OBSTETRICS

Fetal growth restriction and risk of cerebral palsy in singletons born after at least 35 weeks' gestation

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OBJECTIVE: The objective of the study was to improve the understanding of etiological paths to cerebral palsy (CP) that include fetal growth restriction by examining factors associated with growth restriction that modify CP risk.

STUDY DESIGN: In a total population of singletons born at or after 35 weeks, there were 493 children with CP and 508 matched controls for whom appropriateness of fetal growth could be estimated. Fetal growth was considered markedly restricted if birthweight was more than 2 SD below optimal for gender, gestation, maternal height, and parity. We examined maternal blood pressure in pregnancy, smoking, birth asphyxia, and major birth defects recognized by age 6 years as potential modifiers of CP risk in growth-restricted births.

RESULTS: More than 80% of term and late preterm markedly growth-restricted singletons were born following a normotensive pregnancy and were at statistically significantly increased risk of CP (odds ratio, 4.81; 95% confidence interval, 2.7—8.5), whereas growth-restricted births following a hypertensive pregnancy were not. Neither a clinical diagnosis of birth asphyxia nor potentially asphyxiating birth events occurred more frequently among growth-restricted than among appropriately grown infants with CP. Major birth defects, particularly cerebral defects, occurred in an increasing proportion of CP with increasing growth deficit. The factor most predictive of CP in growth-restricted singletons was a major birth defect, present in 53% of markedly growth-restricted neonates with later CP. Defects observed in CP were similar whether growth restricted or not, except for an excess of isolated congenital microcephaly in those born growth restricted. The highest observed CP risk was in infants with both growth restriction and a major birth defect (8.9% of total CP in this gestational age group, 0.4% of controls: odds ratio, 30.9; 95% confidence interval, 7.0—136).

CONCLUSION: The risk of CP was increased in antenatally growth-restricted singletons born at or near term to normotensive mothers. In growth-restricted singletons, a major birth defect was the dominant predictor, associated with a 30-fold increase in odds of CP. Identification of birth defects in the growth-restricted fetus or neonate may provide significant prognostic information.

Key words: birth asphyxia, birth defects, pregnancy-induced hypertension, smoking, term and late preterm birth

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Suboptimal fetal growth is associated with a heightened risk of a range of adverse outcomes of pregnancy, including antenatal or neonatal death, neonatal encephalopathy, perinatal stroke, cerebral palsy, epilepsy, autism, and schizophrenia. The association of fetal growth restriction (FGR) with cerebral palsy (CP) has been especially robust.[1-8] Defined as a birthweight greater than 2 SD below optimal, FGR contributes a larger proportion of CP in term and late preterm singletons than do potentially asphyxial birth events or inflammation or a combination of those risk factors.[9]

Much of the literature has considered FGR as a unitary entity, varying chiefly in severity and gestational duration at onset. The etiology of FGR is known to be varied, however,[10] and some reports distinguish growth deficit arising in normotensive from that in hypertensive pregnancies.[11-13]

Pregnancy-induced hypertension (PIH), which includes preeclampsia, is a recognized antecedent of growth deficit and an important cause of maternal morbidity and mortality and fetal loss, but it is not clear whether PIH is an important antecedent of CP in FGR births. Maternal smoking is the most frequent antecedent of FGR in population studies,[14] but whether it influences CP risk differently from FGR associated with other antecedents is not known.

Given the paucity of information on whether differing antecedents of FGR

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influence neurological outcome, we examined the data of a large population-based study of births from 1980 to 1995 for a relationship between CP with FGR and its major known risk factors: PIH, smoking, acute asphyxial birth, and major birth defects. We focused on singleton births after at least 35 weeks' gestation because, although they contribute to 75% of all CP, their outcomes have received less attention and because the rates of term and late preterm CP have not changed since these data were collected.

Materials and Methods

The population-based case-control study providing the data for this report was designed to investigate factors associated with risk of CP,[9,15-17] defined as a disorder of movement and/or posture and motor function because of a nonprogressive interference/lesion or abnormality of the developing brain. Persons registered with the Western Australian Register of Developmental Anomalies—Cerebral Palsy[18] were selected if born between Jan. 1, 1980, and Dec. 31, 1995, excluding those whose CP was acquired postneonatally or resulted in minimal motor impairment.

Controls and perinatal deaths were selected from the 380,918 births between 1980 and 1995 registered on the Maternal Child Health Research Database, which links statutory birth and death registries with statutory pregnancy and delivery information and includes more than 99.5% of registered births in Western Australia. Neonatally surviving controls not registered as CP were individually matched to CP cases for gestational age (within 1 week), date of birth (within 12 months), and plurality. Representative samples of intrapartum stillbirths and neonatal deaths (live births dying within 28 days) were selected by taking 7 and 4 year birth cohorts, respectively,[9] distributed within the 1980-1995 period.

Information was sought concerning pregnancy, delivery, neonatal, family, and maternal obstetric history from medical records of the hospitals of delivery and neonatal care and private obstetricians or general practitioners who provided antenatal care. These data were recorded by trained midwives or neonatal nurses.[16] Analyses of FGR included singleton births and focused on children with CP and controls born after at least 35 weeks' gestation.

Appropriateness of fetal growth was assessed with the proportion of optimal birthweight (POBW). This method compares the index birthweight with the median estimated weight of fetuses of the same gestational age subsequently live born at term to women without recorded exposure to common factors known to affect fetal growth and of the same height and parity as the index mother.[14,19]

Fetal growth was categorized as mild if POBW was less than 85% (about the 10th percentile of all Western Australian live births) and marked if POBW was 77.3% or less (2 SD below the median of the optimally grown population, approximately the fifth percentile of all Western Australian live births) or, to minimize false-negative results, had been diagnosed neonatally as growth restricted.

PIH was defined as blood pressure reaching or exceeding 140/90 mm Hg, a systolic rise of 20 mm Hg, or a diastolic rise of 15 mm Hg during pregnancy. As found with other adverse perinatal outcomes,[20] the presence of proteinuria did not affect the risk of CP associated with PIH and was not considered further.

Women were classified as smokers in pregnancy if they were reported to smoke after 20 weeks' gestation; this datum was missing for about one-third of study subjects. The number of cigarettes smoked daily before and after 20 weeks' gestation was also recorded if available (83% of smokers). Alcohol and recreational drug use was noted if recorded, but gross underreporting is likely.

Data concerning defects present at birth and recognized at any time before 6 years of age were obtained by linking with the Western Australian Register of Developmental Anomalies—Birth Defects,[21] which records up to 10 diagnoses of birth defects together with the age at which each diagnosis was made. For this analysis birth defects were categorized hierarchically as cerebral defects; cardiac defects; other major defects; and deformational defects and minor defects (which included cosmetic defects and those unlikely to affect physical quality of life). Major defects excluded exclusively minor defects. Because CP is defined by motor disorders not present at birth, it was not considered a birth defect. Recorded teratogenic exposures and chromosomal or genetic defects were classified separately.

Sentinel events were defined as intrapartum events likely to enhance the potential for fetal asphyxia and included significant intrapartum hemorrhage, cord prolapse, uterine rupture, a tight nuchal cord, shoulder dystocia, and maternal collapse. A clinical diagnosis of birth asphyxia or hypoxic ischemic encephalopathy in the medical record was noted.

The risks of CP were estimated for each growth, PIH, and maternal smoking stratum for singleton births after at least 35 weeks of gestation. Associations were sought between CP within high-risk strata for major birth defects, sentinel events, a clinical diagnosis of birth asphyxia, and recreational drug use.

Statistical analysis

SAS version 9.3 (SAS Institute, Cary, NC) was used to generate descriptive statistics and odds ratios estimated from a conditional logistic regression, which effectively adjusts for the matching variables of gestational duration (within 1 week) and year of birth (within 12 months).

This study was approved by the Princess Margaret Hospital/King Edward Memorial Hospital Ethics Committee, the Confidentiality of Health Information Committee of the Western Australia Department of Health, individual hospital and regional ethics committees, the University of Sydney Human Research and Ethics Committee, and the Confidentiality of Health Information Committee of the Western Australia Department of Health, whose documents can be provided on request. All waived the requirement for individual patient consent.

Results

Among the 386,159 infants born in Western Australia from 1980 through

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