Author’s response to reviews

Title: Latin American Consensus: Children Born Small for Gestational Age

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Author’s response to reviews: see over
March 17, 2011

Dear Ms Neilan:

Re: Latin American Consensus: Children Born Small for Gestational Age

As per your request, please find enclosed responses to the BMC Pediatrics referees’ point-by-point revisions for the above manuscript.

We hope that you find the revised manuscript to be of interest and worthy of publication in BMC Pediatrics, and we look forward to receiving your decision.

Yours sincerely,

Margaret C S Boguszewski, MD (on behalf of all authors)
1st Reviewer's report

Major compulsory revisions

1. Epidemiology. There seems to be a wide range in the number of SGA births among Latin American countries. How can this discrepancy be explained? For instance, the authors mention that only 3.6% of the children in Colombia are born with a birth weight <P10 (while 10% is expected). Could this be explained by a bad population reference, a secular trend toward higher birth weight or a local effect?

Added the following at the end of epidemiology section:

“The discrepancy in SGA births among Latin American countries may also depend on which growth chart is being used, if it has been appropriately updated, and if it reflects the ethnicity mixture within a given country. In addition, a wide range of socioeconomic status and percent of malnutrition exists within Latin American countries which may also impact the number of SGA births.”

2. Initial identification. It is difficult to interpret head circumference in the first 2 days of life, especially after a vaginal delivery. Some recommendation about the timing of measurements should be provided.

Added statement:

“Head circumference should be assessed at birth, as well as at first pediatric control during the first month of life in order to derive a more consistent measurement.”

3. Initial identification. The more premature a child is born the more difficult it is to assess his/her body proportions, for a few reasons. First, reference populations often lack extremely preterm infants. In other words, the intrauterine growth curve is not very reliable in the lower range of gestational ages. Second, most population references are based upon liveborn children. A variable degree of growth retardation is common before a preterm baby is born. These points should be acknowledged.

Added statement:

“However, it is important to recognize that defining SGA in preterm infants may be difficult since preterm reference charts do not typically include extremely preterm infants and are based upon liveborn children. Every country should make an effort to collect growth charts that represent a large number of premature infants of different gestational ages for more informed datasets.”

4. Follow-up during GH treatment. Is it really necessary to measure indices of glucose homeostasis every 6 months in all children? I think risk factors for diabetes, such as obesity or a positive family history for diabetes, should be identified prior to testing for metabolic derangements in children at risk.

Revised following statement:

“Blood glucose, thyroid function, HbA1c, and IGF-1 should be monitored every 6 months.”
“Blood glucose, thyroid function, HbA1c, and IGF-1 should be monitored once a year except in cases exhibiting clear clinical evidence of insulin resistance or an HbA1C of 6% at the beginning of treatment.”

Also revised text in abstract:
“Blood glucose, thyroid function, HbA1c, and IGF-1 should be monitored once a year.”

5. SGA and Metabolic Risks. It should be mentioned how insulin resistance is assessed by the studies. For instance, in the study by Soto et al. fasting insulin level is measured. Therefore, the statement that insulin levels and insulin resistance were measured, is incorrect. Insulin resistance was derived from fasting levels of glucose and insulin. This method is different from a glucose tolerance test or clamp techniques.

In the study by Soto et al., a short IV glucose tolerance test was performed. Insulin sensitivity was assessed throughout fasting insulin levels as well as area under the curve of insulin during the short IV glucose test. We agree that fasting insulin levels is not a specific or sensitive test of insulin resistance but it has a high correlation with other more specific tests such as the clamp in prepubertal normal BMI children. However, in this study the short IV glucose TT was also used as a method to evaluate insulin sensitivity. Other methods were considered to be too invasive to be performed in such a big sample of toddlers. Therefore the following highlighted text has been added to clarify the measurement of insulin resistance:

“In the first study to evaluate insulin secretion and sensitivity in both SGA and AGA children from birth to age 1 year [95], investigators from the University of Chile, Santiago, reported that by age 1 year, the SGA children with catch-up weight gain (ie, weight gain SD score >0.67) had higher fasting insulin levels and insulin resistance (insulin area under the curve during IV glucose) than AGA children. In a follow-up study of these subjects, the investigators reported that gains in weight SD scores continued to age 3 yr in the children born SGA, and insulin resistance also progressed during this period [15].”

6. Implementation. In light of the high prevalence of SGA: is it necessary to refer a mother to “a high-risk obstetric clinic with special care for certain diseases.” Earlier in their manuscript the high prevalence of SGA is emphasized by the authors. Is centralization of common conditions really warranted? This should be clarified.

Due to the large variability of public health policies between Latin American countries, this issue cannot be easily solved. Therefore, the following statement has been added:

“Although high-risk clinics are usually located in big cities, public health organizations should be aware of the needs of these patients and develop special networks for them.”

Minor essential revisions
7. General. Page numbers are lacking. These are especially helpful for a reviewer.

Page numbers have been added

8. General. There is a difference between height and length. Length is always measured in supine position. Height is usually standing height.

Replaced height with length where appropriate
9. Abstract. Results and Discussion. Birth weight and/or length of greater than 2 SD below the population reference mean.

Replaced in abstract with the following:

“SGA is defined as a birth weight and/or birth length greater than 2 standard deviations (SD) below the population reference mean for gestational age.”

10. Definition of SGA. What is meant by the definition of SGA is not exact? Do the authors mean unclear?

Revised statement to:

“The definition of SGA is unclear.”

11. Causes of SGA. Fetal growth is mediated through IGF1, IGF2 and insulin. An excess of cortisol negatively influences fetal growth.

Revised statement and added the following highlighted text:

“Fetal growth depends both on genetic factors and an optimal maternal-fetal health environment that allows the free flow of nutrients and oxygen, in addition to the integrity of growth factors IGF-1, IGF-2 and insulin synthesis and action. In addition, an excess of cortisol in fetal circulation produces a derangement in fetal growth.”

12. Adverse effects. A study has demonstrated… While 2 references are provided by the authors.

Revised text:

“Previous studies have demonstrated that discontinuation of long-term GH treatment in SGA adolescents normalized insulin levels (both fasting and stimulated) after a significant increase during GH therapy [56, 57].”

13. Puberty and SGA. What is the difference between the progression and the tempo of puberty?

Tempo is the timing or age of pubertal onset, while duration is length in years or months since the beginning of puberty up to its end.

No new text added

14. SGA and Metabolic Risks. …with a key feature of insulin resistance. I think the authors mean: …with insulin resistance as the key factor.

Revised text:
“When this "adaptation" is inconsistent with postnatal nutrition, it may be associated with a rapid weight gain during infancy, and may result in considerable adaptation that develops a cluster of signs of metabolic syndrome [55, 96] with insulin resistance as the key factor.”

15. SGA and Metabolic Risks. Several explanations have been put forward for the association between SGA and increased metabolic risks. I agree with the authors that the “catch-up growth hypothesis” is the most plausible explanation for these associations but other hypotheses have been put forward, such as the fetal cortisol hypothesis (Edwards et al., Lancet 1993) and the fetal insulin hypothesis (Hattersley et al., Lancet 1999). These should be briefly mentioned.

Added the following text and corresponding references:

“The fetal cortisol hypothesis postulated that maternal nutrient restriction may act to reprogram the development of the pituitary-adrenal axis, resulting in excess glucocorticoid exposure and adverse health outcomes in later life. In this hypothesis, placental 11 beta-hydroxysteroid dehydrogenase (11 beta-HSD) plays a key role by converting active cortisol to inactive cortisone. This enzyme guards the fetus from the growth retarding effects of maternal glucocorticoids.

The second alternative hypothesis is the fetal insulin hypothesis which proposes that genetically determined insulin resistance results in impaired insulin-mediated growth in the fetus, as well as insulin resistance in adult life. There is evidence to support this hypothesis in a minority of low–birth–weight cases. For example, monogenic diseases with impaired sensing of glucose, lowered insulin secretion or increased insulin resistance are associated with impaired fetal growth.

The most plausible explanation of this association, however, is the catch-up growth hypothesis. Children born SGA may present with a decreased insulin sensitivity early in life [15, 95]...”
2nd Reviewer's report

Reviewer's report:
Major Compulsory Revisions

R2-1: For this consensus an SGA child is a child whose birth weight and/or birth length is at least 2 standard deviations (SD) below the mean for its gestational age. Since this is a consensus for Latin America the birth reference chart(s) to be used to define SGA should be precisely uptaken into the definition.

This is an extremely important point since ethnicity within Latin America is very dissimilar, especially in populations with very high proportion of native descendants. It is mentioned that “reference birth charts are still unavailable in many areas” (initial identification section). In order to address the comment, the following text has been added in this section:

“There is a critical need to develop reference charts for size at birth in each country, otherwise the definition of SGA could still be misleading in certain areas.”

R2-2: With respect to GH treatment it is described that blood glucose, thyroid function etc should be monitored every six months. A baseline schedule is not described. Monitoring changes from baseline is strongly recommended for all the metabolic and endocrine components that might be influenced by GH treatment and have to be uptaken in the follow up before and during of GH treatment.

The following highlighted text has been added in the follow-up during GH treatment:

"Baseline assessment and follow-up during GH treatment:

Baseline studies including hormonal (thyroid, IGF-1) and metabolic measurements (glucose, insulin and lipid profile) are mandatory before initiation of GH treatment. Careful follow-up during GH treatment is recommended. The child should be evaluated every 3 to 6 months (physical examination and laboratory evaluation) by a physician experienced using GH to determine if dose adjustment is necessary [47]."

Also revised the following statement in abstract:
“Monitoring changes from baseline in insulin and surrogates of insulin sensitivity is essential.”

R2-3: Spontaneous catch up growth has impact on insulin sensitivity and betacell capacity in prepubertal SGA children. I miss two important references to describe the metabolic risks in chapter "SGA and metabolic Risks".


The recommended references have been included in SGA and metabolic risks section.