Blood flow velocity waveforms from fetal peripheral pulmonary arteries in pregnancies with preterm premature rupture of the membranes: relationship with pulmonary hypoplasia

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ABSTRACT

Objectives To measure fetal peripheral pulmonary artery velocity waveforms by Doppler ultrasonography in pregnancies complicated by premature rupture of membranes under 24 weeks’ gestation and to relate the Doppler indices to the development of fetal pulmonary hypoplasia.

Design A prospective longitudinal study of fetal peripheral pulmonary artery velocity waveforms from premature rupture of membranes to delivery.

Subjects Twenty pregnancies complicated by premature rupture of membranes before 24 weeks of gestation and delivering after 26 weeks.

Methods Peripheral pulmonary artery velocity waveforms were recorded by Doppler technique at weekly intervals until delivery and Pulsatility Index (PI) calculated. Pregnancies were managed conservatively according to an institutional management protocol. Pulmonary hypoplasia was defined at autopsy by lung/body weight ratios and radial alveolar counts. Pulsatility Indices of fetuses developing pulmonary hypoplasia were compared with those with a normal lung development.

Results After premature rupture of membranes PI values were higher than normal reference limits for gestation, but no differences were found between the six fetuses which developed pulmonary hypoplasia and the remaining 14 fetuses with normal lung development. In this latter group PI values progressively decreased with advancing gestation (ANOVA for repeated measurements F = 11.61; P ≤ 0.001), while they increased in fetuses developing pulmonary hypoplasia (F = 8.44; P ≤ 0.001). As a consequence of these opposite trends significant differences in PI values were present between the two groups of fetuses from 2 weeks after the premature rupture of membranes. Two weeks after the premature rupture of membranes a PI value from the peripheral pulmonary arteries above the 95th centile had a sensitivity of 62.5%, specificity of 94.6%, positive predictive value of 83.3%, negative predictive value of 78.5% and relative risk of 3.88 (95th confidence interval 1.34–11.28) for the prediction of pulmonary hypoplasia.

Conclusion The measurement of peripheral pulmonary velocity waveforms may help to establish the risk of developing pulmonary hypoplasia in pregnancies complicated by premature rupture of membranes.

INTRODUCTION

Pregnancy complicated by premature rupture of membranes (PROM) in early gestation carries a significant risk of perinatal mortality and pulmonary hypoplasia is the major contributor to this poor outcome. As a consequence methods able to identify prenatally pulmonary hypoplasia are highly desirable in clinical practice.

Several ultrasonographic biometric indices of fetal lungs and chest have been proposed in the past to predict pulmonary hypoplasia, but none of these parameters has reached the diagnostic efficiency useful for the clinical management of these pregnancies.

Recently the fetal pulmonary vasculature has been studied by Doppler ultrasound. Although there are still some discrepancies in the literature regarding the changes occurring during pregnancy in lung hemodynamics, several authors have reported progressive changes in blood flow velocity waveforms occurring with advancing gestation, suggesting a relationship between vascular lung development and Doppler indices.

Since fetuses with hypoplastic lungs have a poorly developed pulmonary vasculature, we hypothesized...
that Doppler assessment of fetal peripheral lung circulation might be useful in identifying pulmonary hypoplasia.

To this end we measured blood flow velocity waveforms from fetal peripheral pulmonary arteries (PPA) in 20 pregnancies complicated by early PROM and we related the Doppler parameters to the presence of lethal pulmonary hypoplasia.

MATERIALS AND METHODS

Study population
The study population consisted of 20 patients selected from those admitted to our institution with the diagnosis of PROM < 24 weeks of gestation between January 1995 and December 1998. During the study period 43 women were admitted with this diagnosis. Among this population, 22 patients met the entry criteria; two were lost to follow-up and thus excluded, leaving 20 patients for the study. Premature rupture of membranes was defined in the presence of obvious leakage of amniotic fluid passing from the cervical os on sterile speculum examination or in the presence of pooling of amniotic fluid in the posterior fornix which showed a positive result to both ferning and nitrazine paper reaction tests. The presence of oligohydramnios was confirmed by ultrasound in all cases. Oligohydramnios was defined as an amniotic fluid index (AFI) ≤ 30 mm. The presence of a cord-free amniotic fluid pocket was confirmed by color Doppler ultrasonography in all cases.

Criteria of inclusion in the study were: (1) singleton gestation with a certain gestational age confirmed by first or early second trimester ultrasonographic examination; (2) absence of fetal anomalies; and (3) pregnancy continuing at least until 26 weeks of gestation. All patients gave their informed consent before entering into the study. Lethal pulmonary hypoplasia was defined at autopsy by a lung/body weight ratio < 0.012 and/or a radial alveolar count < 4.113.

Ultrasound examination
At admission all patients underwent a detailed ultrasound examination, including evaluation of fetal biometry and study of fetal anatomy. Commercially available color and pulsed Doppler ultrasound equipment with a 3.5–5 MHz multifrequency probe (Ansaldo Esaote, Idea AUC 4, Ansaldo Esaote AU 5) was used in all cases.

Doppler recordings from PPA were performed at admission and then repeated using the same equipment at weekly intervals until delivery. The Doppler carrier frequency ranged from 2.5 to 5 MHz. The high-pass filter was set at 100 Hz. This level of high pass filter was selected to avoid interference in the Doppler waveform from the vein or from noise.7–9

The techniques used to record peripheral velocity waveforms have been previously described in detail elsewhere.8 Briefly the fetal chest was imaged in a transverse section at the level of the four-chamber view of the heart. Color flow mapping was then activated over the fetal lung using the power Doppler imaging option. The sample volume of the pulsed Doppler (2 mm) was then placed in the most peripheral area of the fetal lung where vessels were evidenced. Velocity waveforms were recorded from PPA and vein. From this section characteristic velocity waveforms were recorded, characterized by a needle-shaped systolic peak followed by a more gradual decline in velocity waveforms (Figure 1). Care was taken to keep the angle of insonation between the Doppler beam and blood flow direction as low as possible. All the recordings were performed by two of the authors (G.R. and A.C.). The inter- and intraobserver coefficients of variation were 13.8% and 11.3%, respectively.8

Doppler images were video recorded for subsequent
Table 1  Characteristics of the 20 pregnancies studied stratified according to the presence or absence of lethal pulmonary hypoplasia at birth

<table>
<thead>
<tr>
<th>Present (n = 6)</th>
<th>Absent (n = 14)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>28.6 ± 2.9</td>
<td>29.3 ± 3.5</td>
</tr>
<tr>
<td>Parity</td>
<td>1.4 ± 0.8</td>
<td>1.3 ± 0.7</td>
</tr>
<tr>
<td>Gestational age at PROM (weeks)</td>
<td>20.37 ± 1.94</td>
<td>20.13 ± 1.75</td>
</tr>
<tr>
<td>Interval: PROM– delivery (days)</td>
<td>67.16 ± 11.82</td>
<td>77.0 ± 15.53</td>
</tr>
<tr>
<td>Antenatal use of tocolytics: n (%)</td>
<td>5 (83.3%)</td>
<td>11 (78.6%)</td>
</tr>
<tr>
<td>Antenatal use of corticosteroids: n (%)</td>
<td>4 (66.7%)</td>
<td>8 (57.1%)</td>
</tr>
<tr>
<td>Gestational age at delivery (weeks)</td>
<td>29.97 ± 1.75</td>
<td>31.13 ± 1.60</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>1320 ± 312</td>
<td>1534 ± 423</td>
</tr>
</tbody>
</table>

analysis. Permanent records were obtained from the videotape by means of a strip chart recorder and labelled with random numbers. Ten consecutive heart cycles were selected during periods of fetal rest without breathing movements and the values measured were averaged. The PI (PI = (Systolic velocity–diastolic velocity)/mean velocity)\(^{14}\) was calculated with the aid of a computer-interfaced digitizer pad (Cardio 800, Kontron, Oxford, UK) by an investigator unaware of the sequence of the printouts.

Patients’ clinical management

After admission patients were followed by the attending physicians according to the following management protocol. Patients were restricted to bed rest with bathroom privileges and counselled to remain in the hospital until delivery. Ultrasonographic assessment was performed at weekly intervals. Fetal heart monitoring and uterine activity assessment were performed from 26 weeks onwards, at least daily, until delivery. Digital examinations were prohibited in the absence of labor with visual evidence of cervical changes. Patients received prophylactic antibiotics as clavulanic acid 1 g orally every 12 h (in the event of penicillin allergy, erythromycin 500 mg orally every 6 h) from admission to delivery. Tocolytic (intravenous ritodrine) and steroid (betamethasone 12 mg intramuscularly repeated after 24 h) therapies were used at the discretion of the individual physician. Delivery was carried out in the presence of clinical chorioamnionitis, fetal distress at fetal heart monitoring and at a gestational age > 32 weeks of gestation.

Data analysis

Peripheral pulmonary artery PIs were plotted against our reference range for gestation which was previously constructed from the cross-sectional study of 164 normal fetuses. Since PI values change with advancing gestation, data are also expressed as the number of standard deviations from which they differ from the expected mean for gestation (delta values). Comparison between PPA PI values obtained in pregnancies complicated by PROM and our normograms, and between fetuses which developed or did not develop pulmonary hypoplasia were performed using paired and unpaired t-tests after controlling the normal distribution of data with the Shapiro–Wilk W-test. Serial changes in PPA PI were evaluated by using the ANOVA for repeated measurements with Tukey post-hoc analysis. Sensitivity, specificity, positive and negative predictive values and relative risk of PPA PI in predicting pulmonary hypoplasia were calculated at various weekly intervals from PROM. Comparison between the characteristics of the two groups of fetuses which developed or did not develop pulmonary hypoplasia were performed by the Mann–Whitney U-test or the unpaired t-test. A P ≤ 0.05 was considered significant.

RESULTS

Six of the 20 fetuses studied developed lethal pulmonary hypoplasia. The median alvear count was 3.2 (range 2.6–3.7) and the lung/body weight ratio 0.010 (range 0.009–0.0128). Two fetuses had borderline values of lung/body weight ratio (0.0124 and 0.0128) due to edema and hyaline membrane disease, but their alveolar count was 3.1 and 2.8, respectively. When these fetuses were compared to the remaining 14 which did not develop pulmonary hypoplasia no significant differences were found in maternal characteristics, gestational age at PROM, duration of pregnancy after PROM and gestational age at birth as indicated in Table 1. In this latter group three newborns died during the first weeks of life, from sepsis in two cases and massive hemorrhage in one case.

There were no significant differences in AFI values in fetuses which developed pulmonary hypoplasia and those with normal lung development at admission (lung hypoplasia: median 18, range 0–30; normal lung development: median 19.5, range 0–39; z = 0.900; P = 0.125) or before birth (lung hypoplasia: median 12.5, range 0–31; normal lung development: median 20, range 0–39; z = 1.035; P = 0.300). The antenatal use of corticosteroids as well as of tocolysis was similar between the groups (Table 1).

Successful recordings from PPA were obtained in all the fetuses. At admission the PI values from PPA were significantly higher in fetuses with PROM when compared to normal reference limits (Figure 2). This occurred both in fetuses which developed lethal pulmonary hypoplasia (delta value = 1.69, t = 9.4, P ≤ 0.002) and in the remaining fetuses (delta value = 1.74, t = 13.73 P ≤ 0.001) (Figure 3). However, no significant differences were found in delta PI values in PPA at admission when fetuses with PROM which developed or did not develop pulmonary hypoplasia were compared (t = 0.22, \(P = 0.827\)) (Figure 2).

ANOVA for repeated measurements demonstrated a significant decrease in PPA PI values during gestation in
fetuses which did not develop pulmonary hypoplasia ($F = 11.61; P \leq 0.001$). The values obtained at the last recording before delivery were significantly lower than those obtained at the first recording (mean paired difference in delta value $= -1.11, P \leq 0.0003$) (Figure 2). On the other hand a significant increase was found in PPA PI values in fetuses developing pulmonary hypoplasia ($F = 8.44, P \leq 0.001$) and higher PPA values were present at the last recording when compared to first recording (mean paired difference in delta value $= 1.02, P \leq 0.005$).

As a consequence, 2 weeks after PROM PPA PI delta values were significantly higher in fetuses which developed lethal pulmonary hypoplasia than in the remaining fetuses with PROM ($t = 4.49; P \leq 0.001$). This difference remained significant until the last recording before delivery ($t = 4.80, P \leq 0.001$) (Figure 3).

Thus a value of PPA PI above the 95th centile 2 weeks after PROM had a sensitivity of 62.5%, specificity of 94.6%, positive predictive value of 83.3%, negative predictive value of 78.5% and relative risk of 3.88 (95th confidence interval $1.34–11.28$) for the prediction of pulmonary hypoplasia.

**DISCUSSION**

Premature rupture of membranes before 24 weeks of gestation is associated with a poor perinatal outcome. Although we selected a subgroup of pregnancies which delivered after 26 weeks of gestation, nine out of the 20 fetuses died, and in six of them the death was secondary to pulmonary hypoplasia. These findings confirm the results of previous studies and underscore the importance of identifying patients who are more likely to develop a normal lung function from the group with early PROM.

In this study we found that at admission fetuses of pregnancies complicated by PROM had PPA PI values significantly higher than control fetuses. At this time no differences were present between fetuses which would develop pulmonary hypoplasia and those with normal lung development. However, with the progression of gestation PPA PI values changed, with the trend varying according to lung development. Indeed, in fetuses developing lung hypoplasia PPA PI values progressively increased, while in fetuses which did not develop this complication PPA PI values decreased. As a consequence fetuses developing pulmonary hypoplasia presented significantly higher PPA PI values from 2 weeks onwards after PROM.

The causes of these changes in PPA PI are unclear. Furthermore, the intrauterine environment does not allow differentiation between factors that might influence PI values such as the volume flow to the lung, vascular tone and vascular cross-sectional area. The lack of differences at the first recording between fetuses which will develop pulmonary hypoplasia and those with normal lung function suggests that the increased PI values in fetuses with PROM are secondary either to a raised vascular tone or to a reduced volume flow to the lung. Changes in the balance between intrathoracic and intrauterine volumes and pressure secondary to oligohydramnios may explain these findings. Moreover the different trends found in the following recordings may be explained by a different development of lung vasculature. In normal lung, intrapulmonary arteries assume their definitive branching pattern by 16 weeks of gestation and then progressively ramify and merge, dramatically increasing the cross-sectional pulmonary vascular area. This may explain the decrease of PI values occurring with advancing gestation in normal fetuses as well as in fetuses with PROM which do not develop lung hypoplasia. The increase in PI found in fetuses with pulmonary hypoplasia may be explained on the basis of an abnormal vascular development occurring with this disease. Indeed, postmortem studies have shown that lung hypoplasia is characterized by a decreased size of the pulmonary vascular bed, reduced vessel count per unit of lung tissue and an increased muscularization in peripheral vessels.

An alternative explanation of the difference in PI values in fetuses with pulmonary hypoplasia may be due to...
measurement being made in a less peripheral section of the pulmonary circulation secondary to the smaller dimensions of the hypoplastic lungs. However, this hypothesis seems unlikely since care was taken to record velocity waveform from the most peripheral area of the fetal lung in both groups.

Irrespective of the underlying mechanism our data show that after 2 weeks of PROM it is possible to predict pulmonary hypoplasia. Indeed at this time interval a PI value above the 95th centile is associated with an increased risk of developing pulmonary hypoplasia.

This observation is in agreement with the data of Mitchell et al.\textsuperscript{18} who found increased impedance to flow in PPA in the cross-sectional study of 10 fetuses with bilateral multicystic dysplastic kidney and subsequent pulmonary hypoplasia. Similarly, Laudy et al.\textsuperscript{19}, studying a fetus with lung hypoplasia secondary to an obstructive uropathy, evidenced modifications in the waveform profile of the left pulmonary artery consistent with high peripheral pulmonary vascular resistance. More recently, Yoshimura et al.\textsuperscript{20} found increased PI values in the main branches of the pulmonary arteries in five fetuses at risk of pulmonary hypoplasia. Moreover, Achiron et al.\textsuperscript{21} found no significant differences in PI values in the right pulmonary artery of four fetuses at risk of lung hypoplasia. Differences in the sampling site or in the time of recordings may explain these discrepancies.

Our findings may have clinical application. In the presence of PPA PI values within the normal range 2 weeks after PROM, the risk of developing pulmonary hypoplasia is low (specificity = 94.6%). Thus, conservative management aimed at prolonging the pregnancy should be encouraged. On the other hand, in the presence of abnormal PI values 2 weeks after PROM there is an increased risk of the development of lethal lung hypoplasia. Under these conditions a rationale for experimental treatments such as amnioinfusion may be indicated\textsuperscript{22,23}.

In conclusion, after early PROM PI values in PPA are increased irrespective of the future development of the fetal lung. However, in fetuses developing lung hypoplasia PPA PI values progressively increase with advancing gestation, while they decrease in fetuses with a normal lung development. As a result measurements of PPA velocity waveforms 2 weeks after PROM may help to establish noninvasively the individual fetal risk of developing pulmonary hypoplasia among those pregnancies presenting with early PROM.

**REFERENCES**


![Figure 3](image-url)
Blood flow velocity waveforms


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