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Ventilatory requirements for respiratory distress syndrome in small-for-gestational-age infants

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Abstract. Neonatal ventilatory requirements and outcome were examined in 135 very preterm, small-for-gestational age (SGA) infants to determine whether fetal growth retardation protects against severe respiratory distress syndrome (RDS) in very immature infants. Their results were compared to those from gestational age- and gender-matched controls. Although there was no significant difference in the median duration of mechanical ventilation between the two groups, more SGA infants required ventilation and were ventilated because of RDS. In a subgroup also matched for mode of delivery, there was no significant difference between the proportion of SGA infants requiring mechanical ventilation for RDS compared to their matched controls. The mortality was greater in the SGA group. We conclude that fetal growth retardation does not protect against severe RDS.

Key words: Respiratory distress syndrome – Prematurity – Small for gestational age – Mechanical ventilation

Introduction

It has been suggested that fetal growth retardation protects against the development of respiratory distress syndrome (RDS). Gluck and Kuliovitch reported that the lecithin to sphingomyelin ratio (L : S ratio) in the amniotic fluid of pregnancies complicated by fetal growth retardation is increased [11]. They suggested that chronic fetal stress had resulted in raised endogenous steroid production which increased surfactant synthesis. In support of this hypothesis was the finding that exogenous steroids administered to animal subjects increased lung maturity as reflected by an elevation of the L : S ratio [8]. An association between fetal growth retardation and reduced severity of RDS has been suggested to occur in preterm infants [17]. Procianoy et al. reported that the incidence of RDS in small-for-gestational-age (SGA) infants of less than 32 weeks gestation was only 5% compared to 74% in controls matched for gestational age and gender [17]. That study, however, only included 19 patients and took place between 1976 and 1978. More recently hypoxia and acid-base disturbances have been demonstrated in very growth-retarded fetuses by ultrasound guided cord blood sampling [16] and these abnormalities are known to interfere with surfactant production and release [15]. We therefore postulate that fetal growth retardation may not protect against severe RDS in very immature SGA infants. To test this hypothesis we have audited the neonatal ventilatory requirements and outcome of consecutive SGA infants who were admitted to our neonatal intensive care unit and were less than 33 weeks gestational age and compared these findings to those in a group of appropriate controls. We also included in our analysis a subgroup of infants whose birth weight was less than the 3rd percentile. Our aim was to assess whether the effect of growth retardation on the severity of RDS, if present, was even more obvious in this more severely growth retarded group.

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Abbreviations: L : S ratio = lecithin : sphingomyelin ratio; RDS = respiratory distress syndrome; SGA = small-for-gestational age

Methods

All infants of less than 33 weeks gestational age admitted to the neonatal intensive care unit during the 5-year period May 1985 – April 1990 were considered eligible for entry into the study. Gestational age was determined from the mother's last menstrual period, an ultrasound scan prior to 21 weeks gestation, the infant's physical appearance and neurological score. SGA infants, that is, those whose birth weight was less than the 10th percentile for gestational age, [1, 9, 21] were recruited into the study. These SGA infants were then matched with an appropriately grown baby, that is, one whose birth weight was between the 10th and 90th percentiles for gestational age. Infants were individually matched for gestational age, gender and birth date as close as possible to that of the SGA case. Controls for three SGA infants could not be found.

The medical records of the infants were examined and the need for and duration of ventilation were recorded. The indication for ventilation had previously been documented by the clinician in

charge of the case, the diagnosis being made according to the unit's routine clinical criteria. RDS was diagnosed if the infant developed tachypnoea, retractions, grunting and/or cyanosis within 4 h of birth persisting for longer than 24 h, in association with a chest X-ray film appearance demonstrating symmetrically affected opaque lung fields with a ground glass appearance. The diagnosis was further confirmed by failure to isolate bacteria from the blood cultures, ear swabs and gastric aspirate which were taken on admission of the baby to the neonatal intensive care unit. Infants who satisfied the above diagnostic criteria but whose gestational age was equal to or less than 25 weeks were described as suffering from respiratory distress of extreme prematurity. The number of deaths in the SGA infants and their controls was recorded and the cause of death was confirmed by postmortem examination.

Statistical analysis

Differences between groups were assessed for statistical significance using either the chi-square test or the Wilcoxon rank sum test. The confidence intervals were calculated with the appropriate P value from the standard error of the difference between the means of the different groups.

Patients

During the 5-year study period 135 of 497 infants of less than 33 weeks gestational age admitted to the neonatal unit were SGA. Their median gestational age was 30 weeks (range 23–32) and birth weight 916 g (range 398–1480). The median gestational age of their matched controls was 30 weeks (range 23–32) and their median birth weight of 1458 g (range 510–2545), was significantly heavier than that of the SGA infants ($P < 0.0001$). Of the 135 SGA infants, 26 (19.2%) were delivered vaginally compared to 66 (50%) of the controls ($P < 0.001$). Of the SGA infants 55 (41%) had a birth weight between the 3rd and 10th percentiles. Their median birth weight was 1090 g (502–1480) which was significantly lower than that of their gestational age-matched controls (median 1500 g, range 566–2304), $P < 0.0001$. The 80 infants (59%) with a birth weight less than the 3rd percentile had a median birth weight of 728 g (range 398–1294) which was significantly lower than that of their gestational age-matched controls (median 1458 g, range 510–2545), $P < 0.0001$.

Of the 135 SGA patients, 41 (34 with birth weight less than the 3rd percentile) had been referred antenatally for further investigation of fetal growth retardation. This included a cord blood sample for fetal karyotyping and determination of fetal acid base status [16]. No chromosomal abnormality was demonstrated. Twenty-three fetuses were found to be both acidotic and hypoxic, seven were hypoxic only and a further three were acidotic only. Corticosteroids were administered routinely between 26 and 32 weeks to any patient in whom preterm delivery seemed likely or elective delivery was planned [10]. Tocolytic agents were given to patients presenting in preterm labour to delay delivery for at least 24 h wherever possible to allow the dexamethasone to take effect, but these were not used in mothers who had evidence of sepsis or who were already in established labour (cervical dilatation greater than 4 cm). No infant received exogenous surfactant replacement therapy during this period.

This study was approved by the King's College Hospital Ethics Committee.

Results

A greater proportion of the SGA infants (112 of 135) required ventilation in the neonatal period compared to their controls (88 of 132, $P = 0.00394$). The duration of ventilation, however, did not differ significantly between the groups, being a median of 5 days (range 1–103) in the SGA group and 3 days (range 1–120) in the controls. The 95% confidence intervals of the difference of the means of the SGA infants (10 days) and the controls (7.8 days) were −2.60 to 6.94 days. Of the 80 infants whose birth weight was less than the 3rd percentile, 67 required ventilation for a median of 5 days (range 1–103) and 54 controls required ventilation for a median of 4 days (range 1–120), (not significant). RDS was the main indication for mechanical ventilation. More SGA infants (88 of 135), were ventilated because of RDS than their controls (57 of 132), ($P < 0.001$). Similarly, more infants with a birth weight less than the 3rd percentile were ventilated because of RDS than their gestational age-matched controls ($P < 0.01$) (Table 1). The proportion of infants requiring mechanical ventilation for RDS did not differ significantly between those infants whose birth weight lay between the 3rd and 10th percentiles (35 of 55) and those who were less than the 3rd percentile (53 of 80). The median duration of ventilation was also not significantly different, being 5 days (range 1–82) and 4 days (1–103) respectively. There was no significant difference in the number of infants requiring mechanical ventilation who were ventilated for reasons other than RDS in the two groups.

Table 1. Diagnoses of ventilated infants. Infants with birth weight less than 3rd percentile and their controls are depicted in brackets

	SGA infants $n = 135$ ($n = 80$)	Controls $n = 132$ ($n = 77$)
RDS	88 (53)	57 (36)
Transient tachypnoea of the newborn	10 (9)	11 (8)
Pneumonia	1 (0)	6 (4)
Septicaemia	4 (1)	4 (2)
Respiratory distress of extreme prematurity	8 (3)	5 (1)
Pulmonary hypoplasia	1 (1)	4 (2)
Spontaneous pneumothorax	0 (0)	1 (1)

In view of the significant difference in mode of delivery between the two groups a further comparison was made between 26 vaginally delivered SGA infants with a median gestational age of 28 weeks (23–32) and controls matched for mode of delivery, gestational age and gender (median gestation age 28 weeks, range 23–32). Of the 26 SGA infants, 21 required ventilation, median duration 4 days (1–70) and 22 of the controls, median duration 4 days (1–120 days). These differences were not significant. Of the vaginally delivered SGA infants who were ventilated for RDS, 12 had a median gestational age of 29 weeks (range 26–32), duration of ventilation 4 days (range 1–56). Of the 26 controls matched for gestational age, gender and mode of delivery, 12 were also ventilated for RDS. The duration of ventilation of the controls (median 4 days, range 1–120) did not differ significantly from that of the SGA infants.

The mortality of the SGA group was greater than that of the controls ($P = 0.0021$) 19 of the 35 SGA infants

Table 2. Causes of death. The infants with birth weight less than the 3rd percentile are shown in the brackets ( )

	SGA infants	Controls
n	35 (19)	14 (11)
Respiratory failure	14 (9)	5 (4)
Intraventricular haemorrhage	5 (2)	2 (2)
Septicaemia	6 (2)	0 (0)
Pulmonary haemorrhage	4 (2)	0 (0)
Bronchopulmonary dysplasia	2 (0)	2 (2)
Necrotising enterocolitis	1 (1)	0 (0)
Hepatic failure	1 (1)	0 (0)
Pulmonary hypoplasia	2 (2)	5 (3)

who died had a birth weight below the 3rd percentile. Septicaemia was the only cause of death found to be significantly more frequent in the SGA group that in the controls, $P < 0.02$ (Table 2). There was no significant difference in the proportion of infants who died whose birth weight lay between the 3rd and 10th percentiles (16 of 55) and whose birth weight was less than the 3rd percentile (19 of 80).

Discussion

The present results do not support the hypothesis that fetal growth retardation protects against the development of severe RDS. Indeed, significantly more of the SGA infants required mechanical ventilation for RDS. These results are supported by the earlier findings of Ruys-Dock and de Leeuw [18]. They reported a very low incidence of ventilation in both their SGA infants and controls, but had studied a population who were relatively mature with a mean gestational age of 33 weeks (range 29–37 weeks). Nonetheless, in that series all 10 of the 55 SGA infants who developed RDS required mechanical ventilation and 7 died but of the 55 controls 15 developed RDS, 7 required ventilation and only 1 died [18].

Our groups differed in their mode of delivery, more of our SGA infants being delivered by caesarian section, and mode of delivery may affect the severity of neonatal respiratory distress [5]. We did not, however, find a difference in the proportion of SGA or control infants who required ventilation for RDS nor in the duration of ventilation when the SGA infants were further matched with controls for mode of delivery. A further possible explanation for our results is the difference in antenatal steroid use between the two groups [10]. If such a difference did exist it would be most likely to work in favour of the SGA group. Many of the SGA patients were already undergoing antenatal investigation, as evidenced by the number who had had cord blood sampling and this should have made it easier to plan the delivery after an appropriate course of antenatal steroid therapy had been given. This hypothesis is supported by the greater number of caesarian sections in the SGA group.

The most likely explanation for our results is that the SGA group were so severely compromised antenatally that there was interference with surfactant production. Chronic asphyxia results in a redistribution of fetal blood flow with decreased flow to the lungs [12] which would be expected to limit surfactant production. This suggestion is supported by the high proportion of fetuses who underwent cordocentesis and had hypoxia and acid base abnormalities. Both hypoxia and acidosis can interfere with surfactant production and release [15]. Gluck and Kuliovitch [11] had studied pregnancies which were more advanced than ours. It is possible that the consequences of fetal growth retardation may differ depending on the gestational age at which it occurs. Certainly mortality is greater in the very immature SGA infant. The very immature infant seems less capable of withstanding and compensating for those insults which lead to growth retardation and may, for example, be less able to produce a cortisol surge in response to stress.

We found a higher mortality amongst the SGA infants than their matched controls. Pulmonary haemorrhage and necrotising enterocolitis [12] are both known complications of fetal growth retardation and in this series deaths due to those conditions only occurred in our SGA group and not in the controls. There was a significantly increased proportion of SGA infants dying from septicaemia compared to the controls. Ruys-Dock and de Leeuw [18] also found a significant increase in minor infections among relatively mature SGA infants compared to matched controls. SGA infants with reverse diastolic flow in the umbilical artery suffer from a number of complications including a low platelet count [12]. It is our clinical experience that SGA infants have other features of bone marrow suppression including a low white blood cell count and this has also been demonstrated in more mature SGA infants [18]. These factors may well account for the higher incidence of septicaemia in our present population of SGA infants. Defence against infection is further impaired in SGA infants as it has been demonstrated in those born at term, there is a lower IgG and C_3 complement concentration compared to controls [19] and that cell-mediated immunity is also impaired [6, 7].

Interestingly, five of the controls died of pulmonary hypoplasia but only two of our SGA infants. This would seem to be the converse of what would be expected, as it seems likely that with such abnormal fetal acid base balance and severity of growth retardation, that these pregnancies would also have been complicated by oligohydramnios [14]. We have previously found, however, that absence of breathing movements leading to pulmonary hypoplasia [3] is more likely with the oligohydramnios due to premature rupture of the membranes rather than uteroplacental insufficiency [1]. It is possible that some of the pregnancies in the controls were complicated by premature membrane rupture which frequently predates preterm labour [2] and thus were predisposed to pulmonary hypoplasia.

We found no difference in the proportion of infants requiring ventilation for RDS, in the duration of ventilation nor in the number dying when comparing these infants with a birth weight between the 3rd and 10th percentile and those less than the 3rd percentile. These results suggest that neonatal morbidity and mortality may not be related to the degree of growth retardation if the

infant is very immature. This initially may seem surprising as morbidity has previously been reported to differ in different forms of growth retardation [20]. The risk for low Apgar scores at 1 and 5 min, aspiration syndrome, hypoglycaemia and perinatal asphyxia was reported to be significantly higher in those infants with a low ponderal index or disproportionate intra-uterine growth retardation compared to those with proportionate intrauterine growth retardation [20]. That study was comprised of infants whose mean gestational age was 39 weeks, whereas the present study only included infants of less than 33 weeks gestational age. The high mortality and morbidity imposed by the extreme prematurity of our study population may mask any differences between the two subgroups of SGA infants. We did not, however, set out to record many of the complications documented by Villar [20] and cannot therefore exclude the possibility that the severity of growth retardation may affect the occurrence of minor forms of morbidity.

In summary, these data support our hypothesis that fetal growth retardation does not protect against severe RDS of infants who are very preterm at birth. Indeed, our results demonstrate that the chronic intra-uterine hypoxia to which SGA infants may be exposed, not only increases their mortality rate but may also increase the severity of their respiratory distress.

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