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Short children born small for gestational age outcomes in the era of growth hormone therapy

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ABSTRACT

Small-for-gestational age (SGA) infants are at risk for short and long term medical and metabolic complications. Most SGA infants (85–90%) demonstrate spontaneous catch-up growth, typically in the first year after birth. Although catch-up growth (CUG) is a desired goal, it is important to note if CUG is too rapid the infants are at increased risk for insulin resistance and type 2 diabetes mellitus as they become adults. On the flip side, infants who do not exhibit CUG are also at increased risk of adverse adult outcomes including those for cardiovascular disease, insulin resistance and type 2 diabetes mellitus, neurodevelopmental and cognitive impairments, in addition to adult short stature. Treatment with growth hormone is safe and effective not only in increasing adult height, but also in improving body composition and decreasing metabolic complications. The aims of this review are to summarize the current knowledge on what constitutes "healthy" catch-up growth in children born SGA as well as provide an update on the role of growth hormone treatment for short children born SGA.

1. Introduction

Small-for-gestational age (SGA) denotes infants who may be at risk for short or longer term medical and metabolic consequences. In the newborn period, these neonates are at risk for multi-system diseases including pulmonary, cardio-vascular and gastrointestinal (especially, necrotizing enterocolitis). Thermoregulatory and feeding issues often accompany these major systemic conditions. Most SGA infants overcome these short term complications and go on to demonstrate catch-up growth (CUG); defined as height velocity above the limits of normal for at least 1 year after a period of growth retardation [1]. However a small cadre, approximately 10–15%, fails to demonstrate CUG. Appropriate CUG may be considered a precursor to relatively normal physiology and low risk of long term metabolic complications. Conversely, infants who do not demonstrate CUG are at increased risk for cardiovascular disease, insulin resistance and type 2 diabetes mellitus, neurodevelopmental and cognitive impairments in addition to adult short stature [2]. The tempo of post-natal weight gain is also important with respect to the risk of adverse metabolic and cardiovascular outcomes in adult life [3–6]. As such, too rapid CUG, particularly in the early postnatal period, has been associated with increased risk of insulin resistance and type 2 diabetes [7].

Here, we aim to review the impact of SGA and CUG patterns on adult outcomes specifically as they relate to metabolic and cardiovascular complications. The role of (rhGH) therapy for short children born SGA will also be reviewed.

2. Small for gestational age definition

The term intrauterine growth restriction (IUGR) is often conflated with the term SGA. However, although the two may be appropriate to describe an individual, IUGR refers specifically to sub-normal growth (estimated fetal weight < 10th percentile is the most widely used parameter) in utero confirmed by at least two intrauterine measurements [8,9]. The term IUGR implies growth delay and a baby who has not attained its biologically determined growth potential. This definition is irrespective of birth weight centiles such that some IUGR infants may in fact be appropriate for gestational age. In contrast, SGA is based on cross-sectional evaluations, not individual trajectories, and may be diagnosed in the absence of any prenatal complications such as IUGR. For the purpose of this review we will focus on the concept of SGA.

The accurate identification of SGA neonates requires accurate knowledge of the gestational age, which may be challenging in pregnancies with suboptimal prenatal care. Obstetric assessments of GA in

Abbreviations: CHD, coronary heart disease; CUG, catch-up-growth; DOHaD, developmental origins of health and disease; GH, growth hormone; IGF1, insulin-like growth factor 1; IGFBP-3, insulin-like growth factor binding protein 3; IUGR, intrauterine growth restriction; rhGH, recombinant human growth hormone; SD, standard deviation; SDS, standard deviation score; SGA, small for gestational age; SRS, Silver-Russel syndrome

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the first trimester are fairly accurate (± 7 days). However, these estimates become much less accurate with advancing pregnancy such that beyond 20 weeks GA determination may be off by 1–2 weeks. At birth, the infant growth is then assessed by anthropometry and weight, length and head circumference are measured and plotted on a set of agreed upon growth curves. Most commonly and for infants born at term, the World Health Organization (WHO) child growth standards curves are used [10,11].

Multiple definitions of SGA have been put forth. In the late 1960's two specific but different definitions were brought forward. The first one from Battaglia and Lubchenco in 1967 [12] classified neonates from Colorado into 9 groups: 3 by gestational age and then 3 by weight within each gestational age group. Their analysis was that those who were under the 10th centile (by weight) at each gestational age cohort were at increased risk for mortality and morbidities and that point was chosen as the cut-off [13]. This classification and its multicolored charts served generations of neonatologists and pediatricians leading to the more appropriate triage of infants at increased risk to a high level of surveillance and care. The second one from Usher and McLean in 1969 [14] evaluated measurements in 7 dimensions (including weight and length) in neonates from 25 to 44 weeks gestation born at sea level (Montreal). Their "convenience" cutoff and that of many others since was ± 2 standard deviation (SD), the 2.3 percentile. This was used in preference to the 10th centile (at the lower end) because the "definition" of an abnormality is restricted to about 3% (at the lower end) rather than 10% of the newborn population. Others have used these numbers and more (10%, 5%, − 2 SD, etc.) [15]. Additionally some sub-divide the SGA population by weight, length or both [16]. In 2007, a consensus statement recommended that SGA be defined as weight and/or length > 2 SD below the mean [10].

However, despite this consensus, multiple definitions continue to be used and investigators may arrive at different conclusions when examining the health implications of being born SGA, as was illustrated by the report from Zeve and co-workers [17]. The authors reported significant differences in the prevalence of metabolic syndrome; 40% versus 11% of children born SGA defined as < 10th percentile and > 2 SDs below the mean, respectively. Further, the incidence of CUG is > 86% when SGA is defined as > 2 SDs versus 79% if defined as < 5th percentile [17]. These discrepancies emphasize the need for an updated consensus with respect to the definition of SGA.

3. SGA etiology

While an in depth review of SGA etiology is beyond the scope of this review, the differential diagnosis for SGA can be broadly classified into one of three major categories: (1) maternal factors, such as malnutrition or tobacco use; (2) placental abnormalities and (3) fetal factors, including genetic disorders and congenital infections (see [18,19] for in-depth reviews). The cause of the SGA status cannot be identified in as many as 40% of neonates [18].

Identifying the cause of SGA whenever possible is important as it may influence therapeutic options [16] and in some cases can predict whether or not neonates are at risk to not experience CUG (i.e. Silver-Russel syndrome (SRS), and others). In general, however, it does impact CUG or response to rhGH.

4. Catch-up growth

4.1. Postnatal CUG epidemiology

Children born SGA have a 5- to 7-fold increased risk of short stature than their appropriate for gestational age counterparts [20]. Most neonates born SGA (85–90%), however experience CUG during the first year after birth, often recognizable at age two to three months. CUG may be defined (at least in terms of length) as "a height velocity above the statistical limits of normality for age or maturity during a defined period of time, following a transient period of growth inhibition [which may be in utero]. The effect of CUG is to take the child towards his/her pre-retardation growth curve" [21]. One might add that in the neonate born SGA this "undeclared growth channel" may be that of the mid-parental target height.

In a large population study of 3650 Swedish term infants, 94.6% were considered within the normal range (within ± 2 SD for length and weight), 1.6% low birthweight, but normal length; 2.4% short, but of normal weight; and 1.5% short and of low birthweight [22]. 87% of those considered SGA showed CUG by two years of age (the majority within 6 to 12 months), but 13% remained small throughout childhood and adolescence. Those with CUG had adult height that was − 0.7 SD from the Swedish norm, but those without had adult heights that averaged 1.7 SD below the mean. Similarly Hokken-Koelega and colleagues [23] studied a group of Dutch SGA (third percentile, − 1.88 SD) neonates who were either preterm or term gestation. After those with well-defined causes of for growth retardation were removed from consideration the investigators found that approximately 85% had CUG to above the third percentile. They also noted that birth length SD score was a more sensitive marker than birth weight to predict CUG in premature children born SGA [23].

Most CUG occurs within this first year and is virtually complete by two years [10], but some very premature babies may take up to four years to show complete CUG [24]. Those who do not have complete CUG by 2 years may have subnormal growth during all of childhood and adolescence. Some members of this group are responsive to therapy with rhGH (see below) [2,25].

4.2. CUG and metabolic outcomes in adulthood

Is catch-up growth always in the infant's best interests? It is clear that robust rapid CUG in infancy in previously SGA infants is a major risk factor for obesity in adults with varying odds ratios from 1.17 to 5.7 depending on the individual study criteria [26]. In addition, children born SGA and who demonstrate a too rapid CUG have higher fasting insulin and may be at increased risk for type 2 diabetes [7]. A similar increase in cardiovascular risk and type 2 diabetes is seen in normal birthweight infants who demonstrate rapid weight gain especially in the first 3 months after birth [27], but the SGA children tend to gain central and intra-abdominal fat (with its concomitantly greater cardiovascular risks compared to a more peripheral distribution of body fat) [28]. Insulin resistance is thought to play a central role [29]. Insulin resistance and the central fat distribution may also be responsible for the early onset and often rapid progression through puberty particularly prominent in some SGA adolescents who were born SGA, adding to their adult height deficit [30]. Polycystic ovary syndrome is also more prevalent in women born SGA and a history of catch-up growth and, may also derive from the same disordered carbohydrate metabolism [31].

4.3. Benefits of adequate CUG

The data on the effects of CUG on neurodevelopmental suggest that perhaps there are benefits of CUG in terms of cognitive function. In a large cohort study of > 250,000 Swedish military conscripts [32,33] there was an apparent "dose response" relationship between cognitive outcomes in adulthood and birth weight. In this study, the absence of CUG in length was the most important predictor of subnormal intellectual and psychological performance. However, because the effect size for neurodevelopmental issues is small, other studies with smaller study populations have failed to demonstrate a similar association [34–36]. Additional benefits for those showing CUG are more short term with resistance to infections, especially in developing nations [37].