OBSTETRICS

Early onset preeclampsia and cerebral palsy: a double hit model?

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BACKGROUND: Cerebral palsy (CP) is a late sequel of pregnancy, and the role of preeclampsia is debatable.

OBJECTIVE: The aims of this study were to determine the association between preeclampsia and cerebral palsy and to determine the risk factors for the development of cerebral palsy in these patients.

STUDY DESIGN: A retrospective population-based cohort study was designed that included 229,192 singleton pregnancies. The study population was divided into 2 groups: (1) patients with preeclampsia (n = 9749) and (2) normotensive gestations (n = 219,443). Generalized Estimating Equation multiple logistic regression models were performed to study the associations among preeclampsia, small for gestational age, gestational age at delivery, and the risk factors for the development of cerebral palsy in neonates of women with preeclampsia.

RESULTS: The rate of cerebral palsy was double in patients with preeclampsia than in the normotensive group (0.2% vs 0.1%; $P = .015$); early onset preeclampsia and small for gestational age were independent risk factors for the subsequent development of cerebral palsy (odds ratio, 8.639 [95% confidence interval, 4.269—17.480]; odds ratio, 2.737 [95% confidence interval, 1.937—3.868], respectively). A second model was conducted to determine the risk factors for the development of cerebral palsy in women with preeclampsia. Birth asphyxia, complications of prematurity, and neonatal infectious morbidity, but not small for gestational age or gestational age at delivery, were independent risk factors for the development of cerebral palsy.

CONCLUSION: In a comparison with normal pregnant women, the rate of cerebral palsy is double among patients with preeclampsia, especially those with early-onset disease. Early-onset preeclampsia is an independent risk factor for cerebral palsy. Among women with preeclampsia, the presence of neonatal infectious morbidity, birth asphyxia, and complications of prematurity are independent risk factors for the development of cerebral palsy, which further supports the role of a multi-hit model in the pathogenesis of this syndrome.

Key words: asphyxia, gestational age, infection, inflammation, multi-hit model, prematurity, SGA

Premature birth, especially at <28 weeks of gestation, is the leading risk factor for the development of cerebral palsy (CP) at 2-3 years of age.[1] This late sequel of pregnancy is a children's disease that is a diagnostic term used to describe a group of permanent disorders of movement and posture that cause activity limitation. These disorders are attributed to nonprogressive disturbances in the developing fetal brain, alteration in fetal development, or pathologic intrauterine processes or are considered as prematurity complications.[2] The prevalence of CP rises in a positive correlation with the severity of premature delivery and can reach up to 15% in preterm neonates who are delivered at 24—27 weeks of gestation.[3] CP is the most common form of chronic motor disability that begins in childhood; its incidence varies from 1—3.6 per 1000 live births. The overall proportion of CP did not change in recent years; yet, it decreased in neonates who were born at term and increased in those who were delivered prematurely.[4] Nevertheless, most of the children with CP are born at term.[5,6] Indeed, in the Collaborative Prenatal Project research in which 45,000 7-year-old children were examined; most of those who had CP were born at term and had no complications during delivery.[6]

Recent studies suggested that preeclampsia may be an additional risk factor for the subsequent development of CP.[7-9] A Norwegian study reported that children born to mothers with preeclampsia were more likely to experience CP than those delivered of normotensive women.[8] Preeclampsia, a major obstetric syndrome, is 1 of the leading causes for indicated preterm birth and perturbation of fetal growth,[6] Indeed, mild preeclampsia is associated with a 5% reduction in fetal weight; in the severe form of this syndrome, it can reach up to 12%. Moreover, neonates of mothers who experience preeclampsia are 4 times more likely to be small for gestational age (SGA).[10] Although the cause of CP is unknown, it is correlated strongly with preterm delivery and SGA[11,12]; it has been proposed that the delivery of an SGA neonate mediates the correlation between early onset preeclampsia and CP.[8] Because both preeclampsia and SGA result, in many cases, from abnormal placental implantation, it might be that the processes that affect fetal growth in women with preeclampsia also predispose their fetuses to the development of CP. Therefore, the aims of this study were to determine (1) the association between preeclampsia and CP and (2) the risk factors for the development of CP in these patients.

Material and Methods

This is a retrospective population-based cohort study that includes all the

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TABLE 1
Risk factors for cerebral palsy, with the use of our Generalized Estimating Equation multivariate logistic model

Variable	Odds ratio	95% Confidence interval	*P* value
Late onset preeclampsia	1.005	0.549–1.84	.957
Early onset preeclampsia (<34 weeks of gestation)	8.707	4.301–17.628	< .001
Small for gestational age	2.856	2.025–4.028	< .001
Maternal age	0.972	0.946–0.998	.034
Multiparity	1.329	0.981–1.799	.066
Year of delivery[a]	0.906	0.887–0.924	< .001

[a] Intended as the year the patient delivered (between 1990-2013).
Mor et al. Preeclampsia and cerebral palsy. Am J Obstet Gynecol 2016.

deliveries that occurred at Soroka University Medical Center from 1990-2013 that met the inclusion criteria. Data were collected from an electronic database that included demographic, obstetric, and general information about the mother and fetus of all the deliveries at our medical center. The use of the database was possible because the Soroka University Medical Center is a tertiary medical center that serves the population of the Negev, and all the deliveries of the region take place in its labor and delivery suites.The Department of Obstetrics and Gynecology has a computerized database of all the deliveries. The information was captured from patient medical records and coded by trained secretaries according to the International Classification of Diseases, 9th edition (ICD-9) diagnosis. Our database is tested constantly and validated by the Department of Epidemiology at the Ben-Gurion University of the Negev (Beer Sheva, Israel).

TABLE 2
Maternal demographic characteristics

Variable	Group		*P* value
	Preeclampsia (n = 9749)	Normotensive (n = 219,443)	
Maternal age at delivery[a]	29.18 ± 6.525	28.51 ± 5.77	< .0001
Bedouin origin, % (n)	46.9 (4574)	53.8 (118,158)	< .0001
Gravidity[b]	2 (1–5)	3 (2–5)	< .0001
Parity[b]	2 (1–4)	3 (2–5)	< .0001
History of preterm birth, % (n)	5.7 (552)	4.4 (9,725)	< .0001
Infertility treatment, % (n)	3.7 (356)	1.7 (3696)	< .0001
Hospitalization, d[b]	4 (1–35)	2 (1–34)	< .0001
History of placental abruption, % (n)	0.5 (52)	0.4 (823)	.016
History of small for gestational age, % (n)	4.1 (399)	4.1 (8,952)	.990
History of preeclampsia, % (n)	12.4 (1206)	1.9 (4,079)	< .0001
Placental abruption history, % (n)	0.5 (52)	0.4 (823)	.016

[a] Data are given as mean ± standard deviation; [b] Data are given as median (25–75 percentile).
Mor et al. Preeclampsia and cerebral palsy. Am J Obstet Gynecol 2016.

The study was approved by the Institutional Review Board Committee of the Soroka University Medical Center.

Patients who had perinatal death (ante-, intra- and postpartum death), multiple gestation, gestational hypertension, chronic hypertension without preeclampsia, or missing data were excluded from the study.

There were 229,192 pregnancies that met the inclusion criteria and comprised the 2 study groups: (1) pregnancies that were affected by preeclampsia (n = 9749) and (2) normotensive pregnancies (n = 219,443). Preeclampsia, CP, and all other diagnoses were coded according to ICD-9 codes (642.42 for mild preeclampsia, 642.52 for severe preeclampsia, 343.9 for CP).

Clinical definitions

Ethnicity was divided in Jews and Bedouins (an Arab ethnic group, descended from nomadic tribes who historically have inhabited the Arabian and Syrian Deserts). Parity groups were defined in the following manner: multiparous (2-5 deliveries) and grand-multiparous (≥6 deliveries). Preeclampsia was diagnosed in the presence of elevated blood pressure and proteinuria of at least +1 in dipstick. Its severity was defined according to the severity of hypertension and/or 1 of the following events: +3 proteinuria by dipstick; thrombocytopenia ≤ 100,000; elevated liver enzymes; persistent headache, and/or blurred vision.[13] Gestational diabetes mellitus was diagnosed according to oral glucose tolerance test and classified according to White's classification.[14] *Preterm delivery* was defined as delivery before complete 37 weeks of gestation; late preterm birth was any delivery between 34 and 36 6/7 weeks.

Newborn infants were classified by their birthweight with the use of Leiberman sex-specific birth curves in the following manner: SGA, birthweight <10th percentile; appropriate for gestational age, birthweight from 10-90th percentile; and large for gestational age, birthweight >90th percentile, according to regional growth curves.[15] *Pathologic Apgar score* was defined as <5 at 1 minute and <7 at 5 minutes. *Neonatal*