Chapter 12
Children Born with Intrauterine Growth Restriction: Neurodevelopmental Outcome

Ronny Geva, Yael Leitner, and Shaul Harel

Abstract Intrauterine growth restriction (IUGR) is a pathological prenatal process that is characterized by a decrease in fetal growth velocity, resulting in a fetus that did not attain its full growth potential. It has heterogeneous parental, placental, and fetal triggering mechanisms. IUGR rates are increased in multiple rearing conditions where fetal under-nutritional processes are evoked. IUGR is thought to elicit a fetal programming process that has lifelong repercussions. IUGR is often accompanied by increased prenatal, perinatal, and postnatal complications. Processes aimed at conserving vitality take place, but these processes do not suffice to preserve neurodevelopmental integrity. The neurodevelopmental deficits are often mild, comprised of changes in muscle tone, arousal, coordination deficits, visuo-motor and visuospatial organizational deficits, lower verbal skills, lower intellectual competence, attention and executive disorders, and emotion regulation difficulties. Increased risk for learning disabilities is noted as well. Neurodevelopmental outcome is mediated primarily by growth catch-up velocity. Weight and height gain rates are of particular predictive value during early infancy, while head circumference is of added value later on during childhood. Socioeconomical support systems and socioemotional processes may moderate outcome. Intervention with IUGR-related processes requires the attention and care of well-coordinated multidisciplinary medical and paramedical teams. Practical guidelines are presented.

Abbreviations

CI	Cephalization index
HPA	Hypothalamus-pituitary-adrenal axis
IUGR	Intrauterine growth restriction

12.1 Introduction

Intrauterine growth restriction (IUGR) is a pathological prenatal process characterized by a decrease in fetal growth velocity, resulting in a fetus that did not attain its full growth potential and is therefore at risk of significant perinatal complications and compromised neurodevelopment (Kok et al., 1998).

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Fetal growth measures are typically lower than the expected 10th percentile for gestation age. "True IUGR" is considered when growth measures are lower than the 10th percentile and are lower than expected, taking familial constitutional features into account, i.e., true IUGR diagnosis excludes those fetuses which are constitutionally small but have reached their full growth potential.

IUGR effects 3–10% of all fetuses, depending on the diagnostic criteria (Pollack and Divon, 1992). Perinatal mortality is four to eight times higher in these neonates (Fernández-Carrocera et al., 2003). At least 20% of fetal deaths are associated with IUGR in the western world, and rates are still as high as 30% in many developing countries (World Health Organization, 2008).

Higher neurodevelopmental morbidity at short term or long term is generally expected in most circumstances in up to a third of children born with IUGR (Geva et al., 2006; Fernández-Carrocera et al., 2003). It is currently under debate whether neurodevelopment is compromised due to very-extreme birth weight values, irrespective of gestation age (Procianoy et al., 2009), or is markedly effected when weight is disproportionally smaller than expected for fetal age (Fattal-Valevski et al., 2009). A resolution of the debate is rather complex since the interrelation between severity of IUGR and subsequent physical and intellectual development has not yet been fully comprehended due to differences among cohorts in heterogeneity of preterm infants with IUGR due to differences in etiologies of IUGR, differences in management, and differences in outcome measures selected. The literature seems to indicate an array that ranges from a neurodevelopmental trajectory that is not distinguishable from that of controls, up to a notion that the IUGR preterm infant faces a double insult: prematurity with its own perinatal complications and IUGR with its potential deleterious effects (Leitner et al., 2007; Sung et al., 1993; Walther, 1988).

Overall, there is support to the notion that IUGR is associated with a higher incidence of perinatal complications and is often thought to be related to specific long-term neurodevelopmental sequels (Kok et al., 1998; Leitner et al., 2000; Leitner et al., 2007; Walther, 1988). There are several very long-term follow-up studies of infants born with IUGR, all of whom demonstrate some physical undergrowth, along with a range of expected long-term neurodevelopmental outcomes. In the following section we will delineate possible mechanisms that may account for differences in the neurodevelopmental trajectory of children born with IUGR.

Risk magnitude of abnormalities in neurodevelopment secondary to IUGR in term and preterm infants has not been well established. The dominant notion posits the *Barker hypothesis*, according to which under-nutritional deficits during ontogeny trigger a long-term programming effect that redirects resources for brain-sparing purposes. Even though this process is relatively effective in increasing the likelihood of survival, it results in specific physiological and neurodevelopmental aftermaths (Fig. 12.1).

The *Barker hypothesis* model has been introduced as a more comprehensive view of IUGR effects that in many ways represents a paradigm shift from the pre-existing "mediator model" (Fig. 12.2), according to which perinatal complications, *secondary to IUGR*, particularly asphyxia, nutritional deficiencies, in addition to obvious genetic or congenital abnormalities, are the causes of neurodevelopmental disabilities observed in these children (Nilsen et al., 1984).

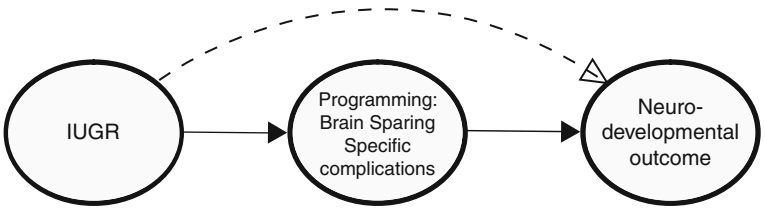

Fig. 12.1 IUGR-related, long-term mediation mechanism of neurodevelopmental outcome

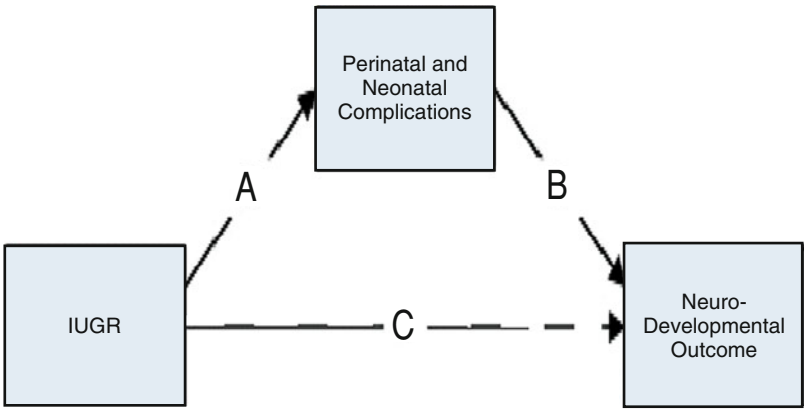

Fig. 12.2 Neurodevelopmental outcome of IUGR: Alternative model

This model is partly supported by two primary classes of findings: First, findings of various studies evaluating low-risk term IUGR neonates which indicate that even though there is an increased risk of physical, intellectual, neurological, and behavioral disability, the majority of these infants perform within normal limits at follow-up.

The advantage of this model may reside in highlighting effects that are considered to be related to IUGR, such as socioeconomical effects on outcome in this population. An extension of the model may thus accommodate evidence that while the neurological problems are related to perinatal and postnatal aberrations, neurodevelopmental outcome is not only associated with biological factors but also moderated by psychosocial ones.

A resolution of this debate may be possible by developing an integrated framework that will posit weightings for IUGR as a main effect, programming processes as mediating factors along with secondary biological complications and a socioeconomic umbrella, as moderating mechanisms to account for neurodevelopmental outcome in this population (Fig. 12.3). Figure 12.3 presents an extended integrative model of alternative pathways effecting neurodevelopments of infants born with IUGR

This new model integrates schematically current literature with regard to mechanisms that are involved in accounting for variance in neurodevelopmental outcome of IUGR. It presents four main avenues: Path A highlights the mediating effect of IUGR-related perinatal and neonatal complications as a primary factor affecting neurodevelopmental outcome; Path B sums up the Barker hypothesis that highlights a general lifelong IUGR programming mechanism that determines neurodevelopmental outcome; Path C extends this view by highlighting the interrelationships between IUGR and parental socioeconomic ecology in accounting for neurodevelopmental outcome; finally, Path D proposes an integration of the above paths while highlighting the importance of growth catch-up processes as important mediating factors in determining neurodevelopment.

Current knowledge cannot yet fully quantify this theoretical framework, with appropriate weightings, as the various reports are not fully comparable with regard to socioeconomic level, prenatal processes, maternal pathology, among others (Fernández-Carrocera et al., 1993; Fattal-Valevski et al., 2009). Nevertheless, a general notion seems to arise from the available literature and support the proposed framework. The following sections will detail the major long-term IUGR-related programming effects, currently known, along with relevant moderating biological and socioecological effects as we currently understand them. A summary of this section is presented in Table 12.1.

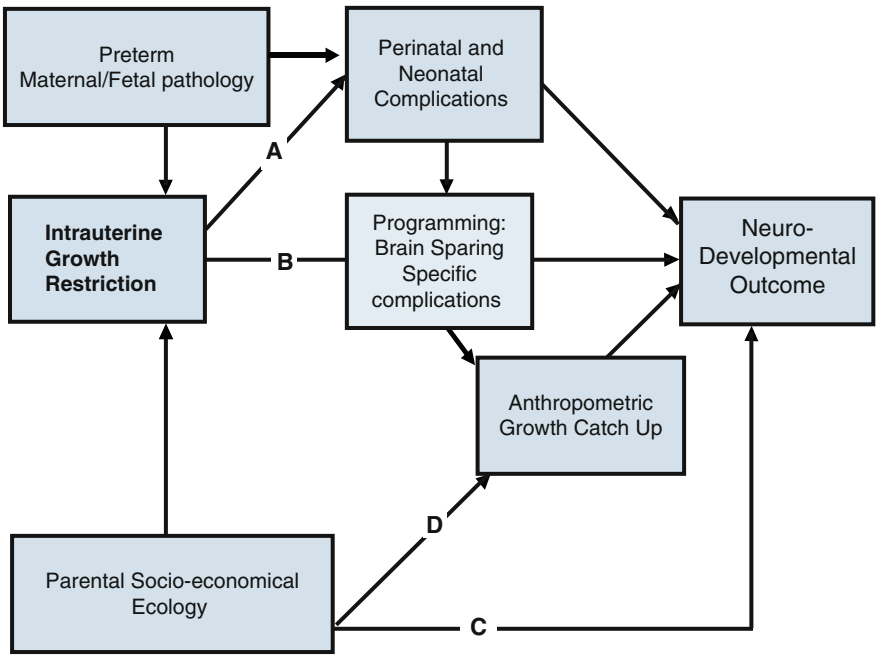

Fig. 12.3 An extended integrated model of mechanisms involved in neurodevelopmental outcome in IUGR. Path A presents the mediating effect of IUGR-related perinatal and neonatal complications as a primary factor effecting neurodevelopmental outcome; Path B highlights a general IUGR programming mechanism that determines neurodevelopmental outcome; Path C highlights the interrelationships between IUGR and parental socioeconomic ecology in accounting for neurodevelopmental outcome; and Path D proposes an integration of the above paths while highlighting the importance of growth catch-up processes as an important mediating factor in determining neurodevelopment

Table 12.1 Key features of neurodevelopmental outcome of children with IUGR as a function of age at test

Developmental period	Key neurodevelopmental features	Frequency (%) of abnormality in general population[a]	Frequency (%) of abnormality in IUGR cohorts
Neonatal	– Regulation disorders of sensory processing	7	
	– Neuromotor deficits	3	30 (Zuk et al.)
Infancy	Mild neuromotor deficits	3	25 (Zuk et al.)
	Hypotonia		
Childhood	Attention and executive deficits	3–7	15 (Geva, 2006)
	Visuospatial deficits	Unknown	40–70
	Expressive verbal disorder	10–15	30
	Learning difficulties	2–15	30–75
	Coordination disorder	6	30 (Zuk)
Adolescence	Lower cognitive scores	3–10	25 (Geva, 2005)
	Anxiety/depression	3–6	30
Adulthood	Lower achievements		
	Lower vocational positions		
	Satisfying social and marital relations		
Aging	Not yet known		

[a]According to the ICD-10, DSM-IV-TR, or the Zero-Three diagnostic manual

12.2 Neonatal Neurodevelopmental Deficits

In the neonatal period, specific IUGR-related neurodevelopmental changes are notable. Early reports from the 1980s noted that neonates born with IUGR were more passive, less aroused, and had less stable sleep–wake states relative to controls. More recent reports which have used the Brazelton Neurobehavioral Assessment Scale repeatedly during the first 2 weeks of life showed that behavior of AGA babies, whose weight matches their estimated gestation age is characterized by optimal performance in habituation, range of state, regulation of state, and autonomic stability, while the behavior performance of SGA babies, whose weight is significantly smaller than expected for their gestation age, was lower in most clusters. Nevertheless it was noted that the percentage improvement of scores normalized quickly during the first 2 weeks at the neonatal intensive care unit, and some of the SGA babies outperform normal controls in alertness (Padidela and Bhat, 2003).

Alongside these behavioral changes, neonatal changes in physiological regulation of the HPA axis are also apparent in SGA and IUGR infants. Elevated levels of cortisol excretion relative to controls are reported during the first months of life (Jackson et al., 2004). Relationships between these elevated excretions and neurodevelopmental output in the neonatal phase are not fully discerned, but seem to be related to changes in self-regulation of behavior, particularly under more stressful conditions.

Deviation from the normal trajectory as a result of IUGR may be accountable in part by specific neurostructural changes evident in MRI studies. Such that the gyrification of IUGR newborns is discordant to the normal developmental trajectory, with a more pronounced reduction of surface in relation to the sulcation index compared to normal newborns. These changes were recently reported to be related to neurobehavioral performance at term equivalent age (Dubois et al., 2008).

12.3 Neurodevelopmental Deficits at Infancy

At the age of 1 year, mild psychomotor deficits are the most common symptoms diagnosed in children born with IUGR (Fernández-Carrocera et al., 1993). Deficits are common at this age but are rarely severe. Rate of cerebral palsy, for example, is not increased in IUGR samples, relative to other neonatal risk groups. Evaluation of spontaneous upper hand movements (arms, forearms, and hands) is considered of predictive value for neurodevelopmental outcome at 2 years (Zuk et al., 2008). Neonates with IUGR tend to score lower than controls in the writhing (term–2 weeks), early fidgety (9–11 weeks), and particularly so in the late fidgety (14–16 weeks) period. The mean score is typically lower in infants born with IUGR than the controls and in the IUGR group lower scores are evident in infants with abnormal neurodevelopmental outcome at 2 years of age.

12.4 Early Childhood Neurodevelopmental Deficits

At early childhood, lower neurodevelopmental scores and lower IQ scores are expected (Fattal-Valevski et al., 2001).

Lower neurodevelopmental scores are also noted. At this age, growth indices are the best predictors of neurodevelopmental outcome. Of the various growth indexes, the cephalization index (CI = head circumference/birth weight) at term age is particularly strong. It is followed by birth weight

and neonatal head circumference. Obstetric and neonatal risk indexes add further to the variance explained (Fattal-Valevski et al., 2001). Gestation age in this context has limited predictive power on its own (Fattal-Valevski et al., 2001).

Neurodevelopmental outcome at this age is comparable for infants that were diagnosed with IUGR during pregnancy and those diagnosed only at birth. This may attest to the strength of current gynecological management protocols of IUGR.

The particular neurodevelopmental domain that is most often affected by IUGR at this age is motor function. In the gross motor area, children born with IUGR at 3 years of age tended to have difficulties walking up stairs, using one foot on each stair without support, and walking on tiptoes. In the fine motor domain, they often showed difficulties grasping and could not cut paper with scissors. Early grapho-motor deficits are noticeable, such as difficulty to copying circles or bisecting graphic lines with a crayon (Fattal-Valevski et al., 2001).

A specific neurodevelopmental profile emerges at 6–9 years of age. It is comprised of a mild decrease in IQ, yet well within expected ranges, mild general hypotonia (both axial and radial), fine motor coordination difficulties, attention deficit and hyperactivity, restricted short-term memory span, visuo-spatial organization deficits, lateralization confusion, and increased mixed hand dominance. Less elaborated language skills are fairly common at this age. Associated movements are also noticeable at 6 years of age. This constellation of mild neurodevelopmental deficiencies may be an early marker for learning disabilities (Leitner et al., 2000).

During this period, from 6 to 9 years of age, core executive functions are expected to appear. At this age children born with IUGR tend to demonstrate specific deficits in this domain. Specific learning disabilities are also reported at this age (Geva et al., 2006, 2009). Klevanov and colleagues (1994) suggested that the increase in learning disabilities identified in IUGR infants may be secondary to mild neurological signs and behavioral characteristics, such as hyperactivity, poor concentration, and lack of coordination; nevertheless, this notion has not been replicated in other, more recent studies. The latter highlights the importance of growth catch-up processes in mediating the frequency of severity of learning disabilities in IUGR.

12.5 Early Adolescence Neurodevelopmental Deficits

Research projects have explored the relationship between intrauterine nutritional restriction and menarche characteristics. Restricting prenatal growth that is evident by very low birth weight for gestational age is thought to be related to long-term programming that reduces growth potential during childhood and adolescence. Indeed, there are reports that puberty occurs slightly earlier and at a different tempo, with an earlier but attenuated growth spurt resulting in reduced final height (Wilson et al., 2007). Earlier menarche often follows increased weight gain in childhood in this group. The roles of non-skeletal postnatal growth in determining pubertal changes in IUGR are not yet understood.

Emotional difficulties may arise at this period. It is not yet clear if early menarche is expected to be related to lower self-esteem, particularly in girls born with IUGR. IUGR is related to increased susceptibility of the hypothalamus-pituitary-adrenal axis (HPA axis), altering neuroendocrine responses to stressors throughout lifetime (Walker et al., 2002). It has been conceived of as part of the long-term aftermath of IUGR. In particular, high cortisol levels and more frequent diagnoses of anxiety and depression disorders are reported.

12.6 Adulthood Neurodevelopmental Deficits

Neurodevelopmental evaluations of young adults who were born with IUGR are indicative of a fairly stable performance, which resembles the adolescence trajectory. In a very long prospective study of a small sample, cognitive outcome at 18 years of participants who had had IUGR as compared with that of control subjects, the results were indicative of the same pattern of results that characterized the cohort that we are studying at 10 years of age (Geva et al., 2006).

Under-vocational and under-academic achievements are notable in adulthood in subjects born with IUGR as compared with AGA controls who were born into the same socioeconomic backgrounds. In a prospective cohort study of 7806 individuals in Norway, aged 20–30 years. Individuals who were born SGA were found to have lower educational levels, lower socioeconomic functioning levels, and more frequent mood disorders in adulthood. Post hoc analyses of a subgroup of subjects born at term showed almost identical results. Overall growth retardation is thought to increase moderately the risk for lower education and socioeconomic level and for greater anxiety and/or depression in young adulthood (Berle et al., 2006).

12.7 Growth Catch-Up Processes in IUGR

IUGR is related to preprogramming processes that effect life span neurodevelopment. A restricted set of functions that are thought to be related to IUGR seemed to be more closely tied to the initial IUGR-related programming processes. Nevertheless, other skills seem to be amenable to postnatal growth catch-up. Growth efficiency in children with IUGR seems to be the strongest mediating factor of neurodevelopmental outcome. A summary of the highlights of this section is presented in Table 12.2

A set of large-scale, long-term prospective studies, focusing on neurodevelopmental outcome of children born with IUGR, has set a fairly convincing support for the importance of growth catch-up processes as mediating mechanisms in determining outcome in IUGR.

Overall, as specified above, children born with IUGR tend to score lower on neurodevelopmental evaluations. The best predictor of 3-year old outcome is first the neonatal cephalization index (CI). The CI was originally introduced by our group in 1985 (Harel et al., 1985). Since then, it has been shown to be a strong "player" in IUGR programming models. Its simplest formulation: head circumference/birth weight ratio is quite straightforward and very useful clinically. First, it may be used to

Table 12.2 Key features of anthropometric and complicating-developmental outcome of children with IUGR as a function of age at test

Developmental period	Key anthropometric features	Key complicating conditions
Neonatal	Low weight	Maternal
	Head circumference catch up-(may be more appropriate for age than weight/height ratio measure)	Perinatal
Infancy	Weight and height catch-up	Growth catch-up
Childhood	Head circumference catch-up	Socioeconomic
Adolescence	Early puberty?	Co-morbid conditions
Adulthood	Cardiovascular disease?	
Aging	Cardiovascular disease?	
	Pancreatic d/o?	

predict neonatal course at the neonatal intensive care unit. CI interacts with neonatal complications, such that infants born with IUGR who have higher CIs tend to have significantly more neonatal complications and a more complex neonatal course ($p < 0.001$). CI also has long-term predictive power. Children born with IUGR that had increased CI ratios are at higher risk for lower neurodevelopmental status at 3 years of age, relative to those who had minimal neonatal complications ($p < .01$, Fattal-Valevski et al., 1999). Furthermore, it seems to mediate outcome at this age, but it does not account for outcome. Upon comparison between children born with IUGR who had no neonatal complications and well-matched controls with comparable gestation ages, neurodevelopmental outcome of the controls was significantly higher ($p < 0.05$, Fattal-Valevski et al., 1999). This latter finding may undermine the power of path A in the model as a unitary path to account for neurodevelopmental outcome in children born with IUGR.

The power of growth catch-up later in development has been suggested as a power mediator as well. Indeed, correlations were reported between height at 3 years of age and neurodevelopmental outcome at this age (Fattal-Valevski et al., 1999).

There is some debate concerning the expected growth catch-up rates in children born with IUGR. We have found that in samples that are comprised of participants with asymmetric IUGR, approximately a third of the children do not demonstrate a full catch-up potential by 3 years of age. Differences between children born with IUGR relative to a matched for gestation age and socioeconomic level cohort showed a notable difference in attained weight ($p < 0.001$), height ($p < 0.005$), and head circumference ($p < 0.05$). The rate of catch-up for height between 1 and 2 years of age is reported to be significantly higher than the catch-up for weight in children born with IUGR ($p < 0.001$). Thereafter the rates of catch-up in height and weight seem to advance at similar trajectories up to 10 years of age. These findings may have a practical value in reassuring parents of children born with IUGR, whose height may be indicative of a faster catch-up rate than their weight during the first 2 years of age.

Rate on non-catch-up, as defined by dimensions that are below 2 SD from expected mean of age and gender, is not uniform and operates based on different functions. Rate of non-catch-up in height is expected to be as high as 40% at 1 year of age and to be reduced drastically to less than 15% risk by 2 years of age (Fattal-Valevski et al., 2009). This is comparable with findings in adulthood, from other samples of children born small for gestation age, who reported a limit of less than 10% risk of unattained expected height by 18 years of age (Karlberg et al., 1995). This finding supports the notion that the great majority of height catch-up is expected to occur within the first 2 years of life in children born with IUGR, particularly of symmetric type. Rate of height catch-up seems to be faster than rate of weight catch-up in this pathogenic process. It also seems to be present significantly more frequently in children born with IUGR than catch-up for weight or head circumference, particularly during the first 6 years of life.

Rate of non-catch-up in weight is expected to be linear, such that it is expected to be apparent in all IUGR children at birth, to be as high as in 50% of the children born with IUGR at 1 year of age, to be reduced to 33% by 2 years of age and to less than a 20% risk by 10 years of age. Reports are indicative of significant correlations between weight ($p < 0.05$) and height at 6–7 years ($p < 0.05$) and the children's neurodevelopmental score at this age. Each correlation accounts for approximately 30% of the variance explained in neurodevelopmental scores at 6 years of age (Leitner et al., 2000). At 9–10 years of age, height no longer correlates with neurodevelopmental outcome, but concurrent weight and concurrent head circumference both do ($p < 0.005$ and $p < 0.01$, respectively; Leitner et al., 2006; Fig. 12.4).

Rate of risk of non-catch-up in head circumference is not linear in IUGR. Non-catch-up in head circumference is expected to increase modestly between 1 and 6 years of age from 20% of the infants born with IUGR at 1 year to 30% at 6 years of age. Thereafter the trajectory tapers off

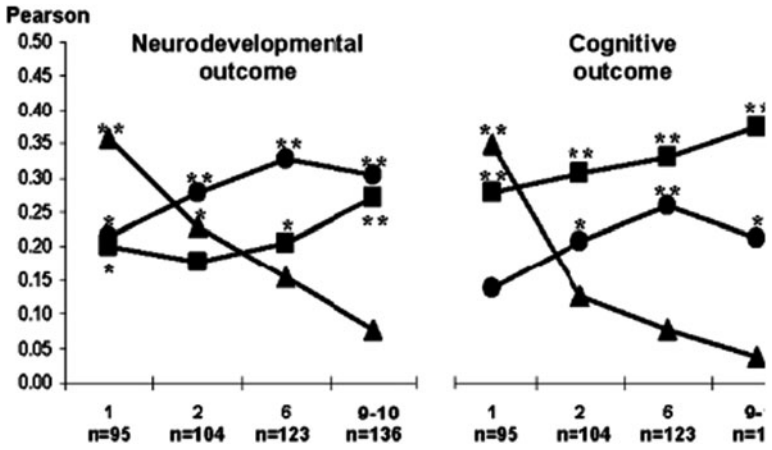

Fig. 12.4 Correlations among weight, height, and head circumferences standard scores over time with neurodevelopmental outcome and IQ at 9–10 years of age. *Note:* $^{*} = p < 0.05$, $^{**}p < 0.01$, ▲ = height; ■ = head circumference; ● = weight. This Figure is published with permission from Sage Publications # 2351931088984. It first appeared in Fattal-Valevski et al. (2009)

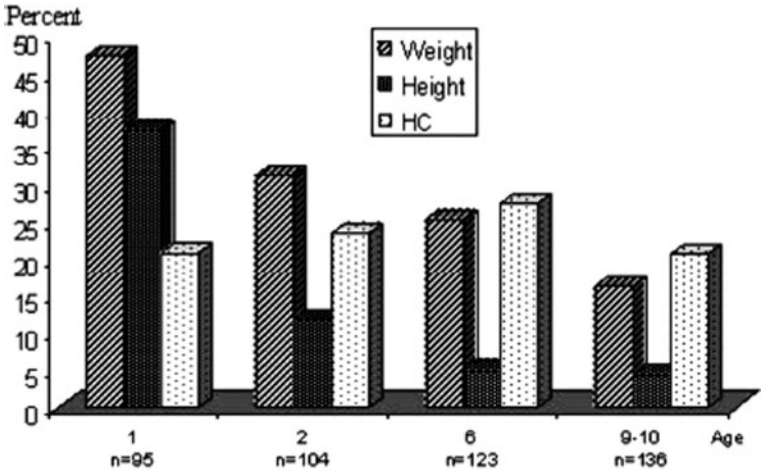

Fig. 12.5 Frequency of children born with IUGR with non-catch-up growth between 1 and 9–10 years of age, as defined by at least 2 standard deviations below the mean for age and gender. This figure is published with permission from Sage Publications 2351931088984. It first appeared in Fattal-Valevski et al. (2009)

(Fattal-Valevski et al., 2009; Fig. 12.5). The rate of catch-up in head circumference is related to cognitive outcome (Fattal-Valevski et al., 2009).

These growth catch-up findings are of high importance for well-being of children and adults born with IUGR. The findings are important for estimating somatic growth risk and for estimating neurodevelopmental outcome. Relationships between somatic growth and neurodevelopmental outcome are significant. A decade-long prospective study of anthropometric measures of children born with IUGR shows that the neurodevelopmental outcome at 9 to 10 years is correlated with weight at all ages during the first decade of life (Table 12.3).

Correlations of weight values were stronger with the neurodevelopmental scores than with other outcome measures such as IQ. Furthermore, a comparison of children born with IUGR who exhibited

Table 12.3 Significant correlations among anthropometric growth measures and neurodevelopmental outcome of children born with IUGR as a function of age

Developmental period	*Neurodevelopmental scores*				
	Growth feature	At 2–3 years	At 6–7 years	At 9–10 years	At adulthood
Neonatal	CI	−0.36**(F3)		−0.33***(L9)	
	Head circumference				
	Weight	0.29*(F3)		0.28**(L9); 0.27***(F)	
	Height				
	Length			0.19*(F)	
At 1 year	CI				
	Head circumference			0.20 ns(F9)	
	Weight	0.22*(F9)			
	Height				
	Length			0.38*(F9)	
At 2–3 years	CI				
	Head circumference	0.18*(F9)		0.44***(L)	
	Weight	0.32*(F3); 0.28(F9)			
	Height			0.22*(F9)	
	Length				
At 6–7 years	CI				
	Head circumference			0.22*(F9)	
	Weight		0.32*(L6); 0.35**(F9)		
	Height		0.29*(L6)		
	Length			0.15 ns	
At 9–10 years	CI				
	Head circumference			0.24*(L9); 0.27**(F9)	
	Weight			0.26***(L9); 0.30**(F9)	
	Height			0.05 ns	
	Length				

Note: * = $p < 0.05$, ** = $p < 0.005$, *** = $p < 0.001$, ns = non significant

catch-up for weight by 2 years of age showed better neurodevelopmental outcome at 9–10 years of age, relative to children born with IUGR who showed non-catch-up for weight during their first 2 years.

At the same time, a note of caution is warranted concerning this finding. Growth optimality by 10 years of age is a predictor of neurodevelopmental outcome at this age, but the same may not hold for growth optimality attained by 2 years of age. More specifically, the use of an optimal somatic growth, indicating children who attain above the 10th growth percentile in height, weight, and HC at age 9–10 as having "optimal" somatic growth as compared with those who were below the 10th growth percentile in at least one growth parameter thus defined as "suboptimal" has been suggested by our group (Leitner et al., 2006). The subgroups were then analyzed to establish whether they differed in neurocognitive outcome at age 9–10. We also examined whether the same criteria of "optimal" somatic catch-up at age 2 were predictive of outcome at age 9–10. Analysis showed that the performance of children with suboptimal somatic catch-up at age 9–10 was significantly worse in the neurodevelopmental assessment ($p < 0.005$) than in IUGR children with optimal catch-up in somatic growth. However, somatic catch-up at 2 years of age is predictive only of IQ at age 9–10 ($p <$

0.05), but not of neurodevelopment at the same age. A more specific dimension-dependent approach is warranted.

In general, height at 1 and 2 years of age was a significant predictor for IQ and neurodevelopmental outcome at 9–10 years, though its correlation with neurodevelopmental outcome was weaker than that of weight.

Head circumference was correlated with neurodevelopmental outcome at 6 and at 9 years of age. Hence it seems that of the three major somatic growth indexes, weight is the most general and consistent with concurrent neurodevelopmental measures. Height is of most importance during the first 2 years of life and head circumference is of concurrent predictive value at later ages during childhood. These findings are of distinct importance for prediction of subsequent neurodevelopmental outcome in children with IUGR.

At the same time, it is important to note that others report some concern regarding rate of growth catch-up as a risk factor on its own with regard to weight catch-up rates, in particular. According to this body of literature, an unexpected, super fast growth catch-up during the first 3 years of life in children born with IUGR may increase their risk of developing obesity and diabetes later on in life.

12.8 Applications to Other Areas of Health and Disease

IUGR is currently understood as a process that has multi-system effects due to a fetal programming process. The systems involved are dependent on the prenatal phase at which IUGR was initiated. Since asymmetrical IUGR typically occurs post mid-gestation, most vital organs are fully formed prior to the aberration; nevertheless, neural migration is often effected and minor, yet significant structural and functional neural changes are expected in multiple domains (Table 12.4).

12.8.1 Neonatology

Neonatal complications have been reported to interact with IUGR programming and augment both short- and long-term neurodevelopmental outcomes. A specialized neonatological protocol may be contemplated for preventative treatment of neonates with IUGR to limit neonatal complications in these fragile children.

Table 12.4 IUGR programming effects: Application to medical and paramedical domains as a function of age

Developmental period	Application medical care specialty	Application paramedical care specialty
Neonatal	Neonatology	Clinical psychology
Infancy	Pediatrics Neurology	Physiotherapy
Childhood	Neurology Clinical psychology	Occupational therapy Teaching aid Neuropsychological consult
Adolescence	Endocrinology Psychiatric	Educational consultant Teaching aid
Adulthood	Cardiovascular	Not yet determined
Aging	Diabetes? Obesity?	Not yet determined

12.8.2 Cardiac

Since IUGR is typically thought of as a stress arousing condition, it involves cardiovascular susceptibility. Animal models seem to indicate that subjects who were under-nourished during pregnancy may be more susceptible for hypertension. Indeed, there are some reports of increased cardiovascular disease in selected groups of subjects born with IUGR (Evensen et al., 2009). Reports include higher values of systolic and diastolic blood pressures and mean arterial pressure at 4 years of age. Susceptibility rates seem to increase in preterm IUGR samples (Fattal-Valevski et al., 2001).

Increased frequencies of hypertension in offspring whose mothers were fed a low-protein diet during pregnancy are reported.

One of the mechanisms involved in hypertension in IUGR has been proposed to be inhibition of renal development and lower counts of renal glomeruli (Bassan et al., 2000).

12.8.3 Endocrine

There is some indication of diminished pancreatic growth and development, insulin resistance, and diabetes. All are more common among adults who were smaller-than-normal at birth due to IUGR, particularly those who had a high placental-to-fetal weight ratio. This line of findings is often based on a variety of animal studies, including the greater incidence of obesity, glucose intolerance, and plasma lipid abnormalities in offspring whose mothers were fed a low-protein diet during pregnancy. Applicability of these models to primates and humans is not yet known.

Restricted uterine nutrition is thought to be related to increased risk of the adult diseases comprising "the metabolic syndrome," which often involve reduced insulin sensitivity in childhood and pathological insulin resistance in later life. There are reports of an increased incidence of premature and exaggerated adrenarche, ovarian hyperandrogenism, and instances of polycystic ovary syndrome.

Inconsistent literature points to increased susceptibility for obesity secondary to these changes (Wilson et al., 2007). Changes in appetite regulation may present an increased risk for obesity in this population. The latter has been supported by a recent epidemiological study (Hay et al., 1997). Mechanisms responsible for these later life morbidities in adults whose growth was restricted in utero are not yet clearly established.

12.8.4 Sleep Regulation

Sleep–wake regulation changes are reported in children born with IUGR at a slightly higher rate than controls (Leitner et al., 2002). These were primarily related to shortened "real" sleep episode lengths in children born with IUGR. This profile does not appear to be related to the child's attention or concentration abilities, but may augment deficits in learning and memory.

12.8.5 Mental Health

Literature with regard to increased attention deficits (Geva et al., 2006) and increased impulsivity rates (Geva et al., 2009) may be indicative of increased rates of attention deficit hyperactivity disorder.

Furthermore, increased rates of anxiety disorder and depression are reported. These may be particularly relevant at pubertal and young adulthood ages. Stress has been targeted as a potential triggering mechanism for programming process related to IUGR during pregnancy. Stress has also been described as being a mediating factor in various emotional and behavioral difficulties recognized by mothers in their children who were born with IUGR (Geva et al., 2005). These difficulties include deficits adjusting to changing circumstances, low self-esteem, self-regulation deficits, mood disorders, attention deficits, and hyperactivity. It is of interest to note that at particular risk for stress-related emotional deficits were mother–child dyads whose prenatal management protocol was fairly conservative, typically comprised of bed rest along with increased follow-up visits, and specific prescribed medication. Mothers whose pregnancies were managed more aggressively, such as by eliciting birth, often reported stress alleviation and showed less stress-related long-term effects on their child's emotional maturation (Geva et al., 2005). This finding may encourage early support groups for parents-to-be of children diagnosed with IUGR.

12.9 Practical Guidelines

An integration of the data presented thus far, with regard to fetal management of IUGR diagnosis and its effects on behavioral characteristics of children with IUGR may very well reflect the significance of the interaction between technological advances, medical practices, and parental resiliency (Geva et al., 2005). We suggest that this interaction is a significant factor in understanding long-term neurodevelopmental outcome of high-risk infants with IUGR.

The findings with regard to the mechanisms involved in determining neurodevelopmental outcome in patients born with IUGR underscore the relationship between prenatal management of risk in pregnant women, diminished fetal growth, and long-term maternal stress, particularly when pregnancy is managed conservatively and emotional, familial, and educational resources are lacking. Psychological support and specifically interventional therapies with conservatively managed parents-to-be who are carrying fetuses whose growth indicators are smaller than expected are highly encouraged. Such programs may yield a threefold benefit: (1) they may restrict the psychological stress that could directly augment fetal well-being; (2) they may alleviate some of the long-term emotional strain on the child and on the emerging parent/child relationships (Field et al., 2008; Geva et al., 2005; Ulman, 2000; Villar et al., 1992); and (3) they may serve to strengthen the neurodevelopmental trajectory by early targeting of dyads that are at increased neurodevelopmental risk early on in development.

Ongoing pediatric follow-up of anthropometric growth is highly recommended early on, preferably during the first year of life for those children born with IUGR whose growth catch-up for height and weight is unsatisfactory. Neonatal increased head circumference/weight percentile ratio is a strong predictor of neurodevelopmental outcome during childhood. Height measurements are expected to approach typical ranges for age and gender at a faster rate than weight. Both height and weight measurements are of predictive value to target neurodevelopmental risk and may serve as part of preliminary screening indicators for a thorough developmental neurological evaluation. Weight seems to be a consistent correlate of neurodevelopment through the first decade of life with IUGR. Nevertheless, a note of caution needs to be added concerning unexpected accelerated weight gain in this population. Reports denote an increased risk for later emerging obesity and diabetes risk in this sub-cohort.

The role of mediating factors and their interactive effects should not be overlooked: Parental risk factors, such as parental age (teenage or late pregnancies), low maternal education, parental co-morbid medical and mental diagnosis; low or unavailable prenatal care; limited socioeconomic

resources; and co-morbid prenatal, neonatal, and childhood pathological processes may further effect neurodevelopmental outcome in children born with IUGR.

Neurodevelopmental outcome in children born with IUGR is typically mildly deficient. It is typically first noticeable by a mild general hypotonia (both axial and radial). As the child grows, fine motor coordination difficulties appear. Upon entry to kindergarten, attention deficits (with/without hyperactivity), restricted short-term memory, visuo-spatial organization deficits, lateralization confusion along with associated movements, increased mixed hand dominance, and less elaborated language skills are fairly common at this age. Specific impulsivity and problem-solving deficits are notable. This constellation of mild neurodevelopmental deficiencies may be an early marker for attention deficit hyperactivity disorder and specific learning disabilities (Leitner et al., 2000). Neurodevelopmental outcome may be within expected age and gender norms in 30–60% of these children.

Valuable markers for neurodevelopmental risk may be detected early on in development, starting during the fetal period and thereafter. This phenomenon may be harnessed to encourage early referrals for suitable medical and paramedical intervention teams to limit IUGR-related aftermath.

Summary Points

- Intrauterine growth restriction (IUGR) is a pathological, prenatal process that is characterized by a decrease in fetal growth velocity, resulting in a fetus that did not attain its full growth potential.
- Higher mild neurodevelopmental morbidity is expected in most circumstances in up to a third of children with IUGR.
- IUGR is caused by under nutritional deficits during ontogeny.
- IUGR triggers a long-term programming effect that redirects resources for brain-sparing purposes.
- IUGR-related programming is relatively effective in increasing the likelihood of survival, but it results in specific physiological and neurodevelopmental and neuropsychological aftermath.
- Neurodevelopmental outcome of IUGR is dependent upon biological factors which are mediated by psychosocial and socioeconomic processes.
- The deficits are often mild, comprised of changes in muscle tone, arousal, coordination deficits, visuo-motor and visuospatial organizational deficits, lower verbal skills, lower intellectual competence, attention and executive disorders, and emotion regulation difficulties.
- Specific relationships between somatic growth catch-up velocity and neurodevelopmental outcome are significant and have predictive value.

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