

Neurobehavior of full-term small for gestational age newborn infants of adolescent mothers

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Abstract

Objective: To compare the neurobehavior of small (SGA) and adequate (AGA) for gestational age full-term neonates born to adolescent mothers.

Methods: This prospective cross-sectional study included full-term newborn infants aged 24-72 hours, free from central nervous system malformations and born to adolescent mothers at a single center in Brazil. Infants were assessed with the Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS) for: habituation, attention, arousal, regulation, handling, quality of movement, excitability, lethargy, nonoptimal reflexes, asymmetry, hypertonia, hypotonia, and stress/abstinence signals. The chi-square test and analysis of variance were used to compare SGA and AGA infants. Multivariate regression was used to analyze factors associated with the score of each NNNS variable.

Results: Of 3,685 infants born in the study hospital, 928 (25%) had adolescent mothers. Of these, 477 infants met the inclusion criteria: 419 (88%) were AGA and 58 (12%) were SGA. Univariate analysis did not show any differences between AGA and SGA neonates in terms of NNNS variables. Multivariate analysis showed that SGA neonates born by vaginal delivery had lower scores for quality of movements than those born by caesarean section. The SGA neonates born with local or without anesthesia had higher scores for excitability than those born with spinal anesthesia. Additionally, female SGA neonates had lower scores for stress/abstinence signals than males.

Conclusion: SGA neonates born to adolescent mothers showed poorer quality of movements, more excitability and more signals of stress in association with sex of infant and variables related to delivery.

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Introduction

Small for gestational age (SGA) newborns are the result of intrauterine growth restriction, which can be triggered by a series of factors inherent to the health of the mother and fetus, in addition to those related to the family's socioeconomic conditions. Pregnancy during adolescence, the absence of a fixed partner, low educational level, insufficient prenatal care, the use of both legal and illegal drugs, exposure to sexually transmitted diseases, violence and psychological disorders can, in

combination or in isolation, lead to inadequate fetal growth.^{1,2} Regarding teenager pregnancies, they are associated to violence exposure and to mental disorders. Violence during pregnancy is reported to be associated with the birth of SGA infants, while mental diseases are associated with prematurity.³ On the other hand, pregnancy during adolescence is not alone a risk factor for low birth weight when the influence of unfavorable clinical, gestational and psychosocial factors is subtracted.⁴

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It is known that intrauterine malnutrition may alter the anatomic and functional maturation of the central nervous system. Chronic placental insufficiency, which results in fetal growth restriction, leads to deficits in neural connections and myelination and alters the function of auditory and visual systems during the postnatal period.⁵ Volumetric studies using magnetic resonance have indicated reduced grey matter in full-term SGA neonates, with the hippocampus being especially vulnerable to the effects of placental insufficiency.⁶ Furthermore, cortical growth is compromised in fetuses with severely restricted intrauterine growth, with reduced numbers of cells in the cerebral cortex.⁷ These changes in the growth and development of the central nervous system can trigger neurobehavioral alterations that are already detectable in the first days of life.⁸

The classic description of the SGA newborn includes increased motor ability, exaggerated responses to reflex tests, prolonged periods in a state of arousal and more appetite than newborns of the same weight but younger gestational ages.⁹ However, studies of specific aspects of the neurological performance of SGA infants, such as muscle tone assessment by objective methods, indicate the presence of reduced muscle tone.¹⁰ Assessment of the global neurobehavioral performance of infants born at full term with intrauterine growth restriction, compared with appropriate for gestational age (AGA) neonates, demonstrates worse performance in items related to orientation to stimuli, motor responses and reflexes, in addition to reduced muscle tone, during the first days of life. SGA infants spend less time awake and need more comforting maneuvers, and they have problems with self-quieting.¹¹⁻¹⁴ Nevertheless, these alterations are not observed in a uniform manner and some authors have observed better orientation in response to external stimuli among SGA newborn infants.¹⁵⁻¹⁶

The neurobehavior of SGA newborn infants, in addition to having been little studied, is also complicated by a lack of homogeneity in terms of the definition of "small for gestational age" and of neurobehavioral assessment methods. In this context, this study goal was to compare the neurobehavioral of SGA and AGA full-term infants born to adolescent mothers with the Neonatal Intensive Care Unit Neurobehavioral Network Scale (NNNS).

Methods

This was a single-center cross-sectional study, with prospective data collection, carried out at a tertiary hospital in the city of São Paulo, Brazil, during the period between July 2001 and November 2002. The study was approved by the Research Ethics Committees at the hospital where data collection was carried out and at the educational institution to which the researchers are affiliated and was financed by the Fundação de Apoio à Pesquisa do Estado de São Paulo.

The patient sample was selected based on the following inclusion criteria: signature of a free and informed consent

form by the mother, newborn infant with adolescent mother (age 10-19 years), born full term (gestational age 37-41.6 weeks), based on gestational age calculated from the last menstrual date or, when this information was not available, by the New Ballard method.¹⁷

Neonates were excluded if they exhibited one or more of the following conditions that could interfere with neurobehavioral responses: mothers with positive serology for congenital infections either during pregnancy or at delivery; mothers who were given opiates, sedatives and/or anticonvulsants during the 24 hours before delivery or general anesthetic during delivery; newborn infants who had been exposed to tobacco, alcohol, marijuana, cocaine or other drugs during gestation; products of multiple gestations; 1 minute Apgar score < 3 or 5 minute Apgar < 7; newborn infants with major congenital malformations; and presence of clinical problems on the day of data collection. Jaundiced neonates were included if not in phototherapy at the time of the test, as were infants who had exhibited adaptive respiratory distress, but did not need oxygen therapy and were in normal nursery at time of the test.

The study included interviews with the mothers and physical examination and neurobehavioral assessment of the newborn infants. The adolescents were interviewed soon after delivery regarding demographic, clinical, antenatal, labor and delivery data.

The neurobehavioral assessments of the neonates were carried out by neonatologists using the NNNS.¹⁸ The NNNS is a scale that assesses neurological integrity, behavioral function and the presence of signals of stress and abstinence in newborns.¹⁹ The test was applied after 24 hours of life, when the stress response to delivery has subsided, and before 72 hours of life, in a calm, dimly lit, heated room by one of four neonatologists. One of the investigators (MMCB) was certified to apply the NNNS at the Women and Infants Hospital, Brown University (Rhode Island, USA) and trained the other three neonatologists. Reliability of the NNNS was verified by simultaneous weekly applications by the lead researcher and each of the three neonatologists, throughout the study, in order to detect and correct possible discrepancies. After the assessment, the items analyzed were grouped into the 13 variable categories described by Boukydis et al.¹⁹ as follows: habituation, attention, arousal, control, handling, quality of movement, excitability, lethargy, nonoptimal reflexes, asymmetry, hypertonia, hypotonia, and stress/abstinence signals.

The information on the adolescent mothers' consumption of legal and illegal drugs during pregnancy was obtained by interview and by toxicological analysis of samples of the mothers' hair and newborns' meconium. The mothers were interviewed by psychologists soon after delivery. Three centimeter samples of the mothers' hair were taken from close to the scalp to be assayed for marijuana and cocaine metabolites by

Table 1 - Characteristics of the mothers of AGA and SGA infants

	AGA (n = 419)	SGA (n = 58)	p
Mother's age (years)	16.9±1.5	16.8±1.7	0.650
White race	209 (50%)	25 (43%)	0.401
Fixed partner	270 (64%)	39 (67%)	0.397
Years in education	7.1±2.2	6.8±2.3	0.295
Number of pregnancies	1.2±0.5	1.2±0.6	0.659
Prenatal care present	404 (96%)	55 (95%)	0.378
Prenatal consultations	7.0±2.7	5.7±2.4	0.001
Vaginal delivery	306 (73%)	43 (74%)	0.499
Regional anesthesia	313 (75%)	34 (59%)	0.009

AGA = appropriate for gestational age; SGA = small for gestational age.

semi-quantitative enzymatic immunoassay, with confirmation by gas chromatography and/or mass spectrometry. The sample was considered positive when both results, screening and confirmation, were positive. Intrauterine marijuana and/or cocaine exposure was detected by toxicological analysis of a meconium sample collected during the first 2 days of life and processed by semi-quantitative homogenous enzymatic immunoassay. With relation to tobacco, newborn infants were excluded if their mothers had smoked any number of cigarettes during pregnancy. With relation to alcohol, neonates were only included in the sample if their mothers stated that they had not drunk during pregnancy or just once, on a special occasion. All newborn infants exposed to illegal drugs were excluded, irrespective of the frequency or quantity of maternal consumption.

The newborn infants were divided into two groups depending on the appropriateness of their birth weight to their gestational age, according to the curve described by Alexander et al.²⁰ Birth weights between percentiles 10 and 90 for gestational age were defined as AGA and weights below the 5th percentile as SGA. Newborn infants with birth weights between the 5th and 10th percentiles were excluded from the study. AGA and SGA neonates were compared using the chi-square test for categorical variables and Student's t test for numerical variables.

Analysis of variance (ANOVA) and multivariate linear regression were applied to identify whether intrauterine growth restriction influenced the scores for NNNS variables, controlling for other factors that could affect the newborns' behavior. Each of the 11 numerical variables from the NNNS (habituation, attention, arousal, control, handling, quality of movement, excitability, lethargy, nonoptimal reflexes, asymmetry and signals of stress and abstinence) were taken as dependent variables and the following as independent variables: appropriateness of weight to gestational age (AGA

vs. SGA), anesthesia during delivery (none/local vs. regional block), type of delivery (vaginal vs. caesarean), sex, gestational age, birth weight, 1st and 5th minute Apgar scores and age of the newborn at neurobehavioral assessment. Two of the 13 NNNS variables were analyzed as qualitative categories: hypertonia and hypotonia. For both, the effect of intrauterine growth restriction was determined by logistic regression, with the independent variables being the same used for the multivariate linear regression and ANOVA.

The sample size was determined based on the need to study 15 to 20 newborn infants per independent variable to be assessed in the multivariate linear regression or logistic regression. Since all of the 13 variables on the NNNS were considered dependent variables and each of them was tested for associations with nine independent variables, the minimum sample size was 135 to 180 newborn infants. Statistical procedures were carried out using SPSS 10.0 and significance was set at $p < 0.05$ for all tests.

Results

A total of 792 infants were born at full term during the study period and 264 of these were excluded due to one or more of the conditions defined in the exclusion criteria. Intrauterine growth restriction was detected in 109 of the remaining 528 neonates, 51 of whom had weights between the fifth and 10th percentiles for gestational age. Therefore, the final study sample comprised 477 patients: 419 AGA and 58 SGA infants.

Both groups were similar in terms of maternal characteristics, with the exception of prenatal care and anesthesia for delivery. The mothers of the SGA infants attended fewer prenatal care visits and more frequently received regional anesthesia (Table 1).

Table 2 - Characteristics of the AGA and SGA infants

	AGA (n = 419)	SGA (n = 58)	p
Male sex	221 (53%)	18 (31%)	0.001
1st minute Apgar score	8.2±1.3	8.1±1.3	0.534
5th minute Apgar score	9.6±0.6	9.5±0.7	0.215
Gestational age (weeks)	39.4±1.1	39.1±1.1	0.049
Birth weight (g)	3,205±299	2,473±191	< 0.001
Head circumference (cm)	34.3±1.1	32.7±0.98	< 0.001
Age of infant when assessed (hours)	33.2±6.9	32.4±6.5	0.386
Assessment duration (minutes)	22.5±5.4	21.6±4.2	0.148
Time between feed and assessment (minutes)	48.7±54.2	57.9±55.0	0.242

AGA = appropriate for gestational age; SGA = small for gestational age.

In relation to neonatal characteristics, there were fewer males and mean gestational age, birth weight and head circumference were lower in the SGA group (Table 2).

The neurobehavioral assessment was applied by four previously trained neonatologist, with the number of assessments carried out by each being 106 (22.2%), 114 (23.9%), 123 (25.8%) and 134 (28.1%). There were no differences between the AGA and SGA groups regarding the age at which the newborn infants were examined, duration of assessment or time elapsed between the last feed and starting the assessment (Table 2).

In the univariate analysis, the two groups exhibited similar scores for all NNNS variables: habituation, attention, arousal, control, handling, quality of movement, excitability, lethargy, nonoptimal reflexes, asymmetry, hypertonia, hypotonia and signals of stress and abstinence (Table 3).

In the multivariate analysis there was no effect from being born SGA on the following items of the neurobehavioral assessment: habituation, attention, arousal, control, handling, lethargy, nonoptimal reflexes, asymmetry, hypertonia or hypotonia. However, being SGA did have an impact on the

Table 3 - Mean (± standard deviation) scores for the 13 NNNS variables for AGA and SGA infants

	AGA (n = 419)	SGA (n = 58)	p
Habituation	6.86±1.49	6.54±1.65	0.255
Attention	5.73±1.32	5.56±1.18	0.335
Arousal	3.70±0.70	3.60±0.66	0.245
Control	6.06±0.74	5.98±0.66	0.394
Handling	0.36±0.26	0.42±0.27	0.109
Quality of movement	5.11±0.49	5.09±0.43	0.776
Excitability	2.48±1.68	2.55±1.69	0.777
Lethargy	4.04±1.82	3.86±1.65	0.460
Nonoptimal reflexes	3.67±1.35	3.79±1.18	0.453
Asymmetry	0.71±0.94	0.71±0.90	0.973
Hypertonia	0.18±0.39	0.16±0.37	0.679
Hypotonia	0.13±0.37	0.12±0.33	0.901
Signals of stress/abstinence	0.07±0.05	0.07±0.05	0.747

AGA = appropriate for gestational age; NNNS = Neonatal Intensive Care Unit Network Neurobehavioral Scale; SGA = small for gestational age.

following variables: quality of movement, excitability and signals of stress and abstinence.

For "quality of movement", there was an interaction between type of delivery and appropriateness of weight to gestational age ($p = 0.057$). Those SGA neonates who were delivered vaginally had lower scores than the caesarean-born infants (5.01 ± 0.74 vs. 5.34 ± 0.13), controlling for type of anesthesia and sex. This difference was not observed among the AGA.

With relation to "excitability", there was an interaction between type of anesthesia and appropriateness of weight to gestational age ($p = 0.038$). SGA neonates born with local anesthesia or without anesthesia scored higher on this variable than SGA born under regional anesthesia (3.18 ± 0.35 vs. 2.09 ± 0.29), controlling for type of delivery and sex. This difference was not observed among the AGA.

Finally, with relation to "signs of stress/abstinence", an interaction was detected between sex of infant and appropriateness of weight to gestational age ($p = 0.039$). Female SGA patients exhibited less signals of stress and/or abstinence than their male counterparts (0.059 ± 0.008 vs. 0.093 ± 0.012), controlling for type of anesthesia and delivery. This difference was not observed among the AGA.

Discussion

Approximately 900,000 adolescents get pregnant every year in United States²¹ and, in 2004, 22% of the 3,026,548 live births in Brazil occurred among adolescent mothers.²² Adolescent pregnancy is associated with low socioeconomic status, absence of a fixed partner, a lack of access to education in general and health education in particular and risk behaviors such as the use of tobacco, alcohol and drugs, among others. Many of these factors, in isolation or together, can lead to intrauterine growth restriction.^{1,2}

The 14% (109/792) frequency of SGA newborn infants observed in this sample of full-term newborn infants, although elevated, has also been observed in other Brazilian studies.^{23,24} This high proportion of SGA is observed in our country when North-American intrauterine growth curves are used. It is controversial whether it reflects an elevated prevalence of intrauterine malnutrition or simply a different constitutional pattern among the Brazilian population.²⁰ In order to avoid including in the sample newborn infants with weights below the North American standard for gestational age who did not suffer intrauterine growth restriction, it was decided to study just those SGA infants below the fifth percentile of the reference scale, excluding those whose birth weights were between the 5th and the 10th percentiles.

With relation to the neurobehavior of SGA neonates, Als et al. assessed 10 vaginally-delivered full-term neonates with low weights on their first, third, fifth and 10th days of life. Compared with heavier babies, patients exhibited worse performance in interactive behavior, with less capacity to respond

to stimuli.¹¹ Lester et al. studied 37 healthy full-term neonates on their 2nd-3rd day of life. Those with weight, length or weight below the 10th percentile performed worse on items related to orientation to stimuli, motor responses and reflexes, in addition to being less alert.²⁵ Costas i Moragas et al. assessed 41 SGA infants born at full term at 3 days of life, comparing them with full-term babies with birth weights between the 25th and 75th percentiles for gestational age. The SGA infants exhibited lower capacity to respond to external stimuli, less motor activity and muscle tone and they needed greater number of quieting maneuvers, presenting difficulties self-quieting.¹³ Abrol et al. also analyzed the behavior of 25 SGA babies born by vaginal delivery at 1, 5, 10 and 30 days of life. Compared with AGA infants, the SGA exhibited poorer performance in all items that assessed their interaction with the environment and in their motor performance.¹⁴ The authors attributed these findings to changes to nervous system development and cerebral organization in newborn infants subjected to nutritional restriction during gestation.^{14,25} In this study, using a scale validated for neurobehavioral assessment during the first days of life and with established reference values,^{26,27} the findings differed from those described above, since, in the univariate comparisons similar performance was observed in the 13 neurobehavioral variables examined for both SGA and AGA infants. However, being born SGA influenced the neonatal neurobehavioral performance in association with other factors that stress the mother-baby pair (anesthesia and type of delivery) or with characteristics of the infants themselves (sex).

Those SGA newborn infants who were delivered under local anesthesia or without anesthesia were more excitable, with greater irritability, lability of skin color and state of arousal, tremors and startles than those delivered with regional anesthesia. In the same way, babies with birth weights below the 5th percentile for gestational age who were delivered vaginally exhibited poorer quality of movements compared with those delivered by C-section. Studies with animal models have demonstrated that the concentrations of growth factors, particularly brain-derived neurotrophic factor, and cytokines are significantly altered in the hippocampus of fetuses with intrauterine growth restriction and that these changes to the mediators are amplified by acute events and may mediate neuronal and white matter lesions.^{5,28} Therefore, it is possible that modifications to the organization of the nervous system associated with intrauterine growth restriction may be enhanced by the release of stress hormones during labor and delivery, interfering with the neurobehavior of SGA newborn infants.

It is intriguing that male SGA newborn infants exhibited a greater number of stress/abstinence signals compared to females. The influence of sex on the neurobehavior of newborn infants during the first week of life has not been systematically assessed. However, Brown et al. analyzed

neurobehavioral changes in extreme preterm infants using the NNNS and reported that female babies exhibited better performance than males for "quality of movement".²⁹ It is known that higher levels of stress hormones are found in male newborn infants when they are subjected to stressful procedures.³⁰ It is possible that intrauterine growth restriction causes different cortical growth and organization changes during intrauterine life for male and female fetuses, depending on the predominant hormonal influence, which would explain the neurobehavioral differences observed in male and female SGA newborn infants during their first days of life.

This study is subject to limitations related to its cross-sectional design, providing no data on the progression of neurological and behavioral performance over time, as the SGA and AGA infants develop. Nevertheless, the research aimed to detect alterations during the first days of life in neonates by means of a scale validated to assess the neurobehavior of babies exposed to risk situations. Assessing this group of SGA children using the Neonatal Intensive Care Unit Network Neurobehavioral Scale adds objective results to the literature regarding analysis of predefined areas of neurological performance and behavior soon after birth. This period is crucial for establishing healthy family emotional bonds, particularly between the mother and her baby.

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