

# Outcome of Small-for-Gestational Age and Appropriate-for-Gestational Age Infants Born Before 27 Weeks of Gestation

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**ABSTRACT.** *Objective.* To evaluate the consequences of being small-for-gestational age at extremely low gestational age.

*Methodology.* Comparison of two historical cohorts of small-for-gestational age (SGA) and appropriate-for-gestational age (AGA) infants born between 24 and 26 6/7 weeks of gestation (gestational age estimated by early ultrasound at 16 to 18 weeks). Data were collected retrospectively on 191 successive admissions to the neonatal intensive care unit between January 1, 1983, and December 31, 1992. These included: demographic and maternal information, delivery mode and condition at birth, mortality, neonatal intensive care unit morbidities (respiratory distress syndrome, intraventricular hemorrhage, patent ductus arteriosus [PDA], chronic lung disease [CLD], retinopathy of prematurity [ROP], necrotizing enterocolitis, infection), nutrition, and length of hospitalization.

*Results.* Forty-one (21%) of the 191 infants were classified as SGA. Those with congenital anomalies (10% in the SGA and 2% in the AGA group) were excluded from further analysis. Despite a similar rate of respiratory distress syndrome (50%), the SGA infants had a greater rate of failure of indomethacin treatment for PDA closure (54% vs 32% for AGA), a higher risk for CLD defined as a need for supplementary oxygen at 36 weeks (65% vs 32% for AGA), a more prolonged need for oxygen supplementation and ventilatory support (94 days vs 68 days for AGA and 58 days vs 40 days for AGA, respectively). SGA infants were also at greater risk for developing severe ROP (stage III) (65% vs 12% for AGA).

*Conclusions.* For infants born before 27 weeks, being small-for-gestational age confers additional risks for severe morbidity, ie, PDA ligation, CLD, and ROP. *Pediatrics* 1997;100(2). URL: <http://www.pediatrics.org/cgi/content/full/100/2/e4>; *extreme prematurity, small for gestational age, mortality, morbidity.*

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ABBREVIATIONS. SGA, small-for-gestational age; NICU, neonatal intensive care unit; AGA, appropriate-for-gestational age; ELGA, extremely low gestational age; ELBW, extremely low birth weight; LMP, last menstrual period; RDS, respiratory distress syndrome; IVH, intraventricular hemorrhage; PDA, patent ductus arteriosus; CLD, chronic lung disease; ROP, retinopathy of prematurity.

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Small-for-gestational age (SGA) infants represent a significant percentage of infants admitted to neonatal intensive care units (NICU). There is abundant literature on the neonatal course and long-term outcome of SGA infants born at or near term.<sup>1-5</sup> For those born prematurely, comparisons between SGA and appropriate-for-gestational age (AGA) infants have generally shown that SGA infants have fewer respiratory difficulties in the neonatal period than AGA infants.<sup>6-8</sup> However, these conclusions were drawn when the birth weight rather than the gestational age served as the basis for comparison.<sup>9,10</sup> The limited number of studies comparing premature AGA and SGA infants of similar gestational age have shown inconclusive outcomes.<sup>11-14</sup> Furthermore, there is a paucity of information regarding the outcome of infants born at extremely low gestational age (ELGA).

The present study addresses the issue of outcome of SGA infants born between 24 and 26 6/7 weeks of gestation, an age group which was very difficult to study earlier. Nowadays, with the routine use of ultrasound between 16 and 20 weeks of gestation in the province of Quebec, it is possible to accurately date a pregnancy. Furthermore, the survival rate of infants of extremely low birth weight (ELBW) and ELGA has increased in the last decade. This permits the evaluation of the impact of early intrauterine growth retardation on the outcome of infants born before 27 weeks of gestation.

## MATERIALS AND METHODS

### Patient Population

The 191 infants enrolled in the study were born at the Sir Mortimer B. Davis Jewish General Hospital, Montreal, between January 1, 1983 and December 31, 1992. Their gestational age, calculated by ultrasonography performed between 16 and 20 weeks of gestation and LMP, ranged from 24 to 26 6/7 weeks. If there was a discrepancy greater than 1 week between last menstrual (LMP) and ultrasound dating, the gestational age determined by ultrasound was taken as reference. An infant was classified as SGA if the birth weight was at or below the third percentile, using the Usher and McLean grids of intrauterine growth, constructed from patients born in the province of Quebec<sup>15</sup> and extrapolated to 24 weeks.

Forty-one infants were classified as SGA and 150 as AGA. Four infants in the SGA group and three in the AGA group had lethal congenital anomalies ( $P = .05$ ) and were thus excluded from further analysis.

### Outcome Variables

The following clinical conditions were evaluated:

1. Early neonatal course describes the infant's condition upon admission to the NICU.
2. Respiratory distress syndrome (RDS): The diagnosis of RDS was made on the basis of clinical and radiologic criteria. Surfactant replacement therapy became available in our NICU in 1990 and has been used early in the treatment of infants with RDS in respiratory failure.
3. Intraventricular hemorrhage (IVH): Ultrasonographic evaluation of the ventricular system was routinely done in the first week of life and repeated 1 week later. If pathology was present, ongoing evaluation would proceed on a weekly basis. The ultrasounds were evaluated by the same ultrasonographer who was unaware of the SGA/AGA status of the infant. IVH was reported according to Papile's classification.<sup>16</sup>
4. Periventricular leukomalacia: A head ultrasound was done between 36 and 40 weeks of gestation for the diagnosis of periventricular leukomalacia.
5. Patent ductus arteriosus (PDA): PDA was diagnosed clinically and by echocardiography. In the absence of contraindications (active bleeding or renal failure), indomethacin was the treatment of choice for ductuses with clinical signs of failure. Two to three courses of indomethacin were attempted before surgery was considered.
6. Sepsis: Infection was diagnosed either by a positive blood culture or an abnormal white blood cell count and differential in the presence of obvious clinical signs of infection. Infections were classified as early (occurring during the first week of life) or late.
7. Chronic lung disease (CLD): CLD was defined as an oxygen need beyond 36 weeks of gestation.
8. Retinopathy of prematurity (ROP): Each infant's retina was assessed by an ophthalmologist 4 to 6 weeks after admission to the NICU with repeat examinations until maturity of the retina. The diagnosis and staging of ROP was done according to the International Classification.<sup>17</sup>
9. Time of discharge: Infants were discharged home when they reached a weight of 2200 g and were free of medical problems.

### Statistical Analysis

The data were analyzed by the SPSS statistical program. Between group differences on categorical variables were analyzed with  $\chi^2$  statistics or Fisher's exact test if cell sizes were less than 5. Student's *t* test was used to compare the groups on continuous variables. A *P* value of <.05 was considered significant.

## RESULTS

### Perinatal Outcome

Pregnancy complications, mode of delivery, and the infant's condition at birth are described in Table 1. Except for an increased incidence of preeclampsia in the mothers of SGA infants, all other parameters were similar in the two groups. The percentages of

**TABLE 1.** Perinatal Data

	SGA (n = 37)	AGA (n = 147)	<i>P</i>
Birth weight (g)*	586 ± 74	793 ± 95	<.00
range	(395–720)	(600–1000)	
Gestation (weeks)*	25.2 ± 0.8	25.5 ± 0.7	NS
Gender male/female	17/21 (43/57)	80/67 (54/46)	NS
Betamethasone‡	18 (49)†	64 (44)†	NS
Preeclampsia	6 (16)†	3 (2)†	<.00
Prolonged rupture of membranes >24 h	15 (40)†	44 (30)†	NS
C-Section	16 (42)†	52 (35)†	NS
Apgar scores			
At 1 min*	3.2 ± 2.5	3.5 ± 1.9	NS
At 5 min*	5.3 ± 2.5	6.1 ± 2.0	NS
<5 at 5 min	12 (32)†	27 (19)†	.05

\* Values are expressed as mean ± SD.

† Values in parentheses are percentages.

‡ Betamethasone: antenatal administration of 2 doses of 12 mg of betamethasone 24 hours apart.

SGA and AGA infants born after prolonged rupture of membranes (greater than 24 hours) were comparable (40% and 30%, respectively). At birth, more SGA infants were depressed as indicated by the greater percentage of SGA infants with an Apgar score of ≤5 at 5 minutes (32% vs 19%) (*P* = .05). The distribution of SGA and AGA infants by gestational age was as follows: at 24 weeks, 19 SGA and 42 AGA; at 25 weeks, 11 SGA and 50 AGA; and at 26 weeks, 7 SGA and 55 AGA. The distribution of infants according to gender was similar.

### Early Neonatal Course

Table 2 presents data on neonatal morbidity after admission to the NICU. The incidence of RDS was similar in the two groups (50%). Surfactant replacement therapy was given to 12% of SGA and 14% of AGA infants. The incidence of IVH of any grade was 22% for SGA and 30% for AGA infants. There was a trend for severe IVH (grade III or IV) to occur more frequently among the AGA infants (23% vs 12%).

The need for ventilatory assistance was similar in the two groups, but the reasons for intubation differed. Among the SGA infants, 27% were intubated for RDS, 30% for depression, and 42% for immaturity. Among the AGA infants, 27% were intubated for RDS, 14% for depression, 41% for immaturity, 11% for intractable apnea, and 7% for other causes. All 33 SGA infants who required ventilatory support were intubated within the first 3 hours of age (32/33 by 1 hour of age), compared with 85% of the AGA infants (*P* = .02). The incidence of air leaks was 24% for the SGA and 21% for the AGA infants. All the SGA infants required oxygen supplementation at some time during their hospitalization, compared with 90% of the AGA infants (*P* = .05).

### Mortality

Mortality to discharge home was somewhat higher for the SGA group, although not statistically significant (46% vs 35%). The mean birth weight and gestational age of the 17 deceased SGA infants were 556 g and 25.4 weeks, and for the 52 AGA infants, 773 g and 25.3 weeks. The causes of death were not different for SGA and AGA infants (Table 3). Causes other than respiratory or infectious included intractable hyperkalemia, massive IVH, and renal failure. The median age at death was 7 days for the SGA and 2.5 days for the AGA infants.

**TABLE 2.** Early NICU Course

	SGA	AGA	<i>P</i>
RDS	19/37 (51)†	76/147 (52)	NS
Need for:			
Oxygen supplementation	37/37 (100)	137/147 (90)	.05
Ventilation	33/37 (89)	139/147 (95)	NS
IVH:			
None	24/31* (77)	97/139* (70)	NS
Grade III/IV	4/31* (13)	33/139* (23)	NS

\* No information on IVH is available on 6/37 SGA and 8/147 AGA infants who died soon after birth and for whom autopsy consent was not granted.

† Values in parentheses are percentages.

**TABLE 3.** Mortality

	SGA	AGA	P
Death	17/37 (46)†	52/147 (35)	NS
Age at death (days)*	24 ± 38	11 ± 19	NS
Causes of death:			
Respiratory	7/17 (41)	24/52 (46)	NS
Infectious	5/17 (29)	14/52 (27)	NS
Other	5/17 (29)	14/52 (27)	NS

\* Values are expressed as mean ± SD.

† Values in parentheses are percentages.

**TABLE 4.** NICU Outcome, Survivors

	SGA n = 20	AGA n = 95	P
Apnea	1 (5)†	24 (25)	.05
Infection			
early	10 (50)	23 (24)	.02
late	15 (75)	53 (55)	NS
Necrotizing enterocolitis	3 (15)	7 (7)	NS
PDA			
Indomethacin	13 (65)	44 (46)	NS
Surgery	7 (35)	14 (15)	.05
ROP			
Any stage	18 (90)	55 (58)	<.01
Stage III/IV	13 (65)	11 (12)	<.01
Nutrition			
Full PO (days)*	64 ± 19	50 ± 14	<.001
Hospitalization			
Duration (days)‡	115	95	<.01

\* Values are expressed as mean ± SD.

† Values in parentheses are percentages.

‡ Values are expressed as median.

**TABLE 5.** Respiratory Outcome, Survivors

	SGA n = 20	AGA n = 95	P
RDS	9 (45)*	38 (40)	NS
Oxygenation			
F <sub>IO</sub> <sub>2</sub> at 24 hrs†	0.39 ± 0.23	0.33 ± 0.19	NS
F <sub>IO</sub> <sub>2</sub> at 72 hrs†	0.30 ± 0.14	0.27 ± 0.12	NS
CLD			
Days O <sub>2</sub> †	94 ± 40	68 ± 37	<.01
O <sub>2</sub> at 28 days	20 (100)	79 (83)	<.05
O <sub>2</sub> at 36 weeks	13 (65)	30 (32)	<.01
Ventilation	17 (85)	88 (93)	NS
Duration (days)†	58 ± 16	40 ± 22	<.01
PIP at 24 hrs‡	11 ± 3	9 ± 7	NS
PIP at 72 hrs‡	13 ± 5	9 ± 7	.02

Abbreviations: F<sub>IO</sub><sub>2</sub>, fraction of inspired oxygen; O<sub>2</sub>, oxygen; PIP, peak inspiratory pressure.

\* Values in parentheses are percentages.

† Values are expressed as mean ± SD.

‡ Expressed as cm H<sub>2</sub>O.

### Neonatal Complications Among the Survivors

The outcome of the surviving infants (20 SGA, 95 AGA) is described in Tables 4 and 5. Although the incidence of RDS and need for oxygen were similar in AGA and SGA infants, appropriate oxygenation and ventilation were achieved with significantly higher peak inspiratory pressure at 48 and 72 hours for the SGA infants (Table 5). A clinically significant PDA was diagnosed more frequently in the SGA group. Indomethacin treatment was unsuccessful in 7/13 (54%) SGA infants and 14/44 (32%); these infants subsequently required surgical ligation of the ductus arteriosus. Infection was suspected or con-

firmed more frequently in SGA infants, especially during the first week of life. The number of positive blood cultures was 2 (10%) for SGA and 2 (2%) for AGA infants during the first week of life, and 7 (38%) for SGA and 11 (12%) for AGA infants after 7 days of life.

With reference to long term neonatal outcome, SGA infants required an average of 58 days of mechanical ventilation and 94 days of oxygen supplementation compared with 40 days and 68 days, respectively, for the AGA infants ( $P < .01$ ). At 28 days of life, 100% of the SGA and 83% of the AGA infants were oxygen-dependent ( $P < .05$ ), and at 36 weeks of gestation 65% of SGA and 32% of AGA still required oxygen supplementation ( $P < .01$ ). Retinal changes were present in 90% of SGA infants and in 58% of AGA ( $P < .01$ ) and severe ROP (stage III or IV) occurred in 65% of the SGA infants versus 12% of the AGA infants ( $P < .01$ ). Two of the 20 SGA infants and 5 of the 95 AGA infants are now considered legally blind. Even though the incidence of necrotizing enterocolitis was not significantly different between the two groups, the SGA infants had more difficulties with enteral feedings. Achieving full enteral feeding took 64 days for the SGA infants versus 50 days for the AGA infants ( $P < .01$ ). That the neonatal course of the SGA infants was more complicated is reflected by the fact that their median hospital stay was 20 days longer than that of the AGA infants (115 days for SGA vs 95 day for AGA,  $P < .01$ ).

### DISCUSSION

The prognosis of SGA infants with chromosomal anomalies, genetic syndromes, or congenital infections is relatively predictable. However, for the others, the outcome is much less certain. Furthermore, very little information is available concerning SGA infants who are born extremely premature. In view of the increasing survival of ELBW infants, a better knowledge of the consequences of the combination of severe prematurity and intrauterine growth retardation becomes imperative for proper parental counseling and decision making.

Published data comparing premature SGA and AGA infants of similar gestational age indicate serious discrepancies in their findings. Sung et al<sup>12</sup> compared 27 SGA to 27 AGA infants with a mean gestational age of 29 weeks. There were no differences in neonatal morbidities between the two groups of infants. In Pena et al's report,<sup>13</sup> there were no differences in the incidence of RDS, apnea, necrotizing enterocolitis, or need for ventilatory assistance but there was a decreased incidence of IVH and an increased duration of ventilation and number of days of hospitalization for SGA infants at a mean gestational age of 30.8 weeks. Morley et al<sup>18</sup> and Thompson et al have found an increased need for ventilation for SGA infants of 30 to 31 weeks gestational age. In Thompson's study,<sup>10</sup> this need was secondary to an increased incidence of RDS among the SGA infants. On the other hand, Robertson<sup>11</sup> described a decreased need for assisted ventilation among 36 SGA infants of mean gestational age

33.5 weeks compared with 36 AGA infants of similar gestational age, but no increased length of hospitalization or increased incidence of CLD. Tyson et al<sup>9</sup> reported an increased risk of RDS and respiratory failure in SGA infants born between 27 and 38 weeks compared with AGA infants. In terms of mortality, Thompson<sup>10</sup> found greater mortality (19% vs 11%) in SGA infants of mean gestational age of 30 weeks attributable to an increased incidence of sepsis. In a study by Teberg et al,<sup>3</sup> none of the seven SGA infants of less than 26 weeks gestation survived, compared with 18% survival in AGA infants. Similarly, Chen et al,<sup>19</sup> comparing AGA and SGA twins from 23 to 34 weeks, found an increased risk of death and sepsis among the smaller twin. All these studies clearly underline the important role that gestational age plays in the prognosis for SGA infants.

Our study of ELGA infants confirms the previous reports of increased incidence of congenital anomalies among SGA infants.<sup>20</sup> After exclusion of infants with congenital anomalies, the mortality remained higher in SGA infants; 46% vs 35% in AGA. SGA infants were more depressed at birth, as indicated by the lower 5-minute Apgar score and the need for more aggressive resuscitation. This is in agreement with the findings of Williams<sup>21</sup> and Wilcox,<sup>22</sup> who demonstrated increased mortality as birth weight decreases at any specific gestational age.

During their hospitalization, all SGA infants required oxygen supplementation and most of them needed early assisted ventilation attributable to neonatal depression in one-third of the cases. Despite the high incidence of early neonatal problems (need for resuscitation, PDA, more severe lung disease), we observed a trend for a lower incidence of severe IVH in the SGA group (12% vs 23%), in accordance with the findings of Pena et al.<sup>13</sup> One may speculate that chronic hypoxic state in utero alters the levels and balance of prostanoids, leading to wider autoregulatory range and a better protection of cerebral blood flow.<sup>23</sup> The higher failure rate of indomethacin therapy for the closure of the PDA among SGA infants may also be related to altered levels of prostaglandins or altered number or sensitivity of their receptors.<sup>24</sup>

Although the incidence of RDS and the need for exogenous surfactant were similar in SGA and AGA infants, the initial pulmonary disease was more severe for the SGA infants as demonstrated by the need for more aggressive ventilatory support in the first days of life. Many factors may be responsible for this difference: remodeling of the pulmonary vasculature attributable to chronic intrauterine hypoxia, which in turn can predispose to pulmonary hypertension. Depression at birth can add additional hypoxic injury to the lung. Finally, smaller muscle mass can lead to fatigue and respiratory failure. The SGA infants also demonstrated a much higher incidence of CLD, with 65% of them requiring oxygen supplementation at 36 weeks postconception. Although the etiology of CLD is multifactorial, some factors such as more severe early lung disease and persistence of PDA requiring higher oxygen concentration and more ventilatory support are to be emphasized. Furthermore, chronic

malnutrition can aggravate the deficiency in antioxidants already present in low concentration in premature infants.<sup>25</sup>

In our ELGA population, the incidence of infection was greater in the SGA group. Tolerance of enteral feeding, already a problem in ELBW infants, was significantly aggravated by intrauterine growth retardation. Indeed, full enteral nutrition was achieved on the average after 64 days in SGA infants versus 50 days in AGA infants.

The increased incidence of severe ROP in SGA infants in comparison to AGA infants is a new observation which has significant implications in terms of ophthalmologic intervention, parental counseling and potential medico-legal issues. As to the reasons for this increased risk for ROP among SGA infants of ELBW, one can speculate that it could be a combination of many factors, such as chronic intrauterine hypoxia, altered levels of prostanoids, growth factors, and endothelins, and antioxidant deficiency.

Finally, the length of stay in hospital for SGA infants of ELGA was substantially longer than for AGA infants. This is not a surprising finding in view of the complexity and severity of their medical problems.

In conclusion, our data indicate that intrauterine growth retardation in extremely premature infants is associated with higher mortality. Moreover, the risk of CLD and ROP is much higher in SGA than in AGA infants. Parental counseling before delivery is based mostly on the gestational age of the pregnancy. Thus, after the birth of an SGA, ELGA infant, counseling and treatment must reflect the increased difficulties potentially faced by these infants. Furthermore, because of the seriousness of the early problems and the impact that these may have on their future health, long term outcome in SGA, ELBW infants needs to be carefully evaluated.

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