Preterm birth, early growth and adult metabolic health

Finken, M.J.J.

3 Long-term height gain of prematurely born children with neonatal growth restraint:

parallellism with the growth pattern of children born small-for-gestational-age

Martijn J.J. Finken, Friedo W. Dekker, Francis de Zegher, Jan-Maarten Wit,
on behalf of the Dutch POPS-19 Collaborative Study Group

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Abstract

Objectives:

It is unknown whether children born very preterm (<32 weeks' gestation) with appropriate size for gestational age (AGA), who grow poorly in the first postnatal months (i.e., preterm-growth-restraint, PGR), show a similar growth pattern as children born small-for-gestational age (SGA). In this study, childhood growth and adult height of very preterm AGA PGR children were compared to those of very preterm SGA and AGA non-PGR children.

Methods:

Data were drawn from the Project On Preterm and Small-for-gestational-age infants cohort. PGR was considered to have occurred after AGA birth, if length and/or weight was <-2 SD score (SDS) at the age of 3 months post-term.

Results:

Among 380 very preterm children, 274 experienced no PGR and showed near-normal growth, whereas 79 (21%) experienced PGR and subsequently displayed a growth pattern similar to that of very preterm SGA children (N=27). Adult height of these children was -1.1 to -1.2 SDS. Very preterm AGA PGR and SGA children with a height <-2 SDS at 5 years had an adult height of approximately -2.5 SDS.

Conclusions:

Childhood growth and adult height were similar in very preterm SGA and AGA PGR children. These long-term findings further strengthen the plausibility of extending the SGA indication for growth hormone (GH) therapy in such a way that very preterm AGA PGR children are no longer excluded from GH therapy, if they have a short stature persisting beyond the age of 5 years.

Introduction

There is increasing evidence that children who experienced a transient phase of preterm-growth-restraint (PGR) display a persistent ensemble of sequelae that are independent of whether the PGR occurred in utero (resulting in a small-for-gestational-age (SGA) infant), ex utero (preterm birth followed by poor neonatal growth), or in both perinatal phases. To date, this evidence already encompasses features like body composition, insulin sensitivity, and blood pressure (reviewed in Wit et al (1)). From the age of approximately 6 to 8 years onward, the PGR subgroups converge their pathophysiological patterns so that, in the absence of a perinatal history, they become nearly indistinguishable on clinical, biochemical, endocrine, or metabolic grounds. Here, we extend this concept further: up to adult height, the growth pattern of very preterm appropriate-for-gestational-age (AGA) PGR children was compared with that of very preterm SGA and AGA non-PGR children.

Methods

Population

Growth data were extracted from the prospective Project On Preterm and Small-for-gestational-age infants (POPS), which follows a nationwide cohort of very preterm (<32 weeks' gestation) and/or very-low-birth-weight (<1,500 g) infants born in The Netherlands in 1983 (2). For this specific study, only the very preterm non-syndromic white subjects were included, provided that their growth data (length and weight) at birth and at 3 months post-term were complete (N=380). Size at 3 months post-term was used as proxy for size at term.

Study protocol

Length until the age of 2 years post-term was measured to the nearest 1 cm in supine position, fully extended with the heels in contact with a baseboard. At ages 5 and 19 years, standing height was measured to 1-mm accuracy. Sizes at birth and beyond birth were converted to SD score (SDS) using Swedish and Dutch references, respectively (3;4).

By definition (5), very preterm subjects (<32 gestational weeks) with birth length and/or weight <-2 SDS were classified as SGA, whereas those with birth length and weight ≥-2 SDS and length and/or weight at 3 months <-2 SDS were labelled as AGA PGR, and those with birth length and weight ≥-2 SDS and length and weight at 3 months also ≥-2 SDS were labelled AGA non-PGR. Target height was calculated as: mid-parental height + 6.5 (-6.5 for females) + 4.5 cm (correction for Dutch secular trend). Ethical approval and written informed consent was obtained from all of the participants.

Statistical analysis

All of the auxological data were normally distributed. Length/height measurements were compared between AGA PGR and AGA non-PGR groups, as well as between AGA PGR and SGA groups, using the unpaired t test. These comparisons were repeated after adjustment for perinatal morbidity, using linear regression analysis. Statistical significance was defined as a P value <0.05. To adjust for possible bias caused by the relatively greater availability of growth data of taller persons at the age of 19 years, missing data for adult height SDS was predicted from the available height SDS data at 5 years through imputation for each group separately by linear regression analysis.

Results

There were 1,338 children in the original cohort, of whom 1,012 were born before 32 weeks of gestation. Of those, 683 were still alive at the age of 1 year. After exclusion of 7 syndromic children and persons from non-white ancestry, 571 subjects were left. Complete data for size (length and weight) at birth and at 3 months post-term was available for 380 children. The

Table 1. Prevalence of prenatal and postnatal characteristics of very preterm infants.

Characteristic	SGA	AGA PGR	AGA non-PGR	P	
				AGA PGR vs. AGA non-PGR	AGA PGR vs. SGA
N	27	79	274		
Obstetric					
Parity > 0 (%)	10 (37%)	44 (56%)	137 (50%)	0.32	0.08
Multiple pregnancy (%)	3 (11%)	28 (35%)	65 (24%)	0.04	0.02
Maternal hypertension (%)	12 (44%)	15 (19%)	36 (13%)	0.19	0.009
Gestational diabetes (%)	0	5 (6%)	18 (7%)	0.96	0.33
Maternal smoking (%)	12 (44%)	23 (32%)	99 (38%)	0.34	0.25
Maternal intake of drugs/alcohol (%) [a]	18 (67%)	45 (57%)	157 (57%)	0.96	0.38
Neonatal					
Gestational age (weeks)	30.9 (28.3 to 31.9)	29.3 (25.4 to 31.7)	30.4 (25.6 to 31.9)	<0.001	<0.001
Respiratory distress syndrome (%)	11 (41%)	55 (70%)	134 (49%)	0.001	0.008
>7 Days on assisted ventilation (%)	5 (19%)	37 (47%)	50 (18%)	0.02	0.009
Intracranial hemorrhage (%)	5 (19%)	22 (28%)	36 (13%)	0.002	0.34
Convulsions (%)	0	5 (6%)	8 (3%)	0.16	0.18
Postnatal corticosteroids (%)	2 (7%)	11 (14%)	10 (4%)	0.002	0.51
Sepsis (%)	10 (37%)	26 (33%)	74 (27%)	0.31	0.70
Necrotising enterocolitis (%)	6 (22%)	4 (5%)	9 (3%)	0.50	0.02

Values represent N (%) or median (range). Continuous variables were compared with the unpaired t test.

Dichotomous variables were compared by the χ^2 test or Fisher's exact test.

[a] Smoking, drinking alcohol, or using soft drugs, hard drugs or methadone during pregnancy.

AGA PGR condition (N=79; 21%) was 3-fold more prevalent than SGA (N=27; 7%). Among AGA PGR children, 22 were PGR for weight, 21 for length, and 36 for both.

Table 1 lists a selection of conditions that may have contributed to prenatal and/or postnatal growth restraint. Comparing AGA PGR with AGA non-PGR and SGA children, the AGA PGR group was characterized by a low gestational age and, accordingly, by a high prevalence of respiratory distress syndrome and prolonged ventilation. There was also a greater proportion with intracranial hemorrhage and on glucocorticoid therapy among AGA PGR children than among those born AGA without PGR.

Table 2 summarizes the growth patterns of the groups up to adult height. The growth patterns of AGA PGR and SGA groups were similar from the age of 3 months post-term onwards. At birth, AGA PGR children were somewhat shorter and lighter than AGA non-PGR children. Throughout childhood, stature of AGA PGR children was shorter than that of AGA non-PGR children. These differences persisted after correction for the variables listed in Table 1 (data not shown).

Table 2. Spontaneous growth of very preterm infants.

Variable	SGA			AGA PGR			AGA non-PGR			P	
	N	Median	Range	N	Median	Range	N	Median	Range	AGA PGR vs. AGA non-PGR	AGA PGR vs. SGA
Neonatal size SDS											
Birth weight	27	-2.1	-3.2 to 0.7	79	-0.2	-2.0 to 1.3	274	0.1	-2.0 to 2.7	<0.001	<0.001
Birth length	27	-2.5	-4.4 to -1.4	79	-0.2	-1.6 to 2.8	274	0.2	-2.0 to 3.6	0.01	<0.001
3 mo eight	27	-2.6	-5.3 to 0.4	79	-2.3	-4.2 to 0.3	274	-0.3	-2.0 to 2.6	<0.001	0.61
3 mo lenght	27	-2.4	-5.4 to 0.2	79	-2.3	-4.8 to -0.8	274	-0.4	-2.0 to 3.3	<0.001	0.31
Length/height SDS at follow-up visits											
1 yr	26	-1.6	-5.6 to 0.3	71	-1.3	-5.5 to 2.8	252	-0.3	-6.0 to 2.3	<0.001	0.18
2 yrs	26	-1.2	-4.8 to 1.2	70	-1.1	-4.5 to 1.4	244	-0.2	-2.8 to 4.3	<0.001	0.76
5 yrs	27	-1.0	-3.1 to 1.6	75	-0.7	-4.6 to 1.6	259	-0.1	-4.1 to 2.7	<0.001	0.40
19 yrs (available data)	19	-0.8	-2.9 to 0.7	51	-0.8	-2.7 to 0.4	157	-0.3	-2.9 to 2.1	<0.001	0.88
19 yrs (with data imputation)	27	-1.2	-2.9 to 0.7	76	-1.1	-3.9 to 0.4	264	-0.4	-3.4 to 2.1	<0.001	0.92
Target height SDS	27	-0.2	-1.6 to 1.0	77	-0.1	-1.6 to 1.5	270	0.1	-2.1 to 2.4	0.06	0.36

Table 3 shows that, among AGA PGR children, the prevalence of short stature is close to 20%, as it is among very preterm SGA children. A short stature at the age of 5 years in these 2 groups points to a high risk (~90%) of short stature in adulthood, whereas a stature ≥-2 SDS at 5 years old was associated with a low prevalence (~10%) of short stature in adulthood. AGA PGR and SGA children with a height <-2 SDS at the age of 5 years had a median adult height of approximately -2.5 SDS.

Discussion

In this population-based study of very preterm children, the AGA non-PGR children displayed a virtually normal growth pattern, whereas the AGA PGR and SGA children grew in a way that has previously been described for SGA children born at term (6;7). The present data are the first to document the spontaneous growth pattern of AGA PGR children up to adult stature. Hence, they are also the first to evidence that AGA PGR children, if still short (height <-2 SDS) at the age of 5 years, have a similar risk (~90%) to become short adults as do SGA children (whether born preterm or not) who are still short at that age. The striking long-term parallellism between AGA PGR children and SGA children is herewith extended to linear growth up into adulthood.

The present findings corroborate the rationale to extend the current growth hormone (GH) indication for short SGA children in such a way that it harbours also those very preterm born AGA PGR children who still have a height <-2 SDS at the age of 5 years. Departing from the numbers in this article, it can be estimated that a PGR extension of the current SGA indication for GH would increase the number of eligible children by 10 %. Because average adult height SDS is very close to mean height SDS in childhood and as younger children respond more to exogenous GH (8), such therapy should preferably start at an early age.

In our study, no bias could have been introduced by the high neonatal mortality rate (2), since the indication for GH therapy is determined beyond the toddler age range. However, because mortality of very preterm infants has dramatically declined between 1983 and the mid-1990s, especially because of a reduction in mortality from respiratory distress syndrome (9), the sicker children – presumably with PGR – survive nowadays. This increasing survival rate has also resulted in a rising incidence of bronchopulmonary dysplasia (9), which implies that the prevalence of short stature may be higher in the next generation of very prematurely born children.

Conclusions

In conclusion, prematurely born children who experienced PGR were found to have a growth pattern similar to that of SGA children. These data corroborate a concept in which short AGA PGR children are considered to be pathophysiological equivalents of short SGA children. The present evidence undermines the current policy to exclude PGR survivors from GH therapy if their small size evolves toward a short stature in childhood.

Table 3. Short stature at age 5 years points in AGA PGR and in SGA children to a high risk (~90%) of short stature in adulthood; conversely, a stature ≥-2 SD at age 5 years implies a low risk (~10%) of short stature in adulthood.

Height SDS at 5 yrs	SGA		AGA PGR	
	<-2 SDS	≥-2 SDS	<-2 SDS	≥-2 SDS
N	6	21	11	64
Height SDS at 19 yrs	-2.6 (-2.9 to -1.8)	-0.8 (-2.1 to 0.7)	-2.4 (-3.9 to -1.4)	-0.8 (-2.7 to 0.4)
N <-2 SDS at 19 yrs (%)	5 (83%)	1 (5%)	10 (91%)	7 (11%)

Values represent median (range) or N (%).

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