Pediatric Neurology 74 (2017) 68–73

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Article

Gender Affects Long-Term Neurological Outcome of Neonates

Amir Freud MD [a,*], Eyal Sheiner MD, PhD [a], Tamar Wainstock PhD [b], Daniella Landau MD [c], Asnat Walfisch MD [a]

[a] *Department of Obstetrics and Gynecology, Soroka University Medical Center, Ben-Gurion University of the Negev, Beer-Sheva, Israel*
[b] *Department of Public Health, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel*
[c] *Department of Pediatrics, Soroka University Medical Center, Ben-Gurion University of the Negev, Beer-Sheva, Israel*

ABSTRACT

OBJECTIVE: We evaluated the possible association between fetal gender and long-term pediatric neurological morbidity. **METHODS:** We performed a population-based retrospective cohort analysis comparing the risk of long-term neurological morbidity (up to age 18 years) of children born during the years 1991 to 2013 according to their gender. Neurological morbidity evaluated included hospitalizations in childhood involving pervasive developmental disorder, obstructive sleep apnea, cerebral palsy, epilepsy, and infantile spasms and disorders of eating as recorded in the hospital files. Multiple pregnancies and fetal congenital malformations were excluded. Kaplan-Meier survival curves were constructed to compare the cumulative neurological morbidity over the study period. A Cox proportional hazards model was used to control for obstetrical confounders, including gestational age at birth, birth weight, and maternal factors. **RESULTS:** During the study period, 240,953 newborns were included in the long-term analysis: 51.0% (n = 122,840) males and 49.0% (n = 118,113) females. Hospitalizations for neurological problems (up to age 18 years) were significantly more common in males compared with females (1.1% vs 0.8%, respectively, odds ratio 1.31, 95% confidence interval 1.2 to 1.4, $P < 0.001$). Specifically, pervasive developmental disorder and obstructive sleep apnea were found to be significantly more common in males, and cerebral palsy reached borderline significance (0.1% vs 0.04%, odds ratio 1.39, 95% confidence interval 0.9 to 1.9, $P = 0.06$). The Kaplan-Meier survival curves demonstrated males to have a significantly higher cumulative incidence of total neurological morbidity as well as of pervasive developmental disorder and obstructive sleep apnea (all log-rank test P values <0.001). In the Cox regression model, male gender exhibited an independent association with long-term neurological morbidity, while adjusting for birth weight, gestational age, and other confounding variables (adjusted hazard ratio 1.29, 95% confidence interval 1.2 to 1.4, $P < 0.001$). **CONCLUSION:** Males are at an increased risk for pediatric neurological morbidity independent of gestational age at birth and birth weight.

Keywords: pregnancy, gender, epidemiology, boys, outcome

Pediatr Neurol 2017; 74: 68-73

Introduction

Genetics, inheritance, and cumulative exposures throughout life impact one's general health in multiple ways. Some of these effects have been shown to originate from as early as embryonic life.[1-3] Numerous studies demonstrated adult disease to be deeply influenced by events that occur in the uterus. Classical examples include maternal gestational diabetes mellitus and later offspring health,[4,5] as well as fetal growth restriction and later metabolic syndrome in adult life.[6,7] Offspring of mothers with gestational diabetes mellitus possess a higher risk for future obesity and abnormal glucose

Conflicts of interest: The authors have no conflicts of interest relevant to this article to disclose. We confirm that no honorarium, grant, or other form of payment was given to anyone to produce the manuscript.

Article History:
Received February 25, 2017; Accepted in final form April 17, 2017

* Communications should be addressed to: Dr. Freud; Department of Obstetrics and Gynecology; Soroka University Medical Center; POB 151; Beer-Sheva 84101, Israel.
E-mail address: amirfreud@gmail.com

0887-8994/$ – see front matter © 2017 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pediatrneurol.2017.04.020

metabolism during childhood, adolescence, and adulthood as well as for neurological morbidity.[4,5] Similarly, intrauterine growth restriction is associated with the development of obesity, hypertension, and diabetes in the offspring.[6,7]

Prematurity is another example of an obstetrical event with a dramatic impact on later offspring health, with neurodevelopmental handicap being a major concern.[8] Preterm infants frequently experience long-term cognitive morbidity and exhibit lower mean IQ scores.[8,9]

The notion that fetal gender may affect his or her pregnancy course and future health has been explored in several studies. Male gender has been shown to be an independent risk factor for adverse pregnancy outcome such as delivery complications (including labor dystocia, cord pathologies, and fetal distress) and several other immediate adverse perinatal outcomes such as lower Apgar scores and lower umbilical pH values.[10-14] Moreover, an association between male gender and abnormal fetal heart rate patterns has also been suggested.[15-19] Another study found that male newborns are at an increased risk for pediatric cardiovascular morbidity.[20] A leading hypothesis for these gender differences is related to different patterns of fetal growth. Male fetuses grow faster than female fetuses from an early stage of gestation and perhaps even before implantation.[21] This accelerated growth is likely to make them more vulnerable if nutrition is compromised. Thus more newborn boys exhibit growth restriction and placental pathologies, and perinatal mortality rates are higher compared with girls.[11,22]

As for later neurological health, there are notable gender differences in the incidence and manifestations of virtually all central nervous system disorders.[23] Among childhood neurological diseases, it is suggested that pervasive development disorder cerebral palsy and obstructive sleep apnea are more common in males,[24-27] however, it is unclear whether the association is because of the gestational age or other confounders such as birth weight and maternal pregnancy complications.[28,29]

As male gender is significantly related to several pregnancy and delivery complications, we sought to establish whether long-term neurological health of the male offspring is merely a result of these complications, or that gender itself has a role, independent of pregnancy course and immediate outcome. This study was designed to explore the possibility of an independent association between fetal gender and long-term pediatric neurological morbidity while accounting for a large set of pregnancy and delivery characteristics including gestational age at birth, birth weight, and maternal pregnancy complications.

Materials and Methods

A retrospective cohort analysis was performed comparing the risk for long-term neurological diagnoses (up to age 18 years) according to the offspring's gender. Deliveries occurred during the years of 1991 to 2013. The study was conducted at the Soroka University Medical Center (SUMC). This center is the sole hospital in the Negev (southern Israel), which occupies 60% of the land of Israel, and is serving the entire population of the region (14.4% of Israel's population, totaling over one million inhabitants[30]). Thus the study is based on nonselective population data. The institutional review board (in accordance with the Helsinki declaration) approved the study (#0438-15-SOR approved on March, 2016).

Multiple pregnancies and fetuses with major congenital malformations were excluded from the analysis. Perinatal deaths (intrauterine fetal death, intrapartum death, and postpartum death) were excluded from the long-term analysis. A comparison of outcomes between males and females was performed. Outcomes assessed included pregnancy characteristics and adverse perinatal outcome, as well as hospitalizations up to age 18 years involving a predefined set of pediatric neurological morbidities. The different neurological morbidities assessed are detailed in the Supplementary Table. Follow-up time was defined as time to an event (first hospitalization with any of the diagnoses listed in the Supplementary Table), or until censored. Censoring occurred in case of death (during hospitalization, other than neurologically related) or at age 18 years (which was calculated for each child based on the date of birth). The relevant neurological diagnoses were given based on an evaluation performed on admission to the hospital and may have been new or based on the patient's history. It may have been the main reason for admission or a background disorder. Only the first hospitalization involving a neurological condition was counted for each child and included in the analyses. All affected children in our cohort were diagnosed either before or during their first hospitalization.

Data were collected from two databases that were cross-linked and merged: the computerized hospitalization database of SUMC ("Demog-ICD9") and the computerized perinatal database of the obstetrics and gynecology department. The Demog-ICD9 database includes demographic information and ICD-9 codes for all medical diagnoses made during encounters with SUMC.

The perinatal database consists of information recorded immediately after delivery by an obstetrician. Experienced medical secretaries routinely review the information before entering it into the database to ensure its maximal completeness and accuracy. Coding is performed after assessing medical and perinatal records as well as routine hospital documents.

Statistical analysis

Statistical analysis was performed using the SPSS package 23 version (SPSS, Chicago, IL). Categorical data were assessed by the chi-square test for general association. The Student *t* test was used for differences in continuous variables. Kaplan-Meier survival curves were used to compare neurological morbidity incidences over time. The differences between the curves were assessed using the log-rank test.

A Cox proportional hazard model was used with time from delivery to event or censoring (i.e., age 18 years or emigration) as the time-dependent variable and controlled for maternal age at delivery, gestational age and birth weight, parity, maternal diabetes mellitus, and hypertensive disorders. Adjusted hazard ratios (aHRs) are presented with their 95% confidence intervals (CIs). A P value of <0.05 was considered statistically significant.

Results

During the study period, 240,953 singleton deliveries met the inclusion criteria. Of them, 50.9% (n = 122,840) were male newborns and 49.1% (n = 118,113) were females. Maternal characteristics and immediate pregnancy outcomes subdivided male versus female newborns are presented in Table 1. Male newborns were slightly more likely to have been born preterm, both before 37 weeks and before 34 weeks of gestation. Maternal diabetes was more common in the male group as was small for gestational age birth weight (Table 1).

Long-term neurological morbidity, as evident by hospitalizations of the offspring up to age 18 years, is presented (in total and in subcategories) in Table 2. Total pediatric neurological morbidity was significantly more common in boys compared with girls (1.1% vs 0.8% respectively, odds ratio 1.31, CI 1.2 to 1.4, $P < 0.001$). Specifically, pervasive developmental disorder and obstructive sleep apnea were each significantly more common in boys (0.02% vs 0.007%, $P = 0.01$ and 0.7% vs 0.4%, $P = 0.001$, respectively).