OBSTETRICS

Prenatal head growth and child neuropsychological development at age 14 months

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OBJECTIVE: We sought to assess the association between prenatal head growth and child neuropsychological development in the general population.

STUDY DESIGN: We evaluated 2104 children at the age of 14 months from a population-based birth cohort in Spain. Head circumference (HC) was measured by ultrasound examinations at weeks 12, 20, and 34 of gestation and by a nurse at birth. Head growth was assessed using conditional SD scores between weeks 12-20 and 20-34. Trained psychologists assessed neuropsychological functioning using the Bayley Scales of Infant Development. Head size measurements at birth were transformed into a 3-category variable: microcephalic (<10th percentile), normocephalic (≥10th and <90th percentile), and macrocephalic (≥90th percentile) based on the cohort distribution. *P* values < .05 were considered statistically significant.

RESULTS: No overall associations were observed between HC or head growth and mental and psychomotor scores. In particular, no associations were found between HC at birth and mental scores (coefficient, 0.04; 95% confidence interval, −0.02 to 0.09) and between interval head growth (20-34 weeks) and mental scores (0.31; 95% confidence interval, −0.36 to 0.99). Upon stratification by microcephalic, normocephalic, or macrocephalic head size, results were imprecise, although there were some significant associations in the microcephalic and macrocephalic groups. Adjustment by various child and maternal cofactors did not affect results. The minimum sample size required for present study was 883 patients ($\beta = 2$, $\alpha = 0.05$, power = 0.80).

CONCLUSION: Overall prenatal and perinatal HC was not associated with 14-month-old neuropsychological development. Findings suggest HC growth during uterine life among healthy infants may not be an important marker of early-life neurodevelopment but may be marginally useful with specific populations.

Key words: cognitive functions, head circumference, neurodevelopment, neuropsychological development, population-based study, prenatal growth

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The association between early life factors and child development has received increasing attention. Complex conditions and pathologies such as maternal and fetal undernutrition,[1] prematurity, and small body size at birth[2,3] may lead to adverse effects on neuropsychological development, which may in turn reduce the chances of the child to fully develop.[4]

Repeated head circumference (HC) assessments during development are known to be correlated with changes in brain volume. Proxy indicators of brain volume are rarely measured in population studies, in which cognitive development is the usual outcome.[5] The relationship between HC and neurodevelopment has been explored with inconclusive results, some studies reporting null associations[5-14] and others positive associations.[15-20] However, most of the previous research has focused on special populations, such as infants with fetal growth restriction,[6,7,14] spina bifida,[8] or low gestational age.[9,10] These infants may be at higher risk compared to those in the general population for developing various neurological disorders, such as cerebral palsy, hydrocephalus, blindness, deafness, and seizures.[11,12]

Previous general population studies have tended to report positive associations, although others were inconclusive.[13-20] However, most of the HC measurements in these studies were conducted at birth or during the postnatal period and child neurodevelopment assessed at ages usually >56 months. Large studies are also needed to further stratify analyses into normocephalic, microcephalic, and macrocephalic categories, in which we may expect to observe different association trajectories, since some studies observed an inverse U-shaped association between birthweight and cognitive performance.[2]

Little is known about the importance of brain growth during different periods of prenatal and postnatal development. Determinants of prenatal growth may differ from those at older ages. For example, maternal nutrition habits, stress, and complications during pregnancy could affect brain growth during this period and family environment could play a role on brain volume in postnatal periods.[5] Gale et al[5] (2004) conducted prenatal HC measurements in a longitudinal study of maternal nutrition during pregnancy and observed no association with neuropsychological development at age 9 years, contrary to the positive associations observed with postnatal HC measurements. Another cohort study detected that slow prenatal and postnatal HC growth was associated with poorer intellectual functioning in young adulthood.[17]

The aim of this study was to assess whether prenatal head growth and HC at birth were prospectively associated with child neuropsychological development at age 14 months in a large population-based birth cohort.

Materials and Methods

This study was based on 4 cohorts (Asturias province, Gipúzcoa province, Sabadell city, and Valencia city) of the larger Infancia y Medio Ambiente (Environment and Childhood) (INMA) Project. Patient recruitment and follow-up procedures have been reported in detail elsewhere.[21] A total of 2644 eligible pregnant women agreed to participate and met the inclusion (≥16 years of age, singleton pregnancy, intention to deliver at the reference hospital) and exclusion (no communication handicap, no fetuses with malformations, no assisted conception) criteria. Women were followed-up during pregnancy and their children enrolled at birth and followed up until age 14 months. After excluding women who withdrew, were lost to follow-up, or underwent abortions or fetal deaths, a total of 2506 pregnant women were monitored through delivery. The final study sample included 2104 children with complete data on HC measurements and Bayley mental and motor scores. Both preterm (<37 weeks of gestation) and term children were included. All women provided written informed consent prior to participating in the study and the research protocol was approved by the clinical research ethics committee of the Municipal Institute of Health Care, Barcelona, Spain. The revised version of Helsinki declaration was followed. The ethics committees of the individual study centers also provided approval. All data were entered by the data manager of INMA Project (http://www.proyectoinma.org/en_index.html).

Ultrasound examinations for all women were scheduled in weeks 12, 20, and 34 of gestation. Measurements of HC were performed by trained obstetricians. We also had access to the records of any other ultrasound performed in the same hospital unit during pregnancy, thus allowing us to obtain from 2-7 valid ultrasonograms per woman between 7-42 weeks of gestation. Gestational age was established using early crown-rump length when the difference with gestational age based on self-reported last menstrual period was ≥7 days. Data in which this difference was >3 weeks or ±4 SD from the study mean were eliminated (n = 16) to avoid possible bias due to typographical errors in scan records or last menstrual period data. All measurements were performed in millimeters, obtained by transabdominal ultrasound examination (Voluson 730 Pro and 730 Expert; Siemens, Berlin, Germany) and followed standardized procedures. Ultrasonographists conducted a validation study in the Sabadell cohort to determine interobserver reliability. Intraclass correlation coefficients were in the range of 0.80−0.91 and coefficients of variation were <5%.[22] Infant HC at birth was assessed by a nurse when the newborn arrived to the hospital ward within the first 12 hours of life.

Linear mixed models[23] using the Hadlock algorithm[24] were used to obtain longitudinal growth curves for HC. Box-Cox transformations were used to normalize the distribution and were modeled as a polynomial of gestational age in days until degree 3. Physiological determinants of growth and their interactions with gestational age were evaluated using the likelihood ratio test ($P < .05$) through a forward selection procedure. Models were adjusted for physiological factors known to affect fetal growth to get an individualized