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Lung Function following First-Trimester Amniocentesis or Chorion Villus Sampling

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Abstract. Functional residual capacity (FRC) was measured at 2–8 (median 4) weeks of age in 100 infants whose mothers had entered a randomized trial of amniocentesis versus chorion villus sampling (CVS) at 10–13 weeks gestation. At measurement all of the infants were well and none had respiratory problems. No significant difference was found in the FRC of infants whose mothers had undergone amniocentesis (n = 49) compared to those who had undergone CVS (n = 51). The 95% confidence intervals of the difference of the means of the amniocentesis group (29.7 ml/kg) and the CVS group (30.4 ml/kg) were −1.17 and 2.52 ml/kg. Three patients in the amniocentesis group and 2 in the CVS group had an FRC < 24 ml/kg, which is below the 2.5th centile of the reference range. These preliminary results suggest that there is no difference in the effect on antenatal lung growth of these two first-trimester antenatal diagnostic procedures.

Introduction

Chorionic villus sampling (CVS) enables fetal karyotyping to be performed as early as 6 weeks gestation [1]. When the fetus is affected and the parents want to have a termination, this can be performed in the first trimester of pregnancy, which is psychologically and physically less traumatic than at 20 weeks when the results from traditional amniocentesis are available. CVS, however, is associated with a higher risk of miscarriage and false-positive diagnoses [2, 3]. Furthermore, CVS is still a relatively new procedure and the long-term effects on the baby are unknown. A recent study has suggested that

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if this procedure is performed before 66 days gestation it may be associated with severe limb abnormalities [4].

Amniocentesis can now be performed from 10 weeks gestation and the interval between sampling and obtaining a cytogenetic result is similar to that of CVS [5]. However, amniocentesis carried out in the second trimester has been associated with an increase in neonatal respiratory problems. The United Kingdom Medical Research Council study documented a 9.2% incidence of unexplained respiratory difficulties lasting for more than 24 h in infants born at 34–35 weeks gestation and whose mothers had undergone amniocentesis compared to an incidence of 0.9% in controls [6]. Tabor et al. [7] found that following amniocentesis at a mean of 16.4 weeks, respiratory distress syndrome was diagnosed more often than in the control group (relative risk 2.1) and more babies were treated for pneumonia (relative risk 2.5). Furthermore, Vyas et al. [8] examined apparently asymptomatic infants and demonstrated that the crying vital capacity in infants whose mothers had undergone amniocentesis was lower than in controls. Extrapolation from data of pregnancies complicated by premature rupture of the membranes demonstrates that the earlier the reduction in amniotic fluid volume the worse the effect on lung growth [9]. Thus, it is possible that with amniocentesis in the first trimester the adverse effect on lung growth may be even more dramatic.

We are currently conducting a prospective randomized trial to assess the safety and cytogenetic accuracy of amniocentesis versus CVS at 10–13 weeks gestation. Infants of patients who live within the King's College Hospital district are recalled for assessment of lung function at approximately 4 weeks of age.

The aim of the present study was to determine if either procedure was associated with abnormal antenatal lung growth as demonstrated by a significantly lower functional residual capacity (FRC) in the neonatal period. In this preliminary report the results of lung function measurements in the first 100 consecutive cases are presented.

Patients and Methods

The infants were seen in the Paediatric Respiratory Laboratory where their history was taken and they were weighed and examined. Lung function was assessed by measurement of FRC using a helium gas dilution technique [10]. Measurements were made with the infant in the semi-prone position. The infant 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-second 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 of clinical details by A.G. From the trace the end-expiratory level was determined and FRC calculated. The results were converted to body temperature, pressure-saturated conditions and related to the infant'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 intrasubject reproducibility of the measurement in infants and young children had been previously calculated to be 7.3% [10]. 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).

Trial Size

FRC was measured in 30 infants less than 8 weeks of age, expressing the results in millilitres per kilogram. The standard deviation of these 30 FRC results

Table 1. Comparison of FRC results

Compared groups	95% CI of the differences of the means, ml/kg
CVS (30.4) with amniocentesis (29.7)	−1.17 to 2.52
Controls (30) with study population (30.1)	−1.52 to 1.36
Controls (30) with CVS (30.4)	−1.99 to 1.05
Controls (30) with amniocentesis (29.7)	−1.29 to 1.95

In parentheses mean FRC values (ml/kg).

was 2.6 ml/kg. Thus, recruitment of 100 patients into the study gave us 80% power at the 5% level to detect a difference in FRC between the two groups of 2.0 ml/kg.

Statistical Analysis

FRC was compared between infants whose mothers had undergone a single diagnostic procedure and differences between the amniocentesis and CVS groups were assessed for statistical significance using a Student's t test or the chi-squared 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.

Permission for this study was granted by the King's College Hospital Ethical Committee.

Results

FRC results were compared from 49 infants whose mothers had undergone amniocentesis and 51 who had undergone CVS. The median gestational age at amniocentesis or CVS was 11 weeks (range 10–13). The median postnatal age at follow-up for the amniocentesis group was 4 weeks (range 3–8) and the CVS group 4 weeks (range 2–7).

There was no significant difference in the FRC results between the amniocentesis and the CVS groups or between these groups and the healthy controls (figure 1, table 1). The FRC was below 24 ml/kg (2.5th centile of the controls) in three patients from the amniocentesis group and in two from the CVS group and above 36 ml/kg (97.5th centile of the controls) in four patients from the CVS group and five in the amniocentesis group (non-significant).

Discussion

In this study there was no significant difference in the lung volume between infants whose mothers had undergone early amniocentesis and those who had had CVS. Impairment of antenatal lung growth results in abnormal lung function postnatally and in particular small volume lungs [11]. In this study lung volume, as a reflection of lung growth, was assessed by measurement of FRC using a helium gas dilution technique. Although this method of assessment of lung volume may be inaccurate in infants with a high airways resistance, infants with reduced antenatal lung growth are more likely to have low rather than high airways resistance [11]. Furthermore infants with high airways resistance, such as children with severe asthma [12] who suffer from gas trapping are usually symptomatic [13]. Reassuringly none of our

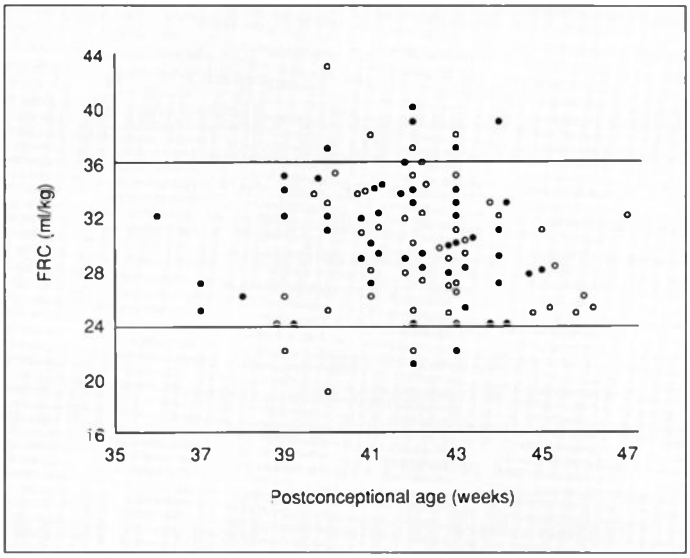

Fig. 1. FRC in 49 infants whose mothers had undergone early amniocentesis (○) and 51 who had CVS (●) plotted on the postconceptional age at the time of measurement. The solid horizontal lines indicate the 95% confidence limit of the reference range.

population at the time of measurement were symptomatic. Thus, it seems likely that in our study population the measurement of FRC does give an accurate assessment of lung volume and hence antenatal lung growth.

Other investigators [8] have assessed postnatal lung function by measurement of crying vital capacity. That test [8], however, relies on measuring the infant's response, i.e. a cry, to a noxious stimulus and it is difficult to guarantee the same strength stimulus to all infants. In contrast, measurement of FRC requires no co-operation from the infant and is very reproducible. Clinical pulmonary complications have also been used to document impaired antenatal lung growth [7, 9]. Such problems, however, are likely to be associated with at least moderate pulmonary abnormality, whereas it is well appreciated that some lung function abnormalities may be asymptomatic [13]. Thus measurement of lung volume using the FRC technique provides a much more sensitive assessment of antenatal lung growth.

The lack of significant difference in the FRC of the two groups suggests that amniocentesis and CVS performed in the first trimester of pregnancy do not have an obvious difference in their effect on antenatal lung growth. We cannot, however, conclude that these procedures are without effect on lung growth. Indeed the FRC was below the 2.5th centile in 3 of the amniocentesis group and 2 of the CVS group, which is slightly higher than expected. Hislop et al. [14] demonstrated that amniocentesis in the monkey *(Macaca fascicularis)* resulted in changes in the fetal lungs. These changes, however, occurred regardless of the amount of fluid removed or indeed if the membranes were simply punctured and no fluid was removed. The authors suggested that the explanation for their findings could be chronic leakage of amniotic fluid due to the amniocentesis. Alteration in fetal activity following the proce-

dure could also explain their findings. Manning et al. [15] documented a significant fall in fetal breathing movements 24–48 h after amniocentesis and attributed this to the increase in uterine activity which is known to occur following amniocentesis [16]. In both experimental studies in rabbits [17] and in clinical studies [18] cessation of fetal breathing activity has been associated with impaired antenatal lung growth.

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 do intend, however, to reassess all our patients at 6 months of age to, hopefully, confirm continuing normal lung growth with postnatal age.

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