A regional follow-up study at two years of age in extremely preterm and very preterm infants.

Rijken, M.

CHAPTER 5

Similar growth in preterm infants with intra- or extrauterine growth restriction

Monique Rijken, MD
Jan M Wit, MD, PhD
Sylvia Veen, MD, PhD

On behalf of the Leiden Follow-Up Project on Prematurity

Submitted

Abstract

Objective: To analyse the influence of preterm growth restraint (PGR) in preterm infants born appropriate-for-gestational-age (AGA) on growth achievement at 2 years of age and to compare their growth with preterm small-for-gestational-age (SGA) infants.

Design: Regional, prospective study of infants born < 32 weeks gestational age (GA). Length, weight and head circumference were measured at term, 1 and 2 years of age and expressed as Standard Deviation Scores (SDS). PGR was defined as length and/or weight at term age < -1.3 SD.

Results: Of the 158 infants, 23 (14%) infants were SGA, 61 (39%) were AGA-PGR and 74 (47%) AGA-nonPGR. At all ages the SGA-infants had the lowest length, weight and head size. At 2 years of age AGA-PGR-infants had a similar mean length as SGA-infants (-0.68 vs. -0.80 SDS), a lightly bigger head circumference (-0.09 vs. -0.40 SDS) and a higher weight (-0.93 vs. -1.50 SDS) and weight-for-length (-0.79 vs. -1.51 SDS). The AGA-nonPGR-infants displayed growth parameters comparable to the Dutch reference group, except for a relatively large head circumference (0.38 SDS). After correction for confounders PGR remained the most important predictor for sub-optimal growth at 2 years in the AGA-infants.

Conclusion: Preterm infants, who experience preterm growth restraint, are at increased risk for sub-optimal growth at the corrected age of 2 years. Their growth is similar to that of SGA-infants concerning length and head circumference.

Introduction

Advances in neonatal care have resulted in an improvement of survival of premature infants, but survivors have remained at an increased risk of neurological sequelae and sub-optimal growth. Sub-optimal growth may be the result of a complex interaction of perinatal factors including inadequate nutrition and is common in extremely preterm children, particularly when the infants are born small-for-gestational-age (SGA)[1], when they have bronchopulmonary disease (BPD)[2] or when prolonged courses of systemic steroids have been given for BPD.[3-5] Most clinicians strive at a normal growth pattern of preterm infants, as a sign of sufficient nutrient intake, which is believed to be crucial for early brain development.[6]

We have recently postulated that the extra-uterine growth restriction of AGA born preterm infants who suffer from medical complications in the neonatal period may have a similar effect on later growth as intrauterine growth restriction leading to SGA at term. Thus, "preterm growth restraint" (PGR) may be the relevant issue, more than the environment where it is experienced (in utero or ex utero).[7] Indeed, in a nationwide cohort of very preterm infants born in the nineteen-eighties, infants who experienced PGR displayed a growth pattern similar to that of preterm SGA-infants.[8] An association between the incidence of in-hospital growth failure in extremely low birth weight infants and growth failure at 2 years of age was described earlier by Dusick *et al.*[9]

In a previous study in a regional cohort of very preterm infants from the nineteen-nineties, we found impaired growth at 2 years of age and postnatal dexamethasone to be related to sub-optimal growth.[10] In the present study we compared various growth parameters until the corrected age of 2 years of three subgroups (SGA, AGA-PGR and AGA-nonPGR) in the same cohort.

Methods

Data were taken from the Leiden Follow-Up Project on Prematurity (LFUPP), a Dutch regional prospective study, which included live born infants < 32 weeks of gestation, born in 1996/1997 in the health regions The Hague, Leiden and Delft (n=266).[11] The infants from the health region Delft were excluded because of a high percentage of missing growth data (59%). At the corrected age of 2 years,

196 of the 225 infants (87%) born in the regions The Hague and Leiden were alive. From 160 survivors (82% of 196) length and weight were measured at the corrected age of 2 years. From 36 children no data could be obtained. No differences were observed between the lost-to-follow-up group and the study group in perinatal parameters, but the parents of the lost-to-follow-up group had lower socio-economic status and were more often non-Caucasian. Head circumference at 2 years was measured in 142 children (72%).

For this analysis small-for-gestational-age was defined as birth weight <-1.3 SD (P_{10}) according to Niklasson.[12] All other infants were considered appropriate-for-gestational-age (AGA), including three infants with birth weights >2 SD. In the AGA-infants preterm growth restraint (PGR) was defined as length and/or weight at term age less than -1.3 SD. When the postmenstrual age (PMA) was <40 weeks (29 infants, 18%) growth parameters were compared to Niklasson[12]; when PMA was >42 weeks (45 infants, 29%) the Dutch nation-wide growth reference was used[13]; and for the children examined between 40 – 42 weeks PMA (84 infants, 53%) the two reference-curves were interpolated. In 2 infants data concerning length and weight at term age were missing, so the final cohort consisted of 158 infants. Seven infants were examined not precisely at term age (resp. at 46, 48, 49, 51 and 58 weeks PMA); when we excluded these infants and analysed the data, results remained the same (data not shown).

Antenatal and perinatal data were collected including health status and diseases of the mother, socio-economic status, diseases and medication during pregnancy, gestational age, birth weight and data about perinatal morbidity and medication. In 28 cases dexamethasone was administered. In 1996/1997 dexamethasone was given in an initial dose of 0.5 mg/kg/day, tapered over 42 days to 0.1 mg/kg/day.

The Medical Ethics Committee of the LUMC approved the study and informed consent of the parents was obtained.

Follow-up

At term age and at the corrected age of 1 and 2 years four neonatologists experienced in developmental examination assessed the infants. A complete physical examination was performed and data about length, weight and head circumference were collected. Length was measured in supine position with straight back and knee on a standardised infantometer. Infants were weighed undressed on a calibrated infant balance scale. Head circumference was measured with a standard

measuring tape taking the largest measurement across the occipito-frontal line. Length (L), weight (W) and head circumference (HC) were expressed as standard deviation scores (SDS) according to the Dutch growth charts at the ages of 1 and 2 years.[13] Because of differences in length due to differences in genetic growth potential, at the age of 2 years another outcome measure for length was added: Lcorr-SDS. In Lcorr-SDS, length was corrected for target height (TH). Target height was calculated as [mean parental height + or – 13 cm]/2 + 4.5 cm, in which 4.5 cm represents the secular trend per generation of 30 years.[13] Height of both parents was obtained in 93% of the infants. At 2 years of age a mental developmental index (MDI) and a psychomotor developmental index (PDI) were assessed by a developmental psychologist using the Dutch version of the Bayley-Scales of Infant Development I (BSID I). During the study period the BSID II were not validated yet for the Dutch population. The BSID I have a mean value of 100 and a standard deviation of 16.

Statistical analyses

SPSS 11 for Windows was used for statistical analyses. Fischer's Exact test and X^2–test were used to evaluate associations in a 2x2 table. The two-sample *t* test was used for comparison of continuous variables. The one-sample *t* test was used to compare means with Dutch growth charts. A multiple regression analyses was conducted with growth parameters at 2 years as dependent variables and GA, BW-SDS, PVL, BPD, dexamethasone and PGR as independent variables. Differences were considered significant when $p < 0.05$.

Results

Twenty-three (14.6%) of the 158 children analysed at 2 years could be classified as SGA, 61 (38.6%) as AGA-PGR and 74 (46.8%) as AGA-nonPGR. Characteristics of the 3 groups including mean gestational age (GA) and mean birth weight (BW) are listed in Table 1. Mean BW, multiple birth, patent ductus arteriosus (PDA), use of surfactant, need of oxygen at 28 days, bronchopulmonary dysplasia (BPD), use of postnatal dexamethasone, still being admitted at term and the MDI and PDI were significantly different in the 3 groups. Among the AGA-infants GA, BW, female gender, respiratory distress syndrome (RDS), use

Table 1. Characteristics of SGA-, AGA-PGR- and AGA-nonPGR-infants

	SGA n (%)	AGA-PGR n (%)	AGA-nonPGR n (%)
Total infants	(n = 23)	(n = 61)	(n = 74)
GA (wks, mean+range)	30.4 (26.1-31.9)	28.4 (23.7-31.9)	30.1 (25.9-31.9)
BW (grams, mean+range)*	943 (530-1210)	1118 (550-1928)	1540 (900-2382)
Male gender	11 (48)	31 (51)	50 (68)
Multiple birth*	2 (9)	20 (33)	27 (37)
PDA*	4 (17)	21 (34)	9 (12)
surfactant*	5 (22)	37 (61)	24 (32)
O2-28 days*	6 (26)	34 (56)	5 (7)
BPD 36 wks*	5 (22)	27 (44)	3 (4)
NEC	3 (13)	7 (12)	3 (4)
Cystic PVL	2 (9)	2 (3)	3 (4)
IVH grade 3/4	-	4 (6)	3 (4)
Dexamethasone*	4 (17)	23 (38)	1 (1)
Still admitted at term*	8 (35)	22 (37)	8 (11)
Normal neurol. exam. at term	6 (26)	31 (51)	41 (55)
Normal neurol. exam. at 2 yrs	15 (65)	36 (59)	59 (80)
BSID MDI – mean (SD)*	96 (30)	91 (25)	104 (23)
PDI – mean (SD)*	92 (20)	92 (20)	102 (20)

GA = gestational age; BW = birth weight; PDA = patent ductus arteriosus; BPD = bronchopulmonary dysplasia; NEC = necrotising enterocolitis: PVL = periventricular leucomalacia; IVH = intraventricular haemorrhage; MDI = mental developmental index; PDI = psychomotor developmental index; SGA = small-for-gestational age; AGA = appropriate-for-gestational age; PGR = preterm growth restraint. *Significant difference between the 3 groups.

of surfactant, patent ductus arteriosus (PDA), need of oxygen at 28 days, BPD, postnatal dexamethasone, abnormal neurological examination at 2 years and both lower PDI and MDI were associated with PGR. Multiple birth, race, necrotising enterocolitis, periventricular leucomalacia (PVL) and intraventricular haemorrhage were not associated with PGR. For all growth parameters, PGR was an important predictor for sub-optimal growth at 2 years in the AGA-infants. Mean differences were 0.97 SD for length, 0.60 SD for length corrected for target height, 0.93 SD for weight, 0.57 SD for weight-for-length and 0.47 SD for head circumference. For length, PGR remained a significant predictor after correction for confounding factors like GA, BW-SDS, PVL, BPD and use of dexamethasone (mean SDS was 0.88 lower in AGA-PGR-infants compared to AGA-nonPGR-infants).

Growth parameters for the 3 groups (SGA, AGA-PGR and AGA-nonPGR) at term age and at 1 and 2 years corrected age are shown in Table 2. Compared to Dutch nation-wide reference diagrams, mean SDS for L, Lcorr, W and W/L were significantly lower in the SGA- and AGA-PGR-infants at all ages. Head circumference was only smaller in the SGA-infants at term age and at 1 year of age; at 2 years of age HC was similar to the reference group. Growth of the infants in the AGA-nonPGR-group was similar to the reference group, except for mean L-SDS at 1 and 2 years of age and the mean HC-SDS at all ages, which were larger than in the reference group. After correction for the target height, length at 2 years was close to the mean of the reference group.

Growth was significantly different in the 3 groups: $p < 0.001$ for L and W, $p = 0.002$ for Lcorr, $p = 0.003$ for W/L and 0.005 for HC. In the AGA-group the infants with PGR grew significantly worse than the infants without PGR. The SGA-infants had the lowest mean SDS for length, weight and head circumfer-

Table 2. Comparison of mean growth-SDS at different ages in SGA-, AGA-PGR- and AGA-nonPGR-infants

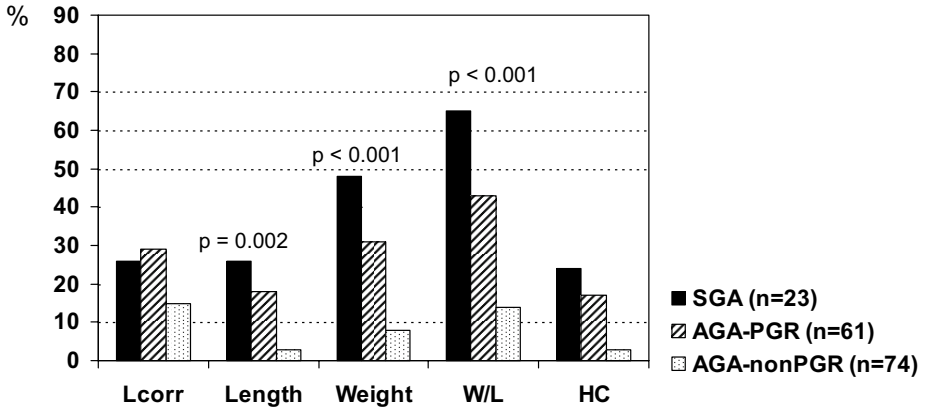
	Age (yr)	SGA (n = 23) Mean-SDS (95% CI)	AGA-PGR (n = 61) Mean-SDS (95% CI)	AGA-nonPGR (n = 74) Mean-SDS (95% CI)
Length	term	-3.38 (-3.93;-2.82)★	-2.00 (-2.22;-1.78)★	-0.04 (-0.22;0.14)
	1	-1.13 (-1.65;-0.60)★	-0.70 (-0.94;-0.46)★	0.37 (0.16;0.59)†
	2	-0.80 (-1.35;-0.25)★	-0.68 (-0.91;-0.44)★	0.29 (0.07;0.51)†
Length-corr	2	-1.03 (-1.59;-0.47)★	-0.70 (-1.08;-0.33)★	-0.11 (-0.36;0.15)
Weight	birth	-1.85 (-2.04;-1.67)★	-0.14 (-0.33;0.05)	0.34 (0.18;0.50)†
	term	-2.76 (-3.15;-2.36)★	-1.69 (-1.89;-1.48)★	0.02 (-0.15;0.19)
	1	-1.72 (-2.22;-1.23)★	-0.82 (-1.10;-0.54)★	0.06 (-0.16;0.27)
	2	-1.50 (-2.00;-1.01)★	-0.93 (-1.25;-0.62)★	-0.01 (-0.25;0.23)
Weight-for-length	1	-1.36 (-1.84;-0.87)★	-0.44 (-0.76;-0.13)★	-0.07 (-0.34;0.19)
	2	-1.51 (-1.95;-1.06)★	-0.79 (-1.13;-0.46)★	-0.22 (-0.50;0.05)
Head circumference	birth	-1.22 (-1.72;-0.72)★	1.46 (-0.36;3.28)	0.28 (0.05;0.51)†
	term	-0.85 (-1.29;-0.42)★	-0.19 (-0.41;0.03)	1.03 (0.82;1.24)†
	1	-0.61 (-1.14;-0.09)★	-0.08 (-0.36;0.19)	0.50 (0.25;0.75)†
	2	-0.40 (-0.95;0.14)	-0.09 (-0.37;0.19)	0.38 (0.13;0.64)†

★ significantly smaller than the reference group; † significantly larger than the reference group
SGA = small-for-gestational-age; AGA = appropriate-for-gestational-age; PGR = preterm growth restraint

ence at all ages. At 2 years the mean SDS for length (L), length corrected for target height (Lcorr) and head circumference (HC) were similar in SGA- and AGA-PGR-infants; W-SDS and W/L-SDS were significantly lower in the SGA-infants compared to the AGA PGR-infants, 0.57 and 0.72 SD respectively.

Figure 1 shows the percentages of the 2 year old children in the three groups, who had a growth parameter of less than -1.3 SD. Significant differences were observed for length, weight and weight-for-length.

Figure 1. Comparison of percentage of infants with growth-SDS < -1.3 (P_{10}) at the corrected age of 2 years, between SGA-infants, AGA-PGR-infants and AGA-nonPGR-infants



Lcorr = length corrected for target height; W/L = weight-for-length; HC = head circumference; SGA = small-for-gestational age; AGA = appropriate-for-gestational age; PGR = preterm growth restraint.

Discussion

In this prospective regional study of very preterm infants, 45% of the infants born AGA experienced extra-uterine growth restriction (preterm growth restraint). After 2 years, their mean length was similar to SGA born children, and significantly lower than AGA-nonPGR children and population references. Weight for age and for length of AGA-PGR children were also significantly lower than population references, but higher than of SGA born children. Head circumference was within the normal range for each group at 2 years. Growth in AGA-nonPGR children was normal for the population and for target height.

These findings support our hypothesis that preterm growth is an important predictor for growth later in childhood, and are in agreement with the similar growth patterns over a period of 19 years of preterm born children either born SGA or AGA with PGR. In that cohort a more strict definition was used of SGA and PGR (-2 SDS instead of –1.3 SDS).[8] We chose -1.3 SD because if we had used -2 SDS in our study only 5 infants (0.6%) would have been classified as SGA; 35 infants (26% of the non-SGA-infants) had a weight or length < -2 SD at term age. Our results are also compatible with those of Jordan *et al.*[2], who described significant catch-up between birth and 36 months which was greater for SGA- than for AGA-infants; in their group AGA-infants with serious neonatal pathology had lower length at term age compared to AGA-infants without serious pathology, but weight and head circumference did not differ. Recently Casey *et al.*[14] published a study in which very-low-birth-weight infants who developed postnatal growth problems demonstrated lower physical size at 8 years of age compared to infants with adequate postnatal growth.

Suboptimal growth of preterm babies is observed in multiple studies. Clark *et al.* described the incidence of extra-uterine growth retardation (defined as growth < P10 at the moment of discharge from the hospital) in a large cohort infants born between 23 and 34 weeks' gestation to be 28%, 34% and 16% for weight, length and head circumference, respectively.[15] In our study these numbers were 23%, 12% and 10% for the whole group but 31%, 18% and 17% for the AGA-PGR-group. Recently the National Institute of Child and Human Development (NICHD) Neonatal Research Network reported that 97% of infants with a birth weight < 1500 grams at 36 weeks post conceptional age had weights less than the 10th percentile and they conclude that optimising nutritional support of these very preterm infants remains a challenge.[16] Clark *et al.* found male

gender, need for respiratory support and exposure to steroids to be associated with extra-uterine growth retardation.[15] We also found RDS and use of postnatal dexamethasone to be associated with PGR, but in our study female gender was associated with PGR.

The decrease in L-SDS, W-SDS and HC-SDS between birth and term age in the AGA-PGR-infants is probably mainly due to significant morbidity in the neonatal period. Indeed, RDS, PDA and BPD occurred more often in the AGA-PGR-group; furthermore these infants received more often postnatal dexamethasone which is also described to have a negative influence on growth.[17] Nowadays however this drug is used much less in neonates.[18] Ehrenkranz *et al*.[19] also reported that preterm infants who survived without developing BPD, severe intraventricular haemorrhage or necrotising enterocolitis, gained weight faster than comparable infants with those morbidities. In our study, it is not clear whether the differences in neurological performance, MDI and PDI at 2 years between the AGA-PGR- and AGA-nonPGR-children, are the result of more significant neonatal morbidities or poorer catch-up growth in the AGA-PGR-children.

In this study data on growth were missing from 36 infants (18%). However, the study group and the lost-to-follow-up group did only differ in socio-economic status and race, and because we found no association between growth and these two parameters, it is not likely that including these infants would have made the results different.

We have now shown evidence, that a proper early postnatal growth is also a good predictor of normal growth in early childhood. However, it was recently suggested that rapid catch-up growth of preterm infants may also have long-term effects that may be harmful, such as the development of insulin resistance[20], particularly if body mass index SDS increases during childhood and adolescence. However, the respective roles of environmental and genetic factors in the development of insulin resistance is still unknown.[21;22]

In conclusion, preterm infants born AGA who grow poorly up to term age, show sub-optimal growth at 2 years of age, similarly to preterm infants born SGA. After correction for confounders the effect of sub-optimal early growth remains. Weight of AGA-PGR infants at 2 years is also low, but not as low as of SGA-infants.

"What is already known on this topic"

- Growth in preterm infants is usually impaired
- Several risk factors can be pointed out for this impaired growth, like bronchopulmonary dysplasia and use of postnatal corticosteroids

"What this study adds"

- Preterm infants who suffer from preterm growth restraint (extra-uterine growth retardation), display similar growth as preterm infants who experience intra-uterine growth retardation
- Preterm growth restraint is an important predictor for sub-optimal growth at 2 years of age

References

1. Gortner L, van Husen M, Thyen U, Gembruch U, Friedrich HJ, Landmann E. Outcome in preterm small for gestational age infants compared to appropriate for gestational age preterms at the age of 2 years: a prospective study. Eur J Obstet Gynecol Reprod Biol 2003;110 Suppl 1: S93-S97.
2. Jordan IM, Robert A, Francart J, Sann L, Putet G. Growth in extremely low birth weight infants up to three years. Biol Neonate 2005;88:57-65.
3. Morris BH, Smith KE, Swank PR, Denson SE, Landry SH. Patterns of physical and neurologic development in preterm children. J Perinatol 2002;22:31-6.
4. Wood NS, Costeloe K, Gibson AT, Hennessy EM, Marlow N, Wilkinson AR. The EPICure study: growth and associated problems in children born at 25 weeks of gestational age or less. Arch.Dis. Child Fetal Neonatal Ed 2003;88:F492-F500.
5. Wang D, Vandermeulen J, Atkinson SA. Early life factors predict abnormal growth and bone accretion at prepuberty in former premature infants with/without neonatal dexamethasone exposure. Pediatr Res 2007;61:111-6.
6. van Wassenaer A. Neurodevelopmental consequences of being born SGA. Pediatr Endocrinol Rev 2005;2:372-7.
7. Wit JM, Finken MJJ, Rijken M, de Zegher F. Preterm Growth Restraint: A Paradigm That Unifies Intrauterine Growth Retardation and Preterm Extrauterine Growth Retardation and Has Implications for the Small-for-Gestational-Age Indication in Growth Hormone Therapy. Pediatrics 2006;117:e793-e795.
8. Finken MJJ, Dekker FW, de Zegher F, Wit JM, for the Dutch Project on Preterm and Small-for-Gestational-Age-. Long-term Height Gain of Prematurely Born Children With Neonatal Growth Restraint: Parallellism With the Growth Pattern of Short Children Born Small for Gestational Age. Pediatrics 2006;118:640-3.
9. Dusick AM, Poindexter BB, Ehrenkranz RA, Lemons JA. Growth failure in the preterm infant: can we catch up? Semin Perinatol 2003;27:302-10.

10. Rijken M, Wit JM, Le Cessie S, Veen S. The effect of perinatal risk factors on growth in very preterm infants at 2 years of age: The Leiden Follow-Up Project on Prematurity. Early Hum Dev. 2007; 83:527-34.
11. Stoelhorst GMSJ, Rijken M, Martens SE, Brand R, den Ouden AL, Wit JM *et al*. Changes in Neonatology: Comparison of Two Cohorts of Very Preterm Infants (Gestational Age <32 Weeks): The Project on Preterm and Small for Gestational Age Infants 1983 and The Leiden Follow-Up Project on Prematurity 1996-1997. Pediatrics 2005;115:396-405.
12. Niklasson A, Ericson A, Fryer JG, Karlberg J, Lawrence C, Karlberg P. An update of the Swedish reference standards for weight, length and head circumference at birth for given gestational age (1977-1981). Acta Paediatr Scand 1991;80:756-62.
13. Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E *et al*. Continuing positive secular growth change in The Netherlands 1955-1997. Pediatr Res 2000;47: 316-23.
14. Casey PH, Whiteside-Mansell L, Barrett K, Bradley RH, Gargus R. Impact of prenatal and/or postnatal growth problems in low birth weight preterm infants on school-age outcomes: an 8-year longitudinal evaluation. Pediatrics 2006;118:1078-86.
15. Clark RH, Thomas P, Peabody J. Extrauterine Growth Restriction Remains a Serious Problem in Prematurely Born Neonates. Pediatrics 2003;111:986-90.
16. Lemons JA, Bauer CR, Oh W, Korones SB, Papile LA, Stoll BJ *et al*. Very Low Birth Weight Outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1995 Through December 1996. Pediatrics 2001;107:e1.
17. Weiler HA, Paes B, Shah JK, Atkinson SA. Longitudinal assessment of growth and bone mineral accretion in prematurely born infants treated for chronic lung disease with dexamethasone. Early Hum Dev 1997;47:271-86.
18. Shinwell ES, Karplus M, Bader D, Dollberg S, Gur I, Weintraub Z *et al*. Neonatologists are using much less dexamethasone. Arch Dis Child Fetal Neonatal Ed 2003;88:F432-F433.
19. Ehrenkranz RA, Younes N, Lemons JA, Fanaroff AA, Donovan EF, Wright LL *et al*. Longitudinal Growth of Hospitalized Very Low Birth Weight Infants Pediatrics 1999;104:280-9.
20. Singhal A, Fewtrell M, Cole TJ, Lucas A. Low nutrient intake and early growth for later insulin resistance in adolescents born preterm. Lancet 2003;361:1089-97.
21. Finken MJ, Keijzer-Veen MG, Dekker FW, Frolich M, Hille ET, Romijn JA *et al*. Preterm birth and later insulin resistance: effects of birth weight and postnatal growth in a population based longitudinal study from birth into adult life Insulin resistance 19 years after preterm birth. Diabetologia 2006;49:478-85.
22. Ingelfinger JR. Prematurity and the legacy of intrauterine stress. N Engl J Med 2007;356:2093-5.