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Abnormalities of lung volume at follow-up after antenatal rhesus iso-immunization

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Rhesus iso-immunization is associated with fatal pulmonary hypoplasia. We have examined the hypothesis that abnormalities of lung volume, as an index of lung growth, may also be found in survivors. At a median age of nine months, lung volume was assessed by measurement of functional residual capacity in 23 patients affected antenatally by rhesus iso-immunization. Seventeen of the patients had required at least one intrauterine transfusion. Five patients (group A) had an FRC <24 ml/kg (median 21 ml/kg, range 19–22 ml/kg) and the other 18 (group B) an FRC ≥ 24 ml/kg (median 27 ml/kg, range 24–36 ml/kg) ($p<0.01$). The only significant difference between these two groups was the timing of the first foetal blood sampling and intrauterine transfusion, being a median of 22 weeks (range 20–23 weeks) in group A and 30 weeks (range 17–36 weeks) in group B ($p<0.01$). □ *Pulmonary hypoplasia, Rhesus iso-immunization*

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Rhesus iso-immunization can be associated with fatal pulmonary hypoplasia. This may result from chronic compression of the lungs by foetal ascites and pleural effusions. A direct immune-mediated injury affecting lung growth has also been suggested (1). It seems likely that abnormalities of lung volume, as an index of lung growth, would also be found in survivors, particularly those most severely affected antenatally, that is patients who required intrauterine transfusions. The aim of this study was to test this hypothesis by measuring functional residual capacity (FRC) at follow-up of patients who had had rhesus iso-immunization and undergone antenatal intervention procedures.

Patients and methods

The study population was recruited from 43 infants who had had rhesus iso-immunization and had been managed antenatally at King's College Hospital (KCH). Patients who lived within travelling distance of KCH had lung function measurements at follow-up. The 23 children (10 boys and 13 girls) were studied at a median postnatal age of 9 months (range 2–24 months). Their median gestational age at their first foetal blood sampling (cordocentesis) was 24 weeks (range 17–36 weeks). Intrauterine transfusions were performed during cordocentesis. The procedures were not undertaken in patients prior to 17–18 weeks of gestation as, in our experience of more than 500 rhesus iso-immunized patients (2), neither foetal death nor the development of hydrops occurs before this gestational age. The site and direction of the umbilical cord at its placental insertion were defined by real-time ultrasound scanning with a curvilinear probe. The cord was then punctured near its placental insertion, foetal blood aspirated and the haematocrit determined. Foetuses were transfused when their haematocrit was at least 2 SD below the normal mean for gestation (2).

The median birth weight of the study group was 2.7 kg (range 0.9–3.97 kg) and gestational age at birth was 36 weeks (range 27–39 weeks). The median number of foetal blood samplings was 3 (range 1–8). Seventeen of the 23 patients had required intrauterine transfusions; the median number of transfusions was 3 (range 1–7). Only 2 infants required neonatal respiratory support; both infants were born at 27 weeks of gestation. One of these 2 infants, the only infant in our series who was hydropic at birth, was ventilated for 28 days and required supplementary oxygen for 8 weeks. The second infant was ventilated for 2 days and oxygen-dependent for 5 days.

This study was approved by the King's College Hospital Ethics Committee and informed parental consent was given.

The patients were seen in the Paediatric Respiratory Laboratory. Lung function was assessed by measurement of FRC using a helium gas dilution technique (3). All measurements were made with the children non-sedated and in a semi-prone position. The children breathed through a face mask, held firmly in place to prevent air leaks, into a water-sealed spirometer (Gould Pulmonet III). The spirometer incorporates a digital display of FRC, which was recorded above the respira-

Table 1. Comparison of infants with low and normal FRC. Values are median (range).

	Group A ($n=5$)	Group B ($n=18$)
FRC at follow-up (ml/kg)	21 (19–22)	27 (24–36)
Gestational age at first foetal blood sampling (weeks)	22 (20–23)	29 (17–36)
No. of patients who underwent intrauterine transfusion	5	12
Gestational age at first intrauterine transfusion (weeks)	22 (20–23)	30 (17–36)
No. of foetal blood sampling/transfusions per patient	8 (3–12)	5 (1–16)
Gestational age at delivery (weeks)	33 (27–38)	36 (31–39)
Age at follow-up (months)	10 (4–16)	11 (2–24)
Weight at follow-up (kg)	8.2 (4.8–12.8)	9.2 (4.5–16)

tory 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 of clinical details by one of the authors (AG). From the trace the end-expiratory level was determined and from this the FRC calculated. The results were converted to body temperature and pressure-saturated conditions and then related to the patient's weight. To assess the reproducibility of the measurement of FRC in young children, two separate measurements had been made in 30 infants. 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%.

Statistical analysis

The patients were separated into two groups according to whether their lung volume at follow-up was or was not reduced (i.e. <24 ml/kg); the mean FRC of 50 healthy "control" infants measured between 1 and 10 months was 30 ml/kg (95% CI ± 6 ml/kg) (4). Differences between the groups were assessed for statistical analysis using the Wilcoxon signed rank sum test.

Results

Five patients had a low FRC (<24 ml/kg) (group A) and 18 patients had an FRC $\geqslant 24$ ml/kg (group B). Non-parametric regression analysis demonstrated that FRC was significantly related to gestational age at first transfusion ($r=0.7$, $p<0.01$), but there was no significant relationship between FRC at follow-up and the number of antenatal intervention procedures (either foetal blood sampling alone or with transfusion) (Table 1). Groups A and B differed significantly only in their gestational age at first foetal blood sampling/transfusion ($p<0.01$) (Table 1). All of group A had had their first intrauterine procedure prior to 24 weeks of gestation. The only infant who was hydropic at birth had a low FRC (19 ml/kg). The other ventilated infant, however, had an FRC of 35 ml/kg.

Discussion

Our data demonstrated that post-neonatal FRC was reduced in some rhesus iso-immunized infants who had undergone intrauterine transfusion. FRC, a measure of lung volume, was assessed by a helium gas dilution technique. The method can be inaccurate in infants with high airways resistance. Infants with reduced antenatal lung growth, however, have low, rather than high, airways resistance (5). Infants who have impaired antenatal lung growth have small volume lungs (6). Thus the data suggest that certain infants with rhesus iso-immunization have impairment of antenatal lung growth.

Only one of the five infants who had a low FRC was hydropic at birth and thus we cannot explain the low lung volumes of the other infants by a compressive mechanism. Neither did the lung function abnormality relate to a need for neonatal ventilation. Group A was born at an earlier gestation than group B, but this difference did not reach statistical significance and, as premature birth tends to be associated with an elevated rather than a reduced FRC (7), an effect of gestational age at birth did not explain our findings. As our patients were not studied immediately after birth we cannot exclude that in some patients postnatal growth had compensated for an abnormality of foetal lung growth. It should be noted, however, that groups A and B were of similar postnatal ages and yet had significantly different FRC values. The only significant difference between the infants with a low FRC and those with an FRC $\geqslant 24$ ml/kg was the timing of their first intrauterine procedure, all the former group having had their first transfusion prior to 24 weeks of gestation.

Lung function abnormalities have been described following antenatal diagnostic interventions, particularly amniocentesis, and thus could be explained by loss of amniotic fluid (8). It has also been suggested, however, that even insertion of a needle into the uterine cavity may increase uterine activity, suppressing foetal breathing movements (9) and thus, if performed at a critical stage of gestation, could affect lung growth (10). Thus intrauterine transfusion via cordocentesis at an early gestation might affect lung growth by a similar mechanism. Our data, however, would suggest it is less likely to be an effect of repeated procedures as we saw no

significant relationship between the number of antenatal procedures (sampling/transfusion) and the FRC at follow-up.

All the intrauterine transfusions were performed in response to the foetal haematocrit. Thus the infants with a low FRC and who had required intrauterine transfusion prior to 24 weeks of gestation had become anaemic at an earlier stage of pregnancy than the remainder of our study group. Our results therefore suggest that abnormalities of lung volume occurred in the most severely iso-immunized patients, as indicated by their need for earlier transfusion.

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