Long-term neurocognitive outcomes of SGA/IUGR infants

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Abstract

With advances in the management of preterm neonates, the chances of survival have increased even among those who are intrauterine growth restricted (IUGR) or who are born small for gestational age (SGA). However, infants who are IUGR/SGA are considered at higher risk of physical and neurodevelopmental abnormalities, although the reported impacts of IUGR and SGA status at birth on neurodevelopmental outcomes in long-term outcomes studies have varied. In particular, some reports have indicated gradual improvement in neurodevelopmental functions over time in these infants. We have therefore reviewed all the available reports describing neurodevelopmental outcomes of preterm and term SGA infants beyond 5 years of age. Preterm SGA infants are at increased risk of impairment in neuromotor, cognitive, behavioural and scholastic attainments compared with preterm non-SGA infants. On the other hand, term SGA infants had problems in scholastic/vocational attainments compared with term non-SGA infants, while adverse neuromotor, cognitive and behavioural outcomes were not consistently observed at higher rates. Limitations regarding the validity of studies of long-term outcomes of SGA infants are discussed and a potential approach is suggested.

Keywords achievement; cognition; growth restriction; performance; shcolastic; vocation

Introduction

Very low birth weight infants are at increased risk of adverse motor and neurobehavioral outcomes in childhood and adolescence. Similarly, intrauterine growth restriction (IUGR) and small for gestational age (SGA) births are considered at higher risk of developing long-term adverse health consequences, both physical and neurodevelopmental. However, it is unclear whether gestational age (GA) at birth has any influence on these outcomes among IUGR/SGA infants.

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Background

Inadequate *in utero* growth can be caused by a multitude of factors, ranging from maternal, placental, fetal, environmental, nutritional, infective and genetic. Underlying pathological mechanisms for IUGR that have been identified include either inadequate supply of nutrients to the growing fetus or excess utilization of nutritional resources. It is perceived that, in response to so-called under-nutrition, the fetus develops an adaptive response that initiates what is described as a "diving reflex". The blood is diverted to the brain, adrenals and heart, mainly at the cost of the liver, muscles, skin and subcutaneous tissues. This could lead to neuroprotection; however, with persistent insult the brain suffers from a lack of nutrients, potentially affecting its growth and development. The clinical phenotypes of this process are classified into symmetrical and asymmetrical growth restriction. If the insult leading to IUGR occurs before the first trimester, growth of the head and brain is affected to a similar degree to the body, and these infants are classified as symmetrically growth restricted. In contrast, later insult leads to head sparing and results in asymmetrical IUGR, with presumed brain sparing. Head growth is very important in the context of later neurodevelopment, as subnormal head circumference at approximately 1 year of age in infants is associated with lower IQ, poor academic achievement, and poor adaptive behaviour.

Several single-centre and multicentre studies have examined outcomes of IUGR or SGA infants at various postnatal ages ranging from 1 year to 26 years. Some of these studies have identified that childhood and adolescent outcomes improve as age advances even in the same cohort. Additionally, some review articles have implied that SGA or IUGR status per se has very little effect on long-term outcomes.

Several factors affect the long-term outcomes of individuals born SGA (Figure 1). Both proximal (related to this pregnancy) and distal (maternal life-long factors) maternal factors are trigger points for growth restriction *in utero*. This could be aggravated by immediate life-course events such as prolonged hospitalization, complications of prematurity, asphyxia and infections. Long-term life-course events of social, neighbourhood and environmental deprivation play a larger role in the later outcomes. It has been suggested that the outcomes of SGA infants are dependent upon GA, with different influences playing important roles in preterm versus term infants. In this article, we summarize the available literature describing long-term (after 5 years of age) outcomes in the domains of neurological, cognitive, behavioural and academic achievements, for both term and preterm IUGR and/or SGA infants.

Before a detailed description of the outcomes can be entered into, a couple of caveats need to be made. First, the biggest limitation of the available literature is that the different studies have not been consistent in their definition of IUGR/SGA. Some studies have used only intrauterine estimation of fetal weight and attempted prognostication, whereas others have used postnatal growth curves. This may lead to comparison of dissimilar populations. Second, there is a lack of consistency as to when and how population cohorts are evaluated in terms of long-term outcomes. Thus the outcome results from different studies may not be comparable.

Neurodevelopmental outcomes are mainly assessed in four domains, as indicated in Table 1. For the purposes of this review, we used a cut-off of 5 years of age for assessment of long-term outcomes, as reports on outcomes prior to 5 years of age are

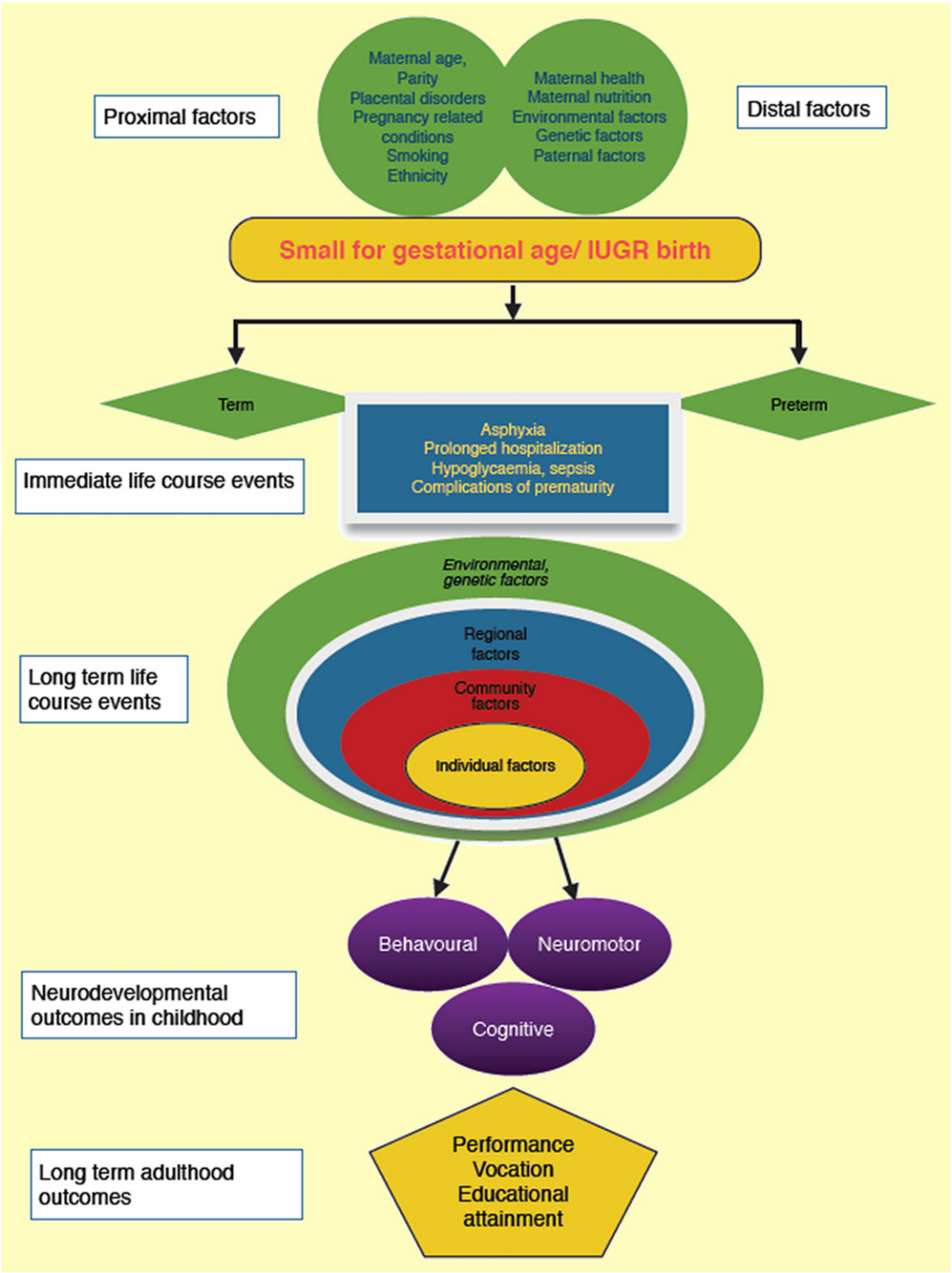

Figure 1 Causes and life time trajectory of SGA/IUGR infants.

subject to debate due to uncertainty regarding correlation of short-term outcomes with long-term outcomes.

Pathophysiological rationale for adverse neurocognitive outcomes in SGA/IUGR infants

The aetiology for SGA/IUGR births is multifactorial, while the primary reason underlying the SGA/IUGR birth may play a significant role in the subsequent pathophysiology of the neurocognitive outcomes. The insult or injury that led to development of fetal growth restriction may directly affect the immature and developing brain, leading to adverse consequences. Animal studies reveal that IUGR animals have reduced brain weight, with volume loss occurring mainly in the cerebellum, hippocampus, and in the cerebral cortex. Delayed migration of

Neurodevelopmental outcomes of interest

Domains	Outcomes
Neurological	Cerebral palsy
	Motor abnormality
	Neuromotor issues
	Minimal brain dysfunction
	Visuomotor problems
Cognitive	Intelligence quotient
	Developmental quotient
Behavioural	Mood
	Behaviour
	Interaction
	Aggression
	Anxiety
	Depression
Scholastic	Performance at school
	School failure
	Grade placement
	Reading score
	Arithmetic scores

Table 1

neurons, reduced myelination and reduction in the number of neurons, superimposed with delayed growth of axons and dendrites, have been identified in growth-restricted animals.

Reduced brain growth, and a reduction in myelin deposition have also been identified in human studies. Effects on brain growth during the intrapartum and postpartum periods are reflected in the development of microcephaly and poor head growth, respectively. Both these postnatal findings have been identified as significant predictors of long-term outcomes. Additionally, complications of SGA/IUGR births such as perinatal hypoxaemia, acidosis, hypothermia, hypoglycaemia, and preterm birth can accentuate existing brain damage and affect neurocognitive outcomes. Prolonged hospitalization and associated complications during the neonatal period can aggravate injury to the developing brain, affecting neurocognitive outcomes. At the same time, plasticity of the neonatal and especially the immature brain may enable the recovery of several aspect of neurocognitive function over time. Thus, long-term studies assessing neurocognitive and motor functions of SGA/IUGR infants are essential.

Long-term outcomes of SGA/IUGR births

Motor, neuromotor, and neurological outcomes

In comparisons of term SGA infants with their counterpart appropriate for gestational age (AGA) infants, many studies have reported no significant differences in visuo-spatial motor ability, motor abnormalities or in motor score. At 17 years of age, the neuromotor disability was reported to be between 9 and 10% in SGA infants and 5 and 7% in AGA infants. On the other hand, a small but significant increase in the incidence of neuromotor disabilities was observed in those who had been born preterm SGA. In particular, when those born preterm SGA were compared with those born preterm AGA, the rates of neurological dysfunction were overall higher in the former.

To tease out differences in outcomes that are associated with being born SGA/IUGR and outcomes that are simply a complication of preterm birth, a few studies assessed three study groups of infants (preterm SGA, preterm AGA and term AGA). These studies confirmed that preterm SGA infants were at the lowest end of the scale in terms of neuromotor scores. Neurological abnormalities varied from mild motor dysfunction to a picture indicative of cerebral palsy.

Timing of *in utero* onset of growth failure has also been indicated to have an important influence. For infants in whom growth failure is identified prior to 26 weeks, higher rates of neuromotor disabilities were identified compared with those who had growth failure after 26 weeks. However, as these data are from one study with a shorter duration of follow-up (only at 2 years of age), further evaluation is needed.

Cognitive/performance abilities

Cognitive abilities and performance measures are reported interchangeably in studies of long-term outcomes of SGA infants. Evaluation of intelligence levels using various tests of performance, verbal intelligence quotient (IQ) and full-scale IQ for term SGA infants have identified that, in most studies, the mean IQ levels for term SGA infants were not significantly different from AGA infants. An average difference of 3–5 points in IQ, (0.25 SD) with a maximum difference of <15 points (<1 SD), was identified in verbal and performance IQ scales among term SGA infants compared with term AGA infants. On the other hand, studies of preterm infants revealed that IQ scores were on average approximately 5–7 points (0.5 SD) lower for preterm SGA infants compared with preterm AGA infants.

Two longitudinal studies, one in a geographical cohort in Canada and another from the US, have reported higher rates of severe delay and cerebral palsy in preterm SGA infants and very low birth weight AGA infants compared with term AGA infants. In the same study, no difference was noted when preterm SGA infants were compared with GA-matched AGA infants and a BW-matched cohort.

Although population cohort studies with a longer follow-up period have been reported, they have not distinguished between term and preterm infants. A 5–7% increase in severe delay and 5–10 point difference in IQ scores have been observed among these population cohort studies that evaluated term and preterm SGA infants in combination. A study with the longest follow-up data on this topic (17 years) reported higher odds of subnormal intellectual and psychological performance among SGA infants.

Another factor suggested to impact long-term neurodevelopmental outcomes of SGA infants is postnatal growth. Infants who demonstrated catch-up growth by 2 years of age had improved neurodevelopmental status compared with those who failed to demonstrate catch-up growth. Similarly, developmental scores were significantly lower for SGA infants who did not demonstrate catch-up growth in the first 2 years after birth compared with those who did. Thus, postnatal nutrition is an important factor that is increasingly being identified as a rate-limiting step.

In response to advances in our understanding of the pathophysiological processes underlying longitudinal growth, a few

studies have attempted to treat SGA infants using growth hormone (GH) for specific situations of persistent growth failure in early childhood, in an attempt to improve physical growth and psychological well-being. This approach has shown significant promise in improving final adult height and some studies report improved head growth following administration of GH. Two studies have assessed neurodevelopmental outcomes, but the results of these studies were conflicting, with one study suggesting benefit and the other suggesting no difference between those who received GH and those who did not. Additionally, long-term effects of administration of GH to infants are unknown, although potential carcinogenesis has been identified in other studies. It is possible that psychosocial and emotional well-being with improved physical stature may result in improved cognition; however, more studies are needed to confirm or refute this possibility. Prolonged exclusive breastfeeding (≥24 weeks) is suggested to prevent some of the intellectual impairment, although again further studies are necessary to validate this hypothesis.

Behavioural outcomes

Behavioural outcomes for SGA infants have been reported from both parental perspectives and from the perspective of the individual themselves as they grow in to adolescence and adulthood. Only one study has compared preterm SGA infants, and reported no difference in parent-reported behaviour scores. For term SGA infants, borderline impacts on in behaviour have been noted, including a higher risk of attention problems or inattention as reported by both the mother and the child. In studies that did not distinguish based on GA at birth, SGA infants had increased risk of inattention, thought problems, behavioural issues, aggression problems, anxiety and depression. Furthermore, late onset problems in socioeconomic functioning have been identified between 20 and 30 years of age. In a longitudinal study, the risk of inattention, aggression and social problems was increased 5-fold between the ages of 4 and 16 years. This issue is surfacing now as more and more population-based studies are reporting their outcomes. However, it is currently unclear whether advances in management such as administration of GH will mitigate these behavioural issues, as psychosocial well-being improves.

Scholastic achievement

Probably the most convincing impact of SGA births is identified in the category of scholastic achievement. Nearly all studies report higher incidences of school problems, reduced school performance or school failure among both preterm and term SGA infants compared with their counterpart AGA infants. Studies of combined populations also revealed similar rates of difficulties with scholastic achievement. Scholastic achievements were significantly lower in SGA infants according to a range of measures. Overall, an increase in problems at school of approximately 10–15% has been identified among SGA infants. The study with the longest follow-up (20–30 years of age) revealed that the odds of low educational attainment were 33% higher among SGA infants. These findings have important implications from both the planning and preventative perspectives. Short-term neurodevelopmental follow-up as assessed in the majority of clinics in developed countries would be unable to recognize these issues, as they arise at later ages. This is compounded by the fact that, since these issues will not surface as medical concerns, caregivers/parents will not seek to report these findings to members of the medical community. Unless a linkage is established between neurodevelopmental follow-up clinics and educational system databases, this lack of achievement will remain underreported.

Issues in the long-term studies of SGA/IUGR infants

Caution must be taken when attempting to understand and interpret the results from studies of neurocognitive outcomes of SGA/IUGR births, as these studies have several limitations with respect to internal and external validity.

1. A major problem in compiling and interpreting studies of long-term neurocognitive outcomes of SGA/IUGR infants is the definition of cases: not all IUGR infants are SGA. Identification of a cohort based on set parameters of intrauterine growth can lead to misclassification and incorrect interpretation of results. Furthermore, the definition of SGA encompasses a one-time measurement of growth in an individual's life course, whereas it is intuitive that growth velocity over time would be more important than a single point measurement in affecting outcomes. Additionally, counting someone as SGA/IUGR based on a set percentile measure will lead to approximately 20% of children being labelled as at risk, even though they may simply be constitutionally of short stature. Indeed, some of the apparent lack of distinct differences between SGA and AGA infants could be due to the inclusion of children with constitutional short stature.
2. Several studies have attempted to counter this by selecting only fetuses with associated alterations in vascular blood flow in umbilical arteries or aorta. However, the accuracy and validity of such findings in predicting long-term outcomes is not completely proven. The theoretical construct implicating that sparing of the blood flow to the middle cerebral artery activates the "diving reflex" – and thus may act as a threshold to detect impairment in cerebral autoregulation – makes sense, but further studies are needed to confirm the hypothesis.
3. Gestational age at birth clearly plays an important role in long-term outcomes; however, clear understanding of the importance of this role is confounded by the fact that many large-scale studies have combined term and preterm infants together in their cohort. Ideal studies comparing preterm SGA, preterm AGA, term SGA and term AGA infants of sufficient sample size to discern the influence of GA and BW on outcomes are scarce.
4. Assessments of neurocognitive outcomes have varied in different studies, while standardization of these tests across different continents has been challenging. Combining results can even be more difficult as domains covered in one assessment are not comparable to others.
5. The age of the infants at the time of assessment has been variable. In particular, many adverse outcomes identified in early childhood analyses have not been sustained in later age assessments.
6. Small sample size, large attrition, variable duration of follow-up and the case–control nature of major studies have

likely resulted in a failure to identify subtle differences in the neurocognitive outcomes.

7. The incidence of major neurocognitive abnormalities such as cerebral palsy, subnormal intelligence, and attention-deficit hyperactivity disorder in the general population are very low; for example, the prevalence of cerebral palsy is in the range of 2–3 per 1000 infants. It is therefore necessary to recruit a large number of infants to achieve significance, which is essential if valid conclusions can be made.
8. The impact of the hypoxia that is associated with infants who are born SGA on neurodevelopment is unclear. In particular, SGA or IUGR fetuses are at higher risk of asphyxia, ischaemia and/or hypoxaemia, which can aggravate existing brain insults. Additionally, the neonatal course of these infants, including prolonged stay in the neonatal intensive care unit, increased risk of neonatal sepsis, and other complications of preterm birth, can influence long-term outcomes, which would be difficult to control for in any statistical model.
9. Many factors that lead to SGA births are also themselves directly associated with adverse neurodevelopmental outcomes, which makes it difficult to tease out whether or not differences in outcomes are specifically a reflection of SGA status.
10. Studies of assessments of SGA/IUGR infants in adulthood are lacking. Very few studies have assessed the impact of SGA status on quality-of-life, functional attainment, and employment status of the individual.
11. Studies assessing long-term outcomes rarely report mortality. Mortality is higher among infants who are SGA compared with AGA. These may influence the numbers for outcomes of neuromotor function, or development of these infants.

What is needed?

How can we overcome these challenges? Large population-based inception cohorts are needed where we can compare SGA cohorts with GA based and weight-based matched cohorts of infants with normal term AGA infants, to differentiate confounding effects. These studies should utilize a standardized neurodevelopment assessment tool, scholastic achievement criteria, and behavioural assessment, as well as including follow-up of functional or performance measures into adult life. Combined data from various regional or national systems that host data on the individual's health, education, employment, and vocational/financial status should be compiled in one large repository to track functional outcomes data. It should be noted that quality-of-life criteria, and the impact of SGA/IUGR on these criteria must be evaluated, as we know from the published literature regarding preterm birth that as adolescents, children born preterm rated their quality-of-life markedly differently from the ratings obtained from health care providers.

Conclusion

SGA/IUGR is a condition with heterogeneous aetiology. Studies with a longer follow-up period reveal that term SGA infants are generally not at an increased risk of adverse neurodevelopmental disabilities, except for a lower level of scholastic achievement. By contrast, preterm SGA infants are at higher risk of neurocognitive disabilities compared with their counterpart preterm AGA infants and term AGA infants. Infants who did not demonstrate catch-up growth, those who had symmetrical growth restriction and those with known contributing factors such as genetic, chromosomal or infectious aetiology are at the highest risk of adverse long-term outcomes. Initial studies have shown potential beneficial effects of GH therapy on functional and quality-of-life related measures for SGA infants; however, the long-term impact has yet to be determined. Concerted efforts at data capturing, including lifetime trajectories of these infants from multiple data sources are essential to enable a full evaluation of long-term outcomes for SGA/IUGR infants. ◆

FURTHER READING

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Practice points

- Small for gestational age or growth-restricted infants are at risk of long-term neurodevelopmental disabilities
- Term SGA infants are not at a significantly higher risk of neuromotor, cognitive or behavioural adverse outcomes, but they have lower scholastic/vocational achievement compared with non-SGA infants
- Preterm SGA infants are at higher risk of adverse neuromotor, cognitive, behavioural and scholastic achievement compared with preterm non-SGA infants
- Postnatal growth appears to be an equally important determinant of neurodevelopmental outcomes in growth-restricted infants
- Well-designed, comparative population cohorts with standardized assessment at specified period and assessment of achievements at or after school years are needed to clearly differentiate the impact of SGA from that of preterm birth

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