Fetal Growth Restriction with Brain Sparing: Neurocognitive and Behavioral Outcomes at 12 Years of Age

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Objective To study neurocognitive functions and behavior in children with a history of fetal growth restriction (FGR) with brain sparing. We hypothesized that children with FGR would have poorer outcomes on these domains.

Study design Subjects were 12-year-old children with a history of FGR born to mothers with severe early-onset hypertensive pregnancy disorders (n = 96) compared with a normal functioning full term comparison group with a birth weight ≥2500 g (n = 32). Outcome measures were neurocognitive outcomes (ie, intelligence quotient, executive function, attention) and behavior.

Results For the FGR group, the mean ratio of the pulsatility index for the umbilical artery/middle cerebral artery (UC-ratio = severity of brain sparing) was 1.42 ± 0.69. The mean gestational age was 31-6/7 ± 2-2/7 weeks. The mean birth weight was 1341 ± 454 g, and the mean birth weight ratio 0.68 ± 0.12. Neurocognitive outcomes were comparable between groups. Parents of children with FGR reported more social problems (mean T-score 56.6 ± 7.7; comparison 52.3 ± 4.3, $P < .001$, effect size = 1, 95% CI 0.52-1.46) and attention problems (mean T-score 57.3 ± 6.9; comparison 53.6 ± 4.2, $P = .004$, effect size = 0.88, 95% CI 0.42-1.33). UC-ratio was not associated with any of the outcomes, but low parental education and lower birth weight ratio were.

Conclusions In this prospective follow-up study of 12-year-old children with a history of FGR and confirmed brain sparing, neurocognitive functions were comparable with the comparison group, but parent-reported social and attention problem scores were increased. *(J Pediatr 2017;188:103-9).*

Early-onset hypertensive pregnancy disorders, such as pre-eclampsia and hemolysis, elevated liver enzymes, and low platelets syndrome are strongly associated with fetal growth restriction (FGR).[1] When FGR is caused by placental insufficiency, which is the case in hypertensive pregnancy disorders, the fetus adapts to insufficient oxygen and nutrient supply by a redistribution of cardiac output to all vital organs including the brain. This is known as "brain sparing." Although brain sparing suggests a positive effect for brain development, it has been associated with impaired long-term cognitive functions and behavioral problems.[2-8]

Recent research shows that in brain sparing, blood flow initially increases to the frontal brain regions, but when FGR worsens, blood flow is redistributed to the basal ganglia.[9] This may lead to alterations in frontal brain development that are observed as deficits in executive function and attention. Executive functions such as impulse control, working memory, mental flexibility, and planning are important for academic, behavioral, and social functioning.[10-14] Although deficits in executive function and attention have been found in preterm and very low birth weight children,[13] no studies have examined these functions yet in detail in children with FGR with proven brain sparing.

This study presents the results of a prospective long-term follow-up of 12-year-old children born with FGR and antenatal evidence of brain sparing after severe early-onset hypertensive pregnancy disorders. The aim was to examine neurocognitive outcomes (ie, intelligence, executive function, and attention) and behavior. We hypothesized that children with FGR would have poorer neurocognitive and behavioral outcomes compared with same aged term-born comparison children, and that severity of brain sparing, FGR severity, gestational age (GA), neonatal morbidity, and socioeconomic status (SES) would be associated with neurocognitive and behavioral outcomes.

ADHD	Attention deficit hyperactivity disorder
AMC	Academic Medical Center
ANT	Amsterdam Neuropsychological Tasks
BWR	Birth weight ratio
FGR	Fetal growth restriction
GA	Gestational age
SES	Socioeconomic status
UC-ratio	Ratio of the pulsatility index of the umbilical artery and the middle cerebral artery

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Methods

Participants of this prospective cohort study were children with FGR born to women with severe early-onset pre-eclampsia, hemolysis, elevated liver enzymes, and low platelets syndrome, or pregnancy induced hypertension with concomitant FGR. The women participated in a trial on plasma volume expansion, executed by the Academic Medical Center (AMC) and VU Medical Center in Amsterdam, The Netherlands. Women were eligible if they were pregnant with a viable singleton and were admitted to the hospital at a GA between 24 and 34 completed weeks between April 1, 2000 and May 31, 2003. Details of the study protocol and the outcome of the trial have been described elsewhere.[15] Children were followed-up to 4 years of age, and thus far no trial effect has been found for any pediatric outcome.[16,17] Children were invited for follow-up at the AMC at corrected age 12.5 years.

Comparison children (ie, same-age with a GA ≥37 weeks and/or a birth weight ≥2500 g) were recruited from 3 mainstream neighborhood schools. Information letters were handed out in class, and parents were able to respond by using a reply form. To create a homogenous comparison group, children with a psychiatric diagnosis confirmed by parents and/or tested IQ below 85 were excluded from analyses after testing. All cognitive measures were administered by one of the authors or by well-trained research assistants.

The medical ethics institutional review board of the AMC Amsterdam, The Netherlands, approved the study protocol. All participating parents and children provided written informed consent.

During the prenatal hospital admission, fetal Doppler measures were performed twice a week. The highest ratio of the pulsatility index of the umbilical artery and middle cerebral artery (UC-ratio) was used to express severity of brain sparing, with brain sparing defined as UC-ratio >0.72.[18] A birth weight ratio (BWR) was used as a proxy for FGR severity.[19] The BWR was calculated as birth weight divided by the expected weight for GA, using the Gardosi customized fetal growth chart 50th percentile values.[20] A BWR <10th percentile was defined as growth restricted.

At 12 years of age, parents reported whether their child had a confirmed psychiatric diagnosis and their child's type of education (mainstream vs special) in a standardized background questionnaire. Parental education also was assessed with a standardized questionnaire. A low SES was defined as at least 1 parent with educational level 0, 1, or 2 according to International Standard Classification of Education.[21]

The IQ was assessed with the Wechsler Intelligence Scale for Children, Third Edition, Dutch Version.[22,23] Executive functions assessed included the most well-known and crucial areas of executive function.[14,24] Impulse control (ie, suppression of responses to irrelevant stimuli), was measured by the stop task.[25] Verbal and visual working memory (ie, the capacity to manipulate information in mind) were assessed with the Digit Span backwards subtest of the Wechsler Intelligence Scale for Children, Third Edition, Dutch Version, and the Spatial Temporal Span backwards subtest of the Amsterdam Neuropsychological Tasks (ANT), respectively.[23,26] Set-shifting (ie, alternation between mental strategies) was assessed with the Shifting-Visual-Set task of the ANT.[27,28] Planning was assessed with a digital Tower of London Test.[29] In addition, parent ratings of executive function were assessed with the impulse control, working memory, set-shifting, and planning scales of the Behavior Rating Inventory of Executive Function Dutch version.[30] Focused attention was evaluated with the Focused Attention 4 Letters task of the ANT, and sustained attention with the stop task.[31] In addition, parent-reported attention was assessed with the Strengths and Weaknesses of attention deficit hyperactivity disorder (ADHD) Symptoms and Normal Behavior scale.[32] Behavior was assessed by parent report on the Child Behavior Checklist (6- to 18-year-olds).[33] Details on all tests and questionnaires are described in the **Appendix** (available at www.jpeds.com).

Statistical Analyses

Missing data were not replaced. Extreme values were defined as a score of <1.5 times the IQR below the first quartile, or >1.5 times the IQR above the third quartile.[34] An extreme value was removed only if it was a result of noncooperative behavior or a technical problem during testing. Baseline characteristics, neurocognitive and behavioral outcomes of children with FGR seen at 12 years of age were compared with those lost to follow-up, and with the comparison children using χ^2 tests, independent *t* tests, or Mann-Whitney-U tests (when assumptions for parametric testing were not met). For measures that comprised a baseline and an executive condition, linear regression analyses were performed with the baseline condition and the group variable as independent variables. To see whether significant group differences were caused by selection bias of the comparison group, we also compared the subgroup of children with FGR who were not in special education, without a parent-reported psychiatric diagnosis, and without IQ <85, with the comparison group. In addition, Glass Delta effect sizes were calculated with the comparison group as baseline measure, with small (0.20-0.50.), moderate (0.50-0.80), or large effects (.80 or higher).

To examine associations between perinatal and neonatal characteristics, SES, and neurocognitive and behavioral outcomes, linear regression analyses were performed. Independent variables entered stepwise were UC-ratio, BWR, GA, neonatal morbidity, and low SES. Outcomes were displayed as unstandardized betas (β), (ie, the mean change in the dependent variable for one unit change in the independent variable).

To reduce type I error because of multiple testing, statistically significant *P* values were set at .002 (0.5/number of tested variables). *P* values from .002 to .01 were considered as a trend. IBM SPSS v 23 (SPSS, Armonk, New York) was used with STATA/IC 14 (StataCorp LLC, College Station, Texas) to calculate effect sizes.

Results

The flow of participants through the trial and in follow-up is shown in **Figure 1** (available at www.jpeds.com). Out of 174