Fetal pulmonary hypoplasia

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Summary

Fetal and neonatal pulmonary hypoplasia is defined as a reduction in the number of lung cells, airways and alveoli resulting in a lower organ size and weight. Pulmonary hypoplasia may be a primary or secondary phenomenon. Most cases are secondary to congenital disorders or complications during pregnancy causing thoracic compression, inhibition of fetal breathing movements or a net loss of lung fluid. Examples of disorders and complications associated with pulmonary hypoplasia are preterm premature rupture of the membranes, renal and urinary tract anomalies, skeletal and neuromuscular malformations, intrathoracic masses like congenital diaphragmatic hernia and other conditions causing compression of the fetal lungs.

Several conventional 2-dimensional (2D) ultrasonographic techniques have been used to predict pulmonary hypoplasia. The best results were achieved using the thoracic circumference (TC) versus gestational age (GA) or femur length (FL), the thoracic/abdominal circumference (TC/AC) ratio and the thoracic/heart area (TA/HA) ratio. But these measurements have not been reliable enough to be used in clinical diagnosis and management of pulmonary hypoplasia. Measuring lung volumes with MRI already has shown benefits over 2-dimensional ultrasonography. However it has limited clinical application because of the relative high costs involved. Recent studies have indicated the value of 3-dimensional (3D) ultrasonography, a technology that has the same advantages as conventional ultrasonography; inexpensiveness, ease and speed of use and high acceptance by patients. It enables us to visualize an entire volume in a single image and to visualize perpendicular planes simultaneously (multiplanar imaging). With the volume rendering mode it is possible to measure volumes of different organ systems.

The aim of this thesis is to determine if lung volume measurements with 3D ultrasonography are feasible and reliable and whether 3D lung volume measurements can predict the occurrence of pulmonary hypoplasia secondary to congenital disorders or complications during pregnancy.

Chapter 1 contains an introduction about the etiology and pathogenesis of pulmonary hypoplasia and the prenatal and postnatal diagnostic methods examined. And the aims of the thesis are described.

Charts and tables of fetal lung volumes from 18 to 34 weeks' gestation measured longitudinally using multiplanar 3D ultrasonography are presented in **Chapter 2**. Seventy-eight women with uncomplicated pregnancies were scanned 3 to 4 times for the purpose of this study. Overall we were able to acquire good image quality in 594 of 616 right and left lungs (96,4%) and the reliability was also good, with intraobserver variability of less than 3% and 5% for the right and left lung volume, respectively. In this Chapter we also present valid references for volumetric measurements of the right and left lung in male and female fetuses. It is well known that the female fetuses, on average, weigh 2-3 % less than male fetuses at any gestational ages. It has been suggested that the use of gender-specific nomograms may improve prenatal assessment of fetal growth. For gestational age the mean lung volume of male fetuses was significantly (4,3 %) larger than that of female fetuses. The difference was not significant when the lung volumes were plotted against the estimated fetal weight. It needs to be investigated if these small differences between male and female fetuses are clinically relevant.

In **Chapter 3** lung volume measurements of 10 uncomplicated pregnancies measured by MRI and multiplanar 3D ultrasonography were compared. Each patient with gestational age between 24 to 34 weeks was examined only once for the purpose of the study. When comparing the lung volumes measured with MRI and 3DUS the intraclass correlation coefficient was for the right lung 0.92 (95% CI 0.71-0.98) and for the left lung 0.95 (95% CI 0.82-0.99). The proportionate limits of agreement between the methods were for the right lung –32.57 to 20.03% and for the left lung –21.26 to 17.13%. The inter- and intraobserver agreement of both the MRI and 3D ultrasonography measurements were high.

Therefore in clinical practice 3D ultrasonography is the method of choice to measure fetal lung volumes, but if 3D ultrasonography causes unreliable visualization, fetal MRI can be a good and interchangeable option. A comparison of lung volume measurements in 10 uncomplicated pregnancies using the free-hand with positioning method and the integrated mechanical sweep method is described in **Chapter 4**. Also the agreement between the multiplanar mode of measuring lung volumes and the rotational (VOCAL) mode is assessed. Again each patient with gestational age between 24 to 34 weeks was examined only once for the purpose of the study. The ICC between the free-hand with positioning method and the integrated mechanical sweep method measurements was for the right lung 0.95 (95% CI 0.79-0.99) and for the left lung 0.94 (95% CI 0.79-0.98). The proportionate limits of agreement between the methods were for the right lung -19.44 % to 34.87 % and for the left lung -28.26% to 22.82 %. The ICC between the multiplanar mode and the rotational mode

measurements was for the right lung 0.96 (95% CI 0.85-0.99) and 0.90 (95% CI 0.65-0.97) for the left lung. The proportionate limits of agreement between the modes were for the right lung -31.49 % to 32.43 % and for the left lung -38.02% to 32.73 %. Although this study only examined the lung volumes of 10 uncomplicated pregnancies we concluded that because of the close agreement of both techniques, the integrated mechanical sweep technique should the method of choice, because it is easier to use in daily practice. When measuring lung volumes, the multiplanar mode should be considered because of the higher interobserver correlation compared to the rotational mode.

A comparison between 3D lung volume measurements and 2D biometric parameters (thoracic circumference versus gestational age or femur length, the thoracic/ abdominal circumference ratio and the thoracic/ heart area ratio) in predicting pulmonary hypoplasia in pregnancies complicated by PPROM is described in **Chapter 5**. Eighteen pregnancies complicated by PPROM at mean 21 weeks' gestation (range 14-32 weeks) were prospectively examined and in total, 32 lung scans were recorded. The incidence of pulmonary hypoplasia was 33.3%. The best diagnostic accuracy for predicting pulmonary hypoplasia was achieved using the 3D lung volume measurements versus gestational age (sensitivity of 83%, specificity of 100%, PPV of 100% and NPV of 92%). The best diagnostic parameter of the 2D biometric measurements was achieved using the TA/HA ratio, with a sensitivity of 100%, specificity of 58%, PPV of 54%and NPV of 100%. So in conclusion, 3D lung volume measurements seem to be promising in predicting pulmonary hypoplasia prenatally in pregnancies complicated by PPROM.

In **Chapter 6** a comparison between 3D lung volume measurements and 2D biometric parameters (thoracic circumference versus gestational age or femur length, the thoracic/ abdominal circumference ratio and the thoracic/ heart area ratio) in predicting pulmonary hypoplasia secondary to congenital disorders or complications during pregnancy is described. In a prospective study 33 pregnancies complicated by various disorders or complications with regard to pulmonary hypoplasia (intrauterine growth restriction (IUGR) (n=8), renal anomalies (n=11), skeletal and neuromuscular malformations (n=8) and various disorders such as hydrops fetalis and gastroschisis (n=6)) were examined and in total, 54 lung scans were recorded. Pulmonary hypoplasia was diagnosed in 16 (48.5 %) infants. 3D lung volume measurements had a better diagnostic accuracy for predicting pulmonary hypoplasia (sensitivity 94%, specificity 82%, PPV 83%, NPV 93%) compared with the best 2D biometric measurement TA/HA (sensitivity 94%, specificity 47%, PPV 63%, NPV 89%).

The role of 2D lung area and 3D lung volume measurements of the contralateral lung in assessing prognosis in 6 infants with congenital diaphragmatic hernia is described in **Chapter 7**. A total of 19 fetal lung measurements of 5 left-sided and 1 right-sided congenital diaphragmatic hernias were examined. Three infants survived, and 3 infants died by the 20th day of life. Lung volume measurements versus gestational age were beneath the 5th percentile for the non-surviving infants and within the normal ranges for the surviving infants. When comparing the observed/expected lung volume and lung area ratios of the first measurements with the ratios at the last visit before birth, the ratios of the dying infants decreased whereas the ratios of the surviving infants remained unchanged or increased. The clinical value of longitudinal measured lung volume measurements, using 3D ultrasonography and lung area measurements in fetuses with congenital diaphragmatic hernia need to be further evaluated.
Pulmonary hypoplasia is also characterised by changes in pulmonary velocity waveforms due to a decreased size of the pulmonary vascular bed, a reduced vessel count per unit of lung tissue and an increased muscularization in peripheral vessels. In **Chapter 8** the question if the pulsatility index (PI) and the resistance index (RI) of the ductus arteriosus can predict the occurrence of pulmonary hypoplasia secondary to congenital disorders or complications during pregnancy is answered. In a longitudinal study 78 uncomplicated pregnancies and 51 pregnancies complicated by various disorders or complications with regard to pulmonary hypoplasia were studied by Doppler sonography between 18 and 35 weeks of gestation.
A PI and a RI above the 97.5 percentile was considered abnormal. Using multilevel modelling reference curves of the PI and RI were created, based on 301 measurements. Of the 51 complicated pregnancies, 22 infants (43 %) were diagnosed with pulmonary hypoplasia. Using the PI a sensitivity of 36%, a specificity of 93%, PPV of 80% and NPV of 66% were found and for the RI a sensitivity of 32%, a specificity of 100%, PPV of 100% and NPV of 66%. Our data demonstrated that PI and RI of the ductus arteriosus is not useful in predicting the occurrence of pulmonary hypoplasia secondary to congenital disorders or complications during pregnancy.