Global Epidemiology


Mortality Risk among Term and Preterm Small for Gestational Age Infants

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Abstract

Globally, 15% of infants are low birthweight (LBW; <2,500 g) each year. Most LBW infants are either preterm (<37 weeks gestation) and/or growth restricted in utero. These etiologies of LBW have different prevalence, risk factors, health and survival consequences, and are attenuated by different interventions. Birthweight has generally been easier to measure than gestational age in low-resource settings. This is now changing rapidly with access to antenatal care and ultrasound and allows providers, researchers and public health practitioners the opportunity to identify infants born too soon or too small, and to better target interventions to reduce mortality and morbidity associated with these conditions. Understanding the mortality patterns and burden of preterm or small for gestational age (SGA) is important for designing programs to prevent these outcomes and improve survival of these infants. We present here estimates of the increased mortality risk, timing of mortality, and attributable mortality burden associated with these conditions. Such data provide estimates of the potential for proven maternal interventions to reduce SGA burden and its associated mortality, as well as identify infants who would most benefit from clinical and public health interventions to improve their survival and health.

Introduction

Low birthweight (LBW) infants have long been known to have higher mortality than those born 2,500 g or heavier, with mortality estimated to be 20-fold greater than for normal birthweight babies [1]. Sixty to 80% of the 3.3 million neonatal deaths annually are estimated to be attributed to this condition [2–4]. While
a small component of size at birth that results in LBW may be genetic, most LBW arises from being born preterm or growth restriction in utero, or both conditions. Furthermore, the cut point of 2,500 g for defining LBW is arbitrary and was originally used to identify preterm infants rather than as a marker of mortality risk [5, 6]. These conditions and their severity (how preterm or how growth restricted), rather than birthweight per se, will impact mortality risk, and the timing and causes of death.

It is estimated that a total of 120.4 million births occurred in 138 low- and middle-income countries (LMICs) in 2010 [7]. Eighteen million (15%) of these births were classified as LBW (<2,500 g at birth) and 32.4 million as small for gestational age (SGA; <10th percentile of the Alexander reference population of weights for gestational age) [7, 8]. The vast majority of these SGA infants (91%) were born after 37 weeks’ complete gestation. Approximately 15 million infants were born preterm in 2010, including in high-income countries, where preterm is an increasing problem [9], and 13.7 million of these were born in LMICs [7]. These preterm infants have well-characterized mortality risk and causes, especially those born very preterm [3, 10]. SGA infants are considered to have higher mortality risk than appropriate for gestational age (AGA) infants [11–15]. However, the mortality risk, timing and causes of death have not been as well studied in LMICs. To date, it has been difficult to compare SGA prevalence and risks in the literature because many different reference populations have been used to define SGA, and this can result in significant variations in these estimates within the same data set [16]. Furthermore, the mortality risks may be quite different for term and preterm SGA infants, and recent studies suggest there are a significant number of infants born SGA but not LBW whose mortality risks have not been well characterized [17, 18]. In this paper, we discuss recent estimates of early, late and postneonatal mortality associated with term and preterm SGA, as well as being born SGA but not LBW.

**Associations between SGA, Low Birthweight and Preterm**

It has been estimated that 32.4 million SGA infants were born in 138 LMICs in 2010 [7]. Of these, 29.6 million were term and the remainder preterm. This pattern of high SGA burden in LMICs is in contrast to higher-income countries where preterm predominates. SGA has been defined as birthweight for a given gestational age that falls below the 10th percentile of a large population-based reference distribution [8]. The use of a reference population from a high-income country results in very high prevalence in LMICs, especially in South Asia [7]. In order to better appreciate the severity of SGA in such settings, the analy-
ses we present here defined more severe SGA as birthweight below the 3rd percentile of the Oken reference population, which is similar to that of the Alexander reference population which does not provide data at percentiles other than the 10th [8, 19]. In an analysis that examined data from 22 population-based cohorts of over 2 million live births (table 1), studies from South Asia had the highest prevalence of SGA, and Latin America the lowest [17]. Within these 22 studies, over half of SGA infants were born with birthweights ≥ 2,500 g (table 1; 54% in Asia, 65% in Africa, and 59% in Latin America). Among LBW SGA infants, about 20% were born preterm in Asia and Africa, but 45% were preterm in Latin America, indicating a much higher proportionate burden of preterm in Latin America.

Mortality Risk and SGA

The risk ratios (RR) for neonatal mortality among SGA infants born below the 3rd percentile were 1.91 (95% CI: 1.40–2.60), 2.23 (95% CI: 1.52–3.28) and 4.01 (95% CI: 2.20–7.28), for Asia, Africa and Latin America, respectively, compared with those who were not SGA [17]. RRs among SGA infants from the 3rd percentile to <10th percentile of the Alexander reference population were 1.20 (95% CI: 0.87–1.66), 1.27 (95% CI: 0.95–1.70) and 1.93 (95% CI: 1.02–3.64) in Asia, Africa and Latin America, respectively [16]. RRs were comparable between Asia and Africa but higher in Latin America. This was primarily due to lower neonatal mortality rates in the reference population of AGA infants in Latin America, relative to Asia or Africa. For example, the median neonatal mortality rate in the 4 Latin American studies was 8.8 deaths per 1,000 live births, compared with 12.0 and 21.6 in Asia and Africa, respectively, where there are many causes of death not present in the Latin American studies.

Neonatal mortality risk was lowest among term SGA infants in all three regions, higher in preterm AGA infants, and highest among those born both preterm and SGA (fig. 1). As with SGA, regardless of whether term or preterm, RRs

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Table 1. SGA infants born normal weight, term and preterm LBW in 22 studies from Asia, Sub-Saharan Africa and Latin America [17]

<table>
<thead>
<tr>
<th></th>
<th>SGA, %</th>
<th>SGA not LBW, %</th>
<th>SGA term LBW, %</th>
<th>SGA preterm LBW, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia</td>
<td>40</td>
<td>54</td>
<td>37</td>
<td>9</td>
</tr>
<tr>
<td>Africa</td>
<td>25</td>
<td>65</td>
<td>27</td>
<td>8</td>
</tr>
<tr>
<td>Latin America</td>
<td>8</td>
<td>59</td>
<td>23</td>
<td>19</td>
</tr>
</tbody>
</table>

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Mortality of SGA Infants
were comparable in Asia and Africa but higher in Latin America. These higher RRs in Latin America were driven by lower neonatal mortality rates in term AGA infants in Latin America (2.4 per 1,000 live births), compared with 7.9 and 8.4 per 1,000 live births in Asia and Africa, respectively. It should be noted that the neonatal mortality risk was higher for preterm infants, whether SGA or AGA, than term SGA infants.

Patterns of mortality risk varied with timing of death among SGA preterm infants compared to those born term AGA (fig. 2). Mortality risk was comparable for term SGA infants in the early, late and postneonatal periods, with a 3-fold higher mortality risk than among term AGA infants. For those who were preterm but not SGA, mortality risk declined from the early through late through postneonatal periods but remained significant in the latter period. For infants who were both preterm and SGA, mortality risk was comparable in the early and late neonatal periods but declined in the postneonatal period. Regardless of time period, infants born preterm and SGA had the highest mortality risk relative to those born term AGA.

Since the prevalence of term SGA infants whose birthweight was ≥2,500 g was large, we estimated mortality RRs for these infants separately from term SGA LBW infants (table 2). As expected, term SGA LBW infants had higher mortal-

**Fig 1.** RRs for neonatal mortality by SGA and/or preterm in 22 studies in Asia, Sub-Saharan Africa and Latin America [17].
Mortality of SGA Infants

Ity risk relative to term AGA infants in both the neonatal and postneonatal periods compared with term SGA infants not born LBW. However, term SGA not LBW infants still had a significantly higher mortality risk compared with term AGA infants [RR: 1.9 (95% CI: 1.5–2.4) for neonatal mortality and RR: 1.5 (95% CI: 1.3–1.7) for postneonatal mortality].

**Fig 2.** RRs for early, late and post-neonatal mortality by SGA and/or preterm in 22 studies in Asia, Sub-Saharan Africa and Latin America (all regions combined) [17].

**Table 2.** RRs for neonatal and postneonatal mortality among term SGA LBW and term SGA normal birth weight infants compared with term AGA infants [17]

<table>
<thead>
<tr>
<th></th>
<th>Term SGA not LBW RR (95% CI)</th>
<th>Term SGA LBW RR (95% CI)</th>
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<tbody>
<tr>
<td><strong>Neonatal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>1.9 (1.35, 2.67)</td>
<td>3.99 (2.46, 6.48)</td>
</tr>
<tr>
<td>Africa</td>
<td>1.46 (1.08, 1.97)</td>
<td>4.05 (2.98, 5.51)</td>
</tr>
<tr>
<td>Americas</td>
<td>2.81 (2.51, 3.15)</td>
<td>9.65 (6.49, 14.34)</td>
</tr>
<tr>
<td>All</td>
<td>1.89 (1.46, 2.44)</td>
<td>4.77 (3.09, 7.36)</td>
</tr>
<tr>
<td><strong>Postneonatal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>2.46 (1.25, 4.84)</td>
<td>2.86 (1.11, 7.38)</td>
</tr>
<tr>
<td>Africa</td>
<td>1.37 (1.16, 1.62)</td>
<td>2.38 (1.99, 2.85)</td>
</tr>
<tr>
<td>Americas</td>
<td>2.15 (1.23, 3.76)</td>
<td>5.10 (2.84, 9.16)</td>
</tr>
<tr>
<td>All</td>
<td>1.47 (1.26, 1.71)</td>
<td>2.85 (2.07, 3.91)</td>
</tr>
</tbody>
</table>
Number of Deaths Attributable to SGA

A total of 1.3 million or 26% of the just over 5 million infant deaths that occurred in 138 LMICs in 2010 were attributable to SGA (table 3) [Lee, unpubl. data]. Of these, 1.3 million SGA deaths, \( \sim 845,000 \) (29% of neonatal deaths attributable to SGA) and \( \sim 442,000 \) (20% attributable to SGA) occurred in the neonatal and postneonatal periods, respectively. Comparable numbers were estimated for 2011 (817,000 attributed to SGA in the neonatal period and 418,000 in the post-neonatal period) [18]. 75% of SGA-attributed neonatal and 80% of postneonatal deaths occurred among term SGA infants. This is because the prevalence of term SGA is much higher than that of preterm SGA, even though the mortality risk in preterm SGA infants is much higher than in those born term SGA.

Conclusions

Infants born SGA are at higher neonatal and postneonatal mortality risk compared with infants born term and AGA. SGA infants born preterm are at higher mortality risk than term SGA ones. Over half of SGA infants are not LBW, especially in South Asia, but these infants are at an almost 2-fold higher neonatal mortality risk than term AGA infants. Hence, clinicians and public health professionals need to pay attention to such infants, even though they may be at lower risk than term LBW SGA infants. SGA is a significant underlying contributor to neonatal and infant mortality, contributing to 29 and 26% of these deaths, respectively. These data suggest that interventions to prevent SGA could have a major impact on neonatal and infant survival in resource-limited settings. Such interventions include iron-folate, multiple micronutrient, or balanced energy protein supplementation during pregnancy [20]. These results also demonstrate that research to identify cost-effective interventions to improve the survival and health of SGA infants could save many lives and contribute to meeting Millennium Development Goal 4.

Table 3. Neonatal, postneonatal and infant deaths attributable to term and preterm SGA among 138 low- and middle-income countries in 2010 [A.C.C. Lee, pers. commun.]

<table>
<thead>
<tr>
<th>Components</th>
<th>Neonatal deaths (2,963,794)</th>
<th>Postneonatal deaths (2,187,393)</th>
<th>All infant deaths (5,151,187)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term SGA</td>
<td>633,504</td>
<td>357,078</td>
<td>990,582</td>
</tr>
<tr>
<td>Preterm SGA</td>
<td>211,362</td>
<td>122,664</td>
<td>334,026</td>
</tr>
<tr>
<td>All SGA</td>
<td>844,866 (29%)</td>
<td>441,686 (20%)</td>
<td>1,324,608 (26%)</td>
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</tbody>
</table>
Disclosure Statement

The authors declare that no financial or other conflict of interest exists in relation to the contents of the chapter.

References
