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Long-term consequences of differences in early growth : epidemiological aspects

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Growth of preterm born children

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Abstract

Background

In this review, we describe the growth of (very) preterm infants or (very) low-birth-weight infants from birth until adulthood.

Methods

A systematic analysis of growth of these infants is thwarted by different definitions (classification by gestational age or birth weight) used in the literature.

Results

The early postnatal period of these individuals is almost invariably characterized by substantial growth failure. In the majority of preterm infants this is followed by a period of catch-up growth, which starts in early infancy and usually stops at 2–3 years of age, although in some cases it may continue into adolescence. Catch-up growth is usually incomplete, so that infants born preterm remain shorter and lighter than term-born peers during childhood, adolescence, and adulthood. Disproportionate catch-up growth in height and weight may lead to an altered body composition in adulthood, especially in females.

Conclusion

Though early catch-up growth has shown to be beneficial for neurodevelopmental outcome, it is also associated with adverse metabolic consequences in adulthood. As the first generation of (very) preterm infants is now reaching young adulthood, future follow-up studies on these effects are warranted.

Introduction

Based on a systematic review of the literature the definitions and determinants of prematurity, prenatal growth, reference charts for preterm born infants, early postnatal growth of the preterm infant, catch-up growth, and growth in childhood, adolescence and adulthood size are discussed, followed by a brief review of late metabolic consequences.

Methods

We conducted a systematic literature search in PubMed of articles published between 1998 and October 2007. Our search strategy is shown in table 1. Relevant articles were selected on title and abstract. We primarily focused on original research conducted in the past 10 years in humans and written in English. Additional articles were sought by checking the reference lists of the included articles. Recent review articles that provided comprehensive overviews were also included. For the present paper, we selected approximately 50% of the encountered articles; a full list can be obtained from the authors.

Table 1. Search strategy for PubMed

Search No.	
1	'infant, premature' (MeSH terms) or 'premature infant' (TiAb) or preterm (TiAb) or 'infant, low birth weight' (MeSH terms) or low birth weight (TiAb)
2	'growth' (MeSH terms) or growth (TiAb)
3	growth (Ti) or 'cohort studies' (MeSH terms) or cohort studies (TiAb) or cohort study (TiAb) or 'body height' (MeSH terms) or body height (TiAb) or 'body weight' (MeSH terms) or body weight (TiAb)
4	1 and 2 and 3
5	4 limits: publication date from 1998, humans

Definitions

Preterm birth is defined by the estimated gestational age as a proxy of maturity. Three subgroups are distinguished by the World Health Organisation (WHO): preterm (< 37 weeks gestation), very preterm (< 32 weeks), and extremely preterm (< 28 weeks).¹ In the United States of America and several other countries a classification according to birth weight is

generally used. Low birth weight infants are defined as those with a birth weight of 2,500 g or less, which may be due to prematurity, being born small for gestational age (SGA), or both. Similarly, lower cut-off limits for weight have been used to describe more severe cases, i.e. very low birth weight (VLBW < 1,500 g)^{2,3} and extremely low birth weight (ELWB < 1,000 g).⁴ In very preterm and/or VLBW infants, gestational age is a better predictor of short-term survival than birth weight.⁵ The decision about which parameter is applied to define a cohort of small infants has considerable consequences for the characteristics of the population studied.

Determinants of prematurity and low birth weight

Determinants of prematurity

Various risk factors have been consistently associated with premature birth, such as multiple pregnancy, low socioeconomic status, African-American origin, second teenage pregnancy, parity and past reproductive history, substance misuse, infection and hypertensive disease during pregnancy.⁶ Approximately 14% of the variation in gestational age is explained by maternal genetic factors, and 11% by fetal genetic factors.⁷ The effect of specific polymorphisms in the foetus, e.g. in genes encoding immunologic or haemostatic proteins, seems to be modest compared to maternal risk factors.⁸

Determinants of a low birth weight for gestational age

The risk factors for SGA are usually divided into foetal, placental, and maternal factors, the latter including maternal age, height, and parity,⁹ for details see.¹⁰ Foetal genetic factors explained 31% of the normal variation in birth weight and birth length and 27% of the variation in head circumference; maternal genetic factors explained 22% of the variation in birth weight, and 19% of the variation in birth length and head circumference.⁷ One of the foetal genes involved may be insulin, as polymorphisms in its promoter are associated with size at birth.¹⁰ Paternally and maternally imprinted genes oppose each other in the regulation of foetal growth and development, illustrated by observations that genomic imprinting of the IGF-II gene has a considerable effect on foetoplacental development and thus delivery of nutrients to the foetus.¹⁰ Although the variation in birth weight may be mainly caused by differences in growth in the third trimester, there is recent evidence that both the growth trajectory of the fetus and its adaptive responses to the prenatal and postnatal environment may be determined as early as the period around the time of conception.^{11,12}

Prenatal growth

SGA

At birth, the newborn can have an appropriate weight and/or length for gestational age (AGA), be small for gestational age in weight and/or length (SGA), or large for gestational age (LGA).¹³ Ideally, the cut-off limit for SGA should best discriminate between infants who are at high risk of short-term and long-term growth impairment, disease, and death, and those who are at a low risk.¹⁴ However, in practice there are various cut-off limits based on arbitrary statistical criteria. Among paediatric endocrinologists there is consensus that a birth weight and/or length of < -2 SDS should be the cut-off value.^{9,15} Neonatologists tend to use the 5th or 10th percentile for gestational age,¹⁶ since these cut-offs are related to later developmental problems.

Within the SGA population, three subgroups can be distinguished; infants with a low weight but normal length for gestational age (SGA W or SWGA), infants with a low length but normal weight for gestational age (SGA L or SLGA), and infants with the combination of both (SGA LW or SLWGA).^{17,18} The growth patterns of the three subgroups are somewhat different^{17,19} and SLWGA males have on average a poorer neurologic outcome than those born SWGA but not SLGA.²⁰

We have previously argued that the third auxological parameter that should be measured at birth is head circumference. SGA H or SHGA could be added to the nomenclature to indicate a small head circumference for gestational age,²¹ which is indicative for early intrauterine growth retardation or, in extreme cases, for a decreased biological effect of IGF-1 due to primary IGF-I deficiency or resistance.²²

SGA versus IUGR

Formerly, the terms SGA and intrauterine growth restriction (IUGR) were used for the same condition, but nowadays there is consensus that the term IUGR should be limited to the process of decreased intrauterine growth rate detected by – preferably several – ultrasound measurements.^{9,15} If prolonged and/or severe enough, this may lead to the delivery of an SGA infant. SGA refers only to the condition at birth.^{15,18,21} When the prenatal growth pattern is unknown, SGA may be regarded as a proxy for IUGR.¹⁴

References and standards for birth size for gestational age

For the classification of prematurity, a reliable estimate of gestational age is necessary. This is usually performed by combining information on the last menstrual period, and early ultrasound assessment,² but neither is perfectly reliable.²³ It is noteworthy that according to international recommendations gestational age is expressed in complete weeks,^{24,25} while in the frequently used reference of Usher and McLean gestational age was calculated to the nearest week from the last normal menstrual period.²⁶ In the former approach, the reference curves are shifted to the left by half a week, which appears irrational.

For the classification of SGA (or LGA) versus AGA, anthropometric data are compared with reference charts for gestational age. Ideally, up-to-date reference data from the same or a similar population are required.¹⁴ The choice of the reference population has a considerable impact on the classification, especially for preterm infants.²⁷

Currently used neonatal charts differ substantially, and there are essentially four types of diagrams:

(1) Most reference charts are based on the birth size of all newborns in a certain area or country and are presented separately for boys and girls. The American charts (by Lubchenco^{28,29} and later by Usher and McLean²⁶) are based on small samples (so that combined charts for males and females were prepared) and it was shown recently that both are inaccurate for use in current populations in the US.³⁰ For Northern European countries the Swedish reference is most appropriate.^{24,31}

(2) In some countries separate reference charts are used for primipara and multipara mothers, and for different ethnic groups.³²

(3) Conditional, customized charts are based on various conditions with a known impact on birth weight weighted in a computer model in order to calculate the degree of normality.³³ On top of adjustments for foetal sex, gestational age and parity, additional adjustments are made for a number of characteristics such as maternal height, weight at first antenatal clinic visit, ethnic group,³⁴ maternal birth weight and birth weight of previous siblings.³⁵ These charts are primarily used by obstetricians.

(4) 'Standard' charts are based on intrauterine growth measurements in babies subsequently born at term, from which birth weight is calculated.³⁶ While these charts have a high sensitivity in detecting a neonate with a growth anomaly, calculating body weight from ultrasound measurements leads to an inevitable loss of precision, so that many centres continue to use regular reference charts based on birth weight data.³⁷

Early postnatal growth

In the first weeks of extra-uterine life, (very) preterm infants often develop cumulative energy and protein deficits, despite caloric and protein supplements at recommended intakes.³⁸ Even with active regimens of parenteral and/or early enteral feeding,³⁹ this causes on average a substantial postnatal growth failure, with growth curves that are sharply deviating from the reference data.⁴⁰⁻⁴⁴

The typical growth pattern is an initial postnatal weight loss (the lowest weight is reached at the fourth to seventh day), followed by an early neonatal peak in growth velocity mimicking in utero growth rates beginning in the second week of life. Birth weight is usually regained in the period between the 8th to the 24th day of life, but earlier in infants with higher birth weights.^{39,40,45} Typically, VLBW infants have weights less than the 10th percentile at 36 weeks

postmenstrual age,⁴² and have an average weight at 40 weeks postmenstrual age of -2.6 SDS.⁴⁶ In cohorts based on a low birth weight, the relatively high proportion of SGA infants has a negative effect on growth outcome. While weight is the most documented auxological parameter during these first weeks, also extra-uterine growth restriction with regard to length and head circumference is common.⁴³

Although preterm infants are usually lighter and shorter at 40 weeks after the last menstrual period than term born infants, no difference in total adiposity was found. Moreover, preterm infants had an altered fat distribution, with a decrease in subcutaneous fat and an increase in intra-abdominal adipose tissue.⁴⁷ At 1 year of age, still a slightly greater fat mass normalized for weight was found in infants born < 34 weeks of gestation.⁴⁸

Factors influencing early growth

Preterm infants are often admitted to a Neonatal Intensive Care Unit (NICU), and face the consequences of unintended postnatal life such as respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, and infections, with concomitant treatment regimens of, e.g., mechanical ventilation, parenteral nutrition, and administration of steroids.^{43,49} Both illness severity and clinical practice in treatment and nutrition vary widely between infants and between NICUs as well.^{50,51}

A low birth weight and gestational age,^{43,44} postnatal dexamethasone,^{43,49} a long duration of respiratory support,⁴⁹ pulmonary and circulatory problems,⁴⁴ severity of illness,⁴⁵ infections,^{43,44} NEC,^{43,44} and male sex⁴³ have been negatively associated with early postnatal growth. On a biological level, an important mediator of the early postnatal growth in preterm infants may be IGF-1.^{52,53} Not surprisingly, a very important factor that has been positively related to growth in early life is caloric intake.^{38,49,54}

Postnatal growth references

The non-physiological situation of preterm birth makes it difficult to provide appropriate postnatal growth references in order to distinguish postnatal growth failure from growth that is normal for this specific group. Separate growth references for infants with parenteral and/or early nutrition have been suggested,^{39,55} but generally the charts of birth weight, length and head circumference for gestational age are used. Postnatal growth failure has been defined as weight below the 10th centile at 36 weeks corrected gestational age,⁴¹ or as a decrease in z-score of 1 > 2 between birth and 36 weeks corrected gestational age.⁵⁶ We have coined the term 'preterm growth restraint' (PGR) to indicate poor growth in the third trimester, either spent in utero (the term born SGA infant) or ex utero (the preterm born infant with a normal weight for gestational age, but a low length and/or weight at term age, i.e. < -2 SDS).⁵⁷

Catch-up growth

Catch-up growth

Catch-up growth is usually defined as reaching an SD score of $1 > -2$ SDS of the reference population,⁹ but in other studies a change $1 > 0.67$ SD has been used as cut-off.⁵⁸ Similar to term infants born SGA, most preterm born infants (approximately 80%) show catch-up growth in weight, length and head circumference after initial postnatal growth failure,⁵⁹⁻⁶² generally starting early in the first months of life and often achieved within the first 2 years of life.^{59-61,63,64} However, late catch-up growth of preterm subjects has been described throughout childhood^{61,62} and even in adolescence.⁶⁵⁻⁶⁷

It is generally considered that catch-up growth in weight, length, and particularly in head circumference is important for neurodevelopmental outcome.⁶⁸⁻⁷⁰ Motor impairment was less common if preterm infants were fed an enriched preterm formula in comparison to a regular term formula in the first month after birth,⁷¹ especially in males.⁷² However, on average adolescents born very preterm have decreased brain volumes compared to term controls.⁷³

Determinants of catch-up growth

Little is known about the factors that determine if catch-up growth occurs in preterm infants and whether it is complete. Also for term born SGA infants these questions have not been fully elucidated, but birth length and target height,⁷⁴ a lower serum leptin, lower birth weight, early weaning from the ventilator and plasma IGF-I are associated with catch-up growth in weight.^{75,76}

In preterm infants early growth and genetic potential as reflected by parental height seem important for catchup growth in height as well, though this effect might be different for different durations of gestation.^{61,62,66,77,78} Examples of specific genetic polymorphisms that have both been related to increased postnatal catch-up growth in preterm infants are the d3-isoform polymorphism of the growth hormone receptor gene,⁷⁹ and the R23K polymorphism in the glucocorticoid receptor gene.⁸⁰

Recently, a prediction model was presented on growth of a cohort of very low birth weight survivors. The following factors explained height SDS at 5 years: height SDS at 1 year, mid-parental height SDS, 1st year weight SDS, and birth weight SDS.⁶¹ We have shown that infants born very preterm who reach the normal range for length ($1 > -2$ SDS) at 3 months post-term display a virtually normal growth pattern in childhood, adolescence and adulthood, but infants who do not catch up (labelled pre-term growth restraint, PGR) show a similar growth pattern as term born SGA babies. In approximately 10% of them length remains below the -2 SDS line.⁶⁴ Most studies have shown that postnatal corticosteroid treatment has a negative effect on postnatal catch-up,^{63,81,82} but others did not find such effect.^{60,83-85} Other factors that have been negatively related to later (catch-up) growth in preterm infants include male gender,³ medical complications,⁸⁶ and being born SGA.^{59-62,87}

Growth and body composition

Growth in childhood

With respect to growth in early and mid-childhood, the general pattern reported is that despite catch-up growth (if defined by reaching a height within the normal range) and a steady increase in SDS or z-score for all anthropometric measurements,^{60,61,88} both male and female infants born preterm remain smaller and lighter with a smaller head circumference than their term-born or normal birth weight peers,^{61,65,77,88} particularly if they were born SGA^{59-62,87,89} (table 2, page xx). The data in table 2, collected from recent studies, however, indicate that there is likely to be a trend towards normal height and weight after a decrease in z-scores in the first years of life. Only one study reported that preterm infants born < 29 weeks of gestation as a group reached normal weight, height, and weight for height before puberty.⁹⁰ With regard to body composition in infancy, a reduced fat mass when normalized for height at age 8-12 years was observed in children born < 37 weeks of gestation.⁹¹

Growth in adolescence and adulthood

In studies describing growth of preterm infants reaching adolescence (table 3), puberty has not always been accurately reported. This complicates a comparison between studies, as puberty has an important effect on growth velocity.⁷⁷ Studies reporting puberty have shown no difference in the timing of puberty between preterm born adolescents and term controls.^{3,65,67} In adolescence, upwards percentile crossing has been reported,^{65-67,92,93} but adolescents born preterm generally continue to be shorter in puberty than term born controls.^{65,78}

Table 3. Growth of preterm and LBW infants in puberty and adulthood

	N	Inclusion criteria birth weight or gestational age	Age (years)	Height z-score	Weight z-score
Hack 2003 ♂ ³	103	<1500 g	20	-0.44	-0.35
Hack 2003 ♀ ³	92	<1500 g	20	-0.26	0.26
Doyle 2004 ⁶⁷	42	500-999 g	20	-0.52	+0.14
Brandt 2005 ⁶⁶	21	<1000 g, SGA* and preterm**	22.8	-1.02	
Euser 2005 ♀ ⁹⁵	216	<32 weeks	19	-0.60	-0.48
Euser 2005 ♂ ⁹⁵	187	<32 weeks	19	-0.55	-0.41
Farooqi 2006 ⁷⁸	83	<26 weeks	11	-0.53	-0.15
Saigal 2006 ♀ ⁶⁵	82	<1000 g	11-16	-0.59	-0.24
Saigal 2006 ♂ ⁶⁵	65	<1000 g	11-16	-0.46	-0.53

* SGA as defined <10th percentile for height and/or weight

** preterm birth undefined

Table 2. Early postnatal and childhood growth of preterm, LWB, VLBW and ELBW infants

	N	Inclusion criteria birth weight/ gestational age	Mean gestational age (wks)	Mean birth weight (g)	Mean birth weight SDS	Percentage SGA at birth	Measure point	Percentage growth failure at measure point	Height z-score at measure point	Weight z-score at measure point
Fevitrel 2000 ⁷⁷	765	'preterm' & < 1850 g	31.0	1364			18 months 7.5-8 years 9 to 12 years		0.91 -0.47 -0.44	
Lemons 2001	4438	501-1500 g				22 ^a	36 weeks ^b	97 ^a		
Niklasson 2003 ⁹⁰	52	<29 wks		28 wk 1180 27 wk 1015 ≤26 wk 720			40 weeks ^b 6 months 3 years 7 years	19.2 5.8 ^c	-1.08 -1.70 -0.60 +0.09	-0.19 -1.73 -0.88 -0.02
Bertino 2006 ⁴⁵	262	500-1500 g	30.4	1140	-0.98	38.5 ^a	40 weeks ^b	100 ^d		
Saigal 2006 ⁶⁵	82	<1000 g	27.2	838		28 ^a	2 years	100 ^e	-1.04	-1.96
Saigal 2006 ⁶⁵	65	<1000 g	27.0	844		20 ^a	1 year 2 years 8 years		-0.77 -0.94 -1.59	-1.68 -1.05 -2.49
Trebar, 2007 ⁶¹	1320	<1500 g	29.17	1097	-1.16	55.3 ^a	1 year 2 years 8 years 1.8 years 4.0 years	13.3 ^c 18.2 ^c	-0.92 -0.84 -0.69 -0.93	-1.90 -1.05 -1.28 -1.32
Hovi 2007 ⁴⁶	166	600-1500 g	29.17 ± 2.22		-1.29 ± 1.51	33.1 ^c	6.1 years 40 weeks ^b	11.1 ^c	-0.62	-0.85
Bracewell 2007 ⁸⁸	241	<25 ⁶			≤23 wks + 0.70 24 wks + 0.37 25 wks + 0.07		6 years		-0.95	-1.18

a as defined <10th percentile for weight at birth b postmenstrual age c as defined <-2.0 SDS for weight and/or height d as defined < 3rd percentile for weight e as defined < 25th percentile for weight

An increasing number of studies have reported data on adult height in preterm born individuals (table 3), but one should note that these studies only concern the very preterm and very or extremely low birth weight population, from which severely handicapped subjects are usually excluded. Growth data of individuals born preterm at a more advanced gestational age are scarce. Mean height of young adults born (very) preterm is shorter than that of term-born controls^{65,67,94} and than target height.⁶⁵ Again, preterm infants born SGA are at higher risk of short stature, as only 46% of SGA-VLBW born young adults showed complete catch-up.⁶⁶

Adult weight and body composition

Young adults born (very) preterm weigh less than the average population⁶⁵ (6.5 and 7.1 kg for males and females).⁶⁵ However, catch-up for weight of individuals born preterm is generally more pronounced than catchup in height (table 3). The mean BMI that has been reported in young adulthood is close to that of the reference population in most studies,^{65,95} but lower⁹⁴ and higher^{3,67} percentages of overweight have been reported, particularly in females.

One of the cohorts that has been followed up to young adulthood is the POPS cohort, consisting of infants born very preterm and/or with a very low birth weight.^{95,96} In young adulthood, the average height SDS was -0.55 and -0.60 for males and females respectively, but BMI SDS was -0.10 and -0.17, and waist circumference SDS +0.24 for males and even +0.73 for females.⁹⁵ This indicates that the altered fat distribution at term age noted in preterm born infants might persist into adulthood, which might in turn contribute to a less favourable cardiovascular disease risk profile.^{47,95}

Late metabolic consequences of preterm birth

Since the original observations of Barker and collaborators,⁹⁷⁻¹⁰⁰ a wealth of studies have shown an association between low birth weight and adult metabolic diseases like obesity, type 2 diabetes, hypertension and cardiovascular incidents. More recently, it has been shown that especially the combination of small size at birth followed by increased catch-up growth in later life is detrimental for adult cardiovascular health.¹⁰¹⁻¹⁰³ Although these findings have been confirmed in animal studies, one should realize that in the human all 'evidence' results from epidemiological studies. The mechanism behind these associations has remained obscure thus far.^{104,105} In the majority of the original publications, no clear distinction has been made between low birth weight due to term SGA or due to preterm birth, and the number of preterm subjects included is very low.

It has been speculated that individuals born preterm experience similar metabolic consequences in adult life as term born individuals with low birth weight.^{106,107} The third trimester is a critical developmental period, and malnutrition during this time span has been related to reduced adult glucose tolerance in the Dutch famine studies.¹⁰⁸ Infants born preterm almost invariably

experience postnatal growth failure during this time window, often followed by later catch-up growth. Evidence for this similarity in adverse metabolic sequelae in adulthood between term SGA infants and infants born preterm mostly results from studies on glucose tolerance and blood pressure during childhood and young adulthood in preterm or VLBW survivors (recently reviewed by Hofman et al.¹⁰⁶). Both in the neonatal period¹⁰⁹ and in childhood,^{110,111} individuals born (very) preterm have a decreased insulin tolerance.

Survivors of preterm birth are still too young to allow for studying the effect on full-blown cardiovascular disease, and studies are limited to early markers of cardiovascular disease in young adulthood. In a recent study, glucose tolerance was reduced in a cohort of VLBW young adults,⁴⁶ and in the POPS study we found that insulin sensitivity at 19 years of age in individuals born very preterm was particularly decreased if BMI in young adulthood was relatively high.¹¹² No associations were observed between early growth and intima-media thickness.¹¹³ With respect to blood pressure, we found an increased incidence of hypertension and borderline hypertension,¹¹⁴ in accordance with other studies,^{115,116} irrespective of nephrocalcinosis.¹¹⁷

Conclusion

Individuals born preterm usually show a substantial growth failure in the early postnatal period, which is usually followed by catch-up growth over 2–3 years, but a slightly lower mean adult height than term born peers. Although catch-up growth is beneficial for neurodevelopmental outcome, it might lead to adverse metabolic consequences in adulthood. Future follow-up studies on these effects are warranted.

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