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Intrauterine Growth-Restricted Neonates Born at Term or Preterm: How Different?

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Late onset intrauterine growth restriction is a common form of growth restriction, mainly caused by placenta-vascular insufficiency. Whether the intrauterine or extrauterine environment offers a better long-term outcome for the growth-restricted fetus remains unclear. We compared the risk factors and long-term outcomes of late onset growth-restricted neonates delivered between 31-36 weeks of gestation vs those delivered at term. This prospective cohort study included 114 preterm and 193 term born growth-restricted neonates. They underwent a neurobehavioral examination (neonatal period), a neurodevelopmental assessment and the Bayley Scales of Infant Development (age 2 years), and neuromotor assessment and the Wechsler Preschool and Primary Scale of Intelligence (age 6 years). Growth-restricted neonates born prematurely exhibited a significantly higher incidence of maternal hypertension, a maternal history of abortions and stillbirths, increased intrapartum and postnatal complication rates, and abnormal neonatal neurobehavioral scores than expected. Both preterm and term born growth-restricted groups, however, exhibited comparable long-term neurodevelopmental and cognitive outcomes at ages 2 and 6 years. Although prematurely born neonates undergo an earlier growth restriction process and exhibit a higher perinatal risk factor profile, their long-term outcomes are comparable to those of growth-restricted neonates born at term.

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Introduction

Intrauterine growth restriction is associated with a higher incidence of perinatal complications and long-term neurodevelopmental sequelae [1-5]. The cornerstones of management for intrauterine growth restriction comprise combined close antenatal surveillance, a well-timed delivery, special postnatal care [6], and long-term neurodevelopmental attention [1,3,7,8]. Late onset intrauterine growth restriction is a common form of intrauterine growth restriction, clinically evident on ultrasonography during the mid-second to third trimester of pregnancy. It is characterized by asymmetric biometry, in which fetal weight and length are small-for-date, whereas head size is relatively spared. Compared with the early symmetric intrauterine growth restriction type, caused by fetal disorders, late onset type is mainly caused by placenta-vascular insufficiency [9].

Vascular disorders of the placenta lead to a chronic decrease of oxygen and nutritional supplies to the growing fetus. Under such conditions, particularly when with evidence of evolving fetal distress, the definitive treatment constitutes the induction of early delivery, so that the fetus is immediately separated from its hostile environment, thereby terminating its continuous chronic stress. Clearly, the main disadvantage of this approach would involve a preterm delivery that potentially carries the inherent risks of immaturity and increased risks of short-term and long-term sequelae [6].

Extreme prematurity (i.e., birth at <32 weeks of gestation) is well established to confer a significantly higher risk for perinatal mortality, morbidity, and long-term neurocognitive sequelae [10]. After 32 weeks of gestation, however, whether the intrauterine or extrauterine environment offers a better long-term outcome for the growth-restricted infant remains unclear. Indeed, obstetric dilemmas regarding the advisability of initiating the delivery of a fetus with intrauterine

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growth restriction often arise between 31 weeks of gestation and term. The long-term outcomes for these survivors of intrauterine growth restriction have not been established.

According to our hypothesis, the combination of intrauterine growth restriction and preterm delivery (between 31-36 weeks of gestation) would additively result in a higher rate of perinatal complications and, consequently, worse long-term neurocognitive outcomes, compared with intrauterine growth restriction neonates delivered at term. To test our hypothesis, data were obtained from a prospective cohort of late onset intrauterine growth restriction live births between September 1992 and 1997 [2,3,7,8,11-13]. We aimed to establish a perinatal risk factor profile and assess and compare the neonatal and long-term outcomes of intrauterine growth restriction neonates delivered at ≥37 weeks of gestation vs intrauterine growth restriction neonates delivered between 31-36 weeks of gestation.

Study Design and Methods

Study Population

All consecutive infants with a gestational age of >31 weeks, born between September 1992 and 1997 at the Lis Maternity Hospital, Tel Aviv Sourasky Medical Center, with a birth weight below the 10th percentile for gestational age, according to the Israeli percentile curves published by Leiberman et al. [14], were eligible to participate. Neonates included in the study were identified by the participating obstetricians and neonatologists. Inclusion criteria comprised mid-second to third trimester late onset intrauterine growth restriction, as verified by ultrasonography or clinically, and an absence of genetic syndromes, major malformations, and congenital infection. Estimated gestational age was calculated according to the date of the mother's last menstrual period. Based on the timing of their delivery, intrauterine growth restriction newborns were categorized as either preterm intrauterine growth restriction (gestational age of 31-36 weeks) or term intrauterine growth restriction (gestational age of 37 weeks and more). Pathologic studies of the placentas revealed vascular pathology in over 85% of our cohort (obliterated vessels, placental infarcts, and increased syncytial knots) [3,11].

The study cohort manifested the asymmetric type of intrauterine growth restriction, defined as a cephalization index (i.e., the ratio between the head circumference in centimeters and the birth weight in grams $\times$ 10^2) >1.5 (for preterm intrauterine growth restriction) and >1.25 (for term intrauterine growth restriction), as adapted from Harel et al. [15].

Study Design

After suitable patients had been identified, relevant clinical data were collected, and the newborns underwent a neurobehavioral examination. Detailed neurodevelopmental and cognitive assessments were administered when the patients were aged 2 and 6 years. A group of 15 patients who could not be located at age 6 years were eventually located and examined at age 9 years, and their scores were combined with those of the others. This study was approved by the Ethics Review Committee of the Tel Aviv Sourasky Medical Center.

Clinical Data Collection

Biometric data collected at birth included birth weight, height, head circumference, and cephalization index, reflecting the severity of intrauterine growth restriction [15]. Risk parameters were then assessed, using three previously published questionnaires [2,3,11]:

(1) A socio-familial risk questionnaire included maternal education (number of years of formal education completed), paternal occupation (on a nine-level scale in which 1 = unskilled, 2 = skilled, 3 = farmer, 4 = artisan, 5 = salesman, 6 = clerk; 7 = manager, 8 = self-employed, and 9 = academic), maternal overweight status (weight gain of >12 kg during pregnancy), and maternal smoking (>1 pack per day).
(2) An obstetric risk questionnaire included hypertension (systolic blood pressure >140 mm HG and diastolic blood pressure >90 mm HG), albuminuria (2+ or more [i.e., > 100 mg%] according to urinalysis), infection (any infectious process, either culture or serologically proven, or clinically diagnosed, e.g., a common cold), premature rupture of membranes >24 hours before the onset of labor, and abnormal fetal heart rate (sustained fetal bradycardia of <100 beats/minute, decreased variability, and late decelerations).
(3) A neonatal risk questionnaire included low Apgar scores at 1 and 5 minutes (scores ≤6), neonatal infection (the occurrence of culture-proven or clinically suspected infection), metabolic and blood disturbances (any abnormality in measurements of glucose and electrolytes, anemia, i.e., hematocrit at <45%, rhesus factor and/or ABO incompatibility, and hyperviscosity, i.e., hematocrit at >65%), hyperbilirubinemia (bilirubin level >16 mg% in a full term newborn, and >10 mg% in a preterm newborn), and temperature disturbance (any temperature outside the zone of 36-37.5°C at least 1 hour after birth).

Outcome Measures

All examiners were blinded to gestational age, birth weight, and all perinatal and clinical data. The final outcome was determined from the scores of neurologic and cognitive assessments. The neurologic and cognitive examinations included:

(1) A neonatal neurobehavioral evaluation, consisting of 47 items, performed at term (between 37-41 weeks of postconceptional age). It included a formal neurologic examination (cranial nerves, tone, posture, movements, and neonatal reflexes), and behavioral items (visual orientation, consolability, response decrement to auditory, and visual and pinprick stimuli).
(2) A neurodevelopmental evaluation consisting of 45 items, performed at age 2 years. It included a formal neurologic examination (cranial nerves, motor, sensory, and cerebellar function) and several developmental items [11].
(3) A detailed neurodevelopmental assessment consisting of 72 items, performed at age 6 years. It included a formal neurologic evaluation (cranial nerves, and motor, sensory, and cerebellar function), and incorporated special tests for the presence of "soft" neurologic signs of brain maturation, i.e., coordination skills, parietal functions (finger agnosia, graphesthesia, stereognosis, and discrimination of stimuli), motor impersistence, associated movements, and visuomotor skills [2].
(4) Cognitive assessments performed by a certified child psychologist, who administered the Bayley Scales of Infant Development, 2nd edition [16] at approximately 2 years of age. Cognitive abilities were assessed using the Wechsler Preschool and Primary Scale of Intelligence [17] at age 6 years.

Scoring and Statistical Analysis

Scoring of the three neurologic examinations (at birth and at ages 2 and 6 years) was performed according to the optimality concept of Prechtl [18], i.e., each test item received an "optimal" vs "suboptimal" binary score, according to published standards [2,3,11]. A total score was then given to each of the three neurologic examinations (maximum score, 100). Cognitive assessments were scored in terms of a Mental Developmental Index for the examinations at age 2 years, and as intelligence quotients for the examinations at age 6 years.

The Fisher exact test and unpaired *t* test were used for comparisons between specific risk factors and perinatal and outcomes measures of the preterm and term intrauterine growth restriction groups. A multivariate analysis (logistic regression) was used to determine the independent effects of specific prenatal risk factors on preterm and term intrauterine growth restriction. In addition, for outcome analyses, we categorized the preterm intrauterine growth restriction group into two subgroups (A, 31-33 weeks; B, 34-36 weeks), and used one-way analysis of variance and the χ^2 test for trend for comparisons between all outcome data of the term intrauterine growth restriction group and the two preterm subgroups. Univariate linear regression was used to investigate the effects of early clinical risk factors on intelligence quotients. A multivariate linear regression analysis was then performed to define the independent contributions of specific risk factors to intelligence quotients. We used SPSS (SPSS, Inc., Chicago, IL) for all computations.

Results

Between 1992 and 1997, 307 infants born at the Lis Maternity Hospital met our criteria for late onset intrauterine growth restriction. They included 193 term-born (gestational age, 37-42 weeks) intrauterine growth restriction neonates, and 114 preterm-born (gestational age, 31-36 weeks) intrauterine growth restriction neonates. Data from all pregnancies and postnatal periods were used for analyzing risk factors and neonatal outcomes (Tables 1-3). At age 2 years, 110 (57%) term intrauterine growth restriction and 70 (61%) preterm intrauterine growth restriction subjects underwent follow-up neurodevelopmental and cognitive examinations. Long-term (at age 6 years) outcome assessments were performed on 201 subjects, consisting of 125 (65%) term intrauterine growth restriction and 76 (67%) preterm intrauterine growth restriction subjects. Subjects in both groups who were prospectively followed and those lost to follow-up were of comparable gestational ages and neonatal neurobehavioral, maternal education, and paternal occupation scores (P = NS).

Prenatal and Postnatal Factors

Several distinct prenatal risk factors were associated with intrauterine growth restriction neonates born both at

Table 1. Pregnancy risk factors of intrauterine growth restriction in term and preterm neonates

Clinical Factors	Preterm Intrauterine Growth Restriction: Number (%) or Mean ± S.D.	Term Intrauterine Growth Restriction: Number (%) or Mean ± S.D.	*P* Value
History of previous pregnancy			
Abortions and miscarriages*	22/112 (19.6)	20/193 (10.4)	0.02
Stillbirths and neonatal deaths	9/113 (8)	3/193 (1.6)	0.01
Interval since last pregnancy of <12 mo	7/113 (6.2)	9/192 (4.7)	0.37
Prolonged (>2 yr) infertility	10/113 (8.8)	20/193 (10.4)	0.41
Lifestyle			
Exposure to radiation during pregnancy	3/112 (2.7)	1/191 (0.5)	0.14
Smoking (1 pack per day)	11/113 (9.7)	28/191 (14.7)	0.14
Weight gain of >12 kg	37/112 (33)	69/190 (36.3)	0.33
Maternal age >35 yr	16/113 (12.9)	25/193 (14.6)	0.47
Vascular factors			
Blood pressure >140/90 (mm Hg)*	37/112 (33.3)	30/190 (15.8)	0.001
Albuminuria	19/112 (17)	12/190 (6.3)	0.003
Maternal edema of legs	19/112 (17.0)	23/190 (12.1)	0.16
RH/ABO incompatibility	7/112 (6.3)	4/187 (2.1)	0.07
Others			
Oligohydramnios	12/107 (11.2)	14/163 (8.6)	0.30
Polyhydramnios	0/95 (0)	2/151 (1.3)	0.38
Infection during pregnancy	15/109 (13.8)	19/182 (10.4)	0.25
Vaginal bleeding during pregnancy	16/112 (14.3)	25/189 (13.2)	0.46
Procedures			
Amniocentesis	23/93 (24.7)	37/171(21.6)	0.34
Laparoscopy/major surgery	4/74 (5.4)	6/140(4.3)	0.48
Poor prenatal care during first trimester	2/112 (1.8)	3/191 (1.6)	0.61
Social			
Unmarried mother	4/113 (3.5)	7/193 (3.6)	0.62
Paternal occupation scores	13.30 ± 2.30	13.26 ± 2.56	0.88
Maternal education scores	4.84 ± 2.71	4.4 4 ± 2.57	0.24

The comparison of dichotomous variables was performed using the Fisher exact test. The comparison of continuous variables was performed using an unpaired *t* test.

* Significant factors in the multivariate logistic regression (see Results section)

Abbreviation:
RH = Rhesus factor

Table 2. Labor risk factors for intrauterine growth restriction in term and preterm neonates

Clinical Factors	Preterm Intrauterine Growth Restriction: Number (%)	Term Intrauterine Growth Restriction: Number (%)	*P* Value
Induced labor	84/109 (77.1)	103/191 (53.9)	0.001
Arrest of labor	0/92 (0)	4/174 (2.3)	0.18
Drugs given to mother during labor and delivery	42/110 (38.2)	72/189 (38.1)	0.54
Abnormal amniotic fluid (meconium-stained, infected, or bloody)	2/97 (2.1)	17/166 (10.2)	0.01
Abnormal fetal heart rate	43/109 (39.4)	50/182 (27.5)	0.02
Placental previa or abruption	7/113 (6.2)	5/188 (2.7)	0.11
Forceps or vacuum extraction	1/34 (2.9)	13/131 (9.9)	0.17
Cesarean section	48/81 (59.3)	49/167 (29.3)	0.001
Abnormal fetal presentation (breech/face/occipito-anterior)	21/110 (19.1)	16/188 (8.5)	0.01
One cord vessel (arteries)	0/112 (0)	1/185 (0.5)	0.62
Premature rupture of membranes (>24 hr)	17/112 (15.2)	24/190 (12.6)	0.32

The comparison of variables was performed using the Fisher exact test.

term and preterm. The univariate analysis revealed a two-fold increase in a maternal history of abortions and miscarriages, and a fivefold greater risk of a history of previous stillbirths or neonatal deaths in cases of preterm intrauterine growth restriction newborns (Table 1). In addition, maternal hypertension and albuminuria were significantly more common in this group. Multiple pregnancies were associated with similar rates in the preterm (8.9%; 10/112) and term (6.8% 13/190; $P = 0.327$) intrauterine growth restriction groups. Other factors, including maternal infection and maternal smoking, were not significantly different between the two groups (Table 1). None of the risk factors listed in Table 1 were detected in 23 (20%) intrauterine growth restriction neonates delivered prematurely and in 49 (25%) intrauterine growth restriction neonates delivered at term ($P = 0.029$).

Two antecedent domains were included in a multivariate model, to determine the independent effects of the several variables associated with preterm intrauterine growth restriction. The first domain included factors associated

Table 3. Neonatal outcomes of term and preterm intrauterine growth restriction

Clinical Factors	Preterm Intrauterine Growth Restriction: Number (%) or Mean ± S.D.	Term Intrauterine Growth Restriction: Number (%) or Mean ± S.D.	*P* Value
Gestational age (wk)	34.48 ± 1.63	38.52 ± 1.12	0.001
Birth weight (g)	1473 ± 310	2093 ± 235	0.001
Birth length (cm)	40.58 ± 3.30	44.57 ± 2.77	0.001
Head circumference (cm)	28.78 ± 1.63	31.22 ± 1.36	0.001
Cephalization index	2.03 ± 0.39	1.50 ± 0.15	0.001
Male sex	47/113 (41.6)	75/193 (39)	0.36
Low Apgar scores at 1 min	12/110 (10.9)	14/185 (7.6)	0.22
Low Apgar scores at 5 min	3/110 (2.7)	1/187 (0.5)	0.15
Resuscitation in delivery room	9/106 (8.5)	9/188 (4.8)	0.15
Respiratory distress syndrome	5/107 (4.7)	4/186 (2.2)	0.20
Neonatal infection	14/107 (13.1)	10/186 (5.4)	0.02
Ventilatory assistance	9/106 (8.5)	4/186 (2.2)	0.01
Metabolic or blood disturbance	24/107 (22.4)	29/187 (15.5)	0.09
Hyperbilirubinemia	73/103 (70.9)	87/183 (47.5)	0.001
Temperature disturbance	3/107 (2.8)	4/186 (2.2)	0.50
Umbilical catheterization	13/107 (12.1)	7/185 (3.8)	0.01
Apneic episodes	11/107 (10.3)	11/185 (5.9)	0.13
Neonatal neurobehavioral score	86.04 ± 11.38	92.87 ± 9.23	0.001

The comparison of dichotomous variables was performed using the Fisher exact test, and the comparison of continuous variables was performed using an unpaired *t* test. The cephalization index comprises the ratio between head circumference (centimeters) and birth weight (g) $\times 10^2$.

with abnormal placentation (history of abortions, miscarriages, stillbirths and neonatal deaths, and short duration after previous pregnancy), and the second domain comprised placenta-vascular factors (smoking, exposure to radiation, hypertension, and rhesus factor/ABO incompatibility). We excluded factors that could not be attributed to the pathogenesis of intrauterine growth restriction, e.g., procedures during pregnancy, or labor risk factors, thus avoiding confounding by indication. An independent contribution was evident from maternal hypertension (odds ratio 2.3; 95% confidence interval: 1.3-4.2; $P = 0.004$) and history of abortions and miscarriages (odds ratio 2.3; 95% confidence interval: 1.1-4.7; $P = 0.03$). None of the remaining factors in the multivariate model reached a level of significance. Intrapartum and postnatal complications were more common in the prematurely born intrauterine growth restriction group, compared with those delivered at term (Tables 2 and 3).

Neurodevelopmental and Cognitive Outcomes

The preterm group with intrauterine growth restriction achieved significantly lower neonatal neurobehavioral scores than the term group with intrauterine growth restriction (Table 3), but the neurodevelopmental scores and cognitive assessments at ages 2 and 6 years were comparable for both groups (Table 4). Comparisons between all outcome data (neurodevelopmental and cognitive) of the term group with intrauterine growth restriction and the two preterm subgroups with intrauterine growth restriction (34-36 weeks and 31-33 weeks) remained comparable at the 2-year and 6-year assessments. For example, the 6-year intelligence quotient scores of the preterm subgroups with intrauterine growth restriction were 103.21 ± 16.44 (31-33 weeks) and 104.79 ± 14.8 (34-36 weeks), and for the term group with intrauterine growth restriction, 104.88 ± 16.48 ($P = 0.899$).

The univariate linear regression of intelligence quotient scores at age 6 years on neonatal clinical parameters is presented in Table 5. Sociodemographic factors (maternal education and paternal occupation), neonatal neurobehavioral scores, and neurodevelopmental and cognitive assessments at age 2 years were significantly associated with intelligence quotient scores at age 6 years, in both the preterm and term groups with intrauterine growth restriction (Table 5).

We constructed two multivariate linear regression models that included all significant items from the univariate analysis. The first model contained antenatal and perinatal risk factors. Independent contributions from hyperbilirubinemia ($P = 0.001$), premature rupture of the membranes ($P = 0.002$), and neonatal height ($P = 0.017$) were evident in the preterm group with intrauterine growth restriction ($R^2 = 0.32$), whereas independent contributions from maternal age >35 years ($P = 0.004$), neonatal apnea ($P = 0.038$), and neonatal head circumference ($P = 0.048$) were evident in the term group with intrauterine growth restriction ($R^2 = 0.2$). The second model incorporated social scores and postnatal evaluations (neonatal and at age 2 years). Independent contributions from neurodevelopmental examination at age 2 years ($P = 0.002$) and maternal education ($P = 0.01$) were evident in the preterm

Table 4. Sequential neurologic and cognitive outcome examinations of intrauterine growth-restricted term vs preterm neonates

Clinical Factors	Intrauterine Growth Restriction at 31-36 Weeks of Gestational Age: Number (%) or Mean ± S.D.	Intrauterine Growth Restriction at Term: Number (%) or Mean ± S.D.	*P* Value
Examination at age 2 years			
Number of subjects	70	110	
Age at time of testing	2.14 ± 0.14	2.10 ± 0.28	
MDI scores	98.90 ± 17.47	97.66 ± 20.35	0.68
Low MDI score (<85)	17/60 (28.3%)	32/110 (29.1%)	0.38
Neurodevelopmental scores	88.19 ± 8.21	89.53 ± 7.28	0.23
Examination at 6 years of age			
Number of subjects	76	125	
Age at time of testing	6.32 ± 0.71	6.29 ± 0.74	
IQ scores	104.31 ± 15.22	104.88 ± 16.48	0.81
Low IQ (<85)	7/76 (9.2)	13/125 (10.4)	0.49
Neurodevelopmental scores	83.81 ± 10.92	85.36 ± 9.84	0.22

The comparison of dichotomous variables was performed using the Fisher exact test, and the comparison of continuous variables was performed using an unpaired *t* test.

Abbreviations:
Cephalization index = Ratio between head circumference (cm) and birthweight (g) × 10^2
IQ = Intelligence quotient
MDI = Mental Developmental Index

Table 5. Early clinical parameters of term vs preterm intrauterine growth-restricted neonates and intelligence quotient scores at age 6 years

Clinical Parameters	Preterm Intrauterine Growth Restriction			Term Intrauterine Growth Restriction		
	n	Regression Coefficient	*P* Value	n	Regression Coefficient	*P* Value
Pregnancy and labor						
Maternal age >35 yr	63	−0.04	0.77	101	−0.034	0.001*
Blood pressure >140/90 (mm Hg)	75	0.011	0.92	121	−0.028	0.82
RH/ABO incompatibility	75	−0.001	0.99	118	−0.047	0.61
Oligohydramnios	66	−0.32	0.01	104	−0.150	0.12
Abnormal amniotic fluid(meconium-stained, infected, or bloody)	57	−0.008	0.55	105	−0.240	0.02
Premature rupture of membranes (>24 hr)	76	−0.35	0.002*	121	−0.009	0.92
Neonatal factors						
Gestational age (wk)	76	0.452	0.70	125	0.1	0.28
Birth weight (g)	76	0.23	0.04	125	0.133	0.14
Head circumference at birth (cm)	71	0.16	0.18	119	0.266	0.003*
Height at birth (cm)	70	0.28	0.02*	113	0.215	0.02
Male sex	76	−0.016	0.89	125	−0.013	0.89
Resuscitation, delivery room	70	−0.097	0.42	120	−0.250	0.01
Hyperbilirubinemia	66	−0.391	0.001*	117	−0.085	0.36
Apneic episodes	70	−0.099	0.42	119	−0.020	0.03*
Neurologic and cognitive outcome examinations						
Neonatal neurobehavioral scores	73	0.33	0.01	120	0.240	0.01
MDI scores at age 2 yr	54	0.38	0.01	90	0.682	0.001*
Neurodevelopmental score at age 2 yr	59	0.4	0.002*	96	0.510	0.001
Social factors						
Paternal occupation scores	74	0.24	0.004	124	0.410	0.001*
Maternal education scores	75	0.32	0.01*	119	0.360	0.001

Regression coefficient and *P* values are from a univariate linear regression of intelligence quotient on a given risk factor.
* Significant factors in multivariate linear regression analysis (see Results).

Abbreviations:
IQ = Intelligence quotient
MDI = Mental Developmental Index
RH = Rhesus factor

group with intrauterine growth restriction ($R^2 = 0.26$), and independent contributions from the Mental Developmental Index at age 2 years ($P < 0.0001$) and paternal occupation ($P = 0.002$) were evident in the term group with intrauterine growth restriction ($R^2 = 0.52$).

Discussion

The results of this study revealed that neonates with intrauterine growth restriction delivered at mild-to-moderate prematurity demonstrated a significantly higher incidence of antecedents related to placentation abnormalities (previous miscarriages and stillbirths), placental vascular factors (maternal hypertension and albuminuria), and an increased risk of intrapartum and postnatal complications, compared with intrauterine growth-restricted neonates delivered at term. Nevertheless, despite their lower neonatal neurobehavioral scores, the long-term neurodevelopmental and cognitive outcomes of intrauterine growth-restricted subjects born at mild-to-moderate prematurity were comparable to those of term intrauterine growth-restricted subjects.

Prenatal Risk Factors

Our finding that women who gave birth to preterm newborns with intrauterine growth restriction demonstrated an increased frequency of previous miscarriages and stillbirths supports the suggestion that abnormal placentation may be an early effector in this group [19,20]. Other factors that potentially affect placental growth, e.g., parity, maternal overweight or underweight status, younger or older maternal age, previously associated with preterm intrauterine growth restriction [21,22], were evident at similar frequencies in the preterm and term groups with intrauterine growth restriction in our cohort. This disagreement may stem from differences in study groups, such as the absence of teenage mothers and malnourished women in our cohort. An association between preeclampsia, hypertension, and intrauterine growth restriction was reported, reflecting the placenta-vascular etiology of asymmetric intrauterine growth restriction [23,24]. Our finding that maternal hypertension and albuminuria were increasingly associated with preterm intrauterine growth-restricted neonates corroborates the findings of other

studies [9,21,22,25,26], and suggests that the placental vasculature may be more vulnerable to hypertensive injury very early in gestation. A history of smoking, another potential risk factor for placental-vascular injury [22,27], was equally reported in both intrauterine growth-restricted groups, in agreement with other reports [26].

Approximately one fifth of patients with intrauterine growth restriction in both groups exhibited "idiopathic intrauterine growth restriction," meaning no identifiable etiology was evident. Some could have had a constitutional (genetic) source, but given the asymmetric biometry of our entire cohort, we propose that a substantial number of these "idiopathic" cases probably derived from placenta-vascular mechanisms. Thus, the pathogenesis of preterm intrauterine growth restriction may be indistinct from that leading to term intrauterine growth restriction, and could represent an earlier event.

Intrapartum and Neonatal Complications

Compared with term intrauterine growth restriction, the labor and delivery of prematurely born intrauterine growth-restricted neonates was more often associated with a higher perinatal risk profile, which was sometimes the trigger for the induction of labor and delivery by cesarean section, both of which were also more prevalent in this group. Furthermore, as we originally hypothesized, the neonatal period of preterm intrauterine growth restricted neonates tended to be more complicated, compared with that of the term intrauterine growth-restricted neonates. The additive effects of the growth restriction process and system immaturity could have contributed to the increased rates of both intrapartum and neonatal complications in preterm neonates with intrauterine growth restriction. Our finding of lower neonatal neurobehavioral scores among the preterm neonates with intrauterine growth restriction compared with the term-delivered group with intrauterine growth restriction may have been a reflection of such a chain of events.

Neurodevelopmental and Cognitive Outcomes

According to increasing evidence, extremely premature infants (i.e., <32 weeks) with intrauterine growth restriction carry a significantly higher risk for long-term cognitive sequelae [1,4,28-30]. Furthermore, these extremely premature infants with intrauterine growth restriction were described to manifest decreased gray matter volumes at 40 weeks of postmenstrual age. Those studies suggested that very premature birth after intrauterine growth restriction may further interrupt brain growth and development [31,32]. Although we did find lower neurobehavioral scores in preterm neonates with intrauterine growth restriction, both the neurodevelopmental and cognitive examinations of these children at ages 2 and 6 years were comparable between the two groups, suggesting the existence of a catching-up process in the preterm group with intrauterine growth restriction. Several explanations may be postulated: (1) In comparison to the growth-restricted extremely premature newborns, our cohort was at a more advanced phase of brain development (after 31 weeks of gestation), and beyond the critical period for white matter injury. Thus, the brain development of intrauterine growth-restricted infants born after 31 weeks of gestation may be less interrupted after intrauterine growth restriction, and it may better benefit from plasticity processes. (2) The timing of delivery in many patients with intrauterine growth restriction is dependent on obstetric decisions. Therefore, our results of comparable outcomes may indirectly reflect the well-timed delivery of the two groups with intrauterine growth restriction. (3) Compared with term intrauterine growth-restricted infants who do not qualify for routine services, growth-restricted preterm infants qualify for routine neurodevelopmental surveillance that could facilitate their developmental catch-up. Further studies are required to address these explanations.

We investigated the effects of early clinical parameters on intelligence quotient scores at age 6 years, and report that neither maternal hypertension (among other antecedents of intrauterine growth restriction itself) nor gestational age and male sex (both recognized risk factors for adverse outcomes in extremely premature newborns) were associated with intelligence quotient. Of all the prenatal factors that we examined, advanced maternal age (in term intrauterine growth-restricted infants) and oligohydramnios (in preterm intrauterine growth-restricted infants) were significantly associated with intelligence quotient. Advanced maternal age is linked with an increased incidence of chronic illnesses that potentially affect placental growth. Therefore, advanced maternal age may be associated with placental insufficiency. Oligohydramnios indirectly reflects decreased uteroplacental function, and may be a sign of inadequate placental perfusion and abnormal fetal wellbeing. In addition, the height of the term and preterm intrauterine growth-restricted neonates was also significantly associated with intelligence quotient. Thus, we speculate that an infant's height and neurodevelopment may be affected by common hormonal factors in the setting of intrauterine growth restriction. In accordance with this hypothesis, an association between successful growth hormone catch-up growth and improvement over time in nonverbal intelligence quotient was recently reported in adolescents who were born with intrauterine growth restriction [33]. Of the perinatal factors that could augment the adverse effects of intrauterine growth restriction, those associated with perinatal ischemia (i.e., meconium or bloody amniotic fluid, resuscitation, and neonatal apnea) were significantly associated with intelligence quotient in term-born intrauterine growth-restricted infants. In addition, both the premature rupture of membranes (an indirect marker for infection and inflammation) and hyperbilirubinemia (which is more common in premature infants) were significantly associated with intelligence quotient in prematurely born intrauterine growth-restricted infants.

Importantly, examinations at term and at age 2 years were significantly associated with intelligence quotient scores at age 6 years in both groups with intrauterine growth restriction. Multivariate analysis indicated that a neurodevelopmental examination at age 2 years for preterm intrauterine growth-restricted infants and Mental Developmental Index scores at age 2 years for term intrauterine growth-restricted infants were independently associated with intelligence quotient scores at age 6 years, suggesting that these instruments could serve as effective early indicators of outcomes, and could therefore assist in developmental strategies in this high-risk group.

A potential weakness of the present study concerns the unavailability of placental Doppler results, precluding a more in-depth knowledge of the vascular characteristics of participants. Information regarding what had triggered labor and delivery for preterm and term infants with intrauterine growth restriction was also unavailable. Therefore, we cannot provide guidelines for the optimal point at which an intrauterine growth-restricted fetus should be delivered, and thus that decision remains based on multiple obstetric parameters. Although a quarter of the cohort was lost to follow-up, these patients had comparable biometric, neonatal neurobehavioral, and socioeconomic scores to those who were prospectively followed. The strengths of our study include its prospective nature, the relatively large cohort, and our implementation of detailed long term neurodevelopmental examinations.

In conclusion, the results of this study suggest that the pathogenesis of preterm intrauterine growth restriction may be indistinct from that leading to term intrauterine growth restriction, and that it represents an earlier process. Our data suggest that although the perinatal period is more complicated for the premature infant born between 31-36 weeks of gestation, even with state-of-the-art services, the long-term neurodevelopmental outcomes are comparable in both groups with intrauterine growth restriction. Our findings, therefore, suggest that some flexibility may apply when making a decision about the timing for the delivery of an intrauterine growth-restricted infant at more than 31 weeks of gestation. Given the lack of differences in long term neurodevelopmental outcomes between mild-to-moderate preterm and term intrauterine growth-restricted neonates, early delivery may be considered a viable option when evolving fetal-placental abnormalities are evident.

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