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).
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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).
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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*

acidosis was defined as cord blood pH< 7.0 and/or evidence of birth asphyxia.[16]

Short-term neonatal complications were also diagnosed with ICD-9 codes and included pneumonia, jaundice, tachypnea, hypoglycemia, dyspnea, convulsions, polycythemia, bacteremia, sepsis, hemolysis, acidosis, hypothermia, infections, ventilation, intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), respiratory distress syndrome (RDS), packed cell transfusion, and urinary tract infection (UTI). CP was diagnosed by the ICD-9 code, and the diagnosis was made at the age of 3 years old.

Statistical analysis

Categoric variables were processed with Pearson's Chi-square test. Normally distributed quantitative variables were analyzed with either *T*-Test or 1-way analysis of variance test. Not normally distributed quantitative variables were processed with the Mann-Whitney test or Kruskal-Wallis test.

Because the data in our study were collected during a period of 23 years, we have tried to clarify whether the rates of preeclampsia and CP changed over time in 2 manners. The first was to run a trend analysis; however, because there are a small number of cases in our study, such a trend analysis is not statically significant ($P = .711$). We therefore included the year of delivery as a variable in our Generalized Estimating Equation (GEE) model (Table 1), which was found to have a small but significantly protective effect against CP and thus suggests that the data collection and recording were uniform during this period and can be analyzed as 1 cohort.

Multivariate analysis was performed to test the association between preeclampsia and CP by using the GEE to account for multiple births by the same mother. Models were adjusted for confounders that were found statistically significant in the univariate analysis. In the first model, we defined *CP* as the dependent variable; late preeclampsia (>34 weeks of gestation), early onset preeclampsia (<34 weeks of gestation), maternal age, multiparity, SGA, and gestational age at delivery were included as independent variables.

The second GEE model was aimed to study the risk factors for CP among patients with preeclampsia. CP was set as the dependent variable; SGA, birth asphyxia, neonatal infectious morbidity (pneumonia, bacteremia, sepsis, UTI, other infections, chorioamnionitis, and sepsis), sequel of prematurity (BPD, NEC, IVH, ROP, RDS), and gestational age at delivery served as covariates.

The statistical analysis was performed with IBM Statistics SPSS software (version 20; SPSS Inc, Chicago, IL), and statistical significance was determined as a probability value of <.05.

Results

Table 2 presents the demographic characteristics of the patients. Women in the preeclampsia group were older (29.18 ± 6.525 vs 28.51 ± 5.77 years; $P < .0001$), had a lower median gravidity (median, 2 [range, 1−5] vs 3 [range, 2−5]; $P < .0001$) and parity (median, 2 [range, 1−4] vs 3 [range, 2−5]; $P < .0001$) and had a higher proportion of previous obstetric complications that included preterm birth (5.7% vs 4.4%; $P < .0001$), placental abruption (0.5% vs 0.4%; $P = .016$), and preeclampsia (12.4% vs 1.9%; $P < .0001$) than did normotensive pregnancies. In addition, the rate of assisted reproduction technologies (3.7% vs 1.7%; $P < .0001$) and the median length of hospitalization were higher in the preeclampsia group than in the normotensive group ($P < .0001$; Table 2).

Clinical characteristics of the study groups demonstrated that women with preeclampsia had a higher rate of placental abruption, pregestational and gestational diabetes mellitus, oligohydramnios, polyhydramnios, nonreassuring fetal heart monitoring during

TABLE 3
Pregnancy characteristics and complications

Variable	Group: Preeclampsia (n = 9749)	Group: Normotensive (n = 219,443)	*P* value
Mode of delivery, % (n)			< .0001
Forceps	0.1 (7)	0.004 (81)	
Cesarean section	29.3 (2859)	13.3 (29,164)	
Vacuum	3.5 (342)	3.2 (7,088)	
Vaginal	67.1 (6541)	83.4 (183,110)	
Placental abruption, % (n)	1.7 (163)	0.6 (1,291)	< .0001
Placenta previa, % (n)	0.3 (32)	0.4 (915)	.2
Abnormal presentation, % (n)	5.2 (508)	4 (8,678)	< .0001
Gestational diabetes mellitus, % (n)	7 (685)	3.9 (8,634)	< .0001
Diabetes mellitus, % (n)	1.8 (180)	0.6 (1,397)	< .0001
Oligohydramnios, % (n)	3.5 (339)	2.4 (5,264)	< .0001
Polyhydramnion, % (n)	4.4 (432)	3.6 (7,880)	< .0001
Non reassuring fetal heart rate, % (n)	3.1 (298)	1.4 (3,164)	< .0001
Gestational age at delivery, wk[a]	38.03 ± 2.66	39.1 ± 1.914	< .0001
Preterm delivery <37 weeks, % (n)	19.7 (1923)	7 (15,401)	< .0001
Early preterm delivery <34 weeks, % (n)	5.8 (568)	1.4 (3,236)	< .0001

[a] Data are given as mean ± standard deviation.

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labor, cesarean delivery, and a lower mean gestational age at delivery than normotensive patients ($P < .0001$ for all comparisons). In addition, women with preeclampsia had a significantly higher rate of both preterm and early preterm delivery than normotensive patients ($P < .0001$; Table 3).

In terms of early and late neonatal outcomes, neonates of women in the preeclampsia group had a lower mean birthweight and higher rate of SGA, Apgar score <5 at 1 and 5 minutes, and birth asphyxia compared with normotensive pregnancies ($P < .001$ for all comparisons; Table 4). In addition, the rate of jaundice, tachypnea of the newborn infant, hypoglycemia, polycythemia, hemolysis, hypothermia, sepsis, ROP, NEC, BPD, and RDS was higher in patients from the preeclampsia than the normotensive group group (Supplemental Table). Among patients with preeclampsia, the rate of all neonatal morbidities that included convulsions ($P = .006$), sepsis, ROP, NEC, BPD, and RDS ($P < .0001$ for all comparisons) was higher in neonates of women with early-onset preeclampsia than in those with late-onset disease (Table 5).

The rate of CP was double in the preeclampsia group than in the normotensive group (0.2% vs 0.1%; $P = .015$). Although, in general, the rate of CP per 1000 live births decreased during the study period, it was constantly higher among women with preeclampsia than those with normotensive pregnancy (Figure 1). Of interest, there was no difference in the rate of CP according to gestational age at delivery between the study groups (Figure 2).

In the multivariate analysis that was performed with a GEE logistic regression model that included CP as the dependent variable, early onset preeclampsia (odds ratio [OR] 8.639; 95% confidence interval [CI], 4.269−17.480; $P < .001$) and SGA (OR, 2.737; 95% CI, 1.937−3.868; $P < .001$) were independent risk factors for the development of CP. In contrast to SGA and early onset preeclampsia, maternal age (OR, 0.972; 95% CI, 0.946−0.998; $P = .034$), and the year the delivery occurred (OR, 0.906; 95% CI, 0.887−0.924; $P < .001$) had a protective effect against the development of CP (Table 1).

A second model was constructed to determine the risk factors for CP among neonates of patients with preeclampsia. CP was the dependent variable; SGA, birth asphyxia, infectious morbidity, complications of prematurity, and gestational age at delivery were introduced as covariates into the model. Birth asphyxia (OR, 4.421; 95% CI, 1.611−12.134; $P = .004$), neonatal infectious morbidity (OR, 8.089; 95% CI, 1.773−36.890; $P = .007$), and complications of prematurity (OR, 3.845; 95% CI, 1.252−11.803; $P = .019$) were independent risk factors for CP (Table 6).

TABLE 4
Neonatal characteristics and outcomes

Variable	Group: Preeclampsia (n = 9749)	Group: Normotensive (n = 219,443)	*P* value
Birthweight, g	2958 ± 692.8	3207 ± 505	< .0001
Male, % (n)	51.4 (5012)	51.3 (112,615)	.99
Intrauterine growth, % (n)			< .0001
Small for gestational age	11.1 (1078)	5.3 (11,654)	
Appropriate for gestational age	78.3 (7635)	84.4 (185,165)	
Large for gestational age	10 (975)	9.6 (21,013)	
Cerebral palsy, % (n)	0.2 (20)	0.1 (253)	.015
Apgar score, % (n)			
1 min <5	11.6 (1128)	5.5 (11,993)	< .0001
5 min <5	0.6 (62)	0.4 (780)	< .0001
pH[a]	7.35 ± 0.41	7.37 ± 1.07	.974
Asphyxia, % (n)	1.5 (146)	1.1 (2,487)	.001

[a] Data are given as mean ± standard deviation.

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Comment

Principal findings of the study

Women with preeclampsia had a double rate of CP than did normotensive patients. Early onset preeclampsia and SGA neonates are independent risk factors for the subsequent development of CP, even after adjustmen for gestational age at delivery. Infectious morbidity, prematurity complications, and birth asphyxia were all independent risk factors for CP among neonates of women with preeclampsia that further implicated the role of a multi-hit model in the pathogenesis of CP.

CP describes a group of permanent disorders of movement and posture that causes disability that are attributed to nonprogressive pathologic disturbances in the developing fetal or neonatal brain.[17] Motor disorders are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior as well as epilepsy and secondary musculoskeletal problems. The cause of CP is unknown, but many factors that include hostile intrauterine environment because of infection and/or inflammation, vascular disease, acute events such as placental abruption and conditions that lead to birth asphyxia, predisposing genetic factors, and metabolic and ischemic conditions[18-20] have been suggested to participate in the underlying mechanism that leads to CP.

Recently a 2-hit model was suggested as a possible underlying mechanism that leads to CP. This model regards hostile intrauterine environment as the first hit and delivery as well as neonatal complications (ie, birth asphyxia, prematurity

TABLE 5
Additional neonatal morbidities in early-onset preeclampsia group vs late-onset preeclampsia group

Variable	Preeclampsia group, % (n)		*P* value
	Early-onset (n = 789)[a]	Late-onset (n = 8960)[b]	
Pneumonia	8.9 (70)	4.2 (380)	< .0001
Jaundice	51.8 (409)	4.1 (368)	< .0001
Tachypnea	11.3 (89)	1.6 (145)	< .0001
Hypoglycemia	9.9 (39)	2.6 (237)	< .0001
Dyspnea	4.9 (39)	1.9 (170)	< .0001
Convulsions	2.8 (22)	1.5 (134)	.006
Polycythemia	2.5 (20)	1.1 (101)	< .0001
Bacteremia	1.8 (14)	0.8 (70)	.004
Sepsis	1.5 (12)	0.4 (38)	< .0001
Hemolysis	0.4 (3)	0.3 (28)	.519
Acidosis	4.3 (34)	1 (87)	< .0001
Hypothermia	0.5 (4)	0.1 (12)	.013
Infections	1 (8)	0.2 (22)	< .0001
Ventilation	0.5 (4)	0.2 (15)	.038
Intraventricular hemorrhage	3.4 (27)	0	< .0001
Retinopathy of prematurity	6.1 (48)	0	< .0001
Necrotizing enterocolitis	4.2 (33)	0.1 (6)	< .0001
Bronchopulmonary dysplasia	5.6 (44)	0	< .0001
Respiratory distress syndrome	33.8 (267)	0.3 (28)	< .0001
Packed cells transfusion	22.6 (178)	0.7 (63)	< .0001
Urinary tract infection	0.6 (5)	0.2 (16)	.008

[a] Before 34 weeks of gestation; [b] After 34 weeks of gestation.
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complications), especially among premature neonates, as the second hit that leads to neurologic damage and the development of CP.[21]

There are many known risk factors for CP, in which the most significant is prematurity. In the Extremely Low Gestational Age Newborns (ELGAN) study, it was found that there is a correlation between being born at an early gestational age (especially at <28 weeks of gestation) and CP.[1] In addition, it has been proposed that the increase in the survival of early premature neonates, especially at <28 weeks of gestation, was the main contributor to the increased rate of CP among these neonates.[17]

Among the leading mechanisms to be associated with a subsequent development of CP are intraamniotic infection and/or inflammation.[22-25] Intrauterine exposure to infection/inflammation either fetal (chorioamnionitis, inflammation of the umbilical cord, inflammation of the placental membranes) or maternal (maternal fever >38°C, sepsis, and UTI) greatly increases the risk for CP (5 times greater for term neonates and twice as greater for premature ones).[26] A good example for the effect of hostile uterine environment on the rate of CP is the association of the fetal inflammatory response syndrome in which intrauterine exposure to infection/inflammation triggers a systemic fetal inflammatory response that is associated with an increased risk for neonatal complications and the subsequent development of CP.[27] Our novel finding that early onset preeclampsia carries an OR of 8.639 for the development of CP may be representing a different angle of this mechanism that can be, at least in part, attributed to the hostile intrauterine fetal environment that accompanies early onset preeclampsia.

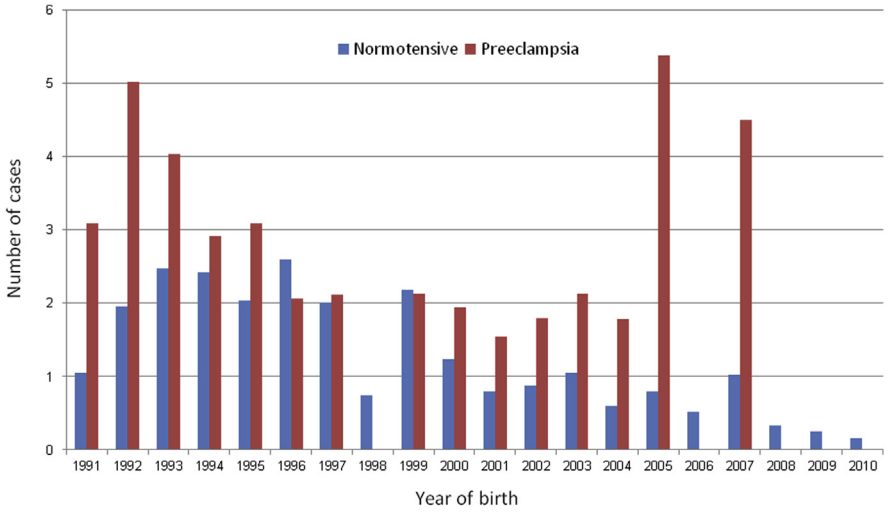
A second aspect is the association of systemic maternal infectious morbidity with the development of CP. Similarly to mothers with systemic inflammation, women with preeclampsia have a proinflammatory profile that is akin to sepsis[28] that, similarly to sepsis, may also influence the subsequent development of CP in their offspring.

The association between SGA and CP is well-documented; it has been reported that SGA at term is associated with a 6-fold increase in the risk for CP, and an SGA born preterm infant has a 4-increase in a risk for this complication.[29] Indeed, in our study, the presence of SGA was an independent risk factor for CP. Similarly, early gestational age at delivery was also an independent risk factor for CP, which is in accord with previous reports.[30-32]

The novel finding of our study that early onset preeclampsia is an independent risk factor for CP with an OR of 8.639 is in contrast to that of Strand et al.[8] During their study, Strand et al[8] adjusted for gestational age and the presence of SGA, and only neonates who were SGA of patients with preeclampsia had a significant risk for the subsequent development of CP. The disagreement between these observations is related to the differences in study design and possible ethnic diversities in the cohort that was studied.

When we further studied the specific risk factors for CP in the preeclampsia group, we found that infectious morbidity of the newborn infant, prematurity complications, and birth asphyxia were all independent risk factor for CP, although in this model gestational age at delivery and the presence of

FIGURE 1
Rate of cerebral palsy per 1000 live births during the study period



The data were collected from women with preeclampsia and normotensive patients.

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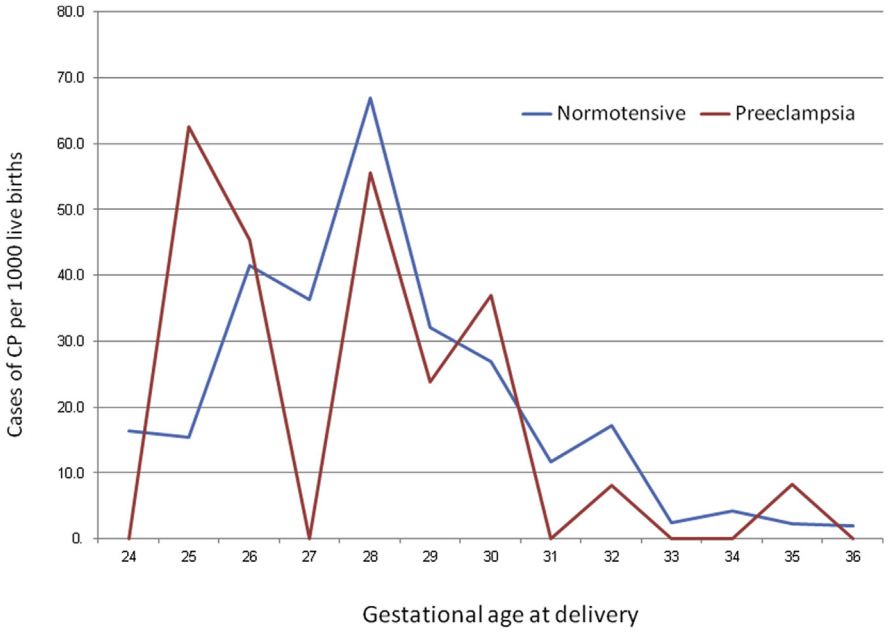
SGA were not. Our findings are important because early-onset preeclampsia often combines early and severe prematurity as well as fetal growth restriction. We propose that, in women with early onset preeclampsia, the combination of prematurity and fetal growth restriction are part of the manifestation of the severity of the disease and that they contribute to the increased risk for CP in these patients by serving possibly as a primary hit that predisposes the fetus to the subsequent development of CP in case they experience additional complications such as infection, birth asphyxia, or prematurity.

FIGURE 2
Rate of cerebral palsy according to gestational age at delivery



The date were collected from neonates who were delivered preterm according to study group.

CP, cerebral palsy.

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The data that were presented in our study support the multi-hit model in the development of CP. Indeed, the cerebral immaturity of preterm neonate results in periventricular leukomalacia and IVH, which are both risk factors for CP.[30, 33-35] Thus, there is actually a vicious cycle that involves delivery in an early gestation week that leads to cerebral immaturity and the subsequent development of IVH and/or periventricular leukomalacia. Evidence in support of this was reported by Korzeniewski et al[21] that the neonate who has evidence for fetal inflammatory response syndrome of acute or chronic chorioamnionitis were at higher risk to develop white matter lesion in the neonatal period, which suggests a multi-hit model for brain injury in preterm infants who were born at <32 weeks of gestation. We would like to expand this approach and propose that the increased risk for CP in women with early onset preeclampsia and the fact that, in these patients, the intrapartum factors (such as asphyxia) and the postpartum factors (such as neonatal infectious morbidity and complications of prematurity [IVH, ROP, NEC, BPD, RDS]) are actually a multi-hit model. In this model, neonates of patients with preeclampsia, especially if it was early onset preeclampsia, are already at a compromised status. The additional hit that results from a fore mentioned listed risk factors further increases that risk for CP. The findings presented in the current study are important in the counseling of women with preeclampsia, especially those with an early onset disease.

Strength and limitations of the study

This was a population-based study that included a large cohort of >200,000 deliveries over a period of >20 years that gives a true representation of even rare complications. The use of such a large

TABLE 6
Risk factors for cerebral palsy in women with preeclampsia, with the use of our Generalized Estimating Equation multivariate logistic model

Variable	Odds ratio	95% Confidence interval	*P* value
Small for gestational age	1.483	0.535–4.118	.449
Asphyxia	4.421	1.611–12.134	.004
Infections	8.089	1.773–36.890	.007
Prematurity complications	3.845	1.252–11.803	.019
Gestational age at delivery	0.947	0.825–1.087	.442

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cohort over a long period enabled us to demonstrate that, in any given year of our study, the rate of CP per 1000 live birth in women with preeclampsia was higher than that of the normotensive patients, which emphasizes the magnitude of the risk for CP in neonates of women with preeclampsia. Moreover, in our study, the rate of CP in both study groups declined during the study period and is within the range reported in the literature, which supports the external validity and the generalization of our findings, although they come from a single-center experience. The fact that our study is based on a database registry has its limitations, which are listed earlier in the article. Another limitation is the long time period (23 years) of our study. This time frame is both a plus and curse. The advantage of our sample size is that it gives us the ability to study such a rare disease. We addressed this matter earlier in the article, but it is still a long study period in which some aspects of the medical practice have changed, the studied population experienced a different prenatal care, there has been an improvement in Neonatal Intensive Care Unit care, and the use of magnesium sulfate was established. Indeed, the protective effect of the year of delivery against the development of CP is a reflection of the improvement that was made in the treatment methods and patients' treatment during the course of the study (Table 1).

Finally, the large difference in numbers between the normal pregnancy group and the preeclampsia group made almost all comparisons significant, which is not necessarily with clinical meaning. We have tried to emphasize only the clinically meaningful findings.

Conclusion

Our study found that women with preeclampsia have a higher rate of CP. Women with early onset preeclampsia are at especially high risk for the development of this dire late sequela of the offspring. Moreover, the association of early-onset preeclampsia with cerebral palsy is independent of other risk factors, such as SGA and early gestational age at delivery. This association must be taken into account when counseling these patients. ■

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SUPPLEMENTAL TABLE

Additional neonatal morbidities in preeclampsia group vs normotensive pregnancies

Variable	Preeclampsia (n = 9735), % (n)	Normotensive (n = 219100), % (n)	*P* value
Pneumonia	4.6 (450)	4.4 (9565)	.224
Jaundice	8 (777)	3 (6746)	< .0001
Tachypnea	2.4 (234)	1.3 (2892)	< .0001
Hypoglycemia	3.2 (315)	1.1 (2492)	< .0001
Dyspnea	2.1 (209)	1.9 (4268)	.165
Convulsions	1.6 (156)	1.3 (2814)	.007
Polycythemia	1.2 (121)	0.5 (1146)	< .0001
Bacteremia	0.9 (84)	0.8 (1787)	.638
Sepsis	0.5 (50)	0.4 (829)	.037
Hemolysis	15.5 (1508)	11.9 (26142)	< .0001
Acidosis	0.3 (26)	0.3 (711)	.361
Hypothermia	1.2 (12)	0.9 (1958)	.001
Infections	0.2 (16)	0.1 (220)	.072
Ventilation	0.3 (30)	0.3 (617)	.697
intraventricular hemorrhage	0.2 (19)	0.2 (436)	1
Retinopathy of prematurity	0.3 (27)	0.1 (216)	< .0001
Necrotizing enterocolitis	0.5 (48)	0.1 (214)	< .0001
Broncopulmonary dysplasia	0.4 (39)	0.1 (116)	< .0001
Respiratory distress syndrome	0.5 (44)	0.1 (212)	< .0001
Packed cells transfusion	3 (295)	0.7 (1597)	< .0001
Urinary tract infection	2.5 (241)	1.3 (2834)	< .0001

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