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FETAL AND NEONATAL MEDICINE

Lung volume measured by functional residual capacity in infants following first trimester amniocentesis or chorion villus sampling

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ABSTRACT

Objective To determine the incidence of respiratory problems and lung volume abnormalities in babies born after first trimester amniocentesis or chorion villus sampling.

Design A prospective randomized study.

Setting Harris Birthright Research Centre for Fetal Medicine, Paediatric Respiratory Laboratory, King's College Hospital.

Subjects: Babies of mothers who had undergone first trimester amniocentesis ($n = 74$) or chorion villus sampling (CVS) ($n = 86$) for fetal karyotyping because of advanced maternal age, parental anxiety or family history of chromosomal abnormality in the absence of parental chromosome re-arrangement.

Main outcomes Respiratory distress in the neonatal period and lung volume as assessed by measurement of functional residual capacity (FRC).

Results CVS was associated with a significantly higher incidence of neonatal respiratory distress, six infants in the CVS group but none in the amniocentesis group required admission to the special care baby unit because of respiratory distress ($P < 0{\cdot}05$). Although there was no significant difference in the mean FRC between the two groups (amniocentesis 29·7 ml/kg *vs* CVS 29·6 ml/kg) the overall incidence of FRC values <2·5th centile of the normal range was 9%.

Conclusion Both amniocentesis and CVS performed in the first trimester of pregnancy may impair antenatal lung growth.

Amniocentesis in the second trimester has been associated with an increased occurrence of neonatal respiratory problems. The Medical Research Council Working Party (1978) found that neonatal unexplained respiratory difficulties lasting for more than 24 h occurred in 9·2% of infants born at 34–35 weeks gestation and whose mothers had undergone amniocentesis compared with 0·9% of controls. Similarly, Tabor *et al.* (1986), in a prospective randomized study, reported that in the group undergoing amniocentesis at a mean of 16·4 weeks gestation the occurrence of neonatal respiratory distress syndrome and pneumonia was more than doubled compared to the control group. Lung function abnormalities are also increased; Vyas *et al.* (1982) examined apparently asymptomatic infants and found that the crying vital capacity in infants whose mothers had undergone amniocentesis was lower than in controls.

Recently, amniocentesis at 10–14 weeks has been introduced as an alternative to chorionic villus sampling (CVS) for first trimester fetal karyotyping. The gestation at sampling and interval between sampling and obtaining a cytogenetic result from cell culture for CVS and amniocentesis are similar (Byrne *et al.* 1991). However, at this early stage in pregnancy, the adverse effect of amniocentesis on lung growth may be even more serious than with second trimester amniocentesis. Extrapolation from data of pregnancies complicated by preterm prelabour rupture of the membranes demonstrates that the earlier the reduction in amniotic fluid volume the worse the effect on lung growth (Blott & Greenough 1988).

We are currently conducting an on-going prospective randomized trial to assess the safety and cytogenetic accuracy of amniocentesis versus CVS at 10–14 weeks gestation and this trial will require 6700 subjects before it is completed (Byrne *et al.* 1991). One aspect of this trial was to examine the possible effect of these techniques on antenatal lung growth by examining the occurrence of neonatal respiratory morbidity and measurement of functional residual capacity (FRC) for assessment of lung volume and therefore antenatal lung growth. Since the smallest different in FRC between the two groups that would have any clinical significance is 1·0 ml/kg, it was aimed to recruit 160 subjects as this would have a 70% power at the 5% level to detect such a difference between the two groups. However, because of concerns regarding the effect of second trimester amniocentesis on lung function (Tabor *et al.* 1986; Vyas *et al.* 1982) an interim analysis of the FRC results was pre-planned after recruitment of 100 babies. At this

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interim analysis there appeared to be no significant difference in the FRC results between the two groups, but the FRC was below the 2·5th centile of our own normal range in a greater proportion of infants (5%) than would have been expected. We now report the occurrence of respiratory problems and lung volume abnormalities in the completed study of the 160 babies.

Subjects and methods

In the CVS *versus* amniocentesis trial the indications for first trimester diagnosis were fetal karyotyping for advanced maternal age, parental anxiety or family history of chromosomal abnormality in the absence of parental chromosomal rearrangement. The exclusion criteria were missed miscarriage, multiple pregnancy, heavy vaginal bleeding at presentation, major fetal abnormalities, multiple fibroids making either procedure impossible, an intrauterine contraception device *in situ* and/or the choice of one procedure because the alternative procedure was considered too difficult. The gestational age at sampling was 10–14 weeks with a minimal fetal crown-rump length of 38 mm. A transabdominal, ultrasound-guided needle (20 gauge) was used for both CVS and amniocentesis; at CVS the amniotic sac was avoided and at amniocentis the placenta was avoided. No local anaesthetic was used for either procedure. At amniocentesis 11 ml of amniotic fluid was removed.

The women with a normal fetal karyotype were requested to have a detailed fetal ultrasound examination at 20 weeks. After this scan, a doctor (P.J.T.), who was unaware of which first trimester procedure had been used asked those women who lived within the district around King's College Hospital whether they would be willing to take part in the present study which would involve examining the postnatal respiratory status of their babies. Of 168 pregnant women approached, four in each group agreed to neonatal follow-up but not to the lung function tests. None of their eight infants had neonatal problems nor did they require admission to the special care baby unit (SCBU). The remaining 160 women agreed to take part in both parts of our study.

All babies were followed from birth and admission and the diagnoses on admission to the SCBU were noted. All diagnoses were made by the clinician in charge who was unaware of the nature of the diagnostic procedure used in the first trimester. Respiratory distress was diagnosed if the baby was tachypnoeic (respiratory rate >60/minute), grunting and had sternal or intercostal recession. Specific respiratory diagnoses were made with regard to the appearance of the chest radiograph, if bacteria were isolated from the baby or if there had been complications at the delivery. Transient tachypnoea was diagnosed if the baby became tachypnoeic with a respiratory rate >60 breaths/min within 6 h of birth but persisting for less than 24 h and if the chest radiograph demonstrated 'wet lungs'. Respiratory distress syndrome was diagnosed if the baby developed respiratory signs which lasted for more than 24 h in association with a chest radiograph demonstrating symmetrically affected opaque fields with a ground glass appearance, the diagnosis was further confirmed by the failure to isolate organisms from either a blood culture or peripheral swabs taken at birth. Pneumonia was diagnosed if the baby had the above abnormal clinical signs with asymmetrical abnormalities on the chest radiograph and organisms were isolated from the endotracheal tube or nasopharyngeal aspirate. Meconium aspiration syndrome was diagnosed if the baby developed signs of respiratory distress and if there had been meconium-stained amniotic fluid at birth and evidence of aspiration at resuscitation.

Babies were recalled for lung function measurements at approximately 4 weeks of life. They were seen in the Paediatric Respiratory Laboratory where their mothers were questioned and the babies were weighed and examined. Lung function was assessed by measurement of functional residual capacity (FRC) using a helium gas dilution technique (Yuksel *et al.* 1991). Measurements were made with the baby in the semi-prone position. The baby breathed through a face mask, held firmly in place to prevent air leaks, into a water-sealed spirometer (Gould Pulmonet III). The accuracy of the spirometer was checked daily with calibrated syringes. The spirometer incorporates a digital display of FRC which was recorded above the respiratory trace at 15 s intervals. When the display remained unchanged for 30 s equilibration was assumed to have occurred and the measurement was discontinued. The traces were coded and analysed blind to the clinical details by A.G. From the trace, the end expiratory level was determined and the FRC calculated. The results were converted to body temperature, pressure saturated conditions and related to the baby's body weight.

To assess the reproducibility of the measurement of FRC in young infants two separate measurements were made in 30 children with a similar postnatal age to the study population. The mean of the differences between the paired measurements was 1·8 ml/kg. The intra-subject reproducibility of the measurement in infants and young children had been calculated previously to be 7·3% The mean FRC of 50 healthy infants (controls) measured in our own laboratory of similar postnatal age to the study population was 30 ml/kg (95% confidence limits ±6 ml/kg).

This study was approved by the King's College Hospital ethics committee.

Trial size

FRC was measured in 30 infants <8 weeks of age, the results were expressed in ml/kg. The standard deviation of these 30 FRC results was 2·6 ml/kg. Thus, recruitment of 160 babies gave us 70% power at the 5% level to detect a difference in FRC between the two groups of 1·0 ml/kg.

Statistical analysis

Differences in the FRC between the amniocentesis and CVS groups were assessed for statistical significance using Student's *t*-test or the χ^2 test. The confidence intervals were calculated, with the appropriate *P*-value, from the standard error of the difference between the means of the two groups.

Results

All the pregnant women had the procedure to which they were allocated, but in two women CVS failed to achieve a satisfactory result and therefore they also had second trimester amnio-

centesis. Both these babies were normal, had no respiratory difficulty and their FRC values were within the normal range; in the comparison between groups the data of these two babies were included in the CVS group. There was no significant difference in the indication for fetal karyotyping, maternal age or parity, mode or gestational age at delivery between the two groups (Table 1). Neither was there a significant difference between the two groups in the postnatal age at follow-up (Table 1).

Ten babies were admitted to the Special Care Baby Unit (SCBU), eight in the CVS group (non-significant). There was no significant difference in the median gestational age between the infants admitted to the SCBU, 40 weeks (range 34–42) and those not admitted 40 weeks (range 35–42). Only two babies were admitted to SCBU from the amniocentesis group; one had congenital septicaemia *(Streptococcus agalactiae)* and the other a congenital cardiac lesion (pulmonary stenosis). Of the eight babies admitted to the SCBU in the CVS group six had respiratory distress, one had bilateral hydronephrosis and jaundice and one had convulsions due to hypoglycaemia. The difference in the number of babies with respiratory distress between the CVS and the amniocentesis group was statistically significant ($P < 0.05$). Of the six babies with respiratory distress, specific diagnoses were made in three: transient neonatal tachypnoea, meconium aspiration syndrome and pneumonia *(Enterococcus faecalis)*. The respiratory signs of the remaining three babies settled spontaneously and within 24 h of birth, they were not associated with any abnormalities of chest radiograph appearance. Only two of the six babies required respiratory support. The baby with meconium aspiration syndrome required 5 days of headbox oxygen, maximum concentration 27%, and the baby who developed pneumonia required 2 days of headbox oxygen, maximum concentration 34%. None of the mothers whose infants developed respiratory distress had had chronic leakage of amniotic fluid following the first trimester procedure.

Table 1. Characteristics of the two study groups

Variable	CVS ($n = 86$)	Amniocentesis ($n = 74$)
Indication for fetal karyotyping		
Advanced maternal age	77	69
Parental anxiety	9	5
Gestational age at sampling (weeks)	11 (10–14)	11 (10–14)
Maternal age (years)	37 (25-45)	37 (26-44)
Parity	2 (1-5)	2 (1-6)
Gestational age at delivery (weeks)	40 (34-42)	40 (34-42)
Mode of delivery		
Caesarean section		
Emergency	9	9
Elective	4*	3†
Forceps	3	3
Ventouse	0	1
Age at follow-up (weeks)	4 (1-16)	4 (1-16)
Infants admitted to SCBU	8	2
Mean FRC (ml/kg)	29·7	29·6

Results are median (range) values.
* Two for breech presentation and two for previous section.
† Two for breech presentation and one for previous section.

There was no significant difference in the mean FRC between the amniocentesis group (29·7 SD 4·3 ml/kg) and the CVS group (29·6 SD 3·9 ml/kg) (*t*-test) (Fig. 1). The 95% CI of the difference between the means of the two groups was −1·38 to 1·62 ml/kg. None of the infants was symptomatic at the time of the FRC measurements. Nine babies in the amniocentesis group and 16 in the CVS group had FRC values outside the 95% CI of the reference range (Fig. 1) this difference was not statistically significant (χ^2 test). The six infants with neonatal respiratory distress had significantly higher FRC values (median 34 ml/kg, range 32–40) than the other 154 infants (median 29 ml/kg, range 17–43) ($P < 0.03$, Wilcoxon rank sum test).

Discussion

This study has demonstrated that first trimester amniocentesis compared with CVS is not associated with an increase in neonatal respiratory morbidity. Neonatal respiratory morbidity was assessed in two ways: firstly, the need for admission to SCBU because of respiratory distress and, secondly, the occurrence of lung volume abnormalities measured at approximately 4 weeks of age. No excess of infants with neonatal respiratory distress was noted in the amniocentesis group, indeed the reverse trend was found. Interestingly our finding of 7% of babies with unexplained respiratory difficulties after first trimester CVS is similar to the 8·6% reported by the United Kingdom Medical Research Council Study (1978), but in that study this was associated with amniocentesis rather than CVS.

Lung volume was assessed by measurement of FRC, using a helium gas dilution technique. This method of assessment of lung volume may be inaccurate in babies with a high airways resistance, but babies who have impaired antenatal lung growth are more likely to have low rather than high airways resistance (Helms 1982). Furthermore infants with high air-

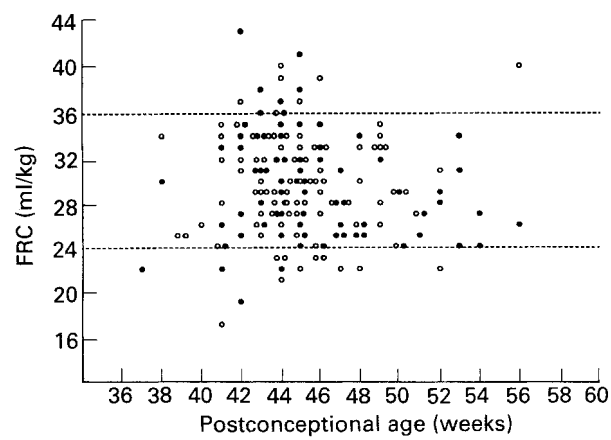

Fig. 1. Functional residual capacity (FRC) in 74 infants born to women who had undergone early amniocentesis (●) and 86 who had chorion villus sampling (○) plotted at the postconceptional age at the time of measurement. The lines indicate the 95% confidence limits of the reference range.

ways resistance, such as children with severe asthma (Greenough *et al.* 1989), who suffer from gas trapping are usually symptomatic (Yuksel & Greenough 1990). Reassuringly none of our population at the time of measurement was symptomatic. Thus, it seems likely that in our study population, measurement of FRC did give an accurate assessment of lung volume and hence antenatal lung growth.

Lung volume may also be measured by plethysmographic estimation of thoracic gas volume (Yuksel *et al.* 1990, 1991). To perform this measurement at 4 weeks of age, the babies must be sedated and we did not feel that it was appropriate to sedate asymptomatic infants solely for the purpose of research lung function measurements. In contrast, sedation is not necessary for measurement of FRC, thus this measurement can be performed throughout the first year of life and facilitate longitudinal determination of the study population's respiratory status. Plethysmographic measurements are time consuming and as a consequence, if we had used this assessment of lung volume, this would have restricted the number of babies who could have been studied. The relatively small, but important, number of babies developing neonatal respiratory distress after second trimester amniocentesis emphasized that we would need a relatively large trial size to avoid a type II error. Thus we felt it appropriate to restrict our assessment of lung volume to measurement of FRC, which we have demonstrated previously to be reproducible and well tolerated in infants (Yuksel *et al.* 1991).

There was a trend towards a greater proportion of babies with abnormal FRC values in the CVS rather than the amniocentesis group, but this was not statistically significant and no statistically significant difference was found in the mean FRC between the two groups. These data suggest that there are no obvious differences between amniocentesis and CVS in the first trimester of pregnancy in their effect on antenatal lung growth. We cannot conclude, however, that these procedures are without effect on lung growth, as the FRC was below the 2·5th centile in four babies in the amniocentesis group and 10 in the CVS group (Fig. 1), which is higher than expected. Amniocentesis in the monkey (*Macaca fascicularis*) resulted in changes in the fetal lungs, which occurred regardless of the amount of fluid removed and even if the membranes were simply punctured and no fluid removed (Hislop *et al.* 1984). The explanation for those findings could be leakage of amniotic fluid continuing for some time after the procedure. Chronic drainage of amniotic fluid following prelabour rupture of the membranes is associated with impairment of antenatal lung growth and the effect is most marked if membrane rupture occurs before 20 weeks gestation (Blott *et al.* 1987; Blott & Greenough 1988).

Some of the babies had an abnormally high FRC and this would not have been expected in babies with impaired antenatal lung growth. The six babies with neonatal respiratory distress had significantly higher FRC values than the rest of the cohort, they represent the major proportion of those whose FRC fell above the reference range. We have demonstrated previously that babies who are born preterm and suffer from neonatal respiratory difficulties tend to have elevated FRC values (Yuksel *et al.* 1991). Although the babies included in the present study were born after 37 weeks gestation, the previous results (Yuksel *et al.*) suggest that neonatal respiratory distress may account for the majority of high FRC values seen in our study population.

This preliminary study suggests that amniocentesis in the first trimester is not associated with a significantly higher risk of impaired fetal lung growth than CVS. We intend, however, to re-assess all the babies at 6 months of age when we hope to confirm that the majority have continuing normal lung growth.

Acknowledgments

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