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Prenatal Prediction of Pulmonary Hypoplasia: Clinical, Biometric, and Doppler Velocity Correlates

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ABSTRACT. *Objectives.* **To determine the value of pulmonary artery Doppler velocimetry relative to fetal biometric indices and clinical correlates in the prenatal prediction of lethal lung hypoplasia (LH) in prolonged (>1 week) oligohydramnios.**

Methods. **Forty-two singleton pregnancies with oligohydramnios associated with premature rupture of membranes ([PROM]; $n = 31$) or bilateral renal pathology ($n = 11$) were examined using color-coded Doppler ultrasound in a cross-sectional study design. Mean gestational age was 28.0 ± 4.3 weeks (range: 20–36 weeks). Thoracic, cardiac, and abdominal circumference and the largest vertical amniotic fluid pocket were measured. Pulsed Doppler measurements of the arterial pulmonary branches were made at the level of the cardiac 4-chamber view. Diagnosis of LH was based on clinical, radiologic, and pathologic criteria. Clinicians were blinded to the prenatal measurements.**

Results. **The prevalence of lethal LH was 43%. In the PROM subset, combination of onset of PROM at ≤20 weeks, duration of oligohydramnios at ≥8 weeks, and degree of oligohydramnios at ≤1 cm presented the highest clinical prediction rate for lethal LH. For both the total group and the PROM subset, the highest prediction rate for lethal LH was presented by thoracic circumference/abdominal circumference ratio, peak systolic velocity in the proximal branch, and time-averaged and end-diastolic velocity in the middle branch of the pulmonary artery. In the PROM subset, the combination of all 3 clinical, biometric, and Doppler parameters revealed the most favorable combination to predict lethal LH (positive predictive value: 100%; accuracy: 93%; and sensitivity: 71%).**

Conclusion. **Doppler velocimetry may detect changes in pulmonary artery waveforms in the presence of LH but fails to be the ultimate test for the prenatal prediction of lethal LH. The best prediction can be achieved by combining clinical, biometric, and Doppler parameters.** *Pediatrics* **2002;109:250–258;** ***human fetus, pulmonary hypoplasia, pulmonary circulation, premature rupture of membranes, oligohydramnios, Doppler velocimetry.***

ABBREVIATIONS. PROM, premature rupture of membranes; LH, lung hypoplasia; PPV, positive predictive value; SD, standard deviation; PSV, peak systolic velocity; PDV, peak diastolic velocity; EDV, end-diastolic velocity; TAV time-averaged velocity; PI, pulsatility index; TC, thoracic circumference; CC, cardiac circumference; AC, abdominal circumference; SDS, standard deviation score; CI, confidence interval.

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Pulmonary hypoplasia is the result of a developmental delay in pulmonary development, which is classically characterized by an abnormal low value of the lung/body weight ratio and radial alveolar count.[1–3] Most commonly, prolonged oligohydramnios attributable to premature rupture of membranes (PROM) or renal and urinary tract malformations may lead to abnormal fetal lung development with subsequent severe respiratory distress immediately after birth and even neonatal death.[1,4,5]

An accurate prenatal test for detecting pulmonary hypoplasia is still highly desirable. Whereas the prediction of nonlethal forms of pulmonary hypoplasia will not really change obstetric management, this will be the case for the lethal form. An accurate and patient-friendly method for early detection and separation of lethal from nonlethal pulmonary hypoplasia should therefore be developed. Ultrasonography can be considered such a methodology that allows appropriate obstetric management and parental counseling in the presence of lethal lung hypoplasia (LH). For this purpose, a positive predictive value (PPV) of 100% is needed.

Various methods have been proposed in this respect. Fetal 2-dimensional biometric indices[6,7] are late indicators of pulmonary hypoplasia, with a sensitivity and specificity not satisfactory for clinical management. Data on the predictive value of the presence or absence of fetal breathing movements are contradictory.[8,9] Furthermore, the applicability of 3-dimensional ultrasonography, computerized tomography, and/or magnetic resonance imaging for accurate measurement of fetal lung volume in the prediction of LH still needs to be determined. The introduction of more sensitive color-coded Doppler systems has led to the visualization of the human fetal pulmonary circulation. Information on normal fetal pulmonary circulation has been obtained in our center.[10,11] As a result, gestation-related changes in pulmonary blood flow velocity waveforms have been reported by us.[10,11] Only sparse data are available on the inverse relationship between Po_2 and downstream impedance in the peripheral pulmonary

arteries, established in growth-restricted human fetuses.[12]

It has been shown in postmortem studies that pulmonary hypoplasia is associated with underdevelopment and structural changes of the pulmonary vascular bed. A decrease in the total size of the pulmonary vascular bed, a decrease in the number of vessels per unit of lung tissue, and an increase of pulmonary arterial smooth muscle thickness have been described.[4,13,14] We hypothesized that these changes may lead to increased pulmonary vascular resistance and decreased pulmonary arterial compliance. These alterations may effect pulmonary blood flow and consequently may induce changes in both systolic and diastolic components of the pulmonary artery flow velocity waveform as suggested previously.[15] On the basis of this hypothesis, we addressed the question of whether 1) Doppler flow velocity waveforms from the fetal arterial pulmonary branches in the presence of prolonged oligohydramnios are predictive of lethal LH and, if so, 2) whether the predictive value of these Doppler recordings is superior to that of fetal biometric indices.

METHODS

Patients and Study Design

A total of 42 women with a singleton pregnancy and prolonged oligohydramnios were evaluated on referral in a random manner. Each woman consented to participating in the study, which was conducted according to a cross-sectional design. Prolonged oligohydramnios was considered the common denominator for the inclusion of patients is this study. Oligohydramnios was either the result of PROM before 30 weeks of gestation and lasting >1 week ($n = 31$) or attributable to the presence of bilateral renal pathology ($n = 11$). The latter subset consisted of bilateral renal agenesis ($n = 5$), bilateral cystic/dysplastic kidneys ($n = 4$), and obstructive uropathy ($n = 2$), suspected prenatally by ultrasonography and confirmed postnatally by postmortem examination. It is realized that the underlying mechanism of oligohydramnios in PROM is different from that in fetal renal malformations.[16] The degree of oligohydramnios was defined as severe, moderate, or mild when the largest vertical amniotic fluid pocket was measured below 1 cm, between 1 and 2 cm, and between 2 and 3 cm, respectively.[5] Other causes of LH, such as diaphragmatic hernia and neurologic and skeletal disorders, were excluded from the study.

The study protocol was approved by the Hospital Ethics Committee and conformed with the principles outlined in the Declaration of Helsinki. Pregnancy duration varied between 20 and 36 weeks (mean: 28 weeks; standard deviation [SD]: 4.3) and was determined from the last menstrual period and confirmed or adjusted by ultrasonic measurement of the fetal crown-rump length (8–12 weeks) or fetal biparietal diameter (12–20 weeks). There was no fetal growth restriction, maternal smoking, drug ingestion, or maternal disease. Abnormal fetal pulmonary vasculature was therefore considered to be associated with pulmonary hypoplasia. No other pregnancy pathology was established. Demographic data are presented in Table 1. Pregnancy duration was beyond 34 weeks in 5 of 31 PROM cases. In the PROM subset, cesarean section was always performed because of fetal distress. In this particular subset, 27 of 31 patients received corticosteroids. Of the remaining 4 patients, we could not traced whether this medication was administered. Two of these patients delivered a fetus with lethal LH, and 2 delivered a fetus without LH.

The mean onset of PROM was 23 weeks (SD: 3.9), and the mean duration of PROM was 8 weeks (SD: 4.4). Within the PROM subset, 11 cases (35%) had a vertical amniotic fluid pocket of ≤1 cm, 13 cases (42%) of >1 cm and ≤2 cm, and 7 cases (23%) of >2 cm and ≤3 cm. All cases with renal pathology displayed amniotic fluid pockets <1 cm. The mean time interval between the sonographic measurements and delivery was 6 days (PROM subset) and 4 days (renal subset), respectively.

Recording Technique

The real-time ultrasound and Doppler studies were performed using a Toshiba SSH 140 with combined transabdominal real-time, color and pulsed Doppler imaging facilities (Toshiba Corp, Medical Systems Division, Tokyo, Japan). The carrier frequency was 5 MHz (real time) and 3.75 MHz (Doppler). The spatial peak temporal average power output was <100 mW/cm² in both imaging and Doppler modes according to manufacturer's specifications. All recordings were performed with the woman in the semirecumbent position and during fetal apnea.

Thoracic, cardiac, and abdominal circumference and the largest vertical amniotic fluid pocket were measured as described elsewhere.[17,18] This was followed by the pulsed Doppler measurements of the arterial pulmonary branches from a transverse cross-section of the fetal chest at the level of the cardiac 4-chamber view after visualization with color Doppler. Depending on fetal position, the right or left lung was examined. Doppler waveforms (sample volume: 0.1–0.3 cm) were first obtained from the most proximal branch of the pulmonary artery, then in the middle lung region at equal distance from the outer border of the heart and the inner thoracic wall and subsequently in the distal lung region as close as possible to the fetal inner thoracic wall (Fig 1).[10,11] The interrogation angle was always kept below 20 degrees. The high-pass filter was set at 100 Hz, and when no end-diastolic or early diastolic reverse flow velocities were present, the filter was set at 70 Hz. All flow velocity waveforms were recorded on hard copies. Each patient was studied by 1 and the same examiner (J.A.M.L.), who also performed the waveform analysis, using a microcomputer (Commodore 386 CX) linked to a graphics tablet. At least 3 consecutive flow velocity waveforms with the highest velocity and of similar appearance were used to calculate the different parameters in each vessel. The flow velocity waveform pattern at all 3 levels has been described previously.[10,11] Adequate accuracy and precision of the recording technique was achieved in a separate control group.[11] Clinicians were blinded to the Doppler results.

From the proximal, middle, and distal arterial pulmonary branches, the following Doppler flow velocity parameters were determined from the same lung: 1) peak systolic velocity (PSV, cm/s), peak diastolic velocity (PDV, cm/s), end diastolic velocity

TABLE 1. Demographics of the Subset of PROM and the Subset of Bilateral Renal Pathology

	PROM ($n = 31$)	Renal Pathology ($n = 11$)
Maternal age (y; mean [SD])	28.8 (4.6)	29.8 (3.6)
Gravida (median [range])	3 [1–6]	2 [1–6]
Para (median [range])	1 [0–4]	1 [0–4]
Interval US–birth (wk; median [range])	0.86 [0.14–6.71]	0.57 [0.14–7.00]
Gestation at birth (wk; mean [SD])	30.48 (2.95)	27.79 (7.13)
Birth weight (g); median [range])	1305 [780–2750]	730 [303–2765]
Mode of delivery		
Spontaneous	25 (81%)	4 (36%)
Cesarean section	6 (19%)	0
Pregnancy termination	0	7 (64%)
Gender (male/female)	18/13	9/2

US indicates ultrasonographic examination.

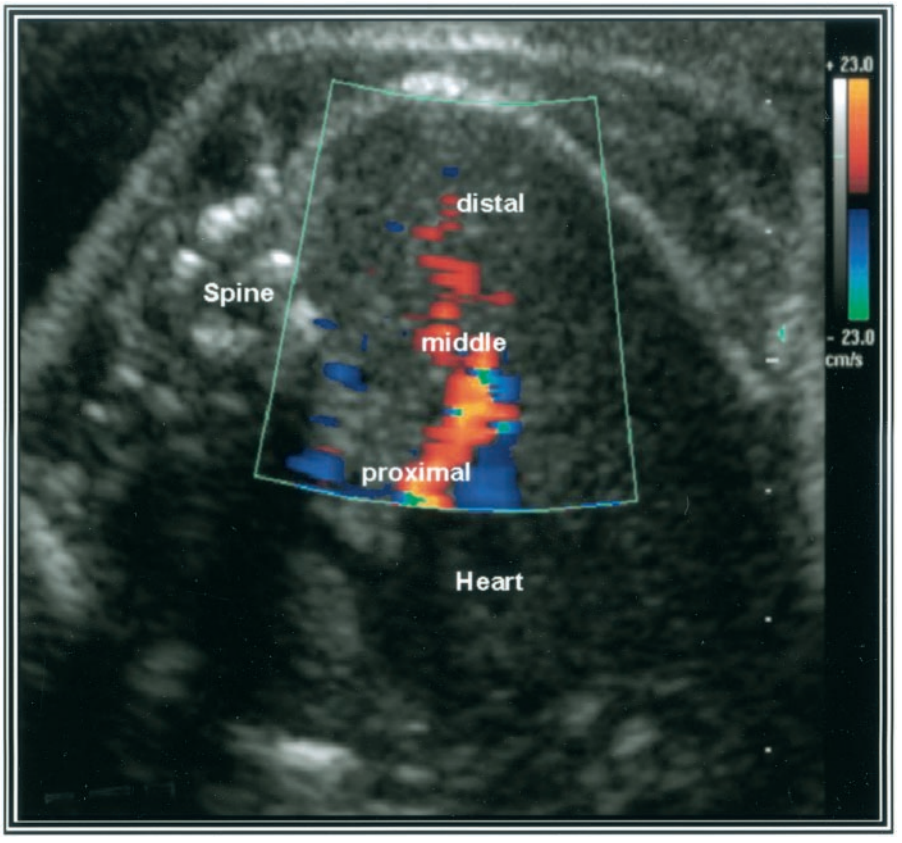

Fig 1. Cross-section of the fetal chest at the level of the cardiac 4-chamber view with color Doppler switched on to visualize the pulmonary circulation. Proximal, middle, distal = proximal, middle and distal Doppler sample site in the arterial pulmonary branch.

(EDV, cm/s), and time-averaged velocity (TAV, cm/s); and 2) the pulsatility index (PI = [PSV − EDV]/TAV).[19]

Postnatal Diagnosis of LH

After birth, LH was diagnosed according to clinical and radiologic criteria and eventually pathologic data. Pathologic data were based on lung/body weight ratios and radial alveolar counts according to Askenazi and Perlman.[2] When the radial alveolar counts could not be determined, which was particularly the case in early pregnancy (20–22 weeks), pulmonary hypoplasia was defined as wet lung/body weight ratio of ≤0.015 before 28 weeks' gestation, or ≤0.012 at 28 weeks or later, including the developmental stage.[3] The clinical criteria were defined as immediate onset of severe respiratory insufficiency after birth, small lung capacity, and requirement of high ventilatory pressures in the absence of obstruction or atelectasis.[5,20] Radiologic criteria constituted small lung fields with diaphragmatic domes elevated up to the seventh rib, downward-sloping ribs, a bell-shaped chest, and/or pneumothorax/pneumomediastinum.[21,22] The radiologist (S.G.F.R.) who scored the radiographs of the neonatal chest was blinded to the sonographic measurements and neonatal outcome.

Lethal LH was defined as death from LH based on criteria described above. Fetuses with autopsy-proven LH after early pregnancy termination were included. Neonates with nonlethal LH developed respiratory insufficiency compatible with clinical and radiologic signs of pulmonary hypoplasia but survived. Absent LH was represented by 1) neonates who did not show any clinical and/or radiologic sign of pulmonary hypoplasia and 2) fetuses in which no pulmonary hypoplasia could be diagnosed on postmortem examination after early pregnancy termination.

From a clinical standpoint, an accurate prenatal prediction of a lethal form of pulmonary hypoplasia is important to both obstetric management and parental counseling. It was decided, therefore, to separate out lethal LH from nonlethal and absent LH in the present study.

Data Analysis

Clinical Parameters (PROM Subset Only)

The onset of PROM and the duration and degree of oligohydramnios served as clinical parameters for the prediction of lethal LH. The selection of these parameters and associated cutoff levels

TABLE 2. Efficacy of the Clinical Parameters in the Prenatal Prediction of Lethal LH in the Subset of PROM

Clinical Parameters	Cutoff Levels	Subset of PROM (n = 31)				
		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Onset of PROM	≤20 wk[1]	78	77	58	89	77
	≤24 wk	100	45	43	100	61
	≤26 wk	100	32	38	100	52
Duration of oligohydramnios	≥8 wk[2]	89	59	47	93	68
	≥6 wk	100	50	45	100	65
	≥4 wk	100	41	41	100	58
Degree of oligohydramnios	≤1 cm[3]	78	82	64	90	81
	≤2 cm	100	32	38	100	52
Combination of parameters with the most accurate cutoff level (1+2+3)		67	95	86	88	87

NPV indicates negative predictive value.

(Table 2) was based on their predictive value of pulmonary hypoplasia suggested in previous reports.[5,23,24] Differences in clinical parameters between lethal LH and combined nonlethal and absent LH were tested (independent sample *t* test). For the onset of PROM, we examined the levels of ≤26 weeks, ≤24 weeks, and ≤20 weeks of gestation; for the duration of oligohydramnios, the levels of ≥4 weeks, ≥6 weeks, and ≥8 weeks; and for the degree of oligohydramnios, a largest vertical amniotic fluid pocket of ≤2 cm and ≤1 cm. Furthermore, sensitivity, specificity, PPV, negative predictive value, and overall accuracy for lethal LH were calculated at the different cutoff levels for each of these clinical parameters separately and in combination. Accuracy was defined as the sum of true "positives" and true "negatives" divided by the total population studied. Data were considered abnormal when situated below a particular cutoff level for onset of PROM or degree of oligohydramnios and above a particular cutoff level for duration of oligohydramnios.

Biometric and Doppler Parameters

Data on thoracic circumference (TC) and ratios of cardiac/thoracic circumference (CC/TC) and thoracic/abdominal circumference (TC/AC) as well as pulmonary Doppler flow velocities were plotted in nomograms constructed from an previous patient cohort of 111 uncomplicated singleton pregnancies.[10,11] All parameters were subsequently converted into the standard deviation scores (SDS) to be independent of gestational age. We tested whether the SDS of both the lethal LH subset and combined nonlethal and absent LH subset were statistically different from the SDS of the mean of the normal controls (= 0) using the 1-sample *t* test. For the latter subset, we also tested whether this result was influenced by the addition of the 3 cases of nonlethal LH to the subset of absent LH. The level of statistical significance was set at $P < .05$. Furthermore, sensitivity, specificity, predictive values, and overall accuracy of the separate and combined biometric and Doppler parameters were calculated for the total study group to evaluate the efficacy of prenatal prediction of lethal pulmonary hypoplasia. A similar procedure was conducted within the PROM subset, including combination of onset of PROM and duration and degree of oligohydramnios. Exact 95% confidence intervals (CI) were computed with the package StatXact 4 (Cytel Software Corporation, Cambridge, UK) for all tested combinations. Measurements below the 5th centile were considered abnormal for TC and TC/AC and the velocity parameters TAV, PSV, PDV, and EDV, and measurements above the 95th centile were considered abnormal for CC/TC and PI.

RESULTS

Pregnancy Outcome

The prevalence of lethal LH in the total study group was 43% (18 of 42), 9 of which were in the PROM subset (9 [29%] of 31) and 9 of which were in the renal subset (9 [82%] of 11). Nonlethal LH was established in 3 cases associated with PROM, and absent LH existed in the remaining 21 cases, 19 of which were related to PROM.

In the renal subset, the mortality rate was 100% (11 of 11); 2 cases (bilateral renal agenesis and bilateral cystic kidneys) displayed normal lung/body weight ratios after termination of pregnancy at 21 weeks of gestation. In the PROM subset, the overall mortality rate was 39% (12 of 31). Of the 9 fetuses with lethal LH, 78% ($n = 7$) died within 24 hours after birth, 70% (5 of 7) of which died in the first hour. Despite vigorous artificial ventilation with 100% inspiratory oxygen and frequencies ranging from 30 to 100 per minute and peak inspiratory pressures reaching 40 cm H_2O in isolated cases, adequate oxygenation was never reached in severely affected neonates. In absent LH ($n = 19$), 3 neonates died from sepsis ($n = 2$) or severe asphyxia ($n = 1$). The remaining 16 neonates survived, although 81% of them (13 of 16) displayed mild to severe respiratory complications. All 3 neonates with nonlethal LH in this PROM subset developed respiratory distress syndrome, complicated by persistent pulmonary hypertension and, later, bronchopulmonary dysplasia.

In the subset of PROM, an intrauterine infection was suspected in 17 cases (55%). In 11 of these cases (65%), there were histopathologic signs of a (chorio)amnionitis. Two of these 11 cases had clinical signs of an infection confirmed by culture, which caused their death. There were no other cases of a clinical infection in the group of PROM. In 6 of the 9 cases of lethal LH, an intrauterine infection was suspected and 5 of them had a chorioamnionitis. However, none of these neonates developed signs of infection. The 3 cases of nonlethal LH cases had no neonatal signs of infection confirmed by negative cultures.

Clinical Parameters (PROM Subset Only)

The median time interval between the onset of PROM and sonographic examination was 7 weeks (range: 1–20 weeks). The mean onset of PROM was significantly earlier (19.7 weeks [SD: 2.1]) vs 23.9 weeks [SD 3.9]; $P = .005$), the mean duration of oligohydramnios was significantly longer (10.0 weeks [SD: 1.2] vs 6.8 weeks [SD 4.9]; $P = .008$), and the mean degree of oligohydramnios was significantly more pronounced (0.9 cm [SD: 0.5] vs 1.7 cm [SD: 0.8]; $P = .01$) in the subset of lethal LH compared with combined nonlethal and absent LH. The highest prediction rate for lethal LH was presented by 1) onset of PROM ≤20 weeks, 2) duration of oligohydramnios ≥8 weeks, and 3) degree of oligohydramnios of ≤1 cm. The best prediction rate (PPV: 86% [95% CI: 42%–100%]; accuracy: 87% [95% CI: 70%–96%]) was reached when combining 1 through 3 (Table 2).

Biometric Parameters

TC and CC/TC and TC/AC ratios could be calculated in ≥98% of all patients and in ≥97% of the PROM subset. Figure 2 demonstrates the TC and CC/TC and TC/AC ratios for the total study group plotted in the normal reference charts. The SDS of all 3 biometric parameters were statistically significantly different from the SDS of the mean of normal control subjects for both the subset of lethal LH and the subset of combined nonlethal and absent LH. For TC and CC/TC, this was independent of the addition of the 3 cases of nonlethal LH to the subset of absent LH. TC/AC ratio displayed the best PPV and overall accuracy in the prenatal prediction of lethal LH for both the total group and the subset of PROM (Tables 3 and 4).

Doppler Velocity Parameters

Technically acceptable proximal, middle, and distal arterial pulmonary branch flow velocity waveforms were obtained in 88%, 81%, and 55%, respectively, for the total study group and in 94%, 84%, and 68%, respectively, for the PROM subset. A significant ($P = .03$) difference existed between lethal LH (6 [33%] of 18) and combined nonlethal and absent LH

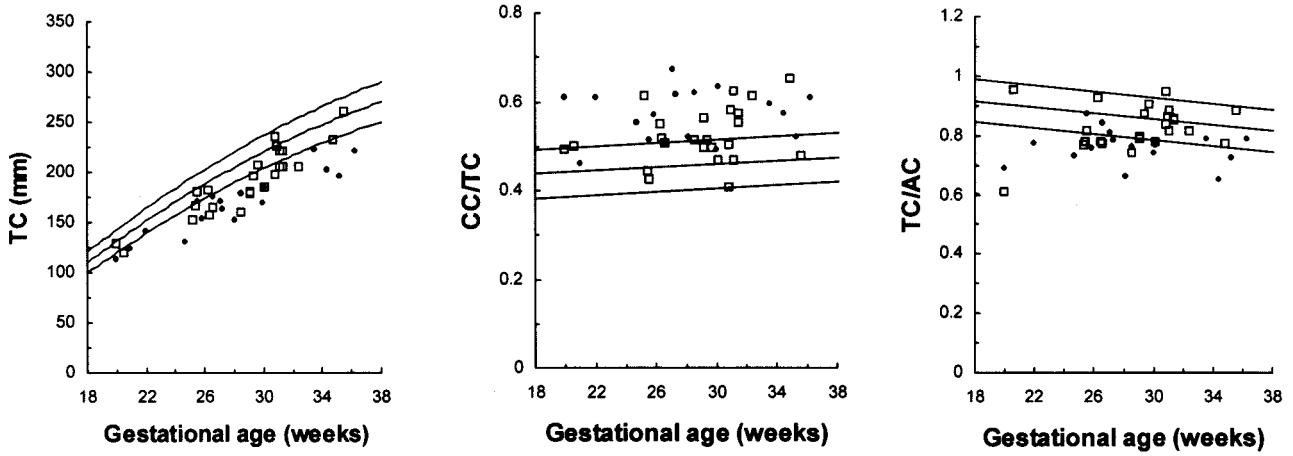

Fig 2. Individual values from the total study group compared with reference ranges (mean, 5th and 95th centiles) for (A) thoracic circumference (TC, mm), (B) ratio of cardiac and thoracic circumference (CC/TC) and (C) ratio of thoracic and abdominal circumference (TC/AC) relative to gestational age. The solid circles represent group 1, ie, fetuses with lethal LH and the open blocks represent group 2, ie, fetuses with nonlethal and absent LH.

TABLE 3. Efficacy of the Biometric and Doppler Parameters in the Prenatal Prediction of lethal LH in the Total Study Group

	Total Study Group (n = 42)					
	Success Rate	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Prevalence LLH 43% (18/42)						
Biometric parameters						
TC	41/42 (98%)	94	38	52	90	61
CC/TC	41/42 (98%)	76	50	52	75	61
TC/AC*	40/42 (95%)	69	71	61	77	70
Doppler parameters						
Proximal pulmonary branch	37/42 (88%)					
TAV		69	76	69	76	73
PSV*		63	90	83	76	78
PDV		44	90	78	68	70
EDV		50	86	73	69	70
PI		56	76	64	70	68
Middle pulmonary branch	34/42 (81%)					
TAV		71	80	71	80	76
PSV		43	80	60	67	65
PDV		43	70	50	64	59
EDV		57	90	80	75	76
PI		29	75	44	60	56
Combination of parameters						
Biometry + Doppler	36/42 (86%)	40	100	100	70	75

NPV indicates negative predictive value.
* Variables used for the biometric and Doppler combination.

(17 [71%] of 24) concerning distal waveforms, which were therefore omitted from further analysis.

For the total study group, the SDS of TAV, PSV, PDV, and EDV from both the proximal and middle arterial waveforms were statistically significantly different from the SDS of the mean of normal control subjects for both lethal LH and combined nonlethal and absent LH. This was independent of the addition of the 3 cases of nonlethal LH to the subset of absent LH. For the PI, this applied only to the proximal arterial waveforms.

For both the total group and the subset of PROM, the highest PPV and overall accuracy in the prenatal prediction of lethal LH were achieved for the PSV of the proximal arterial waveforms and for the TAV and EDV of the middle arterial waveforms. The (nearly) lowest PPV and overall accuracy were presented by the PI (Tables 3 and 4; Figs 3 and 4).

Combination of Clinical, Biometric, and Doppler Parameters

In the total study group, when combining TC/AC and proximal arterial pulmonary PSV, the success rate of obtaining this combination was 86% (36 of 42). Lethal LH existed in 3 of the 6 unsuccessful cases, leaving 15 of 18 cases of lethal LH for analysis of the combined data. Lethal LH was predicted when both TC/AC and PSV were situated below the 5th centile of the normal reference charts, resulting in a PPV of 100% (95% CI: 54%–100%) and an overall accuracy of 75% (95% CI: 58%–88%), with a drop in sensitivity to 40% (6 of 15; 95% CI: 16%–68%; Table 3). Thus, lethal LH was detected in 6 of 18 cases.

In the subset of PROM, further improvement in predictive value was sought in 1) combined clinical parameters and TC/AC; 2) combined clinical param-

TABLE 4. Efficacy of the Biometric and Doppler Parameters Including the Combination With the Clinical Parameters in the Prenatal Prediction of lethal LH in the Subset of PROM

	Subset of PROM (n = 31)					
	Success Rate	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Prevalence LLH 29% (9/31)						
Biometric parameters						
TC	100%	100	36	39	100	55
CC/TC	100%	78	50	39	85	58
TC/AC*	97% (30/31)	63	73	45	84	70
Doppler parameters						
Proximal pulmonary branch	94% (29/31)					
TAV		63	76	50	84	72
PSV*		63	90	71	86	83
PDV		25	90	50	76	72
EDV		38	86	50	71	72
PI		38	76	38	76	66
Middle pulmonary branch	84% (26/31)					
TAV		71	84	63	89	81
PSV		43	84	50	80	73
PDV		14	68	14	68	54
EDV		57	95	80	86	85
PI		29	79	33	75	65
Combination of parameters						
Clinical (Table 2)	100%	67	95	86	88	87
Clinical Biometry	97% (30/31)	38	100	100	81	83
Clinical Doppler	94% (29/31)	50	100	100	84	86
Biometry + Doppler	90% (28/31)	29	100	100	81	82
Clinical + Biometry + Doppler	94% (29/31)	71	100	100	92	93

LLH indicates lethal lung hypoplasia; NPV, negative predictive value.
*, Variables used for the biometric and Doppler combination; clinical, the combination of the 3 clinical parameters with the most accurate cutoff points in the prediction of lethal lung hypoplasia, i.e. onset of PROM ≤20 weeks, duration of oligohydramnios ≥8 weeks, degree of oligohydramnios of ≤1 cm.

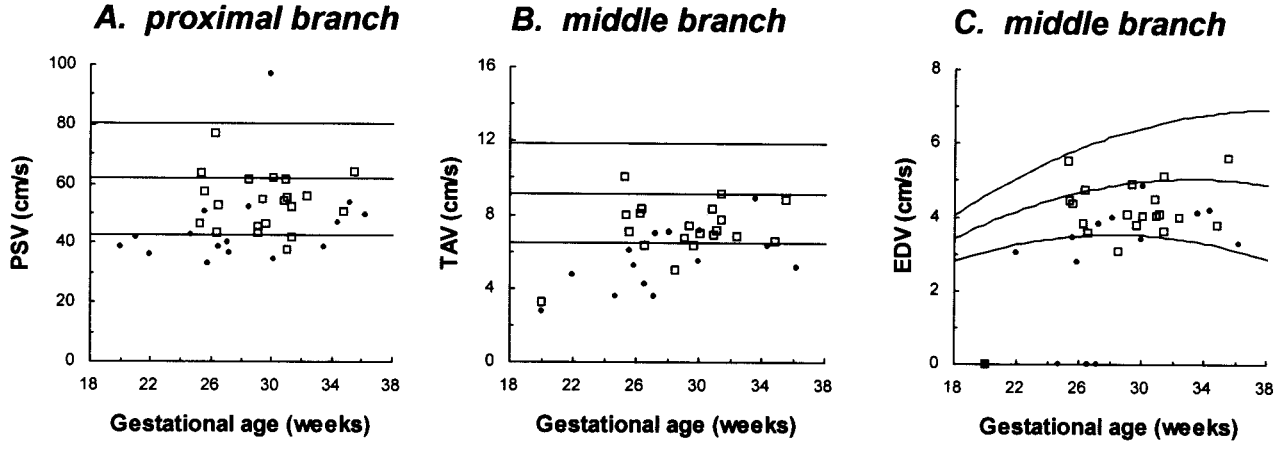

Fig 3. Individual values from the total study group compared with reference ranges (mean, 5th and 95th centiles) for (A) PSV (cm/s) of the proximal arterial pulmonary branch, (B) time-averaged velocity (TAV, cm/s) and (C) end-diastolic velocity (EDV, cm/s) of the middle arterial pulmonary branch relative to gestational age. The solid circles represent group 1, ie, fetuses with lethal LH and the open blocks represent group 2, ie, fetuses with nonlethal and absent LH.

eters and proximal PSV; 3) combined TC/AC and proximal PSV; and 4) combined clinical parameters, TC/AC, and proximal PSV (Table 4). In the first 3 combinations (1–3), lethal LH was considered present when both variables were abnormal. The success rate in obtaining the first combination was 97% (30 of 31), with 1 unsuccessful case of lethal LH, resulting in 8 of 9 cases of lethal LH for further analysis. This combination showed a PPV of 100% (95% CI: 29%–100%), an overall accuracy of 83% (95% CI: 65%–94%), and a sensitivity of only 38% (3 of 8; 95% CI: 9%–76%). The success rate of the second combination was 94% (29 of 31). Lethal LH existed in 1 of the 2 unsuccessful cases, leaving 8 of 9 cases of lethal LH for analysis of the combined data. The PPV of this combination also reached the level of 100% (95% CI: 40%–100%) with an accuracy of 86% (95% CI: 68%–96%) and a sensitivity of 50% (4 of 8; 95% CI: 16%–84%). The third combination was successful in 90% (28 of 31), with 2 cases of lethal LH of the 3 unsuccessful cases, resulting in 7 of 9 cases of lethal LH for analysis. The PPV improved to 100% (95% CI: 16%–100%) with an accuracy of 82% (95% CI: 6%–94%) and a sensitivity of 29% (2 of 7; 95% CI: 4%–71%). With these 3 combined tests, lethal LH could be detected in 3, 4, and 2 of 9 cases, respectively. The

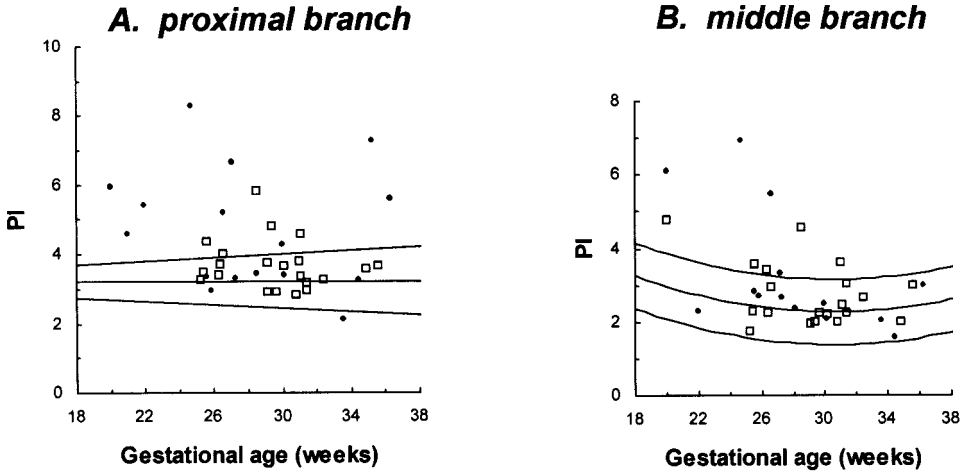

Fig 4. Individual values from the total study group compared with reference ranges (mean, 5th and 95th centiles) for (A) PI of the proximal arterial pulmonary branch and (B) PI of the middle arterial pulmonary branch relative to gestational age. The solid circles represent group 1, ie, fetuses with lethal LH and the open blocks represent group 2, ie, fetuses with nonlethal and absent LH.

success rate in obtaining the last combination (4) was 94% (29 of 31). Lethal LH existed in both unsuccessful cases, leaving 7 of 9 cases of lethal LH for analysis of the combined data. Lethal LH was predicted when at least 2 of the 3 variables were abnormal. PPV, overall accuracy, and sensitivity demonstrated an increase up to 100% (95% CI: 48%–100%), 93% (95% CI: 77%–99%), and 71% (5 of 7; 95% CI: 29%–96%), respectively (Table 4). Lethal LH was detected in 5 of 9 cases.

DISCUSSION

The present study describes the role of clinical, biometric, and Doppler parameters, separate or in combination, in the prenatal prediction of lethal LH in pregnancies associated with prolonged oligohydramnios of renal or nonrenal (PROM) origin.

Surrounding amniotic fluid is important for optimal fetal lung growth. Although the association between oligohydramnios and pulmonary hypoplasia is well documented, the underlying mechanisms for this phenomenon have not been fully elucidated. Several explanations have been put forward: 1) decreased space for lung growth as a result of pressure of the uterine wall on the fetal chest and abdomen; 2) restriction of fetal breathing movements by prolonged thoracic compression; and 3) increased efflux of lung liquid from the intrapulmonary space to the amniotic space, resulting in a decrease of intrapulmonary pressure.[25,26] Oligohydramnios may result from a different cause, such as lack of fetal urinary production associated with renal abnormalities, severe fetal growth restriction, and ruptured membranes.

In case of pulmonary hypoplasia associated with oligohydramnios, the severity of this abnormal condition depends on the degree and duration of oligohydramnios and the stage of lung development.[5,23] The present study confirms the existence of a significant relation among onset of PROM, duration and degree of oligohydramnios, and the development of lethal LH. The PPV of a prenatal test for detecting lethal LH should be 100% to be used in obstetric management. Onset of PROM and duration and degree of oligohydramnios as separate variables displayed the highest prenatal prediction of lethal LH at the cutoff levels of ≤20 weeks, ≥8 weeks, and ≤1 cm, respectively. However, neither the corresponding predictive values and accuracy for each of these clinical parameters separately nor their combination reached an acceptable level for clinical application.

Because only 2 of 31 neonates in the subset of PROM died from sepsis, pre- and/or postnatally confirmed infection was considered not to be a confounder of the predictive variables in the present study.

Prediction of lethal pulmonary hypoplasia has been attempted from fetal TC and sagittal lung length or transversal lung diameter measurements, as well as from CC/TC and TC/AC ratios.[6,7,27] Most biometric studies represent heterogeneous and relatively small patient cohorts and use different definitions of TC and LH. Moreover, none of these biometric tests was reliable enough to be applied in clinical management. Also, in the present study, TC, CC/TC, and TC/AC failed to provide an acceptable prenatal prediction of lethal LH in either the total study group or the subset of PROM. In the latter, the clinical parameters reached an even better prediction rate than the biometric parameters.

Remarkable is the finding that mean SDS of the biometric parameters from not only the lethal LH subset but also the combined nonlethal and absent LH subset was significantly different from the SDS of the mean of the normal control subjects. For the TC and the CC/TC, this was also the case for absent LH alone. We propose that mechanical compression associated with marked oligohydramnios and/or possible interference with fetal breathing movements may play a role in this phenomenon, independent of the occurrence of lethal LH.

Because prenatal fetal biometry has failed to provide an accurate prediction of pulmonary hypoplasia, other methods had to be explored. A prolonged and pronounced oligohydramnios, particularly during the canalicular phase of lung development (from

18 to 26 to 28 weeks of gestation), may cause a delay or even an arrest in pulmonary vascular development, resulting in reduced lung volume and raised pulmonary vascular resistance.[4,13] Consequently, the present study focused on the possible contribution of Doppler velocimetry of the arterial pulmonary circulation for the improvement of prenatal prediction of LH. In the total study group, the success rate of obtaining technically acceptable proximal and middle arterial pulmonary branch flow velocity waveforms was similar to that reported previously in uncomplicated pregnancies.[10,11] Regarding the subset of lethal LH alone, the percentage of technically acceptable distal waveforms was significantly less (33%) compared with the subset of combined nonlethal and absent LH (71%). This suggests that failure to record distal arterial flow velocity waveforms may be indicative of lethal LH. So far, comparison with other studies is not possible because of differences in definition of Doppler sample site for distal pulmonary arteries.[28,29]

Similar to the fetal biometric parameters, nearly all mean SDS of the proximal and middle arterial pulmonary flow velocity waveforms from the subset of combined nonlethal and absent LH were significantly different from the SDS of the mean of normal control subjects, independent of the addition of the 3 cases of nonlethal LH to the subset of absent LH. In the normally developing fetus, fluid leaves the pulmonary vasculature, passes through the interstitium of the lungs entering the potential air spaces, and flows out of the trachea. It has been postulated that oligohydramnios increases efflux of lung liquid from the intrapulmonary space into the amniotic space, resulting in a decrease of intrapulmonary pressure.[25,26] We propose that changes in lung liquid dynamics, even without dramatic influences on lung growth resulting in LH, may affect pulmonary blood flow and consequently pulmonary blood flow velocity waveforms.

The most reliable Doppler velocity parameters in the detection of lethal LH were PSV in the proximal arterial pulmonary velocity waveform and TAV and EDV in the middle arterial pulmonary velocity waveform. The majority of the Doppler velocity parameters from both proximal and middle arterial pulmonary branches showed even higher PPV and overall accuracy than the biometric parameters. Nevertheless, Doppler velocimetry of the arterial pulmonary circulation as a single test also failed to be reliable enough for clinical application. In the subset of PROM, the 3 combined clinical parameters displayed an even higher PPV and accuracy than Doppler velocimetry.

The lowest PPV and overall accuracy for both the proximal and middle arterial pulmonary branches were presented by the PI in the total study group. The PI is known as a reliable Doppler parameter for the detection of changes in fetoplacental resistance. Contradictory views have been reported regarding the clinical significance of the PI in the prediction of lethal LH.[28–31] These reports present data from very small heterogeneous patient series and do not include cases of PROM, which is considered one of the most common causes of pulmonary hypoplasia.

Because we demonstrated that Doppler velocimetry of the arterial pulmonary circulation also fails to be the single and ultimate prenatal test in the prediction of lethal LH, we addressed the question of whether combining clinical, biometric, and pulmonary Doppler parameters could improve the predictive value of lethal LH. In the total study group, first the most accurate biometric parameter, ie, TC/AC, and the most accurate Doppler parameter, ie, the proximal arterial pulmonary PSV, were combined. The PPV improved to 100%. However, this result could be achieved in only 6 of 18 cases of lethal LH, which would limit its clinical applicability. When a similar exercise was conducted in the subset of PROM, all 3 combinations of 1) combined clinical parameters and TC/AC, 2) combined clinical parameters and proximal PSV, and 3) TC/AC and proximal PSV reached a PPV of 100%. Also here, a correct prediction could be made in only 2 to 4 of 9 cases of lethal LH.

Combination of all 3 clinical, biometric, and Doppler parameters demonstrated not only a PPV of 100% but also a considerable improvement in overall accuracy (93%) and sensitivity (71%). Here, a correct prenatal diagnosis of lethal LH was made in 5 of 9 cases of lethal LH, constituting the most favorable combination in the subset of PROM.

It is possible that the performance of the predictive equations defined in the present cohort will not be as accurate as initially projected when evaluated prospectively in a new group of subjects that possess clinical characteristics not encountered in the current group. It is realized that, particularly before 24 weeks of gestation, a highly predictive test for lethal LH would be desirable to allow couples to arrive at a well-balanced decision as to whether to opt for pregnancy termination. In the present study, the mean onset of PROM followed by lethal LH was 19.7 weeks.

It can be concluded that Doppler velocimetry may detect changes in blood velocity waveforms from the proximal and middle arterial branches of the fetal pulmonary circulation in the presence of pulmonary hypoplasia. The best prediction was achieved in the subset of PROM, when a combination of clinical, biometric, and Doppler parameters were applied. The clinical significance of this combined test, however, seems to be limited as a result of the restrictions in obtaining the necessary components of this test and the low sensitivity of the combination.

REFERENCES

1. Sherer DM, Davis JM, Woods JR. Pulmonary hypoplasia: a review. *Obstet Gynecol Surv*. 1990;45:792–803
2. Askenazi SS, Perlman M. Pulmonary hypoplasia: lung weight and radial alveolar count as criteria of diagnosis. *Arch Dis Child*. 1979;54: 614–618
3. Wigglesworth JS, Desai R. Use of DNA estimation for growth assessment in normal and hypoplastic fetal lungs. *Arch Dis Child*. 1981;56: 601–605
4. Hislop A, Hey E, Reid L. The lungs in congenital bilateral renal agenesis and dysplasia. *Arch Dis Child*. 1979;54:32–38
5. Rotschild A, Ling EW, Puterman ML, Farquharson D. Neonatal out-

come after prolonged preterm rupture of the membranes. *Am J Obstet Gynecol*. 1990;162:46–52
6. Yoshimura S, Masuzaki H, Gotoh H, Fukuda H, Ishimaru T. Ultrasonographic prediction of lethal pulmonary hypoplasia: comparison of eight different ultrasonographic parameters. *Am J Obstet Gynecol*. 1996;175:477–483
7. Merz E, Miric-Tesanic D, Bahlmann F, Weber G, Halermann C. Prenatal sonographic chest and lung measurements for predicting severe pulmonary hypoplasia. *Prenat Diagn*. 1999;19:614–619
8. Blott M, Nicolaides KH, Gibb D, Greenough A, Moscoso G, Campbell S. Fetal breathing movements as predictor of favourable pregnancy outcome after oligohydramnios due to membrane rupture in second trimester. *Lancet*. 1987;i:129–131
9. Moessinger AC, Higgins A, Fox HE, Rey HR. Fetal breathing movements are not a reliable predictor of continued lung development in pregnancies complicated by oligohydramnios. *Lancet*. 1987;ii:1297–1299
10. Laudy JAM, de Ridder MAJ, Wladimiroff JW. Doppler velocimetry in branch pulmonary arteries of normal human fetuses during the second half of gestation. *Pediatr Res*. 1997;41:897–901
11. Laudy JAM, de Ridder MAJ, Wladimiroff JW. Human fetal pulmonary artery velocimetry: repeatability and normal values with emphasis on middle and distal pulmonary vessels. *Ultrasound Obstet Gynecol*. 2000;15:479–486
12. Rizzo G, Capponi R, Chaoui R, Taddei F, Arduini D, Romanini C. Blood flow velocity waveforms from peripheral pulmonary arteries in normally grown and growth-retarded fetuses. *Ultrasound Obstet Gynecol*. 1996;8:87–92.
13. Reid LM. Lung growth in health and disease. *Br J Dis Chest*. 1984;78:113–133
14. Barth PJ, Rüschoff J. Morphometric study on pulmonary arterial thickness in pulmonary hypoplasia. *Pediatr Pathol*. 1992;12:653–663
15. Laudy JAM, Gaillard JLJ, Van den Anker JN, Tibboel D, Wladimiroff JW. Doppler ultrasound imaging: a new technique to detect lung hypoplasia before birth? *Ultrasound Obstet Gynecol*. 1996;7:189–192
16. Thurlbeck WM. Prematurity and the developing lung. *Clin Perinatol*. 1992;19:497–519.
17. Hilpert PL, Pretorius DH. The Thorax. In: Nyberg DA, BS Mahony, DH Pretorius, eds. *Diagnostic Ultrasound of Fetal Anomalies. Text and Atlas*. Chicago, IL: Year Book Medical Publishers; 1990:262–299
18. Nyberg DA. Intra-abdominal abnormalities. In: Nyberg DA, BS Mahony, DH Pretorius, eds. *Diagnostic Ultrasound of Fetal Anomalies. Text and Atlas*. Chicago, IL: Year Book Medical Publishers; 1990:342–394
19. Gosling RG, King DH. Ultrasound angiology. In Marcus AW, Adamson J, eds. *Arteries and Veins*. Edinburgh, Scotland: Churchill-Livingstone; 1975:61–98
20. Bhutani VK, Abbasi S, Weiner S. Neonatal pulmonary manifestations due to prolonged amniotic leak. *Am J Perinatol*. 1986;3:225–230
21. Leonidas JC, Bhan I, Beatty EC. Radiographic chest contour and pulmonary air leaks in oligohydramnios-related pulmonary hypoplasia (Potter's syndrome). *Invest Radiol*. 1982;17:6–10
22. Langer R, Kaufmann HJ, Vogel M, Vocks M. Röntgenbefunde bei primärer bilateraler Lungenhypoplasie—Korrelation mit pathologisch-anatomischen Befunden. *Klin Pädiatr*. 1985;197:427–430
23. Vergani P, Ghidini A, Locatelli A, et al. Risk factors for pulmonary hypoplasia in second trimester premature rupture of membranes. *Am J Obstet Gynecol*. 1994;170:1359–1364
24. Kilbride HW, Yeast J, Thibeault DW. Defining limits of survival: lethal pulmonary hypoplasia after premature rupture of membranes. *Am J Obstet Gynecol*. 1996;175:675–681
25. DiFiore JW, Wilson JM. Lung development. *Semin Pediatr Surg*. 1994;3:221–232
26. Kitterman JA. Fetal lung development. *J Dev Physiol*. 1984;6:67–82
27. Roberts AB, Mitchell JM. Direct ultrasonographic measurement of fetal lung length in normal pregnancies complicated by prolonged rupture of membranes. *Am J Obstet Gynecol*. 1990;160:1560–1566
28. Achiron R, Heggesh J, Mashiach S, Lipitz S, Rotstein Z. Peripheral right pulmonary artery blood flow velocimetry: Doppler sonographic study of normal and abnormal fetuses. *J Ultrasound Med*. 1998;17:687–692
29. Mitchell JH, Roberts AB, Lee A. Doppler waveforms from the pulmonary arterial system in normal fetuses and those with pulmonary hypoplasia. *Ultrasound Obstet Gynecol*. 1997;11:1–6
30. Yoshimura S, Masuzaki H, Miura K, Muta K, Gotoh H, Ishimaru T. Diagnosis of fetal pulmonary hypoplasia by measurement of blood flow velocity waveforms of pulmonary arteries with Doppler ultrasonography. *Am J Obstet Gynecol*. 1999;180:441–446
31. Chaoui R, Kalache K, Tennstedt C, Lenz F, Vogel M. Pulmonary arterial Doppler velocimetry in fetuses with lung hypoplasia. *Eur J Obstet Gynecol Reprod Biol*. 1999;84:179–185

FINANCIAL COST OF SOCIAL EXCLUSION

"Costs at age 28 generated to public services (excluding private, voluntary agency, indirect, and personal costs) by individuals who at age 10 had been diagnosed with 1 of 3 levels of antisocial behavior were 10 times higher than for those with no problems. Parental social class had a relatively small effect on how much an individual will cost society. The cost is high and falls on many agencies, yet few agencies contribute to prevention, which could be effective."

Scott S, Knapp M, Henderson J, Maughan B. Financial cost of social exclusion: follow-up study of antisocial children into adulthood. *BMJ*. 2001:323:191–194

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Prenatal Prediction of Pulmonary Hypoplasia: Clinical, Biometric, and Doppler Velocity Correlates

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