Influence of ethnic origin on respiratory distress syndrome in very premature infants

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Abstract

Aim—To determine whether the incidence of respiratory distress syndrome (RDS) is related to ethnic origin in very premature infants (≤32 weeks of gestational age and birthweight ≤2.0 kg).

Method—A retrospective cohort study was performed to determine the incidence of respiratory disorders in African, Caribbean, and caucasian infants. An African infant was matched with two infants (one of Caribbean and one of caucasian descent) for gestational age and birth order and, if several eligible matching infants were found, for gender and approximate birth date. Fifty African infants (median gestational age 28 weeks, range 23–32) were matched with an infant of Caribbean and one of caucasian descent.

Results—Compared with the incidence of RDS in African infants (40%), that in caucasian infants (75%) was significantly higher (p<0.05), while the incidence in the Caribbean infants (54%) did not differ significantly. Regression analysis showed that ethnic origin was related to the occurrence of RDS independent of gestational age, size for dates, antenatal steroids, hypertension during pregnancy, premature rupture of membranes, maternal smoking, mode of delivery and infant gender.

Conclusion—The enhanced lung maturation found in certain ethnic groups, even when born prematurely, has implications for clinical management.

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Black infants have a lower incidence of respiratory distress syndrome (RDS) than white infants. This seems to be due to enhanced lung maturation. That effect, however, may be restricted to relatively mature infants. Logistic regression analysis of 298 infants born between 24 to 35 weeks of gestation failed to demonstrate a lower incidence of RDS in white rather than black babies. A further study showed accelerated lung maturation only in infants beyond 32 weeks of gestation. The situation may also be complicated by the exact ethnic origin of the infant. Lung maturation occurred more rapidly in Ethiopians, but more slowly in South African blacks, than in white or black infants from the United States. The aim of this study was, therefore, to assess if ethnic origin did affect the rate of lung maturation, as evidenced by the occurrence of RDS, in very prematurely born infants of African, caucasian, or Caribbean descent.

Methods

Infants who had been admitted to the neonatal intensive care unit, and of less than 33 weeks of gestational age were retrospectively identified between 1991 and 1995. In 60 infants both parents were of African descent. Matching for gestational age and birth order was then attempted for each subject with an infant whose parents were both of caucasian descent and a second infant whose parents were both of Caribbean descent. If several infants matched a subject, a same sex infant and then the one closest in birth date was chosen. Matching proved impossible for 10 African infants—three sets of twins and four infants all of 31 weeks of gestational age. The latter problem was due to the limited number of Caribbean infants in that age group.

Maternal and newborn inpatient hospital records served as the information source for our study. Data obtained from the mothers’ hospital records included parental ethnicity, antenatal steroids (a standard regimen was used throughout the study period), hypertension during pregnancy, prolonged rupture of membranes (>24 hours) (PROM), antepartum haemorrhage, smoking habit, birth order, mode of delivery and gestational age of the infant calculated from the date of the mother’s last menstrual period to that of birth.

The infant’s hospital records provided information on birthweight, gender, occurrence and diagnosis of respiratory failure, requirement for ventilation and supplementary oxygen and discharge status (alive or deceased). Infants were described as small for gestational age (SGA) if their weight was less than the third percentile on the Gairdner-Pearson growth curves. The diagnosis of the infant’s respiratory failure had been made by the clinician in charge using standard criteria, in particular the appearance of the infant’s chest radiograph taken within four hours of birth. The chest radiograph appearance was independently reported by one paediatric radiologist. Respiratory distress syndrome (RDS) was diagnosed if the infant developed respiratory problems within four hours of birth, which persisted for longer than 24 hours; or if the infant’s chest radiograph appearances showed symmetrical granular opacities in both lung fields with a superimposed air bronchogram, and the infant had received at least one dose of surfactant replacement therapy. Transient tachypnoea of the newborn (TTN) was diagnosed if the infant was tachypnoeic and
had a chest radiograph appearance which showed increased vascular markings, fluid in the horizontal fissure, and overinflation of the lung. Congenital pneumonia was diagnosed if there was chest radiographic evidence of pneumonitis—that is, asymmetrical consolidation, with or without positive blood cultures. Respiratory distress was diagnosed if the infant required supplementary oxygen or ventilatory support, but did not have an abnormal chest radiograph appearance.

Differences in maternal characteristics and in diagnoses of infant respiratory failure in the three ethnic groups were assessed for significance using $\chi^2$ tests. Multiple logistic regression, with presence or absence of RDS as the dependent variable, was used to investigate the effect of ethnic origin on this outcome after controlling for gestational age, size for dates, antenatal steroids, hypertension during pregnancy, PROM, maternal smoking, mode of delivery and infant gender. Non-linear effects of gestational age were not evident, using the various methods suggested by Hosmer and Lemeshow. Thus gestational age was treated as a continuous variable. Sizes for dates were grouped into four categories for the regression analysis (<25th centile, 25–50th centile, 50–75th centile, and >75th centile). The remaining variables were dichotomous.

Fifty subjects were each matched with an infant of caucasian and Caribbean descent (table 1). There were no significant differences between the three groups with regard to the gender distribution or the proportions who were small for gestational age. The caucasian and Caribbean infants had birthweights usually within 10% of those of the African infants; had a lower incidence of RDS in African (significant) and Caribbean (non-significant) infants than in Caucasian infants, 26 of the caucasian and 19 of the Caribbean infants were heavier than their matched subject. All patients had been incorporated into the hospital’s standard policies. In particular, antenatal steroids were given to all women if a preterm delivery was predicted and there was no evidence of maternal sepsicaemia; diabetes and hypertension were not contraindications. Infants less than 29 weeks of gestational age were routinely intubated in the delivery suite; more mature infants only for resuscitation purposes. Infants would then remain intubated and ventilated until arterial blood gas estimation on arrival at intensive care showed this to be unnecessary. Surfactant replacement was given in the first four hours of life to infants whose chest radiograph appearance was suggestive of RDS (see above), who were ventilated, and who required an inspired oxygen concentration of more than 0.29.

Results
The only significant difference in the maternal characteristics among the three groups was in the proportion who smoked ($\chi^2 = 8.44$, df=2, $p<0.02$), smoking being most common in the caucasian group (table 1). The proportions of infants in the three groups who were diagnosed with RDS, congenital pneumonia, TTN and respiratory distress are shown in table 2, along with the other infant outcomes. Each infant received one of these four diagnoses. A diagnosis of congenital pneumonia or of TTN was comparatively rare, so that a statistical analysis which distinguished these diagnoses was not feasible. When numbers of infants with RDS were compared with numbers of infants without RDS, a significant effect of ethnic origin was observed ($\chi^2 = 11.9$, df=2, $p<0.005$). Table 3 shows odds ratios and their confidence intervals for RDS in Caribbean and caucasian infants relative to African infants. It also shows how these odds ratios were relatively unchanged even after being adjusted to take account of gestational age, size for dates, antenatal steroids, hypertension during pregnancy, PROM, maternal smoking, mode of delivery and infant gender. The overall effect of ethnic origin was still significant when allowing for the effects of these other potential risk factors ($\chi^2 = 9.84$, df=2, $p<0.01$). Table 3 shows that the incidence of RDS was significantly higher in caucasian infants than in African infants, while the incidence in Caribbean infants and in African infants did not differ significantly.

<table>
<thead>
<tr>
<th>Variables controlled for in the logistic regression</th>
<th>Caucasian infants</th>
<th>Caribbean infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>4.3 (1.8-10.0)</td>
<td>1.8 (0.8-3.9)</td>
</tr>
<tr>
<td>Gestational age and size for dates</td>
<td>4.6 (1.9-11.1)</td>
<td>1.8 (0.8-4.1)</td>
</tr>
<tr>
<td>Gestational age, size for dates, antenatal steroid therapy, hypertension during pregnancy, PROM, maternal smoking, mode of delivery and infant gender</td>
<td>4.3 (1.7-11.1)</td>
<td>1.6 (0.7-3.9)</td>
</tr>
</tbody>
</table>

Discussion
We have shown a lower incidence of RDS in African (significant) and Caribbean (non-significant) infants than in Caucasian infants,
implying faster lung maturation in the very prematurely born black babies. The tendency for longer requirement for ventilation and supplementary oxygen (Table 2) suggest that the caucasian infants also had more respiratory failure. More African infants had congenital pneumonia, and interestingly, a greater proportion of African mothers had had premature rupture of the membranes. The respiratory diagnoses of all of the infants had been made by the clinician in charge using standard criteria and were not influenced by this study, as it was retrospective.

Black, rather than white, infants have a systematic tendency to be born at lower gestational ages, to weigh less at birth, with a greater proportion of them weighing less than 2500 g. These factors are known to influence the occurrence of RDS. We therefore took care to avoid such bias by matching the infants for gestational age, and the matching process not only considered gestational age and birth order, but gender and birth date if several eligible infants were identified. Our three groups were of similar birthweights, so there were no significant differences in the proportion of infants who were SGA in the three groups. This study was performed retrospectively, but 50 of the 60 eligible African infants eligible for entry were studied, the remaining infants being excluded only because it was not possible to match them with both a Caribbean and caucasian infant.

These results suggest that the association between ethnicity and lung maturation is complex. A larger difference in the incidence of RDS was noted between the African and caucasian infants than between the Caribbean and caucasian infants. Higher lecithin:sphingomyelin (L:S) ratios related to gestational age have been reported in certain black infants, but this difference was not noted between the African and caucasian infants than between the Caribbean and caucasian infants. Higher lecithin:sphingomyelin (L:S) ratios related to gestational age have been reported in certain black infants, but this difference was not noted between the African and caucasian infants than between the Caribbean and caucasian infants. Nevertheless, unmeasured ethnic differences in economic, nutritional, or disease conditions may underlie the ethnic disparities in RDS incidence. The results of one study have suggested the rates of lung maturation were inversely related to maternal body weight. Undernourished mothers have been reported to have low blood pressures and in that group increasing blood pressure to even normal levels had striking effects on fetal growth rate. Differences in uteroplacental blood flow could thus explain a possible effect of differences in nutrition, as a reduction in uteroplacental blood flow would be predicted with low blood pressure.

It has been suggested that the effect of ethnicity may not be apparent until 32 weeks of gestation. Nevertheless, in this review of infants born at less than 33 weeks of gestation, a difference in the incidence of RDS was noted. These data have important implications for clinical management—for example, regarding the timing of interventions such as induction of preterm labour and management of accelerated lung maturation in black infants requires further investigation, as the factors which stimulate fetal lung development in such babies might be applicable to other ethnic groups. The prophylactic effect of antenatal steroids on the development of RDS may be particularly efficacious in non-caucasians, but this is controversial, and does not explain the present results; the African infants had both the lowest incidence of RDS and the lowest administration of antenatal steroids. Other maternal factors such as PROM may also have a positive influence on RDS, although this is also debated. In the present study the incidence of PROM was higher in the African population, but this did not reach significance. We also performed regression analysis, including PROM and other maternal factors known to influence RDS, and this showed that RDS was independently related to ethnic origin.

It has been suggested that environmental factors in the mother such as smoking might explain some of the differences apparently due to ethnicity. Smoking does influence lung maturation and a possible mechanism might be a reduction in uteroplacental blood flow  