Symmetrical and Asymmetrical Growth Restriction in Preterm-Born Children

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KEY WORDS
growth, development, preterm, small for gestational age, appropriate for gestational age, fetal growth, growth restriction, symmetric, asymmetric

ABBREVIATIONS
AGR—asymmetric growth restriction
BW—birth weight
FT—full-term
HC—head circumference
LOLLIPOP—Longitudinal Preterm Outcome Project
NGR—non-growth restriction
OR—odds ratio
P 16—less than 16th percentile
PT—preterm
SGA—small for gestational age
SGR—symmetric growth restriction

Dr Bocca-Tjeertes conceptualized and designed the study, carried out analyses, and drafted the initial manuscript; Ms de Winter carried out analyses and reviewed and revised the manuscript; Dr Kerstjens designed the data collection instruments, coordinated and supervised data collection at all sites, and critically reviewed the manuscript; Drs Bos and Reijneveld reviewed and revised the manuscript and supervised the study; and all authors approved the final manuscript as submitted. Each author read and approved this version of the manuscript for submission and takes full responsibility for its contents.

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abstract

OBJECTIVE: To determine how symmetric (proportionate; SGR) and asymmetric (disproportionate; AGR) growth restriction influence growth and development in preterms from birth to 4 years.

METHODS: This community-based cohort study of 810 children comprised 86 SGR, 61 AGR, and 663 non-growth restricted (NGR) preterms, born in 2002 and 2003. Symmetrical growth restriction was defined as a birth weight below the 16th percentile (−1 SD) compared with full-terms and a head circumference (HC) z score not exceeding that for by 1 SD. Asymmetric growth restriction was defined as a HC z score exceeding that for by >1 SD as a proxy of brain sparing. Developmental delay was assessed by the Ages and Stages Questionnaire at 4 years.

RESULTS: Longitudinal gains in weight and height were similar for SGR and AGR children and less compared with NGR children. At age 4, z scores for weight were −1.1 for SGR and −0.7 for AGR children vs −0.3 for NGR children. z scores for height were −0.8 and −0.5 vs −0.2. HC gain were 2 cm more in SGR, but at 1 year, they were −0.2 vs 0.2 (AGR) and 0.1 (NGR). Developmental delay increased with odds ratios of 2.5 (95% confidence interval 1.1–6.0) for SGR and 2.1 (95% confidence interval 0.7–5.9) for AGR.

CONCLUSIONS: Weight and height gains were similar for AGR and SGR children but poorer compared with NGR children. SGR children caught up on HC. Developmental delay was more likely in growth-restricted preterms independent of HC at birth. Pediatrics 2014;133:1–7

WHAT’S KNOWN ON THIS SUBJECT: Fetal growth restriction, particularly in preterm children, is associated with delayed development and poor growth. Knowledge about the consequences of fetal growth restriction if classified by symmetry is lacking, especially in preterm children.

WHAT THIS STUDY ADDS: In preterm children, symmetric and asymmetric growth restriction at birth results in poorer growth later in life. Both groups are at considerable risk of developmental delay because their long-term development is independent of their head circumference at birth.
Small for gestational age (SGA) birth is associated with neurologic sequelae, even though children born SGA are known for their ability to catch up on weight and height. Nevertheless, in 10% of full-term (FT) children and in up to 40% of preterm (PT) children, this catchup is insufficient. Regarding head circumference (HC), SGA children, despite some catchup, also persist in having smaller heads compared with children born appropriate for gestational age. In PT-born children in particular, being SGA is associated with poorer neurodevelopmental outcomes on, for example, motor and cognitive functions, communication skills, and behavioral conduct. These poorer outcomes are most likely based on a permanently altered brain structure after chronic deficits in nutritional and oxygen requirements in the fetal period.

We distinguish 2 types of growth restriction: proportionate or symmetric growth restriction (SGR) and disproportionate or asymmetric growth restriction (AGR). It is assumed that symmetry or asymmetry depends on the timing and the origin of fetal growth restriction. During early pregnancy, adversities such as viral infections or genetic abnormalities will presumably result in SGR. The effect of placental insufficiency and/or severe nutritional deprivation depends on its onset during pregnancy. If it occurs during early pregnancy, it may lead to SGR. Conversely, if it occurs during late pregnancy, it may lead to AGR. In AGR, which is more common in late pregnancy, the child’s weight is disproportionate to HC due to brain sparing. An explanation for apparent growth restriction may be the constitutionally small child. All forms of growth restriction can result in spontaneous or artificial PT birth.

Although there is a considerable body of evidence on growth and development in SGA infants, longitudinal studies on growth and development in growth-restricted children after classification at birth for symmetry are scarce. Early prediction of outcomes and specific therapies can only be offered confidently if backed by sufficient and solid evidence on the specific subgroup of PT-born children concerned.

Our primary aim was to describe absolute gains and relative growth in weight, height, and HC from birth to the age of 4 in PT-born children who were either SGR or AGR at birth compared with PT-born non–growth restricted (NGR) control children. Additionally, we aimed to determine what type of growth restriction had affected development most at 4 years. We expected that long-term growth and development would be poorest in SGR children.

**METHODS**

**Study Design, Sampling Procedure, and Power Considerations**

This study was part of the Longitudinal Preterm Outcome Project (LOLLIPOP), a large, community-based cohort study on growth and neurocognitive development in PT children in the Netherlands. The LOLLIPOP sample consists of early and moderate PTs born before 36 weeks’ gestation and randomly selected FT control children born between January 1, 2002, and December 31, 2003. All children from the original LOLLIPOP cohort (n = 2517) who were PT and for whom a measurement was available on HC from the first days of life (n = 810) were included in this study. Included children did not differ from the other LOLLIPOP children regarding Ages and Stages Questionnaire (ASQ) total scores ($\chi^2$ tests $P > .05$). We classified the children according to the type of growth restriction based on their weight and HC at birth.

The review board of University Medical Center Groningen approved LOLLIPOP, and written informed consent was obtained from all parents.

**Measures and Procedure**

Gestational age was expressed as the number of completed weeks of gestation. Children whose gestational age could not be defined beyond reasonable doubt were excluded.

Data on growth during the first 4 years after birth were obtained retrospectively from the medical records kept by the preventive child health care centers and augmented by data retrieved from hospital records. During their first 4 years, children in the Netherlands routinely have ~15 well-child checkups. The checkups include assessment of height, weight, and HC (the latter until closure of the large fontanel). Height and weight is measured with standardized measuring devices (ie, an infantometer or stadiometer). Up to age 15 months, the children are examined while supine; thereafter, the children stand upright in their socks. They are weighed uncted. We analyzed an average of 9.9 standardized measurements per child.

We prepared our data by converting birth weights (BWs), heights, and HCs to z scores (mean $= 0$, SD $= 1$) according to gestational age using the medians and SD of the FT controls in the LOLLIPOP cohort. Because we wanted to capture all children with growth restriction, to have enough power to detect real differences, we used cutoffs based on SDS. Classifications by type of growth restriction were made as follows: SGR was defined as a BW $>1$ SD below the median (<16th percentile, P 16) corrected for gestational age and an HC at birth comparable to the child’s BW, that is, not exceeding the BW by $>1$ SD (Table 1). AGR was defined as any BW $>1$ SD less than the corresponding HC, as a proxy of brain sparing. If a BW was higher than the P 16 ($\geq 1$ SD) and or if HC did not exceed the BW by $>1$ SD, the child was classified as NGR.

The Dutch 4-year version of the ASQ was used to measure development at age 4 years. The ASQ is a validated parental...
questionnaire. Its reliability (Cronbach α 0.79) and validity (sensitivity 89% and specificity 80%) have been previously documented.12–14 The questionnaire was sent to the parents before the last check at the Preventive Health Care Center and filled out at home by the parents/caregivers of the included children, which took ∼15 to 30 minutes. After completion, the questionnaires were taken by the parents to the visit and handed over to the Preventive Health Care Center assistant. The ASQ measures development in 5 domains: communication, fine and gross motor ability, problem-solving ability, and personal and social functioning. The scores on each domain add up to an ASQ total score. We considered an ASQ total score =2 SD below the mean score for the Dutch reference group as a sign of developmental delay. For more detailed information on sampling and procedures, we refer readers to our previous publications.5,7,14,15,16,17

Statistical Analysis

Longitudinal Absolute Gains and Relative Growth

To describe longitudinal growth, we assessed each child’s weight and height at birth and HC within the first week of life, and again at calendar ages 1 year (∼1 SD), 2 years (∼1 SD), 3 years (∼1 SD), and at 3 years and 10 months (∼1 SD). HC was measured up to the age of 1 year (∼1 SD), ie, shortly before closure of the large fontanel) and at age 3 years, 10 months (∼1 SD). To compare SGR with AGR and NGR PT children, we first calculated absolute gains and relative weights, heights, and HCs from birth to 4 years. Absolute gains were defined as the number of kilogrammas or centimeters gained during a 1-year period. Relative weights, heights, and HCs were defined as the z score that a child had reached at a certain age compared with the NGR FT-born children from our own cohort (data not shown). Next, we calculated relative growth, defined as the change in z score, also during a 1-year period. We performed all analyses with and without adjustment for prematurity (ie, the number of weeks too early). We determined the statistical significances for all groups using F tests with analysis of variance.

Development of Growth-Restricted PT-Born Children

We compared the long-term development of growth-restricted PT-born children, be they SGR or AGR, to that of their PT-born NGR counterparts by assessing the proportion of children with abnormal total scores on the ASQ. We used multiple logistic regression models adjusted for maternal height, multiple birth, gender, and socioeconomic status for these analyses. For socioeconomic status, we used maternal education level (high/normal vs low) and family income (high/normal vs low). The factors that were significantly associated (P < .15) with abnormal ASQ total scores in the univariate analyses were included in the multivariate models. Within these models, we corrected for gestational age differences by analyzing early PT versus moderate PT birth. All analyses were done with SPSS for Windows (SPSS 19, www.spss.com).

RESULTS

Background Characteristics

Our study group consisted of 810 PT-born children, 147 of whom were growth-restricted at birth (Table 2). Symmetrical growth restriction occurred more often than asymmetric growth restriction, 10.8% vs 7.6%, respectively.

Growth in Growth-Restricted PT-Born Children

We compared absolute gains in weight and height in SGR and AGR PT-born children to those of the NGR PT-born control group from birth to 4 years of age (Table 3). Relative gains in weight and height in SGRs and AGRs was greater than in NGRs. The 2 groups caught up toward the median of the NGR PT-born control group (Table 3). At ages 1 to 4, however, their absolute and relative growth never significantly exceeded that of NGRs, and no further catchup was evident. This resulted in significantly lower z scores for all measures (Table 4). At age 4 median weights and heights for AGRs and SGRs were 0.3 to 0.8 SDS lower, compared with those of NGRs, with worst outcomes for SGRs.

On comparing the 2 growth-restricted groups, we found that absolute gains in weight and height were comparable during the first 4 years of life. Starting with lower z scores at birth, median growth of SGR children at 4 was still 0.3 to 0.4 SDS lower than that of AGR children. Regarding HC, SGR children showed accelerated growth compared with AGR and NGR children. From a lower starting point, the absolute gains and the increase in z scores were largest for SGR children. By and large, these measures were mostly similar for AGR compared with NGR children. Despite their rapid growth, the HC of SGRs were still 0.3 to 0.4 SDS lower than those of AGR and NGR children after correction for prematurity (P = .006).

### Table 1: Classification of Growth Restriction According to Body Proportion Using BW and HC for SGR and AGR Children

<table>
<thead>
<tr>
<th></th>
<th>BW</th>
<th>HC</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGR (n = 86)</td>
<td>∼1 SD</td>
<td>≤1 SD or &lt;1 SD higher than BW</td>
</tr>
<tr>
<td>AGR (n = 61)</td>
<td>Any BW</td>
<td>&gt;1 SD higher than BW</td>
</tr>
<tr>
<td>NGR (n = 863)</td>
<td>BW ≥1 SD</td>
<td>Any HC &lt;1 SD higher than BW</td>
</tr>
</tbody>
</table>

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ASM Total Score. We considered an ASQ score for the Dutch reference group as a sign of developmental delay. For more detailed information on sampling and procedures, we refer readers to our previous publications.5,7,14,15,16,17

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TABLE 2 Characteristics of the Total Sample and Proportions (% of the Group) for SGR, AGR, and NGR Children at Birth

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SGR (n = 86)</th>
<th>AGR (n = 61)</th>
<th>NGR (n = 663)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>86 (10.8%)</td>
<td>61 (7.5%)</td>
<td>663 (81.9%)</td>
<td>810 (100%)</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–31</td>
<td>31 (9.9%)</td>
<td>26 (8.3%)</td>
<td>255 (81.7%)</td>
<td>312 (100%)</td>
</tr>
<tr>
<td>32–35</td>
<td>55 (11.0%)</td>
<td>35 (7.0%)</td>
<td>408 (81.9%)</td>
<td>498 (100%)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>43 (11.4%)</td>
<td>24 (6.4%)</td>
<td>310 (82.2%)</td>
<td>377 (100%)</td>
</tr>
<tr>
<td>Male</td>
<td>43 (9.9%)</td>
<td>37 (8.5%)</td>
<td>353 (81.5%)</td>
<td>433 (100%)</td>
</tr>
<tr>
<td>Multiples/singletons</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singletons</td>
<td>65 (11.8%)</td>
<td>46 (8.3%)</td>
<td>442 (79.9%)</td>
<td>553 (100%)</td>
</tr>
<tr>
<td>Twins</td>
<td>19 (7.9%)</td>
<td>15 (6.3%)</td>
<td>206 (85.8%)</td>
<td>240 (100%)</td>
</tr>
<tr>
<td>Triplets/quadruplets</td>
<td>2 (0.6%)</td>
<td>0 (0%)</td>
<td>1 (0.2%)</td>
<td>3 (100%)</td>
</tr>
<tr>
<td>Maternal height</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1 SD</td>
<td>20 (12.9%)</td>
<td>12 (10.8%)</td>
<td>125 (79.4%)</td>
<td>155 (100%)</td>
</tr>
<tr>
<td>−1 to 1 SD</td>
<td>27 (10.1%)</td>
<td>13 (4.9%)</td>
<td>228 (85.1%)</td>
<td>268 (100%)</td>
</tr>
<tr>
<td>&gt; +1 SD</td>
<td>9 (3.7%)</td>
<td>7 (1.7%)</td>
<td>74 (98.6%)</td>
<td>91 (100%)</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal education level</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal/high</td>
<td>70 (11.8%)</td>
<td>40 (6.8%)</td>
<td>481 (81.4%)</td>
<td>591 (100%)</td>
</tr>
<tr>
<td>Low</td>
<td>16 (7.3%)</td>
<td>21 (9.6%)</td>
<td>181 (83.0%)</td>
<td>218 (100%)</td>
</tr>
<tr>
<td>Family income</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal/high</td>
<td>80 (10.4%)</td>
<td>58 (7.5%)</td>
<td>634 (82.1%)</td>
<td>772 (100%)</td>
</tr>
<tr>
<td>Low</td>
<td>6 (15.9%)</td>
<td>3 (9.7%)</td>
<td>29 (65.9%)</td>
<td>38 (100%)</td>
</tr>
</tbody>
</table>

Per cents are rounded.
* P < .05.

Associations With Developmental Delay According to Type of Growth Restriction

At birth, growth restricted PT infants, be they SGR or AGR, had an increased risk of developmental delay at age 4 as measured by the ASQ total score compared with their NGR counterparts matched for gestational age (Table 5). After adjustment for confounders, the odds ratio (OR) for developmental delay for PTs born SGR was 2.5 (95% confidence interval 1.1–5.9, P < .05). Although not statistically significant, the OR for AGR PT-born infants, still pointed in the direction of an increased risk of developmental delay compared with NGR PT-born children; the OR was 2.1 (95% confidence interval 0.7–6.0, P = .16).

DISCUSSION

We demonstrated that up to age 4 years, SGR and AGR PT-born children failed to catch up on weight and height sufficiently, nor could they keep up with the growth velocity of their NGR counterparts. The HC growth of SGRs exceeded that of AGRs and NGRs, but still remained lower at age 1 year. Our results also showed that growth restriction at birth was associated with poorer developmental outcome at 4 years, independent of the child's HC at birth. Growth-restricted PT children who were classified by symmetry have not been studied often, and we managed to provide answers to several questions.

In SGRs and AGRs, after correcting for prematurity, growth was characterized by comparable absolute and greater relative gains in weight and height during infancy, followed by failure to catch up sufficiently during subsequent years. On these measures, both groups had poorer outcomes compared with NGRs. This means that although the etiology of intrauterine growth restriction differs, any underlying pathology or time of onset can result in poorer long-term growth. Compared with NGRs, all children, be they growth restricted or not, caught up on weight and height during infancy but failed to keep this up in subsequent years. This is in line with the concept of "transient catchup growth" described by Harding et al. It also reflects that long-term outcomes of gains in weight and height beyond the end of the first year could turn out considerably less favorable.
In contrast, for SGRs compared with AGRs and NGRs, growth in HC was characterized by accelerated growth. The AGR and NGR groups, after correcting for prematurity, were born with a HC normal for their gestational age. SGRs, born with smaller heads, showed spectacular catchup growth in HC at the end of their first year. Nonetheless, they failed to catch up completely with their AGR and NGR counterparts. Recently, this phenomenon was also reported for SGRs. From this perspective, we were unable to demonstrate a difference in the risk of developmental delay between both growth-restricted groups. We offer 3 explanations for the heightened risk of developmental delay. The first explanation being that the catchup on weight and height in the 2 groups was insufficient to fully guarantee their normal development because we found that SGRs and AGRs had similar growth patterns in weight and height. This growth pattern did not facilitate gains that caught up completely with the median of NGRs from birth to 4 years, and catchup was associated with a more favorable developmental outcome. Second, we speculate that the accelerated HC growth seen in SGR children and their catchup approaching, but not actually reaching, the medians of AGR and NGR children, safeguarded these children from additional developmental delay. On the basis of their HC at birth as a proxy of brain sparing, we expected less developmental delay in AGRs. A normal HC at birth combined with appropriate HC growth during the first year has been shown to protect against poorer developmental outcome, especially in PT children. Despite normal HC growth in AGRs, this was not the case in our sample. Developmental delay was independent of birth HC. Accelerated growth of HC in SGRs possibly reflected postnatal brain sparing. Recently, Klaric et al reported that in AGRs slower HC growth precedes poorer developmental outcome. Accelerated HC growth may have the opposite effect.

The third explanation may be that fetal growth restriction caused irreversible...
damage to the developing brain. As a consequence, in the case of AGR, brain sparing was insufficient to fully prevent the child from developmental delay. Nevertheless, evidence on the exact mechanisms of growth and development in growth restricted PT-born children does not as yet allow us to fully understand their outcomes.

The major strengths of this study were its large sample of growth-restricted PT-born children over the entire range of gestational ages and its community-based design. Moreover, we analyzed growth longitudinally and assessed development using a validated, easy-to-fill-out developmental screener.25

Our study also has some limitations. First, no data on fetal growth were available to us. Therefore, we were unable to differentiate AGR from normal children with a large HC, nor SGR from constitutionally small children. Our definitions of asymmetric and symmetric growth restriction were specifically designed for this study. They were based on SDS for HC at birth, using 1 SD discrepancy between body weight and HC at birth as cutoff. Even so, we expect that the proportion of misclassified children was small because among PT infants in general, the prevalence of being constitutionally small or having a disproportionately large HC without associated growth restriction has been estimated to be <2.5%.26,27 Second, we used a rather broad definition of symmetric growth restriction (ie, BW <P 16). This definition could have been stricter by using a BW <P 10 or even <P 2.3. If we would have used a cutoff below P 16, it would have led to low power to detect real differences. Finally, AGR occurred less often than SGR in our sample in contrast to what one might expect. Therefore, further research is needed to clarify the underlying mechanisms of growth and development for both groups.

Our study has several implications. Growth-restricted children should be closely monitored because they seem to have an additional risk of growth restriction as well as developmental delay, irrespective of the type of growth restriction or its origin. PT-born children and particularly growth-restricted PT-born children might benefit considerably if we enable them to follow their own “optimal” growth pattern. In PT-born children, catchup growth is a well-documented phenomenon during infancy.20 However, this catchup growth should not extend toward overgrowth or misbalanced growth because children with better catchup growth did not have less risk for developmental delay. The possible metabolic risks that accompany too-rapid growth28 should be prevented. These topics are of particular interest for further research.

Because developmental delay at age 4 was independent of the child's HC at birth, we might need to take this into account when counseling parents on developmental outcomes in growth-restricted children.

Further research is needed to elucidate the effects of growth restriction in PT-born children. It may be that growth-restricted children should not be classified by symmetry. It underestimates the sequelae of growth-restricted birth in AGRs and also underestimates the ability of catchup growth in HC and possible developmental protection in SGR. From this perspective, preventing fetal growth restriction might be the key to preventing poor outcomes in PT-born children.

**CONCLUSIONS**

Gains in weight and height were similar in SGR and AGR PT-born children and poorer than that of NGR PT-born children. The accelerated HC growth of PT-born SGR children facilitated its catchup. Developmental delay was more likely in growth-restricted PT-born children and was independent of HC at birth.

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