prescribed for infants aged 24 to 32 weeks for neuroprotection up to 12 hours.

1. The first Doppler ultrasound imaging examination (Zimens, Acuson Antares, USA) was done with an abdominal convex probe (2-6 MHz) after PPROM was diagnosed and before starting betamethasone administration or 48 hours after the last dosage to eliminate any of its possible effects on Doppler ultrasound imaging indexes. The pulsatility index (PI) (24) was investigated in the middle cerebral, main pulmonary, right kidney, and fetal umbilical

- arteries and descending aorta. All indexes were recorded by an expert operator.
- 2. Doppler ultrasound imaging was done in the fetus' apnea situation and its absence of movement. The kidney artery was evaluated in the axial view at its entrance to the right parenchyma (insolation angel < 30° and Doppler gate 1.5-2 mm). Other arteries included the descending aorta at the diaphragm level, the main pulmonary artery in the three-vessel view (insolation angel < 30° and Doppler gate 2.5-3 mm), and middle cerebral artery at a distance of 2 mm from the middle cerebral artery's origin in the Willis circle, proximal to the probe, (insolation angel < 30° and Doppler gate 1.5 2 mm).

The indications for pregnancy termination were: 1) being in the 34 weeks of gestation; 2) chorioamnionitis clinical evidence that was defined as maternal fever (> 38° C in two 4-hour sets) in combination with leukocytosis > $15000/\mu$ L, or purulent discharge and suprapubic tenderness or maternal or fetal tachycardia; and 3) fetal distress proven by an abnormal non-stress test (category 3) and impaired biophysical profile.

Doppler ultrasound indices were re-evaluated within 24 hours before pregnancy termination in each patient or in urgent cases at the termination time, and were compared with the admission time results. Neonatal outcomes, including the birth weight and Apgar score were recorded. Neonatal complications, such as respiratory distress, early sepsis evidence, and central nervous system complications were evaluated within the first week of birth. In all neonates, respiratory distress was diagnosed by the Downs' scoring system (24). Early sepsis was confirmed by positive results of three consecutive blood cultures obtained immediately after birth. The central nervous system complications were examined by brain ultrasound imaging. Doppler shift in each patient was compared with neonatal outcomes. Written consent was obtained from all patients before their enrollment in the study.

Statistical analysis

The statistical package for social sciences (SPSS Inc., Chicago, Ill., USA) version 17.0 was used for data analysis. Paired T-test was used to compare fetal arteries' Doppler ultrasound imaging indices at admission and pregnancy termination times. Pearson correlation test was used to investigate the relationship between quantitative variables in which r > 0 indicated a direct relationship and r < 0 indicated an indirect correlation. Bootstrap independent samples test was used for low numbered, normally distributed groups' analysis and comparing Doppler ultrasound indexes, including one case of sepsis with non-sepsis cases and eight respiratory distress syndrome cases with non-respiratory distress syndrome cases. P-values less than 0.05 were considered significant.

Results

A total of 23 pregnant women in 24 to 34 weeks of gestational age were enrolled. Elective pregnancy termination was done for nine cases at 34 weeks of gestation (<u>Table 1</u>). In the remaining 14 cases that

terminated their pregnancy before 34 weeks of gestation, nine cases had labor pain and five cases had fetal distress, non-stress test category 3, or placental abruption. The mean latency period was 1.53 weeks in 23 fetuses.

Table 1. Demographic characteristic of 23 PPROM cases

		Mean	Standard Deviation
Estimated Weight at admission (25)		1558.43	498.05
Amniotic Fluid Index (cm)		5.90	2.78
Gestational age at admission (week + day)		30.93	2.30
Birth weight (25)		1828.73	435.52
Gestational age at birth (week + day)		32.46	2.30
Apgar 1 minute		7.91	2.04
Apgar 5th-minute		9.13	1.86
		Frequency	percent
Gender	male	10	43.5
	female	13	56.5
Delivery type	Cesarean section	6	26.1
	Normal vaginal delivery	17	73.9
Early neonatal	yes	1	34.7
Sepsis	no	22	90/5
IVH	yes	2	8.7
	no	21	91.3
RDS	yes	9	8.7
	no	14	91.3

The latency period of all cases based on neonatal complications is shown in <u>Table 2</u>. As the Apgar scores were not normally distributed, the median and 25, 50,

and 75 percentiles for 1-minute Apgar were 9, 8, 9 and 9, respectively; also for 5-minute Apgar scores were 10, 9, 10, and 10.

Table 2. Latency period of all cases in separation of neonatal complications.

Complication	Number of neonates	Latency period (day)
IVH grade 4	1	9
IVH grade 1	1	7
RDS	9	10
Sepsis	1	10
Healthy neonates	11	11.6

Table 3. Differences in Pulsatility index of Doppler parameters for RDS cases and non-RDS cases, *: P<0.05

	Mean Difference	SD	95% Confidence Interval		Dandar
			Lower	Upper	P-value
Admission MCA PI	1.91	0.54	- 0.435	0.4790	0.812
Termination MCA PI	1.74	0.26	- 0.496	0.098	0.188
Admission Aorta PI	1.89	0.31	- 0.366	0.188	.406 •

Admission UMA PI

Termination UMA PI

		_			
	Mean Difference	SD	95% Confidence Interval		P-value
			Lower	Upper	r-value
Termination Aorta PI	1.80	0.20	- 0.420	0.028	.178 •
Admission renal artery PI	1.93	0.24	- 0.632	0.062	0.139
Termination renal artery PI	1.63	0.42	74459	07386	.040**
Admission Pulmonary artery PI	2.60	0.41	- 0.524	0.130	0.307
Termination Pulmonary artery PI	2.76	0.44	- 0.499	0.193	.525 •

0.18

0.29

0.158

- 0.238

1.08

0.92

Key: MCA: middle cerebral artery; UMA: fetal umbilical artery; SD: standard deviation

Discussion

PPROM is the common cause of preterm labor and prematurity (26, 27). After its diagnosis, treatment and decision on pregnancy termination time can have a major influence on the neonatal outcome. The decision regarding the pregnancy termination of women with PPROM is made based on their health status at 34 weeks of gestation, evidence of chorioamnionitis, and intrauterine fetal distress (28-30). Few studies have examined different methods of fetal health assessment to improve maternal and neonatal outcomes; but none of them have reached firm conclusions on how to use these methods to predict outcomes (2, 5, 13). Using fetal assessment methods may lead to early detection of intrauterine infection that has a significant impact on maternal and neonatal outcomes; however, if these methods are not accurate, they can have devastating effects on the outcome by causing preterm birth (3).

A review article evaluated three studies that had used non-stress test, biophysical profile, and vaginal ultrasound imaging for fetal health assessment, but failed to show their impact on the outcome (3). Appropriate blood flow via umbilical cord and fetal arteries has a critical role in prenatal development. Vascular tone regulates this flow and some mediators can change this tone such as nitric oxide, prostacyclin, and thromboxane A₂, which are basically produced during inflammatory processes. Prenatal changes in systemic homodynamic can be evaluated via Doppler ultrasound imaging (31).

In our study, variation in the fetal artery Doppler ultrasound imaging as a noninvasive method was evaluated as a possible method for predicting intrauterine complications and appropriate pregnancy termination time.

Generally, among the 23 cases studied in this study, a significant increase in the kidney artery PI was seen at pregnancy termination time compared to the admission time. According to kidney artery resistance curves, the PI decreases with an increase in the gestational age (32). Similarly, a significant reduction was observed in the

pulmonary artery PI at pregnancy termination time in our patients compared to admission time. This is not consistent with studies that had reported increased pulmonary artery PI with an increase in the gestational age (24). This significant inverse relationship requires further investigation because it may be due to the effect of cytokines on the vascular tone. According to a study, chorioamnionitis, elevated pro-inflammatory and inflammatory cytokine concentrations, and cytokine-associated systemic hemodynamic disturbances in premature infants born after chorioamnionitis can expose infants to many complications (33).

0.158

0.195

0.028*

1.000

The negative correlation between the umbilical artery PI and the 5 minute Apgar score may be due to the lower gestational age in neonates with a higher umbilical artery PI; therefore, future studies should evaluate fetuses at the same gestational age to investigate the relationship between umbilical artery resistance and Apgar score.

Sepsis was confirmed in one neonate who died one day after birth. Through comparing this neonate with other neonates the following results might be reported:

- 1. In this case PPROM occurred at 27 weeks and 4 days of gestational age and pregnancy was terminated at 29 weeks of gestation. According to normal curves (34), a higher level of middle cerebral artery PI was expected in this patient compared to the mean levels of other patients while the PI showed a significant decrease at admission and pregnancy termination times.
- The resistance of the descending aorta does not change at different gestational ages, but a significant decrease in the descending aorta PI in this infant at the time of admission and termination is an interesting finding.
- 3. A reduction in the kidney artery PI was reported with an increase in the gestational age (34); in addition, the kidney artery PI at pregnancy termination time in this patient showed a

- significant decrease in comparison with other neonates at a higher gestational age
- 4. Although we expected an increase in the main pulmonary artery PI with an increase in the gestational age based on normal curves (35), we witnessed a significant decrease in this index at pregnancy termination time
- 5. We found a noticeable reduction in the termination of fetal umbilical artery PI in this 29-week-old fetus compared to other fetuses with a higher gestational age. These changes in Doppler ultrasound imaging indexes in sepsis should be considered in future studies to develop a method to predict sepsis in PPROM fetus. This is maybe due to the vasodilator effect of released cytokines during sepsis.

The kidney artery PI showed a significant decrease in nine respiratory distress cases at pregnancy termination time compared to the admission time; however, there were no obvious changes in the main pulmonary artery PI index. Normally, the kidney artery PI decreases with an increase in the gestational age (32); therefore, its decrease is considerable in fetuses that later develop respiratory distress compared to fetuses without this complication. This may also be due to the effect of inflammatory cytokines. However, sepsis was not proved in these neonates. Similarly, in two neonates with intraventricular hemorrhage (grades 1 and 4) a significant decrease was seen in the umbilical artery PI after PPROM diagnosis and at the end of pregnancy in comparison with other fetuses; however, no significant changes were observed in middle cerebral artery PI.

According to our results, fetal artery's Doppler ultrasound imaging assessment and variations in kidney and umbilical artery PI may predict occurrence of neonatal complications, such as respiratory distress and intraventricular hemorrhage. Since these complications can be influenced by multiple factors, further investigations are needed to clarify the pathophysiology and reproducibility of these findings. The main limitation of this study was its relatively small sample size. As far as the researchers investigated, there were no similar studies in the literature; hence, it is recommended that future studies evaluate this subject more comprehensively and report their own results.

Conclusion

Preterm birth because of PPROM results in many adverse neonatal outcomes; therefore, its early detection is effective in prevention of intrauterine complications and appropriate management of pregnancy termination. We found correlations between changes in the fetal arteries' Doppler ultrasound imaging indexes and neonatal outcomes; variations in the PI of this noninvasive method can be used for accurate prediction of neonatal outcomes of women with PPROM.

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Compliance with Ethical Standards

Disclosure of Conflict of interest

The authors declared that they have no conflict of interest.

Research Involving Human Participants

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from all participants with assurance of confidentiality and anonymity of the data.

Conflict of Interest

Authors declared no conflict of interests.

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