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Growth Patterns in Children With Intrauterine Growth Retardation and Their Correlation to Neurocognitive Development

Aviva Fattal-Valevski, MD, MHA, Hagit Toledano-Alhadef, MD, Yael Leitner, MD, Ronny Geva, PhD, Rina Eshel, PhD, and Shaul Harel, MD

The relationship between somatic growth and neurocognitive outcome was studied in a cohort of 136 children with intrauterine growth retardation. The children were followed up from birth to 9 to 10 years of age by annual measurements of growth parameters, neurodevelopmental evaluations, and IQ. The rate of catch-up for height between 1 and 2 years of age was significantly higher than the catch-up for weight ($P < .001$). The cognitive outcome at 9 to 10 years correlated with head circumference at all ages. The neurodevelopmental outcome at 9 to 10 years correlated with weight at all ages. Correlation with head circumference was more significant with IQ, while with weight it was stronger with the neurodevelopmental score. Height at 1 year was a significant predictor for IQ and neurodevelopmental outcome at 9 to 10 years. These findings are of distinct importance for prediction of subsequent neurodevelopmental outcome in children with intrauterine growth retardation.

Keywords: intrauterine growth retardation; outcome; head circumference; height; weight

Intrauterine growth retardation, the terminology for infants whose birth weight is below the 10th percentile for gestational age,[1] occurs in 3% to 10% of all pregnancies.[2] Intrauterine growth retardation plays a significant role in short- and long-term outcome as reflected in the relatively high incidence of brain dysfunction and neurodevelopmental impairment, as well as in somatic growth failure. These clinical consequences may not be apparent until later in development; therefore, it is crucial to longitudinally follow-up these fetuses and infants.[3-7]

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From the Institute for Child Development and Pediatric Neurology Unit, Tel Aviv Sourasky Medical Center affiliated to the Sackler Faculty of Medicine, Tel Aviv University, Israel.

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Address correspondence to: Aviva Fattal-Valevski, Pediatric Neurology Unit, "Dana" Children's Hospital, Tel Aviv Sourasky Medical Center, 6 Weitzman St, Tel Aviv 64239, Israel; e-mail: afatal@post.tau.ac.il.

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Approximately 10% to 20% intrauterine growth-retarded infants reach a final height below their genetic potential.[1] Most catch-up growth occurs in the early postnatal period within the first 3 to 6 months after birth. Thereafter, growth velocity is similar to that of appropriate-for-gestational age infants.[5,8]

Several longitudinal studies have addressed the question of correlation between cognitive development and somatic growth in intrauterine growth retardation. An increased risk of cognitive (developmental) impairment has been demonstrated in children with small head circumference.[6,7] Others have shown that small head circumference (<3% and 3%-10% at age 8 months) and growth velocity of head circumference (≤10% from birth to 4 months) were strongly associated with school-age learning problems. Assessment of academic performance was based on a teacher questionnaire dealing with aspects of reading, writing, spelling, and mathematics.[4]

The effect of head circumference in a sibling cohort was examined, and the authors found that small-for-gestational age infants with a head circumference ≥3 cm smaller than their siblings had a significantly lower IQ and visuomotor scores.[4] Other studies have demonstrated conflicting results: small-for-gestational age infants with a head circumference <3 cm smaller than their siblings had comparable mental and motor developmental scores.[9] A study of Israeli adolescents revealed that a higher proportion of small-for-gestational age males completed <12 years of schooling or attended vocational schools, compared to controls, having a 2.4-fold greater risk for lower academic achievements than their appropriate-for-gestational age peers.[10] In a retrospective study, Shenkin et al[11] found that birth weight was significantly related to IQ at age 11. Sommerfelt et al[12] ascertained that small-for-gestational age children have lower nonverbal and verbal IQ than controls. Using data from the National Collaborative Perinatal Project (1959-1976),[13] a total of 2719 term infants whose birth weight was <2500 g, small-for-gestational age, were compared with 43 104 term infants not small for date. The IQ scores of children tested at age 7 were 6 points lower for those born small for date. Visuomotor development was also lower in the small-for-gestational age group.[13] The aim of the current study was to document the growth pattern in a cohort of intrauterine growth-retarded children, specify subgroups of catch-up growth versus noncatch-up growth at various ages, and compare the neurodevelopmental and cognitive outcome of these children.

Participants and Methods

Participants

This work is part of a long-term, prospective follow-up investigation of intrauterine growth-retarded infants, aimed at determining their developmental/cognitive outcomes at school age. All infants born consecutively after September 1992 at the Lis Maternity Hospital, Tel Aviv Sourasky Medical Center, with a birth weight <10th percentile for gestational age, according to Israeli birth weight curves previously reported,[14-16] were prospectively followed-up until the age of 9 to 10 years ($n = 136$). Gestational age was calculated according to the date of the last menstrual period. The study group included both term and preterm newborns. Infants born prematurely were also incorporated into the study if their birth weight was <10th percentile for gestational age. Children with genetic syndromes, major malformations, or congenital infections were excluded. All parents provided informed consent for their children's participation in the study.

Methods

The children were followed-up annually from birth by a team of pediatric neurologists and psychologists at the Institute for Child Development. At each follow-up visit, they underwent a detailed neurodevelopmental examination, weight, height, and head circumference measurements, and formal psychological testing. The neurodevelopmental questionnaires were designed in accordance with Prechtl's "optimality concept"[17]; each item was given an "optimal" versus "suboptimal" score according to accepted standards in the literature. The final score was expressed as the percentage of optimal items out of the total number of items in each questionnaire. The content validity of the questionnaires was verified by a team of clinicians (pediatric neurologists and developmental psychologists) who participated in this study. In addition to the standard physical and neurological evaluation, the neurodevelopmental examination at the age of 9 to 10 years included special tests to determine brain maturation, coordination skills, presence of "soft" neurological signs, short-term memory, and a clinical impression of attention abilities and motor hyperactivity.[18,19] Cognitive abilities were assessed using the Wechsler Intelligence Scale for Children-Revised at 9 to 10 years of age.[20] All growth measurements were performed by the same trained nurse. Weight and height percentiles were calculated using the updated growth charts published by the Centers for Disease Control in 2003.[21] Calculations of growth standard deviation scores were performed from means for all biometric parameters using the KIGS Auxology Calculator for PC Software.[22] For the purpose of this study, the neurodevelopmental and IQ scores at 9 to 10 years were the outcome measures used for correlation with growth measurement.

Children who did not display adequate catch-up growth, defined as height at 2 years >2 standard deviations below the means, were compared with those showing catch-up growth. The same comparison was used for weight catch-up at 2 years of age.

The study was approved by the Ethics Review Committee of the Tel Aviv Sourasky Medical Center.

Statistical Analysis

Analysis of variance (ANOVA) with repeated measures was used to analyze the mean standard deviation score of growth parameters (weight, height, and head circumference) at each age over time. The rates of catch-up, as defined by the delta of mean standard deviation scores between 1 to 2 years, 2 to 6 years, and 6 to 9 years for weight and height, were compared using the 1-way ANOVA with Bonferroni correction for multiple comparison tests.

Pearson correlation was used to determine the relationship between neonatal parameters and growth data (standard deviation score of weight, height, and head circumference) at all ages with neurodevelopmental and cognitive outcomes at 9 to 10 years. For the analysis of height, adjustment was made for parental height. Multivariate regression analysis was performed for neurodevelopmental and IQ scores at 9 to 10 years by stepwise regression. The variables that were used for the analysis were neonatal (gestational age, birth weight, and head circumference at birth) and growth variables at all ages that had significant correlation with neurodevelopmental and IQ scores.

Noncatch-up growth was defined as 2 or more standard deviations from the means. The proportion of children who did not catch-up in weight and in height over the study years was analyzed by ANOVA with repeated measures; the percentage of noncatch-up was compared in each age group by the unpaired t test. The unpaired t test was also used for between-group comparison of neurodevelopmental and IQ scores at 9 to 10 years in children with catch-up versus noncatch-up growth for weight at 2 years. One-way ANOVA, with parents' height as covariate, was used for the comparison of neurodevelopmental and IQ scores at 9 to 10 years of children with catch-up versus noncatch-up growth for height.

Results

The study group comprised 136 intrauterine growth retardation children whose mean gestational age was 36.8 $\pm$

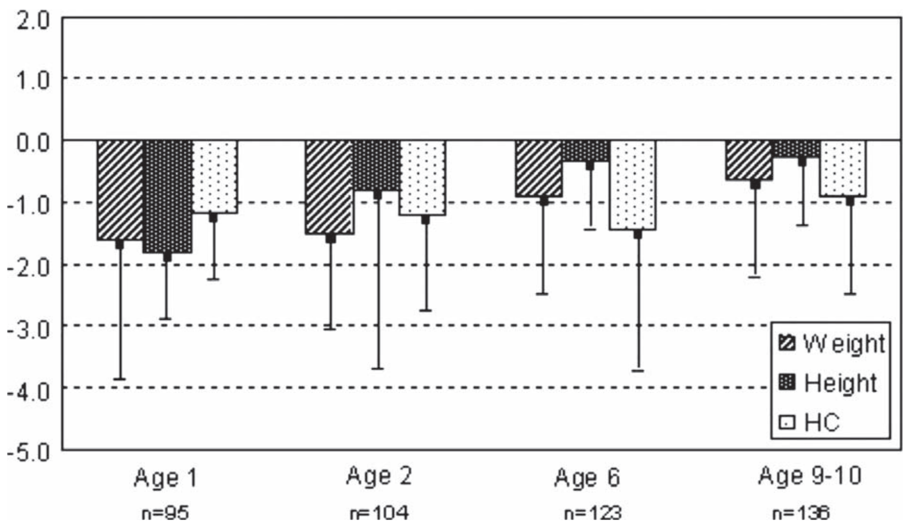

Figure 1. Mean standard deviation scores of growth parameters from 1 to 9 to 10 years of age. HC indicates head circumference.

2.6 weeks, mean birth weight 1822 ± 414 g, and mean head circumference 30.4 ± 1.9 cm. The mean standard deviation score of all growth parameters, that is, weight, height, and head circumference, at 1 to 9 to 10 years of age are shown in Figure 1. All the mean standard deviation scores were below normal at all ages. There was a significant time-effect on the mean standard deviation scores of all growth parameters during the study years (weight, $F = 78.07$, $P < .001$; height, $F = 63.98$, $P < .001$; and head circumference, $F = 4.89$, $P < .05$), presumably due to the catch-up phenomenon. The rate of catch-up growth for height between 1 and 2 years was significantly higher than for weight ($P < .001$). No differences were found for rate of catch-up growth between weight and height at 2 to 6 years and 6 to 9 years.

The correlation of neonatal parameters with neurodevelopmental score at 9 to 10 years was significant for birth weight ($r = .268$, $P = .001$), gestational age ($r = .232$, $P < .01$), and length ($r = .187$, $P < .05$). The correlation of neonatal parameters with IQ score at 9 to 10 years was significant for birth weight ($r = .23$, $P < .01$) and length ($r = .24$, $P < .01$) but not for gestational age. Head circumference at birth did not correlate with neurodevelopmental and IQ scores at 9 to 10 years.

The correlation of growth parameters with neurodevelopmental and IQ scores at 9 to 10 years during the study years is shown in Figure 2. The neurodevelopmental outcome at 9 to 10 years of age correlated with weight at all ages. A strong correlation was found with height at 1 and 2 years, while at 6 and 9 to 10 years it was significantly stronger with head circumference (Figure 2). The IQ score at 9 to 10 years correlated significantly with head circumference at all ages, with height at 1 year and with weight at 2, 6, and 9 to 10 years (Figure 2). It is noteworthy that height correlated only at a younger age (at 1 year with IQ and at 1 and 2 years with neurodevelopmental score) and that correlation with head circumference was more significant with IQ, while with weight it was stronger with the neurodevelopmental score.

By multivariate regression analysis, the height at 1 year was the predictor for the 9 to 10 year neurodevelopmental and IQ scores ($P < .001$, $\beta = .383$ and $P < .005$, $\beta = .372$, respectively).

The percentage of children within the study group who did not catch-up for weight, height, and head circumference at each age is shown in Figure 3. It is notable that during the study years, there was a trend of increased percentage of children who achieved catch-up in weight and height ($F = 12.77$, $P < .001$; $F = 16.7$, $P < .001$, respectively). No similar trend was noted in the head circumference. The percentage of children who achieved catch-up for height was larger than for weight at 1, 2, and 6 years ($P < .001$) but nonsignificant at 9 to 10 years. A comparison of the catch-up versus non-catch-up groups for weight at 2 years revealed significant differences in 9 to 10 year neurodevelopmental and IQ scores ($t = -2.06$, $P < .05$ and $t = -2.63$, $P = .01$, respectively). A comparison of the catch-up versus noncatch-up groups for height and head circumference at 2 years demonstrated significant differences in IQ scores at 9 to 10 years ($t = -2.43$, $P < .05$ and $t = -3.103$, $P < .005$, respectively) but no significant differences in neurodevelopmental scores.

Discussion

Our results clearly showed that intrauterine growth-retarded children lag behind in somatic growth between

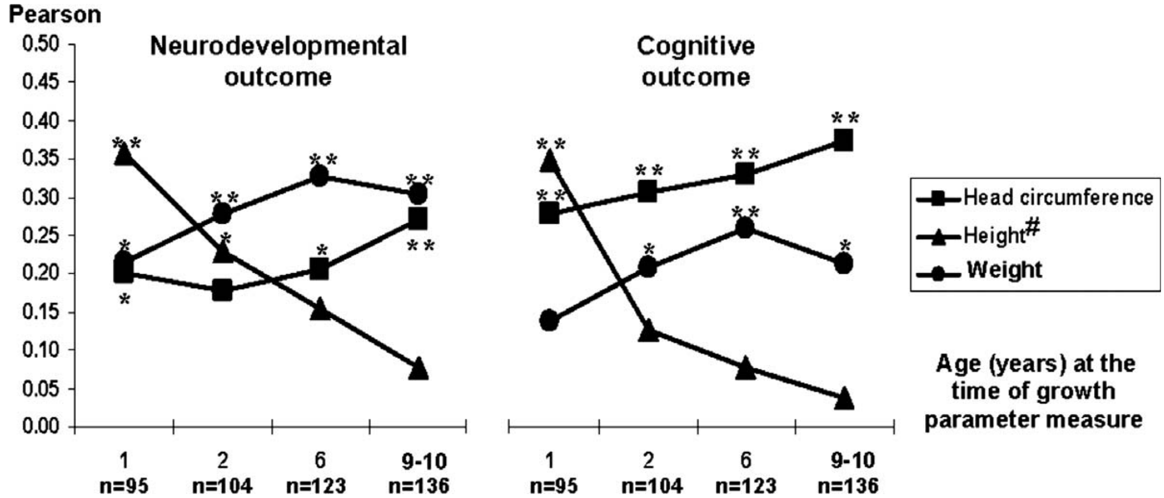

Figure 2. Correlation between weight, height, and head circumference standard deviation score over time with neurodevelopmental outcome and IQ at 9 to 10 years of age. #adjusted for parents' height, $^{*}P < .05$, $^{**}P < .01$.

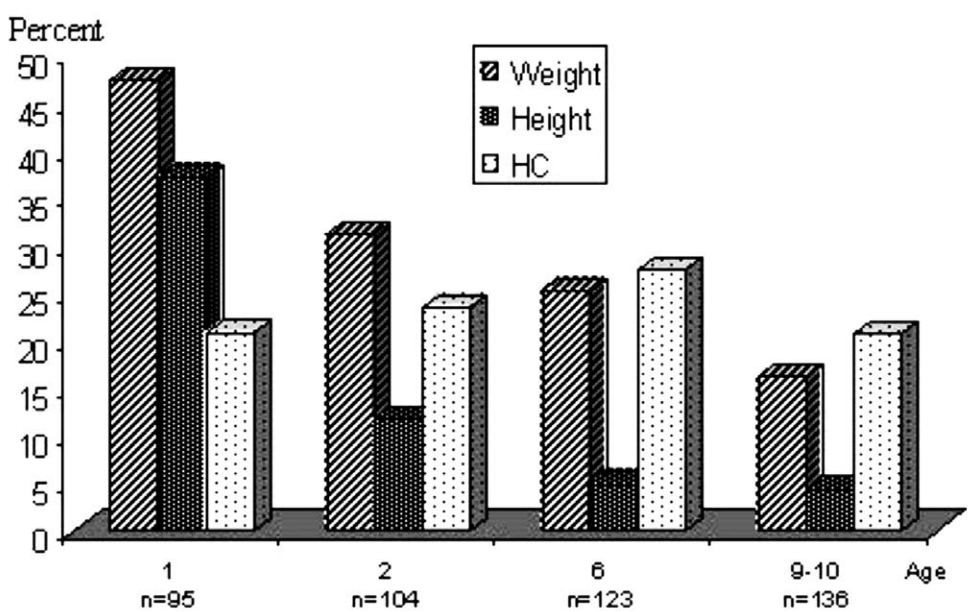

Figure 3. Percentage of children with noncatch-up growth between 1 and 9 to 10 years of age. Noncatch-up was defined as more than 2 standard deviations below the means. HC, head circumference.

1 and 9 to 10 years of age. We found significant time-effect on the mean standard deviation scores of all the growth parameters, presumably due to the catch-up phenomenon. The results demonstrated that the main catch-up of height is achieved in the first 2 years of life (Figure 1). This is in agreement with other studies,[1,23] such as described in a group of 3650 infants in which 13.4% of the small-for-gestational age children were below −2 standard deviation scores in height at 1 year of age, compared to only 7.9% at 18 years of age.[23]

The catch-up for height occurred earlier than the catch-up for weight, and its rate was significantly faster between 1 and 2 years (Figure 1). It was also more prominent than the catch-up for weight between 1 and 6 years as expressed by the significantly higher percentage of children with catch-up in those years (Figure 3). These findings have practical implications in terms of reassurance for parents of 1-year-old intrauterine growth-retarded children who had satisfactory catch-up for height but their weight was too low.

The correlation of neonatal parameters with IQ score at 9 to 10 years is significant for birth weight and length but not for gestational age. This is in agreement with another study[11] and with our previous findings and recommendations for better outcome for intrauterine growth-retarded children delivered earlier, despite the effect of prematurity.[6,7] The significant correlation of gestational age with neurodevelopmental score at 9 to 10 years probably expresses the effect of prematurity on various areas of neurodevelopment. No correlation was found between head circumference at birth and 9- to 10-year outcome, possibly due to the brain-sparing effect in children with asymmetric intrauterine growth retardation. Management of these infants is controversial. They have an increased perinatal mortality and morbidity including behavioral problems, minor developmental delay, and spastic cerebral palsy. Still, the decision whether to induce labor or await spontaneous delivery, with strict fetal and maternal surveillance, has not yet been defined.[24] More studies are needed to establish the optimal management of pregnancies complicated by intrauterine growth-retarded fetuses, to minimize the effect of this stressful environment on the developing fetus.

The correlation of growth parameters at a later age with 9- to 10-year outcome revealed that the height correlated only in the first year with the cognitive outcome, whereas the weight was meaningful mostly after the first year of life. This can be explained by the previous finding of the rapid catch-up for height compared to the slower rate of weight catch-up. The importance of this finding is early detection of intrauterine growth-retarded children who are at risk for impaired cognitive outcome.

Over the studied years, there was a stronger correlation of head circumference with IQ at 9 to 10 years than with either weight or height (Figure 2). This may be explained by the effect of intrauterine growth retardation on brain volume in the severe cases in which the outcome was unfavorable. The intrauterine growth-retarded fetus "enables" sparing of the head while growing in a low-nutrient intrauterine environment and has neuroadaptive modifications aimed at conserving the developing brain.[25,26]

Thus, a newborn with asymmetric intrauterine growth retardation has better neurocognitive outcome compared to a newborn with symmetric intrauterine growth retardation. This finding is consistent with previous studies.[9,10,27] However, head circumference showed lower correlation with the neurodevelopmental outcome than IQ, and especially at 1 and 2 years no such correlation was found. Studies of volumetric magnetic resonance imaging (MRI) findings have shown that fetal growth retardation reduces grey matter volume more than white.[28] This may explain the effect of head circumference on the cognitive function rather than the motor development.

Analysis of catch-up versus noncatch-up children at 9 to 10 years revealed that the process of catch-up continues over the years and that a larger percentage of children had catch-up for height than for weight. However, it emerges that children who did not catch-up for weight at 2 years had lower outcome in both neurodevelopmental and IQ scores. Children who did not catch-up for height and head circumference at 2 years had lower IQ at 9 to 10 years. Thus, the somatic growth correlates with cognitive neurodevelopment in intrauterine growth-retarded children. Children who did not catch-up probably had more severe insult in intrauterine life, which resulted in lower neurocognitive achievements. These results have possible implications for the prognosis and treatment of intrauterine growth-retarded children who should be closely followed-up to identify those who are at risk.

References

1. Lee PA, Chernausek SD, Hokken-Koelega AC, Czernichow P. for the International Small for Gestational Age Advisory Board. International Small for Gestational Age Advisory Board consensus development conference statement: management of short children born small for gestational age, April 24-October 1, 2001. *Pediatrics*. 2003;111(6 pt 1):1253-1261.
2. Gibson AT, Carney S, Cavazzoni E, Wales JKH. Neonatal and postnatal growth. *Horm Res*. 2000;53(suppl 1):42-49.
3. Kutschera J, Urlesberger B, Maurer U, Muller W. Small for gestational age—Somatic, neurologic and cognitive development until adulthood [in German]. *Z Geburtshilfe Neonatol*. 2002;206(2):65-71.
4. Stathis SL, O'Callagahan M, Harvey J, Rogers Y. Head circumference in ELBW babies is associated with learning difficulties and cognition but not ADHD in the school-aged child. *Dev Med Child Neurol*. 1999;41(6):375-380.
5. Tenoveo A, Kero P, Piekkala P, Korvenranta H, Sillanpää M, Erkkola R. Growth of 519 small for gestational age infants during the first two years of life. *Acta Paediatr Scand*. 1987;76(4): 636-646.
6. Fattal-Valevski A, Leitner Y, Kutai M, et al. Neurodevelopmental outcome in children with intrauterine growth retardation: a 3-year follow-up. *J Child Neurol*. 1999;14(11):724-747.
7. Leitner Y, Fattal-Valevski A, Geva R, et al. A six-year follow-up of children with intrauterine growth retardation: long-term, prospective study. *J Child Neurol*. 2000;15(12):781-786.
8. Fitzhardinge PM, Inwood S. Long-term growth in small-for-date-children. *Acta Paediatr Scand*. 1989;349(suppl.):27-33.
9. Strauss RS, Dietz WH. Growth and development of term children born with low birth weight: effects of genetic and environmental factors. *J Pediatr*. 1998;133(1):67-72.
10. Paz I, Gale R, Laor A, Danon YL, Stevenson DK, Seidman DS. The cognitive outcome of full-term small for gestational age infants at late adolescence. *Obstet Gynecol*. 1995;85(3):452-456.
11. Shenkin SD, Starr JM, Pattie A, Rush MA, Whalley LJ, Deary IJ. Birth weight and cognitive function at age 11 years: the Scottish Mental Survey 1932. *Arch Dis Child*. 2001;85(3):189-197.
12. Sommerfelt K, Andersson HW, Sonnander K, et al. Cognitive development of term small for gestational age children at five years of age. *Arch Dis Child*. 2000;83(1):25-30.

13. Yanney M, Marlow N. Paediatric consequences of fetal growth restriction. *Semin Fetal Neonatal Med*. 2004;9(5):411-418.
14. Leiberman JR, Fraser D, Weitzman S, Glezerman M. Birthweight curves in southern Israel populations. *Isr J Med Sci*. 1993;29(4):198-203.
15. Lubchenco LO, Hansman C, Boyd E. Intrauterine growth in length and head circumference as estimated from live birth at gestational ages from 26 to 42 weeks. *Pediatrics*. 1966;37:403-408.
16. Battaglia FC, Lubchenco LO. A practical classification of newborn infants by weight and gestational age. *J Pediatr*. 1967;71(2):159-163.
17. Prechtl HFR. Assessment methods for newborn infant: a critical evaluation. In: Stratton P, ed. *Psychology of the Human Newborn.* New York: John Wiley & Sons; 1982:21.
18. Leitner Y, Fattal-Valevsky A, Geva R, et al. Neurodevelopmental outcome of children with intrauterine growth retardation (IUGR): a longitudinal, 10-year prospective study. *J Child Neurol*. 2007;22(5):580-587.
19. Geva R, Eshel R, Leitner Y, Valevski AF, Harel S. Neuropsychological outcome of children with intrauterine growth restriction: a 9-year prospective study. *Pediatrics*. 2006;118(1):91-100.
20. Wechsler D. *Manual for the Wechsler Intelligence Scale for Children-Revised*. New York: The Psychological Corporation; 1974.
21. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, et al. CDC growth charts: United States. *Adv Data*. 2000:(314):1-27.
22. Ranke MB, Dowie J. KIGS and KIMS as tools for evidence-based medicine. *Horm Res*. 1999;51(suppl 1):83-86.
23. Karlberg J, Albertsson-Wikland K. Growth in full-term small-for-gestational-age infants: from birth to final height. *Pediatr Res*. 1995;38(5):733-739.
24. Boers KE, Bijlenga D, Mol BW, et al. Disproportionate Intrauterine Growth Intervention Trial at Term: DIGITAT. *BMC Pregnancy Childbirth*. 2007;7:12.
25. Scherjon S, Breit J, Oosting H, Kok J. The discrepancy between maturation of visual-evoked potentials and cognitive outcome at 5 years in very preterm infants with and without hemodynamic signs of fetal brain sparing. *Pediatrics*. 2000;105(2):385-391.
26. Inder TE, Wells SJ, Mogridge NB, Spencer C, Volpe JJ. Defining the nature of the cerebral abnormalities in the premature infant, a qualitative magnetic resonance imaging study. *J Pediatr*. 2003;143(2):171-179.
27. Hack M, Weissman B, Borawski-Clark E. Catch-up growth during childhood among very low-birth-weight children. *Acta Pediatr Adolesc Med*. 1996;150(11):1122-1129.
28. Toft PB, Leth H, Ring PB, Peitersen B, Lou HC, Henriksen O. Volumetric analysis of the normal infant brain and in intrauterine growth retardation. *Early Hum Dev*. 1995;43(1):15-29.