What Is Spared by Fetal Brain-Sparing? Fetal Circulatory Redistribution and Behavioral Problems in the General Population


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Intrauterine growth restriction has been linked to infant behavioral problems. While typically only birth weight is examined, here the authors assessed fetal circulatory redistribution, also called the “brain-sparing effect,” which is a fetal adaptive reaction to placental insufficiency. They aimed to investigate whether fetal circulatory redistribution protects against behavioral problems. Within the Generation R Study (Rotterdam, the Netherlands, 2003–2007), fetal circulation variables for the umbilical artery and the middle and anterior cerebral arteries were assessed with Doppler ultrasound in late pregnancy. Ratios between placental resistance and cerebral resistance were related to behavioral problems, as measured by the Child Behavior Checklist, in 935 toddlers aged 18 months. The umbilical/anterior cerebral ratio was associated with the Total Problems summary score from the Child Behavior Checklist (per standard-deviation increase, odds ratio \(= 1.2\), 95% confidence interval: 1.0, 1.5). Children with higher umbilical/anterior cerebral ratios had higher risks of internalizing problems, emotional reactivity, somatic complaints, and attention problems. A high umbilical/middle cerebral ratio was related to higher scores on the Internalizing and Somatic Complaints scales. The authors conclude that infants with circulatory redistribution in gestation are more likely to have behavioral problems. This suggests that “brain-sparing” does not completely spare the brain and indicates underlying pathology with consequences for later behavior.

cerebrovascular circulation; fetal blood; fetal hypoxia; infant behavior

Abbreviations: CI, confidence interval; OR, odds ratio; SD, standard deviation; U/C, umbilical/cerebral.

An adverse intrauterine environment may have lifelong consequences for the developing fetus. A nonoptimal environment in utero is related to somatic (1) and psychiatric (2–5) disorders. Maternal undernutrition during pregnancy has been associated with schizophrenia (2, 3), antisocial personality disorder (4), and depression (5). Moreover, researchers in several population-based studies have described relations between low birth weight and behavior and cognition in childhood and adulthood (6–9). Animal and clinical studies have shown that intrauterine growth restriction is associated with alterations in brain tissue volume (10, 11) and with disabilities in motor skills, cognitive function, concentration, attention, and mood (12–14).

Intrauterine growth restriction is most commonly caused by placental insufficiency (15). Animal studies have shown that in the presence of intrauterine growth restriction due to placental insufficiency, the central nervous system is preferentially perfused, which is intended to maintain oxygen supply to the brain as much as possible (16, 17). In humans, this fetal adaptive mechanism, the “brain-sparing effect,” can be demonstrated with Doppler ultrasound. A raised pulsatility index in the umbilical artery, reflecting a reduced number of arterioles, infarction, and thrombosis (18), identifies fetuses that are growth-restricted due to placental dysfunction. The fetus adapts to placental insufficiency by vasodilatation of the cerebral circulation, which can be detected as a decreased pulsatility index in the cerebral arteries (19). Thus, the indicator of the “brain-sparing effect” is a raised ratio between the umbilical artery pulsatility index and the middle cerebral artery pulsatility index (hereafter called the U/C ratio) (20).
The term “brain-sparing” refers to relative protection of the brain as compared with other organs during fetal development, but this does not guarantee normal development after birth. Scherjon et al. (21) showed in a clinical sample of mainly growth-restricted preterm infants that brain-sparing predicts cognitive deficits at the age of 5 years. Experimentally induced placental insufficiency in animals altered brain structure in the offspring, causing reduced brain weight, ventriculomegaly, and volumetric reductions in the basal ganglia and the hippocampus (22).

We examined the hypothesis that changes in blood flow in the middle and anterior cerebral arteries are associated with behavioral and emotional problems in a population-based cohort. Doppler ultrasound was used to measure U/C ratios for both the anterior and middle cerebral arteries. We investigated whether raised U/C ratios were related to an increased risk of behavioral problems.

MATERIALS AND METHODS

Setting

The study was conducted within a subgroup of the Generation R Study, a population-based prospective study of a cohort from fetal life to young adulthood in Rotterdam, the Netherlands, which has been previously described (23). Briefly, this cohort included 9,778 mothers of different ethnicities and their children. Midwives and gynecologists in the study area informed eligible pregnant women about the study at their first antenatal visit. Detailed prenatal ultrasound assessments were conducted in a subgroup of 1,232 Dutch pregnant women, the Focus cohort, which is ethnically homogeneous, to exclude confounding or effect modification by ethnicity. No other inclusion or exclusion criteria for participation in the Focus cohort were used. All children were born between February 2003 and August 2005 and formed a prenatally enrolled birth cohort.

The study was approved by the Medical Ethics Committee of Erasmus Medical Center, Rotterdam. Written informed consent was obtained from all adult participants.

Study population

A total of 1,232 women and their children were enrolled in the Generation R Focus Study during pregnancy. We excluded twin pregnancies \((n = 15)\) and pregnancies leading to perinatal death \((n = 2)\). Moreover, we randomly excluded 1 child of each sibling pair \((n = 19)\) to avoid bias due to paired data. Of the remaining 1,196 fetuses, interpretable Doppler measurement of the umbilical artery and cerebral arteries was performed in 1,135. Information on behavioral and emotional problems occurring between the ages of 17.5 months and 22 months was available for 935 \((82\%)\) of these children.

Fetal circulation

Three trained sonographers carried out fetal ultrasound examinations in late pregnancy (median gestational age, 30 weeks). Online measurements included Doppler measurements of the umbilical artery and the anterior and middle cerebral arteries (24). The umbilical artery pulsatility index was measured in a free-floating loop of the umbilical cord. Measurements of the middle and anterior cerebral artery pulsatility indices were performed with color Doppler visualization of the circle of Willis in the fetal brain. For reliability analyses, intraclass correlation coefficients between and among observers were calculated in 12 subjects. Intraobserver intraclass correlation coefficients varied from 0.93 to 0.98, and interobserver intraclass correlation coefficients varied from 0.82 to 0.91 for the Doppler measurements (24). During the ultrasound examination, several fetal growth measurements, including head circumference and abdominal circumference, were assessed using standardized procedures. In line with other reports on fetal brain sparing (20, 21, 25–28), we calculated the U/C ratio by dividing the pulsatility index of the umbilical artery by the pulsatility index of one of the cerebral arteries. Although mothers and their caregivers were informed about clinically relevant findings such as small-for-gestational-age birth, pregnant women were not informed of the results of the Doppler examinations.

Child behavioral and emotional problems

The Child Behavior Checklist (29) for toddlers (ages 18 months to 5 years) was used to obtain standardized parental reports of children’s problem behaviors. This questionnaire contains 99 problem items, which are scored with regard to 7 empirically based syndromes that were derived by factor analyses: Emotionally Reactive, Anxious/Depressed, Somatic Complaints, Withdrawn, Sleep Problems, Attention Problems, and Aggressive Behavior. The summary Internalizing scale is a summary score for items on the first 4 syndrome scales, and the Externalizing scale is a summary score for Attention Problems and Aggressive Behavior. The sum for all 99 problem items is the Total Problems score. Each item is scored 0, 1, or 2 \((0 = \text{not true}, 1 = \text{somewhat or sometimes true}, \text{and } 2 = \text{very true or often true})\) on the basis of the child’s behavior during the preceding 2 months. Good reliability and validity have been reported for the Child Behavior Checklist (29). For homogeneity, we included only children in the age range between 17.5 months and 22 months. To investigate the possibility of a “floor effect,” we used data on a Dutch norm sample of 669 children aged 12–60 months (30). Comparing children younger \((n = 79)\) and older than 24 months, we found that younger children on average scored lower on the Internalizing, Emotionally Reactive, Somatic Complaints, and Attention Problems scales. However, the percentage of children scoring at or near the minimum possible score was not statistically significantly smaller in the younger age group than in the older age group. Within our sample, the percentages of children scoring at or near the minimum possible score were 18.7% for Total Problems, 11.0% for Internalizing, 9.8% for Externalizing, 38.1% for Emotionally Reactive, 48.4% for Anxious/Depressed, 32.3% for Somatic Complaints, 60.3% for Withdrawn, 43.3% for Sleep Problems, 22.9% for Attention Problems, and 7.4% for Aggressive Behavior.

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Covariates

Data on gestational age, birth weight, gender, Apgar scores 1 and 5 minutes after birth, infant’s umbilical artery blood pH, and hypertensive complications of pregnancies were obtained from midwife and hospital registries at birth. We established gestational age by using the fetal ultrasound examinations within the Generation R Study. Maternal age, maternal height, and maternal educational level were determined at enrollment. To assess maternal psychopathology in midpregnancy, we used the Brief Symptom Inventory (31, 32). Maternal smoking and alcohol use during pregnancy were assessed using 3 prenatal questionnaires. Postnatal questionnaires administered at ages 6, 12, and 24 months gathered information on breastfeeding, hospitalization of the child, and visits to physicians.

Statistical analyses

We calculated standard deviations (SDs) for the U/C ratios for the middle and anterior cerebral arteries. The Child Behavior Checklist summary and syndrome scales were dichotomized, since the resulting scores were right-skewed and could not be transformed to satisfy the assumption of normality. Primarily, we defined a nonoptimal score as the highest 15% of problem item scores. As a test of consistency, we additionally examined results for Total Problems using the highest 25% and highest 10% of scores as cutoff points for behavioral problems.

Differences in baseline characteristics between children in the top 15% of Total Problems and children without behavioral problems were compared with independent t tests for normally distributed continuous variables, Mann-Whitney U tests for non-normally distributed continuous variables, and chi-squared statistics for categorical variables.

We used linear regression models and logistic regression models to test the associations between SD scores of measures of fetal circulatory redistribution, on the one hand, and growth measures and behavioral problems on the other hand. All covariates were adjusted for gender and age. The other covariates were selected as a result of exploratory analyses and were included in the models if the effect estimate changed meaningfully (defined as more than 5%). Measures of association are presented with 95% confidence intervals. Statistical analyses were carried out using the Statistical Package for the Social Sciences, version 11.0 for Windows (SPSS, Inc., Chicago, Illinois).

Response analysis

Analyses of missing behavioral outcome data showed that mothers of children without information on behavior were 2.1 years younger (95% confidence interval (CI): 1.3, 2.8; \( t = 5.2, P < 0.001 \)), less educated (percent with a university-level education, 25.1 vs. 39.1; \( \chi^2 = 13 \) (1 df), \( P < 0.001 \)), more often continued to smoke during pregnancy (prevalence of 26.4% vs. 11.2%; \( \chi^2 = 32 \) (1 df), \( P < 0.001 \)), and had higher total psychopathology symptom scores (median score of 0.1 (95% range, 0–1.4) vs. 0.1 (95% range, 0–0.7); Mann-Whitney U test: \( P = 0.003 \)) compared with mothers of children with behavioral information. Children with and without behavioral information did not differ in terms of blood-flow parameters for the umbilical and cerebral arteries, birth weight, gestational age at birth, or hospitalization.

RESULTS

Table 1 compares demographic characteristics and potentially confounding variables for the 135 children who showed problem behavior at the age of 18 months and the 800 children who had no behavioral problems. Children with a high score on Total Problems were more often first-born than children with a normal Total Problems score. Maternal psychopathology was also significantly higher in children with behavioral problems than in children without behavioral problems.

The unadjusted and adjusted associations between measures of fetal circulatory redistribution and growth measures are presented in Table 2. For each SD increase in the U/C ratio for the middle cerebral artery, birth weight was 78 g lower and, adjusted for gestational age, 0.14 SDs lower. Similarly, a higher U/C ratio for the anterior cerebral artery was related to lower birth weight. Furthermore, a higher U/C ratio was related to a smaller ratio of abdominal circumference to head circumference.

Table 3 shows the relation between fetal circulatory redistribution and the summary scales of the Child Behavior Checklist. The U/C ratio of the anterior cerebral artery was related to Total Problems and to internalizing problems. A higher U/C ratio for the middle cerebral artery was related to a higher score only on the summary Internalizing scale. Fetal circulatory redistribution did not predict externalizing problems. Odds ratios for the Internalizing scale were not significantly different from odds ratios for the Externalizing scale (for the middle cerebral artery, the mean difference in log odds ratios was 0.12, 95% CI: \(-0.14, 0.37 (P = 0.3\)); for the anterior cerebral artery, the mean difference in log odds ratios was 0.10, 95% CI: \(-0.18, 0.37 (P = 0.5\)). The odds ratios for statistically significant associations were all 1.2 per SD increase in U/C ratio. When analyses were repeated after dichotomization of the determinant on the upper 15% of U/C ratio, the effect size amounted to an odds ratio of 2.11 (95% CI: 1.27, 3.49; \( P = 0.004 \)).

Confounding variables that changed the effect estimates more than 5% were gestational age at birth, birth weight, birth order, maternal educational level, maternal psychopathology, and physician consultations. Although we found no indication that birth weight was directly related to behavioral problems (for Total Problems, per 1-kg increase in birth weight, unadjusted odds ratio (OR) = 1.32, 95% CI: 0.93, 1.88; \( P = 0.13 \)), inclusion of birth weight in the model changed the effect estimates for fetal circulatory redistribution meaningfully. Maternal smoking was not a confounding variable in the association between U/C ratio and behavioral outcome. When mothers smoked during pregnancy, the U/C ratio for the middle cerebral artery was 0.02 SDs lower (95% CI: \(-0.19, 0.15 \); \( P = 0.8 \)), whereas the U/C ratio for the anterior cerebral artery was 0.12 SDs higher (95% CI: \(-0.06, 0.28 \); \( P = 0.2 \)). Since maternal smoking also was
not related to behavioral outcome (Table 1) and did not change the effect estimates meaningfully, it was excluded from the final models in Table 3. Similarly, pregnancy complications such as maternal hypertension or maternal pre-eclampsia did not confound the association between U/C ratio and problem behavior (data not shown).

Additionally, we examined whether a measure of asymmetrical growth—that is, the ratio between abdominal circumference and head circumference at 30 weeks of gestation—was related to behavioral outcome. The odds ratio for Total Problems per SD increase in the ratio of abdominal circumference to head circumference was 1.11 (95% CI: 0.90, 1.37; $P = 0.3$). Similarly, we found no indication that the ratio of abdominal circumference to head circumference was related to internalizing (OR = 1.12, 95% CI: 0.91, 1.38; $P = 0.3$) or externalizing (OR = 1.08, 95% CI: 0.88, 1.32; $P = 0.5$) of problems. When Total Problems score was dichotomized at the 75th or 90th percentile, the odds ratios per SD increase in anterior cerebral artery U/C ratio were 1.20 (95% CI: 1.01, 1.41; $P = 0.03$) and 1.22 (95% CI: 0.97, 1.54; $P = 0.09$), respectively.

Ten fetuses were small for gestational age (<−2 SDs) at 30 weeks of gestation; exclusion of these fetuses did not materially change the effect estimates.

Next, we analyzed the association between fetal circulatory redistribution and specific syndrome scales of the Child Behavior Checklist (Table 4). Fetal redistribution to the anterior cerebral artery was significantly related to 3 subscales of the Child Behavior Checklist. Per SD increase in U/C ratio, the odds for having high scores on the Emotionally Reactive scale were 26% higher. Secondly, a higher anterior cerebral artery U/C ratio also made it more likely that infants would have attention problems or somatic complaints; the increases in odds were 26% and 23%, respectively. Fetal redistribution to the middle cerebral artery was related only to Somatic Complaints (per SD increase in U/C ratio, OR = 1.23, 95% CI: 1.03, 1.47). Physician consultation only marginally accounted for this association.

**DISCUSSION**

The main finding of this study was that signs of fetal brain sparing were associated with infant problem behavior.
Children with fetal circulatory redistribution to the anterior cerebral artery had higher risks of total problems and internalizing problems at the age of 18 months. This preferential perfusion of the frontal lobes during pregnancy was also related to higher scores on the syndrome scales Emotional Reactivity, Somatic Complaints, and Attention Problems. The association between preferential perfusion of the middle cerebral artery and problem behavior was less evident. We found no indication that the effects were specific for internalizing, since the effect estimates for the Internalizing and Externalizing scales were not significantly different.

The present study shows, in line with an earlier report (25), that measures of fetal circulatory redistribution are strong predictors of lower birth weight. Furthermore, Doppler signs of circulatory redistribution were associated with a smaller ratio of abdominal circumference to head circumference, indicating a relative sparing of the growth of the fetal head in a suboptimal environment. However, we found

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<th>Measure of Fetal Circulatory Redistribution</th>
<th>Birth Weight, g</th>
<th>Birth Weight (g) Adjusted for Gestational Age^b</th>
<th>Fetal AC/HC Ratio at 30 Weeks of Gestation^b</th>
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<td>^a Values presented are odds ratios from logistic regression models. Odds ratios from models A were unadjusted, and odds ratios from models B were adjusted for gender, age, gestational age at birth, birth weight, birth order, maternal educational level, maternal psychopathology, and child hospitalization/physician consultations. ^b Standard deviation scores, adjusted for gestational age. ^c Ratio between the umbilical artery pulsatility index and the middle cerebral artery pulsatility index.</td>
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<td>^a Values presented are regression coefficients from linear regression models. Regression coefficients from models A were unadjusted. Regression coefficients from Models B were adjusted for gender, birth order, maternal height, maternal smoking during pregnancy, maternal hypertension, and maternal preeclampsia.</td>
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Abbreviations: AC/HC ratio, abdominal circumference/head circumference ratio; CI, confidence interval; SD, standard deviation; U/C, umbilical/cerebral.

* P < 0.05.
Our findings show that signs of brain sparing in the anterior emotional, cognitive, and motivational processes (39, 40) protects the frontal region of the brain, which is involved in higher-order brain functions and the cerebral arteries (35). Several other studies identified using blood flow parameters of the umbilical artery (36, 37). Animal studies provided information on abnormalities in brain structure and function after unilateral ligation of the maternal uterine artery (10, 22, 38). This work suggests that the goal, to prevent cerebral hypoxia, cannot always be achieved by brain sparing. In other words, the brain is protected at the cost of other organs, but fetal circulatory redistribution does not necessarily spare the brain in absolute terms.

Earlier studies directly related blood flow parameters of brain sparing to visual, neuromotor, and cognitive outcomes in clinical populations. Scherjon et al. (26) found that children with fetal brain-sparing may have accelerated myelination of visual pathways during the first year of life, but they could not demonstrate a difference in visual function at age 11 years (28). Moreover, although gross neuromotor outcome at age 3 years was not affected by fetal circulatory redistribution (27), brain-sparing had a detrimental effect on cognitive outcome at 5 years of age (21). These findings seem contradictory and were not replicated in other studies. Since the authors used different endpoints in time and different outcome measures, it is difficult to interpret the results. Chronic fetal hypoxia may adversely affect specific brain regions, whereas other regions are spared. Dubiel et al. (35) suggested that the redistribution of fetal cerebral blood flow in the presence of chronic hypoxia preferentially protects the frontal region of the brain, which is involved in emotional, cognitive, and motivational processes (39, 40). Our findings show that signs of brain sparing in the anterior cerebral artery were related to a higher risk of attention problems and emotional reactivity, which may indicate less mature frontal-subcortical circuitry (39). Cautiously interpreting our results and the results of the clinical studies of Scherjon et al. (26), those parts of the brain that are involved in higher-order brain functions may be more vulnerable to hypoxemia. Although the fetal adaptive mechanism serves to protect the frontal regions at the expense of temporal and occipital regions in case of chronic fetal hypoxia, cognitive and behavioral functioning may be affected earlier than visual and motor function. Further research into the effects of fetal circulatory redistribution on several neurobehavioral outcomes at similar endpoints in time is needed to strengthen this hypothesis.

Some methodological considerations need to be discussed. First, our sample represented predominantly children with low vulnerability to emotional and behavioral problems, probably because of favorable environmental characteristics. However, this selection also yields advantages, since effects of confounding are smaller in a more homogeneous group. Next to selective nonresponse, selective loss to follow-up of healthier mothers could lead to bias. We found no indication that children with intrauterine growth restriction or raised U/C ratios were more often lost to follow-up. Multiple imputation methods could not be used to complete data on the outcome, since for children with missing data on the outcome, highly related information (e.g., information on temperament at younger ages) was not available. Therefore, the possibility of biased results due to selective attrition cannot be ruled out. Second, we used the Child Behavior Checklist to assess toddler behavior. Although the Child Behavior Checklist has been shown to have good reliability and validity from age 18 months onwards, we used this questionnaire at the lower boundary of its age frame. Although younger children in a Dutch norm sample on average score lower on several subscales, we found no indication that a higher number of children score at or near the minimum possible score. Both in the Dutch norm group and in our sample, there is a considerable floor effect; that is, many children score at or near the minimum possible score. Therefore, the Child Behavior Checklist...
scores were dichotomized at the level of the highest 15%. It is unlikely that the lack of variance in the lower boundaries of the scales influenced our findings. Using a parent-report measure might introduce reporter bias. Differential misclassification of the outcome is less likely, since mothers were blinded to the results of the Doppler velocimetry. Exclusion of small-for-gestational-age fetuses at 30 weeks of gestation did not materially change the effect estimates. Furthermore, we adjusted our associations for maternal symptoms of psychopathology, which are known to color the reporting of actual child behavior (41). Third, residual confounding is a potential limitation. We were able to rule out the possibility that our associations were explained by prematurity, sociodemographic variables, maternal smoking during pregnancy, or medical complications after birth. Although medical complications after birth and maternal psychological symptoms did not fully explain our results, maternal health concerns could be a possible residual confounder. Finally, as indicated by the small-to-moderate effect sizes, the possibility of chance findings cannot be ruled out, although associations were consistent when using different cutoff points.

In conclusion, the brain-sparing mechanism does not protect the child from all neurodevelopmental problems. Infants who experience circulatory redistribution with preferential perfusion of the brain in utero are more likely to have behavioral and emotional problems in young childhood. Our findings suggest that the U/C ratio is a sensitive marker of fetal growth restriction in which the fetal head is relatively spared and is a risk indicator for behavioral outcome. Further research is needed to evaluate the consequences of fetal circulatory redistribution for cognitive and behavioral development at preschool age and school age.

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Author affiliations: Generation R Study Group, Erasmus University Medical Center, Rotterdam, the Netherlands (Sabine J. Roza, Bero O. Verburg, Vincent W. V. Jaddoe); Department of Child and Adolescent Psychiatry, Erasmus University Medical Center, Rotterdam, the Netherlands (Sabine J. Roza, Frank C. Verhulst, Henning Tiemeier); Department of Obstetrics and Gynecology, Erasmus University Medical Center, Rotterdam, the Netherlands (Eric A. P. Steegers, Bero O. Verburg); Department of Pediatrics, Erasmus University Medical Center, Rotterdam, the Netherlands (Vincent W. V. Jaddoe, Albert Hofman, Henning Tiemeier); Department of Child and Adolescent Psychiatry, Erasmus University Medical Center, Rotterdam, the Netherlands (Bero O. Verburg, Vincent W. V. Jaddoe); Department of Epidemiology, Erasmus University Medical Center, Rotterdam, the Netherlands (Vincent W. V. Jaddoe, Henriette A. Moll); and Department of Pediatrics, Erasmus University Medical Center, Rotterdam, the Netherlands (Vincent W. V. Jaddoe, Albert Hofman, Henning Tiemeier).

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REFERENCES


