Preterm birth, early growth and adult metabolic health

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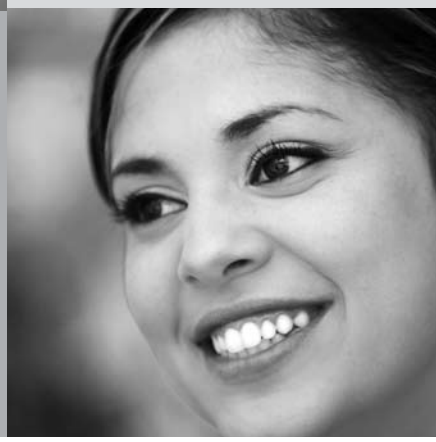

2 Preterm-growth-restraint:

a paradigm that unifies intrauterine growth retardation and preterm extrauterine growth retardation and has implications for the small-for-gestational-age indication in growth hormone therapy

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Abstract

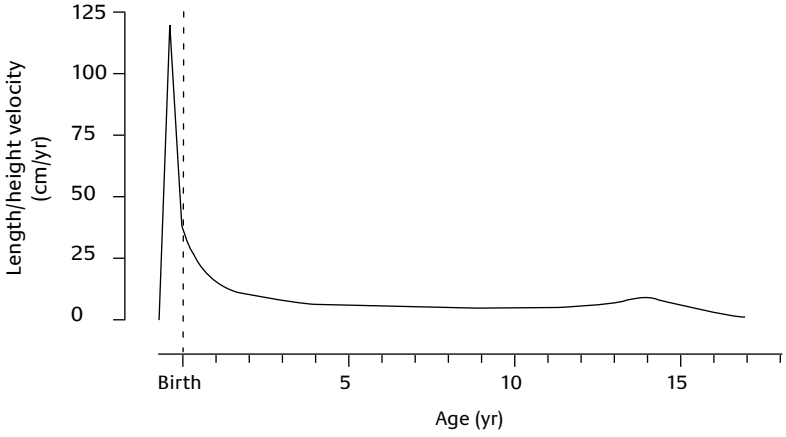
In contrast to children born small-for-gestational-age (SGA), preterm infants with normal size at birth who experienced neonatal growth retardation as part of a stormy postnatal course, resulting in a small size at term, are excluded from growth hormone (GH) therapy if they fail to catch up in height subsequently. Here, we question whether the time has come to update the SGA indication for GH therapy, which requires a birth weight or length >2 SDs below the mean for gestational age, into a preterm-growth-restraint indication, so that this group is no longer excluded from GH therapy in case of persistent short stature.

Small-for-gestational-age (SGA) is defined as a birth weight and/or length >2 SDs below the sex-specific population reference mean for gestational age. However, there is confusion about various aspects of this term, as recently discussed (1;2). The term "intrauterine growth retardation" (IUGR) is often used for the same condition but preferably should be restricted to poor growth during pregnancy according to intrauterine growth diagrams used in obstetrics (3). SGA after a normal duration of gestation (37 to 42 weeks) is usually followed by rapid growth after birth (catch-up growth). It has been demonstrated that almost 90% of term SGA infants catch up in height in the first 2 years of postnatal life (4;5).

On average, the human male has a birth length of 51 cm after term gestation, and a final height, in The Netherlands, of 184 cm. Thus, in the 9 months before birth, he has reached almost 30% of his adult height potential. Fetal length velocity at mid-gestation is >10-fold higher than pubertal peak height velocity (Figure 1).

Thus, very preterm infants are exposed to extrauterine life during a period that is normally characterized by rapid intrauterine growth. To survive, their energy expenditure shifts from growth-promoting actions to survival strategies to cope with the increased requirements of unintended postnatal life. Extrauterine growth retardation (EUGR) is often the result. Preterm infants whose mothers suffered from conditions such as preeclampsia are usually already growth-retarded at birth. Nonetheless, regardless of whether the child is born SGA, very preterm infants tend to be small at term, and a considerable proportion of them even meet criteria for SGA by that age. A study among 52 children born before 29 weeks' gestation showed that 13 (25%) had length at term <-2 SDs (6).

Figure 1. Normal length/height velocity from conception to adulthood (boys).



Fetal length velocity reaches its maximum during mid-gestation, 10 cm/month, and declines to 35 cm/year around birth. In comparison, the median for peak height velocity during puberty is 9.42 cm/year. Postnatal height velocity (median values) is according to Dutch reference values (13).

Thus, among non-syndromatic children with growth retardation before term age, 3 major groups can be differentiated: (I) term children born SGA as a result of IUGR, (II) children born (very) preterm with appropriate size for gestational age who experienced EUGR as part of a stormy neonatal course, and (III) children born (very) preterm who experienced IUGR resulting in being SGA and experiencing EUGR.

According to current legislation across Europe, the second of these groups is excluded from growth hormone (GH) therapy in case of persistent short stature, because these children were excluded – for unspecified reasons – from the pivotal studies that were initiated around 1990, and were maintained up to adult height (7). Here, we question whether the time has come to update the SGA indication for GH therapy, which requires a birth weight or length <-2 SDs for gestational age, into a preterm-growth-restraint (PGR) indication, so that this group is no longer excluded. Approximately 10% of very preterm children have a height <-2 SDs at 4 to 5 years of age (6;8). This is similar to the number of term SGA infants who do not show postnatal catch-up growth (4).

Because neonatal intensive care is a relatively recent and rapidly evolving discipline, there was until now a virtual "absence of evidence" for analogies among the 3 aforementioned groups. Thanks to a set of recent data, this absence of evidence is gradually changing into an "evidence of absence" of major differences between the endocrine-metabolic state of the second group versus that of the other 2 groups. To date, this evidence already includes key features, such as body composition (9;10), insulin sensitivity (11), and blood pressure (12). Beyond the age of approximately 6 to 8 years, the children in these 3 groups seem to resemble each other so closely that, in the absence of a perinatal history, they are virtually indistinguishable from each other on clinical, biochemical, endocrine, and metabolic grounds.

Given that the short-term growth response to exogenous GH in this context may not be indicative of the long-term response (7), there are now 2 major ways to explore GH therapy in former premature infants with short stature. The "absence of evidence for a parallellism" option implies the initiation of long-term studies up to adult height (outcome known around the year 2020). The "evidence of absence of a difference" option would imply an extension of the SGA to a PGR indication, provided the results are monitored until such extension is conclusively validated.

We suggest that paediatric societies, including the American Academy of Pediatrics, the American Pediatric Society/Society for Pediatric Research, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology issue a statement on this specific topic. Below are a few elements to consider in the anticipated debate.

Etiology of PGR – The cause of an intrauterine growth failure that leads to the SGA condition of a baby born at or near term remains often unknown. As a rule, however, the common final pathway includes acidosis, hypoxia, and the equivalent of a fasting state, with serum levels that are low for insulin, insulin-like growth factor-I, and insulin-like growth factor-binding

protein-3 and high for insulin-like growth factor-binding protein-1 and GH. Extrauterine growth failure of very-low-birth-weight premature infants is often attributed to some combination of factors, including low caloric intake, infections, respiratory distress, and pharmacological effects (e.g., of glucocorticoids).

Timing of PGR – In SGA infants born at or near term, it is often unknown whether the PGR started in the last trimester or earlier. In preterm neonates, direct documentation of the extrauterine growth failure is possible (weight, length, and head circumference). In other words, in term SGA infants, the PGR may or may not have started before the third trimester, whereas in preterm appropriate-for-gestational-age (AGA) newborns, the PGR is usually known to have occurred during the third trimester.

Etiology and timing of PGR: relevance for the SGA indication – In the current SGA indication for GH therapy, little attention is given to the etiology of the SGA condition (syndromatic conditions, however, are excluded) or to the timing (early versus late gestation) of the PGR. Given that the net impact of an early growth-restraining insult on subsequent stature may depend more on its timing than on the nature of the insult, the only change that we propose in the current SGA indication for GH therapy is that the timing of the growth restraint should be judged at term age rather than at birth.

Terminology and implementation – We propose to maintain the well-established indicators of size at birth, such as SGA, AGA, and large-for-gestational-age (LGA), and to complement them – for preterm infants – with their equivalents at term: small-at-term (SAT), appropriate-at-term (AAT), and large-at-term (LAT). According to this terminology, the proposed change in the SGA indication for GH would result in a SAT indication for GH therapy. Implementation of this approach would require that neonatologists include "size at term" as an obligatory part of their follow-up (weight, length, and head circumference), and always include information on this size at term in their reports of (very) preterm infants. Such data could then be used as indices of growth in the first 40 weeks if ever the option of GH therapy has to be contemplated because of persistent short stature in childhood.

Impact of a switch from an SGA to a PGR or SAT indication for GH therapy – On the basis of our clinical experience, we estimate that the quantitative impact of an extension from an SGA to a PGR indication will be in the range of 10%. In fact, thus far, the limited number of preterm AGA children with persistent short stature (8) has restrained academic centers, including ours, and the pharmaceutical industry from engaging in long-term GH studies within this patient population.

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