Effects of suboptimal intra-uterine growth on preterm infants between 30 and 32 weeks' gestation

P A Cooper, D L Sandler, I D Simchowitz, J S Galpin

Objective. To investigate the effects of suboptimal intra-uterine growth on the outcome of low-birth-weight (LBW) infants.

Design. Prospective observational study.

Setting. Neonatal unit of a tertiary care hospital.

Patients. A total of 104 LBW infants with a gestation of 30 - 32 weeks were selected from a larger cohort that had previously been studied to ascertain the prevalence of respiratory distress syndrome (RDS) and periventricular-intraventricular haemorrhage (PV-IVH).

Outcome measures. Multivariate analysis was used to examine the association between RDS, PV-IVH and death, and the adequacy of intra-uterine growth.

Results. Infants with a higher birth weight ratio or birthweight ≥ 25th percentile had an increased risk of developing RDS, particularly where ventilatory support was required. However, PV-IVH was associated with immediate perinatal events and not with intra-uterine growth. Mortality was not affected by intra-uterine growth, since those < 25th percentile, in spite of being at lower risk for RDS, showed a trend towards more infection-related deaths.

Conclusions. The 'intra-uterine stress' experienced by infants with suboptimal intra-uterine growth appears to protect partially against RDS, but confers no overall advantage in terms of survival.

S Afr Med J 1997; **87:** 314-318.

The effects of suboptimal intra-uterine growth on low-birth-weight (LBW) infants have been the subject of a number of studies, and conflicting data have been reported in the literature. Of particular interest is how intra-uterine growth retardation (IUGR) may influence two of the major causes of morbidity and mortality in LBW infants, viz. respiratory distress syndrome (RDS) caused by surfactant deficiency and the development of periventricular-intraventricular haemorrhage (PV-IVH). It has been suggested that infants with IUGR may be more 'stressed' than those who are appropriately grown and that this in turn results in protection against RDS,[1,2] while others have suggested that IUGR has no effect on the severity of lung disease or may even result in the need for longer ventilatory support than required for appropriately grown infants.[3,4] Similarly, with regard to PV-IVH, studies have shown that intra-uterine growth retardation may be either protective or an additional risk factor.[2,5-7]

The maternity services for the population of Soweto and surrounding areas are provided by Baragwanath Hospital and seven midwife-run maternity clinics. The total service delivers over 30 000 infants annually. In addition the neonatal unit of the hospital admits in the immediate neonatal period, infants who were born at home and also accepts referrals from outside hospitals. A prospective study was conducted to assess the prevalence of RDS and PV-IVH in this predominantly black population. This showed a prevalence of RDS of 36% for infants of 29 - 34 weeks' gestation compared with 63% for a comparable group of white LBW infants in Johannesburg, with significant differences for each 2-week interval between 29 and 34 weeks.[8] The 52% prevalence of PV-IVH in infants < 34 weeks' gestation was higher than in most reported series.[9]

The population served by the hospital comes largely from poor socio-economic conditions and the high proportion of LBW infants at Baragwanath Hospital with IUGR has previously been described.[10] The purpose of this study was to assess the effects of IUGR on both RDS and PV-IVH in our LBW population.

Methods

A total of 305 infants with birth weights 1 000 - 1 749 g and without major congenital abnormalities who were admitted to the Baragwanath Hospital neonatal unit over a 4½-month period were enrolled as previously described.[8,9] In a study such as this, i.e. within a defined birth-weight range, undergrown infants in the lower gestational age range and well grown infants in the upper range would be excluded. However, analysis of the birth weights and gestational age data showed that almost all infants born at the hospital over this period with a gestation of 30 - 32 weeks inclusive were included in the cohort. Therefore, for the purposes of this analysis, only those of 30 - 32 weeks' gestation were included. Infants born at home or referred from an outside hospital were also excluded because of potential selection bias.

Accurate information on maternal dates and early obstetric ultrasound examination to assess gestational age were not usually available. Therefore gestational age was assessed by the Ballard score performed on each infant by one of two authors (DLS or IDS).[11] The diagnosis of RDS was made on the basis of standard criteria as previously described and those infants with a diagnosis of RDS were further subdivided according to whether or not they required assisted ventilation.[8] With a high prevalence of amnionitis in our obstetric population and the fact that many women do not attend antenatal clinics or may arrive at the hospital in

Departments of Paediatrics and Statistics and Actuarial Science, University of the Witwatersrand, Johannesburg

P A Cooper, FCP

D L Sandler, MMed

I D Simchowitz, MB BCh

J S Galpin, PhD

dvanced preterm labour, antenatal steroids were not ommonly used. Artificial surfactant was not available to us t the time this study was carried out. Diagnosis of PV-IVH vas made by transfontanelle real-time ultrasound xamination, using a portable Kretztechnic Combison 310 ector scanner with a 7.5 MHz transducer. Ultrasound examinations were performed systematically by three members of the neonatal division and a final decision on the grade of PV-IVH for each infant was reached by consensus of all three sonographers, based on Papile's classification of PV-IVH.[12]

The Lubchenco growth charts are used at our institution because they were derived from a population living at an altitude similar to that of Johannesburg.[13] Infants were categorised as small for gestational age (SGA) if they fell below the 10th percentile of Lubchenco's norms, while appropriately grown infants were further subdivided into those with birth weights between the 10th and the 25th percentiles, those between the 25th and the 50th percentiles and those above the 50th percentile. Furthermore, each infant was assigned a birth weight ratio (BR) that was calculated by dividing the birth weight by the expected weight (50th percentile) for gestational age.[3,4] Length and head circumference were measured by a fibreglass tape measure and were also plotted on the Lubchenco charts.

The main statistical techniques used were analysis of variance (ANOVA), Kruskal-Wallis tests, contingency tables and the loglinear model. Continuous variables such as BR were analysed for differences in respect of factors such as RDS and PV-IVH grouping; multifactor ANOVA was used in cases where checks such as residual plots indicated the viability of the assumption that the data were normally distributed around the factor means. In cases where this assumption was suspect, the non-parametric Kruskal-Wallis test was used. For analyses involving categorical variables such as for mode of delivery, the need for resuscitation at birth and the occurrence of a range of neonatal complications, a loglinear analysis was used, supplemented with contingency table analysis and tests on odds ratios.[14,15]

The study was approved by the Committee for Research on Human Subjects of the University of the Witwatersrand.

Results

A total of 104 infants with gestational ages ranging from 30 to 32 weeks met the criteria for this study. Table I shows the mean gestational age, birth weight, head circumference and length of these infants. Also shown are the numbers of infants with birth weights < 10th percentile (SGA), between the 10th and 25th percentiles and > 25th percentile; only 2 (1.9%) in the latter category had a birth weight above the 50th percentile. Four infants did not have length recorded, while 3 infants did not have head circumference measurements recorded. The mean values for birth weight, head circumference and length fell between the 10th and 25th percentile of Lubchenco's norms and, of those who were SGA, 68% had a head circumference measurement and 58% a length measurement below the 10th percentile.

Table I. Mean gestational age, weight, length and head circumference of study infants

		Percentile of Lubchenco's norms for birth weight		
	Total group	< 10th	10th - 25th	> 25th
Gestational age (wks)	104	25	43	36
	31.2	31.3	31.1	31.2
	0.83	0.80	0.88	0.82
Birth weight (g)	104	25	43	36
	1 320	1 118	1 297	1 486
	182	83	121	130
Head circumference (cm)	101	25	42	34
	27.6	26.4	27.5	28.5
	1.4	2.0	1.2	1.1
Length (cm)	100	25	41	34
	39.2	37.6	39.0	40.6
	2.4	1.7	2.3	2.0

Values given are number/mean/standard deviation.

The prevalence and severity of RDS and PV-IVH of the larger cohort of 305 infants, from which the infants in this study were drawn, have been described in greater detail elsewhere.[8,9] Of the 104 infants in this analysis, 48 (46.2%) had RDS and 25 (24.0%) required assisted ventilation. Seven infants died before an ultrasound examination of the head could be performed. Of the remaining 97 infants, 54 (55.7%) had PV-IVH, but only 13 (13.4%) had either grade 3 or 4 PV-IVH.

Respiratory distress syndrome

A significant association between BR and RDS was found ($P = 0.0042$); infants with a greater BR were at higher risk for developing RDS and especially RDS that required ventilatory support (Table II). There did, however, appear to be differences between boys and girls. Table II shows the mean BRs according to whether infants had no RDS, RDS not requiring ventilation or RDS requiring ventilation. While there was a consistent increase in BR for girls as RDS severity increased, this was not so for boys who had no RDS compared with those with RDS not requiring ventilation. However, for both sexes, those with RDS requiring ventilation had the highest BR (Table II).

Table II. BR of study infants according to sex and occurrence/severity of RDS (%)

	No RDS	RDS not ventilated	RDS ventilated
Girls	76.6	81.8	85.5
Boys	85.0	79.4	90.7
All infants	81.1	82.1	88.1

$P = 0.0042$ (ANOVA).
Figures are expressed as the mean BR in each group where 100% is equal to the 50th percentile.

Using the loglinear model to analyse RDS according to whether infants were SGA, a three-way interaction was found ($P < 0.0316$) between SGA, RDS and sex. On examining the RDS versus SGA data separately by sex, no significant relationship could be found. This is probably because of the small sample sizes that were available after splitting by sex. However, if the classification of above or below the 25th percentile was used (as opposed to above or below the 10th percentile), girls showed a trend towards more severe RDS if they were above the 25th percentile ($P = 0.052$) while this did not appear to be so for boys ($P = 0.18$). When both sexes were taken into account, this association was significant ($P = 0.035$) and infants < 25th percentile had an odds ratio of 0.31 (95% confidence interval 0.118 - 0.837) of developing RDS that required ventilation v. no RDS when compared with those ≥ 25th percentile.

RDS was associated with the need for active resuscitation at birth, but not with attendance at antenatal clinic, birth place (hospital or clinic), mode of delivery, Apgar scores, birth weight or gestation (within the narrow range selected for this study).

Periventricular-intraventricular haemorrhage

In the analysis of risk factors for PV-IVH, infants were classified as having no PV-IVH, mild PV-IVH (grades 1 or 2) or moderate-severe PV-IVH (grades 3 or 4). PV-IVH showed no association with BR or any position in relation to the 10th, 25th or 50th percentiles. Like the larger cohort from which this sample was drawn,[9] infants in this study demonstrated significant associations between PV-IVH and the need for active resuscitation at birth ($P = 0.026$), the need for mechanical ventilation ($P = 0.032$) and the development of pneumothorax ($P = 0.040$). Of the SGA infants, 4 of 23 had moderate-severe PV-IVH compared with 9 of 74 who were appropriately grown. This difference was not significant.

Association of RDS and PV-IVH

Table III shows the interaction between RDS and the severity of IVH. This association did not reach statistical significance for the entire group ($P = 0.053$), but there was a greater than expected number of infants with moderate-severe PV-IVH among those requiring ventilation for RDS compared with those without RDS (OR = 9.67; 95% confidence interval 1.74 - 53.85) significant at the 1% level.

Table III. Association between RDS and severity of PV-IVH

	No RDS	RDS not ventilated	RDS ventilated	Total
PV-IVH				
No PV-IVH	29	9	5	43
Grades 1 & 2	21	9	11	41
Grades 3 & 4	3	5	5	13
Total	53	23	21	97

Chi square = 9.33; $P = 0.053$.
Numbers of infants in each category are shown.

Mortality

A total of 32 of the 104 infants died (30.8%). Neither BR nor any category within the percentiles showed a significant association with mortality. Table IV shows the number of infants who died in this study and the causes of death. It can be seen that there was no difference between the proportion of infants above or below the 25th percentile who died; neither were there any significant differences as to the causes of death.

Table IV. Causes of death according to birth weight ≥ or < 25th percentile

	Birth weight ≥ 25th percentile (total = 36)	Birth weight < 25th percentile (total = 68)
Cause of death		
RDS	5	3
PV-IVH	1	3
Septicaemia — congenital	2	4
Septicaemia — acquired	1	7
Necrotising enterocolitis	1	5
Total deaths (% mortality)	10 (27.8%)	22 (32.4%)

None of the group differences was significant.

Discussion

The LBW population in this study would appear to differ markedly in their birth weight/gestational age distribution when compared with two recent studies utilising BR. In Brownlee *et al.*'s study, the mean BR was close to unity while Morley's *et al.* study showed only a slight negative skewness.[3,4] In contrast the infants in this study had a mean BR of 0.83 with only 2 infants having a ratio > 1. Of the infants in this study (24% in all) who fell below the 10th percentile and were classified as SGA, most also had a head circumference and length measurements below the 10th percentile, while the mean values for birth weight, length and head circumference were all located at approximately the same point between the 10th and 25th percentiles. This suggests that in the majority of these infants the cause(s) of the growth retardation had their origin at a relatively early stage of gestation.[16] This pattern of symmetrical growth retardation is likely to be prevalent in most parts of the developing world where nutrition and socio-economic circumstances are poor, and differs markedly from the pattern demonstrated in infants who were the subjects of the above studies utilising the BR in developed countries.

Intra-uterine growth and RDS

The effects of this pattern of intra-uterine growth on our study population appears to be measurable in the prevalence and severity of RDS. It is not clear why this association was more consistent for girls than boys, but may have related to small numbers in each subgroup in this analysis. We speculate that the 'intra-uterine stress' experienced by infants with a lower BR induced more rapid maturation of the surfactant system, resulting in relative protection against the development of RDS, especially RDS severe enough to require ventilatory support. This is in keeping with the studies of Gluck and Kulavich[1] and Procianoy *et al.*[2] Infants ≥ 25th percentile in this study had a prevalence of RDS of 56% compared with 69% in white ıfants of 30 - 32 weeks' gestation in the Johannesburg ·ea. This difference is much smaller than the almost two-›ld black/white difference found for all infants of 29 - 34 ·eeks' gestation as previously reported.[8] The difference ·etween RDS prevalence in black and white infants in the ·ohannesburg area can therefore be explained at least in ›art by the high prevalence of suboptimal intra-uterine ›rowth in black infants.

Morley *et al*. reported that SGA infants developed more ·evere lung disease as evidenced by the requirement for ·onger periods of mechanical ventilation.[4] Our data do not ·upport this association, but the number of infants requiring ·nechanical ventilation in our study was much smaller and ·ve could not exclude the possibility that, in those SGA ·nfants actually requiring ventilation, RDS was more severe. The differences between studies may relate to different populations studied as well as to the cause and duration of IUGR.

This study supports previous data suggesting that the BR allows for a more sensitive analysis of outcome.[3] This is probably due to the fact that, since it is a continuous variable, associations involving infants who are suboptimally grown but remain above the 10th percentile can still be demonstrated.

Intra-uterine growth and PV-IVH

Analysis of the risk factors for PV-IVH in this study failed to reveal an association with any measure of intra-uterine growth. Our data are not in keeping with those of Bada *et al*.[6] and Heinonen *et al*.,[7] who showed IUGR to be an added risk factor, or with those of Procianoy *et al*.[2] and Pena *et al*.,[5] who suggested a protective effect.[6,7] The numbers of infants in our study with either grades 3 or 4 PV-IVH were small, but our study did not support the finding that SGA infants were at greater risk for more severe grades of PV-IVH, as suggested by Heinonen *et al*.[7] The lack of association with intra-uterine growth and the association of PV-IVH with the need for resuscitation at birth, the need for mechanical ventilation and the development of pneumothorax in our study, suggests that PV-IVH in our population is largely determined by events that occur in the immediate perinatal period.

The prevalence of 55.7% of any grade of PV-IVH in this study was high, as previously reported.[9] In keeping with the postulate that PV-IVH is largely determined by perinatal events, this high prevalence can at least in part be explained by the fact that more than half of the mothers did not attend antenatal clinics, many arrived at the hospital in advanced preterm labour and delivered within a relatively short period of time and, due to a shortage of ventilator facilities, infants with respiratory distress may have had to wait longer than would be desirable before being ventilated.

Relationship between RDS and PV-IVH

This study showed no clear association between RDS and PV-IVH. Although PV-IVH was associated with mechanical ventilation, it should be noted that a number of infants in our institution are ventilated for reasons other than RDS, e.g. congenital pneumonia, birth asphyxia and severe apnoea.

While a number of studies have shown that preterm infants with RDS are at increased risk for PV-IVH,[17-19] Philip *et al*. reported a decline in PV-IVH without a concomitant decrease in RDS, while Leviton *et al*. could find little impact on PV-IVH from the literature on prophylactic and rescue trials of surfactant.[20,21]

Apart from the need for active resuscitation at birth, RDS in this study was associated with the adequacy of intra-uterine growth long before the onset of labour, while PV-IVH appeared to be associated largely with perinatal events. This would explain the lack of a strong association demonstrated in this study and lends support to the theory that the two conditions may rather be independent indicators of immaturity of organ systems.[21]

Gestational age assessments

The basis of the conclusions reached above depended on an accurate assessment of gestational age. We, however, did not have the benefit of accurate antenatal gestational age assessments in most cases and therefore relied on postnatal clinical assessments. We attempted to minimise inter-observer variability by only having two observers. However, it has been suggested that both IUGR and race may affect these assessments, resulting in an over-estimation of gestational age.[22,23] If, in fact, gestation was overestimated in our study, the conclusions reached would still be valid in respect of the BR analysis since it is a continuous variable and does not depend on absolute cut-off values.

Mortality

The relative protection against RDS experienced by infants in this study with lower BR may have predicted a more favourable outcome for them. However, mortality did not differ in our study according to position on the growth percentiles. Although there were no significant differences in the causes of death as shown in Table III, the numbers were small. There did, however, seem be a trend towards more deaths from acute RDS in those ≥ 25th percentile, while those < 25th percentile seemed to have more deaths from nosocomially acquired infections and necrotising enterocolitis. Van Heel and de Leeuw[24] showed an increased incidence of gastro-intestinal problems and infections in SGA infants, in keeping with the trend shown in our study.

We speculate that although infants with a lower BR are partially protected against RDS, this does not result in improved neonatal survival because of a trend towards more gastro-intestinal and/or infectious complications. The pattern of symmetrical intra-uterine growth demonstrated by this population of LBW infants cannot therefore be regarded as conferring any overall advantage. The long-term outcome of surviving infants with birth weights < 1 500 g in our institution is currently being investigated with a view to assessing, among other factors, the later effects of chronic suboptimal intra-uterine growth.

This study was supported in part by a grant from the South African Medical Research Council.

REFERENCES

1. Gluck L, Kulovich MV. Lecithin-sphingomyelin ratio in amniotic fluid in normal and abnormal pregnancy. *Am J Obstet Gynecol* 1973; **115:** 539-546.
2. Procianoy RS, Garcia-Prats JA, Adams JM, Silvers A, Rudolph AJ. Hyaline membrane disease and intraventricular haemorrhage in small for gestational age infants. *Arch Dis Child* 1980; **55:** 502-505.
3. Brownlee KG, Ng PC, Roussounis SH, Dear PRF. Birthweight ratio revisited. *Arch Dis Child* 1991; **66:** 418-421.
4. Morley R, Brooke OG, Cole TJ, Powell R, Lucas A. Birthweight ratio and outcome in preterm infants. *Arch Dis Child* 1990; **65:** 30-34.
5. Pena IC, Teberg AJ, Finello KM. The premature small-for-gestational-age infant during the first year of life: Comparison by birth weight and gestational age. *J Pediatr* 1988; **113:** 1066-1073.
6. Bada HS, Korones SB, Anderson GD, Magill HL, Wong SP. Obstetric factors and relative risk of neonatal germinal layer/intraventricular hemorrhage. *Am J Obstet Gynecol* 1984; **148:** 798-804.
7. Heinonen K, Matilainen R, Koski H, Launiala K. Intrauterine growth retardation (IUGR) in pre-term infants. *J Perinat Med* 1985; **13:** 171-178.
8. Cooper PA, Simchowitz ID, Sandler DL, Rothberg AD, Davies VA, Wainer S. A comparison of the prevalence of hyaline membrane disease in black and white low-birth-weight infants. *S Afr Med J* 1994; **84:** 23-25.
9. Sandler DL, Cooper PA, Bolton KD, Bental RY, Simchowitz ID. Periventricular-intraventricular haemorrhage in low-birth-weight infants at Baragwanath Hospital. *S Afr Med J* 1994; **84:** 26-29.
10. Stein H, Ellis U. The low birthweight African baby. *Arch Dis Child* 1974; **49:** 156-159.
11. Ballard JL, Novak KK, Driver M. A simplified score for assessment of fetal maturation of newly born infants. *J Pediatr* 1979; **95:** 769-774.
12. Papile L-A, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular haemorrhage: a study of infants with birth weights less than 1 500 gm. *J Pediatr* 1980; **92:** 529-534.
13. Lubchenco LO, Hansman C, Dressler M, Boyd E. Intrauterine growth as estimated from liveborn birthweight data at 24-42 weeks of gestation. *Pediatrics* 1963; **32:** 793-800.
14. Christensen R. *Log-Linear Models*. New York: Springer-Verlag, 1990.
15. Upton GJG. *The Analysis of Cross-Tabulated Data*. New York: Wiley, 1978.
16. Kliegman RM, Hulman SE. Intrauterine growth retardation: determinants of aberrant fetal growth. In: Fanaroff AA, Martin RJ, eds. *Neonatal-Perinatal Medicine*. St Louis: CV Mosby, 1987: 69-102.
17. Levene M, Fawer CL, Lamont RF. Risk factors in the development of intraventricular haemorrhage in the premature neonate. *Arch Dis Child* 1982; **57:** 410-417.
18. Goddard-Finegold J. Periventricular, intraventricular hemorrhages in the premature newborn: update on pathologic features, pathogenesis, and possible means of prevention. *Arch Neurol* 1984; **41:** 766-771.
19. Volpe JJ. Intraventricular hemorrhage in the premature infant — current concepts, part I. *Ann Neurol* 1989; **25:** 3-11.
20. Philip AGS, Allan WC, Tito AM, Wheeler LR. Intraventricular hemorrhage in preterm infants: declining incidence in the 1980's. *Pediatrics* 1989; **84:** 797-801.
21. Leviton A, VanMarter L, Kuban KCK. Respiratory distress syndrome and intracranial hemorrhage: cause or association? Inferences from surfactant clinical trials. *Pediatrics* 1989; **84:** 915-922.
22. Ballard JL, Khoury JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R. New Ballard score, expanded to include extremely premature infants. *J Pediatr* 1991; **119:** 417-423.
32. Parkin JM. The assessment of gestational age in Ugandan and British newborn babies. *Dev Med Child Neurol* 1971; **13:** 784-788.
24. Van Heel IR, de Leeuw R. Clinical outcome of small for gestational age preterm infants. *J Perinat Med* 1989; **17:** 77-83.