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Antenatal and Intrapartum Risk Factors for Seizures in Term Newborns: A Population-Based Study, California 1998-2002

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Abstract

Objective—To assess antenatal and intrapartum risk factors for seizures occurring during the birth admission.

Study design—Using multivariable logistic regression analysis, we evaluated the association between maternal characteristics and birth admission seizures in a cohort of 2.3 million California children born ≥ 36 weeks gestation from 1998-2002 using the California Office of Statewide Planning and Development database containing birth certificates linked to infant and maternal hospital discharge abstracts.

Results—The incidence of seizures during the birth admission was 0.95/1000 live births. In an adjusted analysis, infants of women who were 40 or older, were nulliparous, had diabetes mellitus, intrapartum fever or infection or who delivered ≥ 42 weeks had an increased risk of seizures. Infants of Hispanic and Asian mothers had a lower risk when compared with infants of white mothers.

Conclusions—Several maternal antenatal and intrapartum factors increased the risk of seizures during the birth admission. Identifying and avoiding risks for neonatal seizures may lead to lower infant neurological morbidity and mortality.

Keywords

Population attributable risk

The estimated incidence of seizures in term newborns is 1-3.5 per 1000 live births (1-4) (5,6). Seizures in the neonate frequently reflect significant underlying brain injury such as hypoxic ischemic injury, stroke, intracranial infection or hypoglycemia (2,7). Neonates with seizures have a high incidence of mortality and adverse long-term neurological outcome (5,8).

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Identifying and avoiding risks for neonatal seizures may lead to lower infant neurological morbidity and mortality. Past studies evaluating risk factors for seizures in term newborns were limited by small size of the affected cohort (3,5,6), focus on a single (9) or only a restricted number of maternal risk factors (3,5) or use of only those variables available on birth and death certificate data (5,10,11). We evaluated antenatal and intrapartum risk factors for seizures during the birth hospitalization in newborns ≥ 36 weeks gestational age in a large population using birth certificate data linked to California statewide maternal and infant hospital discharge diagnoses from 1998-2002.

Methods

We examined a population-based cohort using a California Office of Statewide Planning and Development (OSHPD) linked Vital Statistics/Patient Discharge Data file created specifically to study perinatal outcomes (12). The linkage was performed using probabilistic record linkage techniques. The matched file links 97% of California birth certificates to the corresponding newborn and maternal hospital discharge record (www.health-info-solutions.com/links.html). The dataset includes demographic data and up to 25 International Classification of Diseases, ninth revision (ICD-9-CM) maternal and infant discharge diagnoses (13).

The study group included all live-born infants between January 1, 1999 and December 31, 2002 who were ≥ 36 weeks gestation at birth. Demographic data including maternal age (≤ 18 , 19-24, 25-29, 30-34, 35-39, ≥ 40), parity, race/ethnicity, infant sex, gestational age at birth and birth weight were obtained from birth certificates. We analyzed the source of payment for the birth admission as an indicator of socioeconomic status (SES). High SES included individuals with private insurance or health maintenance organization (HMO) coverage, and low SES consisted of those who were indigent, self-pay, or had Medicaid or Medicare. Post-term delivery was a dichotomous variable defined as delivery ≥ 42 weeks. Maternal and infant medical complications were identified from hospital discharge records by searching ICD-9-CM codes for primary and secondary diagnoses generated during the infant's birth admission. Maternal and pregnancy variables of interest included prolonged second stage of labor (ICD-9-CM 662.2-662.21), catastrophic delivery (abruption 641.2-641.22; umbilical cord prolapse 663.0-663.01 and uterine rupture 665.0-665.02, 665.1-665.12), chorioamnionitis (762.7, 658.4-658.41), isolated fever during labor (659.2-659.21, 780.6) and other infection during labor (659.3-659.31, 646.61-646.62). Diabetes mellitus was defined as either pre-existing diabetes (i.e. diagnosed prior to pregnancy with or without concurrent gestational diabetes, 648.01-648.02) or gestational diabetes (648.81-648.82). Hypertension was categorized as pre-existing hypertension (642.0-642.02, 642.21-642.22, 642.91-642.92), transient gestational hypertension (642.31-642.32) or pre-eclampsia/eclampsia, with or without pre-existing hypertension (642.41-642.42, 642.51-642.52, 642.61-642.62). Mode of delivery was categorized into four groups: routine vaginal, operative vaginal (using vacuum or forceps), daytime cesarean (during the hours 6:00-17:00) and nighttime cesarean (17:01-5:59). Potential infant confounding variables included meningitis (320-320.9, 322.9) and other infection, not meningitis (771.4, 771.8-89).

Our outcome of interest was defined as convulsions (780.3) or seizures in a newborn (779.0) diagnosed during the birth hospitalization.

Statistics

Continuous variables were compared using a two-tailed Student's *t*-test. The association between the predictors and seizure was assessed using logistic regression analysis to derive odds ratio (OR) and 95% confidence intervals (CI). A *P* value ≤ 0.05 was considered significant. The adjusted analysis model included all maternal antenatal, intrapartum and infant characteristics (including maternal age, nulliparity, maternal race/ethnicity, multiple gestation,

socioeconomic status, diabetes, hypertension, prolonged second stage of labor, catastrophic delivery, mode of delivery, maternal infection and delivery ≥ 42 weeks, male sex and birth weight) analyzed in the unadjusted models. All statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC). The population-attributable risk was calculated using the formula by Levin (14).

RESULTS

Of the 2,332,803 infants born at ≥ 36 weeks in the state of California during the four-year study period, 2213 were diagnosed with seizures during the birth admission, giving a population incidence of 0.95/1000. The annual incidence of seizures did not change significantly during the study period. The mean gestational age at birth was similar in newborns with and without seizures (39.8 vs. 39.9 weeks, $P = 0.6$). The affected group had a higher proportion of males (57.3% vs. 50.9%, $P = 0.002$) and a smaller average birth weight than the unaffected group (3365 ± 596 grams vs. 3421 ± 489 grams, $P = 0.002$).

In the unadjusted analysis, numerous antenatal and intrapartum risk factors were associated with seizures during the birth admission (Table I; available at www.jpeds.com). The adjusted analysis included *all* antenatal, intrapartum and infant factors. In the adjusted analysis, the association between risk factors and seizures during the birth admission remained similar except for maternal hypertension, which was no longer significant. Unless stated otherwise, the odds ratios (OR) listed below refer to the adjusted estimates.

Maternal Antepartum Risk Factors

When categorized into 5-year age groups the risk of seizures in infants born to mothers ≥ 40 years was increased when compared with infants of mothers aged 25-29 (OR 1.3, 95% CI 1.0-1.6). Maternal nulliparity was significantly associated with seizures (OR 1.3, 95% CI 1.2-1.5). Maternal race/ethnicity was significantly associated with seizures, with a lower incidence in infants of white, Hispanic (OR 0.8, 95% CI 0.7-0.9) and Asian (OR 0.5, 95% CI 0.4-0.6) descent when compared with those of white, non-Hispanic descent, and a higher risk in infants of black mothers when compared with white, non-Hispanic mothers (OR 1.1, 95% CI 1.0-1.3). Low socioeconomic status was not a risk factor for seizures (OR 1.1, 95% CI 1.0-1.2).

Several maternal medical complications impacted the risk of seizures. Maternal diabetes mellitus was associated with an increased risk of seizures, and the effect of pre-existing diabetes (OR 2.6, 95% CI 1.9-3.5) was greater than that of gestational diabetes (OR 1.5, 95% CI 1.3-1.8) when compared with infants of mothers without diabetes.

Intrapartum Risk Factors

Maternal intrapartum infection was significantly associated with seizures. The adjusted risk was highest for infants of women diagnosed with chorioamnionitis (OR 2.9, 95% CI 2.4-3.4). The risk was smaller but still significant in infants born to women with infection other than chorioamnionitis (OR 1.5, 95% CI 1.2-2.0) or fever only (OR 1.9, 95% CI 1.4-2.5) when compared with women without a diagnosis of infection. The effect persisted with similar point estimates in infants without a diagnosis of meningitis or other perinatal infection.

In the unadjusted analysis, the effect of intrapartum infection was different in multiparous women as compared with nulliparous women such that the risk of seizures was higher in infants of multiparous women with chorioamnionitis (unadjusted OR 6.6, 95% CI 5.0-8.8 vs. OR 3.4, 95% CI 2.7-4.1), other infection (unadjusted OR 2.2, 95% CI 1.6-3.1 vs. OR 1.6, 95% CI 1.1-2.5) and isolated fever (unadjusted OR 2.2, 95% CI 1.2-4.0 vs. OR 2.0, 95% CI 1.5-2.7).

We did not have access to information regarding epidural use and were, therefore, unable to measure its relationship to intrapartum fever.

A catastrophic delivery involving placental abruption, uterine rupture or cord prolapse (OR 6.9, 95% CI 5.9-8.1) was significantly associated with seizures, as was prolonged second stage of labor (OR 2.3, 95% CI 1.8-2.4). Delivery ≥ 42 weeks was also associated with an increased incidence of seizures (OR 1.2, 95% CI 1.1-1.4). There was no difference in the risk of seizures when the analysis was performed for each gestational week over 42 weeks.

Among the four modes of delivery, cesarean section performed at night carried the highest risk when compared with routine vaginal delivery (OR 2.7 95% CI 2.4-3.1). Cesarean section during the day (OR 2.2 95% CI 2.0-2.5) and operative vaginal delivery (OR 1.7, 95% CI 1.4-1.9) were also associated with an increased risk of seizures.

Population-Attributable Risk

In our cohort, the population attributable risk of nulliparity for seizures during birth hospitalization was (15.9%) (Table II). Other conditions with clinically important population attributable risks included diabetes (4.0%), maternal infection or fever (7.9%) and delivery ≥ 42 weeks (2.1%).

DISCUSSION

This population-based study identifies antenatal and intrapartum risk factors for seizures in infants ≥ 36 weeks gestation at birth. The incidence of seizures during the birth admission (0.95 per 1000) was on the lower end of what has been observed for neonatal seizures in other studies, which ranges from 1-3.5 per 1000 in term infants (1-6). The lower incidence of seizures in this study likely reflects a difference in case definition because other studies included seizures up to the first 28 days of life (2-4). Other reasons for the discrepancy may be differences in the rates of etiologic factors or lower reporting by local physicians.

Two previous studies suggested an increased risk of neonatal seizures in nulliparous women, though adjusted analysis was either not performed (5) or not significant (10). In our analysis, the association between nulliparity and seizures persisted after adjusting for numerous possible confounders including maternal age, prolonged second stage of labor, post-term delivery ≥ 42 weeks, assisted vaginal delivery, and low infant birth weight, suggesting that nulliparity is an independent risk factor for seizures in the newborn. Although the increased odds of seizures in infants of nulliparous mothers were modest, the population attributable risk was large due to the high incidence of nulliparous deliveries in the population.

The reported effect of maternal age on the risk of newborn seizures has been inconsistent (10,11,15). The increased risk of seizures during birth hospitalization among women ≥ 40 in our cohort was small but significant when compared with women aged 25-29. The reason for increased seizures in this population is unknown and may be related to changes in uterine function seen with advancing age (16,17).

A previous study suggested an association between pre-existing diabetes mellitus and neonatal seizures (11), but not with gestational diabetes. Others have suggested infant macrosomia and advanced maternal age as reasons for increased adverse outcome in infants of diabetic mothers (18). However, this does not appear to be the case in this cohort because maternal diabetes remained an independent risk factor after adjusting for these variables. Alternative reasons may include higher rates of maternal medical risk factors (obesity, inadequate prenatal care) or diabetic placental vasculopathy (19,20).

Our finding that maternal hypertension is not associated with seizures in the newborn is in keeping with one population-based study (11). In our unadjusted analysis, maternal hypertension was associated with seizures. However, in our adjusted analysis, which included all antenatal, intrapartum and infant co-variables, the risk of maternal hypertension was no longer significant. We evaluated each of the variables individually in a regression with hypertension and no single variable had a significant effect on the point estimate.

Our study confirms that maternal intrapartum fever and infection are risk factors for seizures in the newborn (9,15) and that the risk remains elevated even in infants without a diagnosis of meningitis or neonatal infection. Interestingly, the risk of seizures was lower in infants born to febrile nulliparous women than in infants born to febrile multiparous women. Others have reported a similar interaction (9). Why maternal fever is more detrimental to infants of multiparous mothers is unknown and could be related to differences in the etiology of fever, virulence of the infecting organism or differences in the timing of antibiotic administration.

Cesarean section and assisted delivery were associated with seizures in previous studies(5,6,10,11). In our cohort, this association was strongest in infants born between 17:00 and 6:00. The reason for higher rate of seizures during the birth admission in infants born by cesarean section during the night may be related to higher rates of emergent deliveries, differences in staffing or other unmeasured factors and is the topic of a separate study by our group.

The small but significant association between delivery after 42 weeks and seizures during birth hospitalization is in keeping with studies showing that post term delivery is a risk factor for early seizures (5) and for later epilepsy (21). A recent randomized controlled trial found that induction of labor at 41 weeks did not reduce neonatal morbidity (22) and, therefore, the American College of Obstetrics and Gynecology does not recommend routine induction for women with gestation >42 weeks and an unfavorable cervix (23).

In keeping with previous studies, the risk of seizures was higher in male infants (1,5,6,10,11). The protective effect seen in Asian and Hispanic populations persisted after adjusting for potential confounders such as socioeconomic status, maternal age and infant birth weight. This result has not been shown previously, but is consistent with studies showing lower infant mortality in these populations (24-26). The cause for the protective effect is unknown, and may relate to differences in health care or genetic factors.

Though this is a large population-based study to examine risk factors for seizures in newborns, the data were limited in two important ways. First, we relied on ICD-9-CM diagnoses of seizure rather than chart review for descriptions of clinical events consistent with definitions of seizure proposed by Mizrahi and others (27) or gold standard electrophysiologic diagnosis by EEG. Second, as in any investigation that relies solely on administrative data, our study is susceptible to coding errors. The accuracy of OSHPD data for identifying primary and secondary diagnoses varies widely depending on the nature of the medical condition (28). Even though the coding accuracy for major obstetric diagnoses such as cesarean section is known to be very high (approximately 95-99%) (29-31), the accuracy of coding for seizures in the newborn is unknown. When compared with other administrative data sources, the OSHPD contains relatively high quality data, and it includes 25 diagnoses, making it unlikely that important conditions would be omitted due to limited availability in the database. Also, linked datasets containing information from birth certificates and hospital discharge files have improved sensitivity and specificity when compared with hospital or birth certificate data alone (32). Though these limitations may have lead to differences in the incidence of seizures, we expect that any potential misclassification of seizures related to lack of gold standard diagnosis or reliance on ICD-9-CM administrative data would act to *reduce* our ability to find important antenatal and intrapartum risk factors rather than enhance these associations.

In this large study, delivery past 42 weeks was the only truly modifiable risk factor. Maternal medical risk factors including diabetes mellitus, intrapartum fever and infection together accounted for a small but significant proportion of seizures in the newborn. Past studies suggest that improving maternal care improves neonatal outcomes (33,34). The extent to which preventing or treating these and other risk factors would reduce the incidence of seizures in the newborn is unknown and deserves further study.

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Abbreviations

OSHPD

Office of Statewide Planning and Development

ICD-9-CM

International Classification of Diseases

SES

Socioeconomic status

HMO

Health maintenance organization

Table 1

Frequency and odds ratio for antenatal, intrapartum and infant characteristics among 2213 newborns ≥ 36 weeks gestation at birth and seizures during the birth admission in a California population of >2.3 million births 1998-2002.

<i>Antenatal Characteristics</i>	Seizures (%) N = 2213	No Seizures (%) N = 2,332,803	Univariate OR (95% CI)	Multivariate OR (95% CI)
<i>Maternal Age</i>				
< 18	7.0	6.4	1.13 (0.95- 1.36)	1.05 (0.87- 1.26)
19-24	24.7	26.9	0.95 (0.85- 1.07)	0.94 (0.83- 1.06)
25-29	25.5	26.6	-	-
30-34	24.1	24.2	1.04 (0.92- 1.17)	0.99 (0.88- 1.12)
35-39	14.1	12.8	1.15 (1.00- 1.32)	1.03 (0.89- 1.18)
≥ 40	4.6	3.0	1.60 (1.30- 1.98)	1.28 (1.04- 1.59)
Nulliparous	48.7	39.0	1.49 (1.37- 1.61)	1.32 (1.20- 1.45)
<i>Maternal Race/Ethnicity</i>				
White, Hispanic	42.9	47.7	0.78 (0.71- 0.86)	0.80 (0.72- 0.89)
White, non-Hispanic	37.9	32.9	-	-
Asian	4.1	6.4	0.56 (0.45- 0.69)	0.51 (0.41- 0.64)
Black	8.4	6.1	1.19 (1.02- 1.40)	1.12 (0.95- 1.32)
Other	6.7	7.0	0.83 (0.70- 0.99)	0.76 (0.64- 0.91)
Multiple gestation	1.7	1.8	0.95 (0.69- 1.31)	0.50 (0.36- 0.69)
Low socioeconomic status	40.5	41.0	0.98 (0.9- 1.07)	1.07 (0.97- 1.18)
<i>Diabetes Mellitus</i>				
None	91.5	95.3	-	-
Pre-existing	1.9	0.6	3.43 (2.52- 4.67)	2.58 (1.89- 3.53)
Gestational	6.7	4.1	1.69 (1.43- 2.00)	1.50 (1.27- 1.78)
<i>Hypertension</i>				
None	91.9	95.1	-	-
Preeclampsia or eclampsia	3.9	2.3	1.72 (1.38- 2.13)	1.06 (0.85- 1.32)
Pre-existing	1.7	0.8	2.05 (1.48- 2.84)	1.33 (0.96- 1.85)
Transient gestational	2.5	1.7	1.50 (1.15- 1.96)	1.08 (0.82- 1.41)
<i>Intrapartum Characteristics</i>				
<i>Maternal Infection</i>				
None	87.9	95.7	-	-

	Seizures (%) N = 2213	No Seizures (%) N = 2,332,803	Univariate OR (95% CI)	Multivariate OR (95% CI)
Chorioamnionitis	7.0	1.7	4.55 (3.87- 5.36)	2.86 (2.42- 3.39)
Other infection	2.6	1.5	1.93 (1.49- 2.51)	1.52 (1.17- 1.98)
Isolated fever	2.4	1.2	2.29 (1.75- 3.01)	1.89 (1.44- 2.49)
Catastrophic delivery *	8.2	0.9	10.51 (9.03- 12.24)	6.89 (5.89- 8.07)
Prolonged second stage	2.3	1.0	2.30 (1.74- 3.05)	1.79 (1.35- 2.39)
Mode of Delivery				
Routine vaginal	45.6	69.9	-	-
Operative vaginal	9.2	7.2	1.96 (1.68- 2.28)	1.65 (1.41- 1.92)
Cesarean day (6:00-17:00)	27.2	15.8	2.63 (2.38- 2.91)	2.23 (2.01- 2.48)
Cesarean night	18.1	7.1	3.90 (3.47- 4.38)	2.71 (2.39- 3.06)
Delivery ≥42 weeks	11.0	9.1	1.23 (1.08- 1.41)	1.22 (1.07- 1.40)
<i>Infant Characteristics</i>				
Male	57.3	50.9	1.29 (1.19- 1.40)	1.24 (1.14- 1.35)
Birth Weight				
2500-4000	79.4	85.9	-	-
<2500	7.3	3.0	2.63 (2.23- 3.09)	2.20 (1.85- 2.61)
>4000	13.4	11.1	1.31 (1.15- 1.48)	1.09 (0.97- 1.24)

* Abrupton, uterine rupture or cord prolapse

Table 2

Population attributable risk (PAR) for antenatal and intrapartum risk factors among 2213 newborns ≥ 36 weeks gestation at birth and seizures during the birth admission in California 1998-2002

Risk Factor	PAR (%)
<i>Antenatal Characteristics</i>	
Maternal age ≥ 40	1.7
Nulliparous	15.9
Diabetes Mellitus	
Gestational	2.7
Pre-existing	1.3
<i>Intrapartum Characteristics</i>	
Delivery > 42 weeks	2.1
Prolonged second stage of labor	1.3
Catastrophic delivery	7.4
Maternal infection	
Chorioamnionitis	5.4
Infection, no chorioamnionitis	1.2
Isolated fever	1.3