Postnatal Steroids and Febrile Seizure Susceptibility in Preterm Children

Yi-Fang Tu, MD, PhD, a, b Lan-Wan Wang, MD, PhD, c, d Shan-Tair Wang, MD, PhD, e Tsu-Fu Yeh, MD, d Chao-Ching Huang, MD a, d, f

abstract

OBJECTIVE: To investigate risk factors, seizure characteristics, and outcomes of febrile seizure (FS) in children born very preterm.

METHODS: This study used a prospective registry data set of 844 preterm infants (birth weight <1500 g and gestational age <32 weeks) admitted to NICUs from 2001 to 2009 in southern Taiwan. We investigated the prevalence, risks, seizure patterns, and outcomes of FS in children aged 5 years.

RESULTS: Among 575 children (follow-up rate, 85.8%) followed up for 5 years, 35 (6.1%) developed FS. The FS and non-FS groups were comparable regarding their mean gestational age, birth weight, 5-minute Apgar score <6, and prenatal and postnatal complications. No difference was observed in the use of prenatal corticosteroids between the 2 groups. The FS group had a significantly higher rate of postnatal corticosteroid treatment than the non-FS group, even after adjusting for confounding factors (odds ratio, 5.4 [95% confidence interval, 1.9–15.8]; P = .006). No differences were observed in IQs or subsequent epilepsy rates between the 2 groups. Although no difference was observed in the age of FS onset or neurodevelopmental outcomes between the 2 groups, children with FS who received postnatal corticosteroid treatment had a significantly lower mean body temperature during the first FS attack compared with those who did not receive postnatal corticosteroid treatment (38.6 ± 0.4°C vs 39.2 ± 0.6°C; P = .034).

CONCLUSIONS: Children born very preterm have a higher rate of FS, and postnatal corticosteroid treatment was associated with FS susceptibility in these children.

WHAT’S KNOWN ON THIS SUBJECT: Febrile seizure (FS) is a common neurologic disorder in children. Low birth weight and perinatal complications are risk factors for FS. No population study has focused on FS in a preterm population, which has a higher rate of perinatal and neonatal complications.

WHAT THIS STUDY ADDS: The cumulative incidence of FS was high (6.1%) in 5-year-old children who were born very preterm. Postnatal corticosteroid treatment increased the FS risk and seizure susceptibility during febrile illness in children born very preterm.

Dr Tu designed the study, interpreted the data, and drafted the manuscript; Dr S.T. Wang and Dr L.W. Wang performed statistical data analysis and interpretation; Dr Yeh interpreted the data and critiqued the manuscript; Dr Huang conceptualized the study, interpreted the data, and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DOI: 10.1542/peds.2015-3404

Accepted for publication Jan 26, 2016

Address correspondence to Chao-Ching Huang, MD, Department of Pediatrics, College of Medicine, Taipei Medical University, #250, Wu-Hsing St, Hsin-Yi District, Taipei City, 11031, Taiwan. E-mail: huangped@tmu.edu.tw

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2016 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

Febrile seizure (FS) is the most common neurologic disorder in children, with an incidence of 2% to 5% in children aged <5 years.\(^1,2\) Epilepsy develops in 2% to 6% of children with a history of FS.\(^1,2\) In addition to genetic factors, biological and environmental factors are critical sources of risk for FS. Previous studies have shown that maternal illness, low birth weight, perinatal complications or medications, and certain neonatal characteristics increase the risk of FS.\(^3-7\) Moreover, FS risk is higher in children born with a low gestational age and perinatal complications or those requiring perinatal medication, suggesting that exposure to adverse events in early life can predispose young children to FS.\(^8\)

Advances in neonatal intensive care have improved the survival rate of very preterm infants; however, the incidence rate of neurodevelopmental impairments is high.\(^9\) Preterm infants often experience hypoxic-ischemic and infectious insults during the prenatal, perinatal, and postnatal periods.\(^10\) Adverse events in the early life of preterm infants may therefore increase the occurrence of FS. A case–control study of seizures at a university hospital found that the incidence of FS was 13.5% (8 of 59) in children born very preterm, compared with 5% (3 of 60) in term control children.\(^11\) However, to the best of our knowledge no population study has focused on FS in children born very preterm. The goal of the present study, therefore, was to explore the risk factors, seizure characteristics, and neurodevelopmental outcome of FS in young children born very preterm by using a prospective registry data set of preterm infants in southern Taiwan.

**METHODS**

**Study Population**

This prospective study enrolled 844 very preterm infants (birth weight <1500 g and gestational age <32 weeks) admitted to the NICUs of 4 tertiary referral centers in Tainan City, southern Taiwan, from June 2001 to December 2009. Infants with congenital or chromosomal anomalies and those who died before discharge were excluded. Data on demographic factors and medical complications during the prenatal, perinatal, and postnatal periods were collected after obtaining parental consent. After discharge, all infants were followed up at 6, 12, and 24 months and again at 5 years. During the follow-up visits, pediatricians performed neuromotor examinations, and psychologists administered developmental assessment tests.\(^10,12\) Parents were interviewed and completed a questionnaire on the seizure history of their children. This follow-up study was approved by the institutional review board of National Cheng Kung University Hospital. Informed consent was obtained from the parents of preterm infants.

**Neurodevelopmental Outcome Assessment**

At 6, 12, and 24 months, cognitive and motor outcomes were assessed by using the mental and psychomotor development indices of the Bayley Scales of Infant Development–Second Edition.\(^10\) The Chinese version of the Wechsler Preschool and Primary Scale of Intelligence–Revised was used to assess the verbal, performance, and full-scale IQs of 5-year-old children born very preterm.

**Parent Interview and Questionnaire**

At the follow-up visits, the parents completed a questionnaire on their child’s history of FS or afebrile seizure (including related seizure types) and medication used. After the assessment, the pediatrician examined the responses and discussed the history and neurologic findings with the parents. Medical records were further reviewed in cases in which a history of seizures was reported.\(^13\)

**Definition of FS**

FS is defined as a seizure occurring in children aged between 6 months and 5 years that was associated with fever (body temperature >38°C) not caused by infection of the central nervous system. Diagnosis of FS cannot be made for patients with a history of neonatal seizures, unprovoked seizures, or other acute symptomatic seizures.\(^1,2,13\) Simple FS is characterized by single, generalized, and brief seizures (<15 minutes), whereas complex FS is characterized by focal onset and prolonged duration (>15 minutes) or the occurrence of multiple seizures within 24 hours.\(^14\) Febrile status epilepticus is defined as an FS lasting >30 minutes.

**Definition of Predictor Variables**

Predictor variables of FS were categorized according to FS occurrence during the prenatal, perinatal, or postnatal period. During the prenatal period, gestational diabetes mellitus was defined as any degree of glucose intolerance with onset or first recognition during pregnancy.\(^10,15\) Preeclampsia was defined as pregnancy-induced hypertension (arterial blood pressure >140/90 mm Hg) during the second half of gestation. The use of prenatal magnesium sulfate or corticosteroids was recorded. During the perinatal period, prolonged rupture of membranes was defined as the occurrence of ruptures >18 hours before delivery. During the postnatal period, infants with respiratory distress syndrome who received mechanical ventilation and those with symptomatic patent ductus arteriosus who required indomethacin therapy or surgical ligation were recorded. Bronchopulmonary dysplasia was defined as a supplemental...
oxygen requirement at 36 weeks of postconception age.\textsuperscript{16} Retinopathy of prematurity was graded into 5 stages (I–V) according to the International Classification of Retinopathy of Prematurity.\textsuperscript{17} Intraventricular hemorrhage was classified into 4 grades (I–IV), and cystic periventricular leukomalacia was defined as periventricular echolucent cystic lesions on ultrasonography.\textsuperscript{18, 19} Preterm infants with evolving or established bronchopulmonary dysplasia were treated with low-dose hydrocortisone for 12 days (1 mg/kg/d for 9 days followed by 0.5 mg/kg/d for 3 days).\textsuperscript{20, 21} The demographic factors assessed included gender, gestational age, birth weight, and head circumference.

**Statistical Analyses**

Differences in demographic factors, medical complications, and the neurodevelopmental outcome between children born very preterm who developed FS and those who did not were determined by using Fisher’s exact test for categorical variables and the Mann-Whitney U test for numerical variables. The potential predictors with significance levels of \( P < .05 \) in univariate analysis or with clinical significance were entered into a multivariate logistic regression model to calculate odds ratios (ORs) and 95% confidence intervals (CIs). All analyses were performed by using SPSS version 17 (IBM SPSS Statistics, IBM Corporation, Armonk, NY).

**RESULTS**

Among the 844 very preterm infants enrolled in this study, 165 (19.5%) died before discharge from the NICU. Among the 679 infants who survived, 7 infants with congenital anomalies (3 with chromosomal anomalies and 4 with congenital brain anomalies) were excluded, and another 97 infants were lost to follow-up. A total of 575 children (follow-up rate, 85.8%) were available for analysis at the age of 5 years (mean ± SD, 5.0 ± 0.1 years). Among them, 36 patients developed FS, although 1 child was excluded because of a history of neonatal seizure, thus yielding an FS prevalence rate of 6.1% (35 of 575) in young children born very preterm (Fig 1).

The mean age of FS onset was 2.7 ± 1.3 years. The demographic and medical factors of the FS and non-FS groups are listed in Table 1. No significant differences were observed in gender, mean gestational age, or mean birth weight and head circumference between the FS and non-FS groups. The 2 groups were comparable regarding maternal complications during pregnancy (eg, gestational diabetes, preeclampsia, eclampsia), 5-minute Apgar score (<6), and postnatal complications related to preterm birth (eg, respiratory distress syndrome requiring surfactants, symptomatic patent ductus arteriosus requiring surgical ligation, retinopathy of prematurity, bronchopulmonary dysplasia, intraventricular hemorrhage, cystic periventricular leukomalacia). No difference was observed in the use of prenatal corticosteroids or magnesium sulfate or postnatal indomethacin between the 2 groups. The FS group had a significantly higher rate of postnatal corticosteroid treatment than the non-FS group (OR, 5.4 [95% CI, 1.9–15.8]; \( P = .006 \)).

We also examined the association between postnatal corticosteroid exposure and FS susceptibility by using a multivariate logistic regression model. After adjustment for potential confounding factors (gender, gestational age, birth weight, 5-minute Apgar score <6, bronchopulmonary dysplasia, grade III–IV intraventricular hemorrhage, and cystic periventricular leukomalacia), postnatal corticosteroid therapy still

---

**FIGURE 1**

Flowchart of the recruitment of very preterm infants admitted to NICUs and follow-up of the infants who survived to the age of 5 years.
demonstrated prognostic significance for FS (OR, 7.9 [95% CI, 2.0–30.7]; \( P = .003 \)) (Table 2).

At follow-up, no significant difference was observed in the cognitive or motor developmental scores at 24 months or in the IQs at 5 years between the FS and non-FS groups. The 2 groups were also comparable regarding the rate of subsequent epilepsy (Table 3). Moreover, we investigated the association of postnatal corticosteroid use with the neurodevelopmental outcome and seizure characteristics of children with FS (Table 4). In the FS group, children with postnatal corticosteroid treatment did not have worse 24-month neurodevelopmental outcomes or IQs at 5 years of age compared with those without postnatal corticosteroid treatment. No difference was observed in the age of FS onset, occurrence of complex FS or febrile status epilepticus, recurrence rate of FS, or development of epilepsy between the 2 groups. However, in the FS group, children with postnatal corticosteroid treatment had a significantly lower mean body temperature during the first FS attack than did those without postnatal corticosteroid treatment (38.6 ± 0.4°C vs 39.2 ± 0.6°C; \( P = .034 \)).

**DISCUSSION**

Based on our research, the present study is the first to focus specifically on FS in a population of children born very preterm. Our study revealed a high cumulative FS incidence of 6.1% in children born very preterm. The FS and non-FS groups were comparable regarding maternal complications during pregnancy, gestational age, postnatal complications, and neurodevelopmental outcomes at 5 years of age. However, the children in the FS group had a significantly higher rate of postnatal corticosteroid treatment. In the FS group, children with postnatal

**TABLE 1** Demographic Factors and Complications During the Prenatal, Perinatal, and Postnatal Periods in Children Born Very Preterm With or Without FS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FS (n = 35)</th>
<th>Non-FS (n = 539)</th>
<th>OR (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>22 (62.9)</td>
<td>285 (52.8)</td>
<td>—</td>
<td>.296</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>28.8 ± 2.7</td>
<td>28.0 ± 2.8</td>
<td>—</td>
<td>.896</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>1120 ± 245</td>
<td>1141 ± 273</td>
<td>—</td>
<td>.563</td>
</tr>
<tr>
<td>Head circumference, cm</td>
<td>25.9 ± 2.1</td>
<td>25.8 ± 2.3</td>
<td>—</td>
<td>.737</td>
</tr>
<tr>
<td><strong>Prenatal complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>1 (2.8)</td>
<td>8 (1.5)</td>
<td>1.9 (0.2–15.8)</td>
<td>.440</td>
</tr>
<tr>
<td>Preeclampsia/eclampsia</td>
<td>4 (11.4)</td>
<td>78 (14.7)</td>
<td>0.7 (0.3–2.1)</td>
<td>.805</td>
</tr>
<tr>
<td><strong>Postnatal complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged rupture of membranes</td>
<td>11 (31.4)</td>
<td>164 (30.4)</td>
<td>1.0 (0.5–2.2)</td>
<td>.923</td>
</tr>
<tr>
<td>5-min Apgar score &lt;6</td>
<td>4 (11.4)</td>
<td>82 (15.2)</td>
<td>0.7 (0.2–2.0)</td>
<td>.633</td>
</tr>
<tr>
<td><strong>Medical treatments</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prenatal period</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium sulfate</td>
<td>3 (8.6)</td>
<td>49 (9.1)</td>
<td>0.9 (0.3–3.1)</td>
<td>.888</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>20 (57.1)</td>
<td>308 (57.1)</td>
<td>1.0 (0.5–2.0)</td>
<td>.910</td>
</tr>
<tr>
<td>Postnatal period</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>5 (14.3)</td>
<td>16 (3.0)</td>
<td>5.4 (1.9–15.8)</td>
<td>.006</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>10 (28.6)</td>
<td>151 (28.0)</td>
<td>1.0 (0.5–2.1)</td>
<td>.987</td>
</tr>
<tr>
<td>Oxygen, d</td>
<td>38.3 ± 32.1</td>
<td>40.4 ± 31.9</td>
<td>—</td>
<td>.724</td>
</tr>
<tr>
<td>Ventilator, d</td>
<td>8.4 ± 15.3</td>
<td>7.2 ± 12.9</td>
<td>—</td>
<td>.642</td>
</tr>
</tbody>
</table>

Data are presented as \( n \) (%) or mean ± SD. IVH, intraventricular hemorrhage.

**TABLE 2** Postnatal Corticosteroids and the Risk of FS in Children Born Very Preterm

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Crude OR (95% CI)</th>
<th>( P )</th>
<th>Adjusted OR (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>—</td>
<td>.296</td>
<td>—</td>
<td>.524</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>—</td>
<td>.896</td>
<td>—</td>
<td>.696</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>—</td>
<td>.563</td>
<td>—</td>
<td>.132</td>
</tr>
<tr>
<td>5-min Apgar score &lt;6</td>
<td>0.7 (0.2–2.0)</td>
<td>.633</td>
<td>0.5 (0.2–1.8)</td>
<td>.311</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>1.8 (0.8–3.3)</td>
<td>.220</td>
<td>1.2 (0.4–3.8)</td>
<td>.715</td>
</tr>
<tr>
<td>Postnatal corticosteroids</td>
<td>5.4</td>
<td>.006</td>
<td>7.9 (2.0–30.7)</td>
<td>.003</td>
</tr>
<tr>
<td>(1.9–15.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade III/IV IVH</td>
<td>1.6 (0.5–5.4)</td>
<td>.448</td>
<td>1.7 (0.5–6.3)</td>
<td>.434</td>
</tr>
<tr>
<td>cPVL</td>
<td>1.3 (0.3–5.6)</td>
<td>.673</td>
<td>1.1 (0.2–5.5)</td>
<td>.897</td>
</tr>
</tbody>
</table>

cPVL, cystic periventricular leukomalacia; IVH, intraventricular hemorrhage.

**TABLE 3** Neurodevelopmental Outcome at 24 Months and 5 Years in Children Born Very Preterm With or Without FS

<table>
<thead>
<tr>
<th>Outcome</th>
<th>FS (n = 35)</th>
<th>Non-FS (n = 539)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurodevelopmental outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-mo BSID-II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental development index</td>
<td>87.1 ± 15.6</td>
<td>86.4 ± 16.8</td>
<td>.980</td>
</tr>
<tr>
<td>Psychomotor development index</td>
<td>86.2 ± 18.0</td>
<td>87.6 ± 16.3</td>
<td>.754</td>
</tr>
<tr>
<td>5-y WPPSI-R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performance IQ</td>
<td>85.3 ± 17.2</td>
<td>85.7 ± 16.0</td>
<td>.803</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>87.6 ± 15.3</td>
<td>90.8 ± 14.8</td>
<td>.341</td>
</tr>
<tr>
<td>Full-scale IQ</td>
<td>85.3 ± 15.2</td>
<td>87.4 ± 14.7</td>
<td>.595</td>
</tr>
<tr>
<td>Subsequent epilepsy</td>
<td>2 (5.7)</td>
<td>13 (2.4)</td>
<td>.231</td>
</tr>
</tbody>
</table>

Data are presented as \( n \) (%) or mean ± SD. BSID-II, Bayley Scales of Infant Development–Second Edition; WPPSI-R, Wechsler Preschool and Primary Scale of Intelligence–Revised, Chinese version.
corticosteroid treatment did not have worse neurodevelopmental outcomes compared with those without postnatal corticosteroid treatment. In addition, in the FS group, children with postnatal corticosteroid treatment had significantly lower body temperatures during the first FS attack than those without postnatal corticosteroid treatment. Our findings suggest that children born very preterm are susceptible to FS, and postnatal corticosteroid treatment is associated with the FS risk and seizure susceptibility during febrile illness in children born very preterm.

The incidence of FS is 2% to 5% in children aged <5 years, with the peak incidence occurring in the second year of life. The prevalence of FS in Europe and the United States is estimated to be 2% to 5% in the pediatric population, whereas the prevalence is ~1.5% in other countries such as China. A previous population study in southern Taiwan (in which only 2% of the patients were born preterm) revealed a cumulative FS incidence of 2.4% in children aged 3 years. Other studies have also shown that low birth weight and prematurity are risk factors for FS. In the present study, we found that the cumulative incidence of FS was 4% (23 of 575) at the age of 3 years in children born very preterm and 6.1% (35 of 575) in those at age 5 years; both of these outcomes are considerably higher than the reported incidence in the general population. The reason for this discrepancy remains unknown. FS may be associated with the vulnerability of the developing brain or complications or medication used during early life.

Premature infants are at a high risk of various hypoxic-ischemic and infectious insults because of pulmonary immaturity, cardiovascular insufficiency, and sepsis. Hypoxic-ischemic or infectious events in early life can alter neuronal excitability and are associated with seizure susceptibility in later life. Therefore, the increase in FS occurrence in children born very preterm could be due to several related adverse events of hypoxia-ischemia or infection during early life.

In addition, studies have indicated that early changes in the function and structure of the neural system after stress contribute to susceptibility to FS and epilepsy. A previous study suggested that the excitatory neuropeptide corticotropin-releasing hormone (CRH), the genetic expression of which is activated by stress, is associated with developmental seizures. CRH, a proconvulsive molecule, functions not only as a hypothalamic-releasing factor but also as a modulator of limbic circuit excitation. Neuronal populations that synthesize CRH or possess CRH receptors are abundant in the limbic system, particularly the amygdala and hippocampus. Young children may be particularly susceptible to seizure because the CRH receptor is the main receptor bound during stressful experiences in young animals, and increased levels of CRH, CRH receptors, and CRH-binding protein have been observed postmortem in the brains of children with generalized epilepsy. CRH is a likely candidate for modulating excitability in response to triggers such as fever in the developing brain.

During the neonatal period, corticosteroids are commonly used to treat bronchopulmonary dysplasia, which is a common cause of long-term adverse pulmonary and neurodevelopment outcomes in preterm infants. Our study found that postnatal corticosteroid exposure is associated with a high FS risk and low seizure susceptibility during febrile illness in children born very preterm; however, the underlying pathophysiology remains unknown. Hippocampal glucocorticoid receptors and CRH, which are involved in neuronal seizure susceptibility and behavior, have been identified as possible targets of early-life...
corticosteroid effects. Excess early-life glucocorticoid exposure may lead to decreased glucocorticoid receptor expression and increased CRH expression in neurons.\textsuperscript{31} These findings suggest that the use of neonatal corticosteroids may be associated with a risk of FS by upregulating CRH in the brain regions involved in the circuitry that processes stressful stimuli.\textsuperscript{26} Furthermore, in numerous animal models, corticosterone supplementation has led to morphologic or functional changes in hippocampal structures that are similar to those in patients with temporal lobe epilepsy.\textsuperscript{24, 32} Administration of high-dose glucocorticoids has resulted in hippocampal atrophy, loss of pyramidal cells in the CA1 and CA3 regions, and inhibition of dentate granule cell neurogenesis.\textsuperscript{33} These abnormal changes are supported by the observation that early-life stress facilitates seizure development.\textsuperscript{34} This effect on seizure development can be mediated by corticosterone: the facilitating effect of corticosterone on chemical-induced status epilepticus in rat pups is inhibited by a corticosterone synthesis blocker, thus confirming the crucial role of corticosterone in seizure susceptibility.\textsuperscript{35} High corticosterone levels in early life are believed to irreversibly impair the inhibitory control of the hypothalamic–pituitary–adrenal axis; the disinhibition of this chronic stress axis may induce upregulation of CRH from the paraventricular nucleus.\textsuperscript{26} In addition, Qaheri et al\textsuperscript{36} reported that neonatal dexamethasone exposure in rat pups decreased the convulsion threshold in adult life. Collectively, these reports regarding corticosteroid use during early life support our finding that postnatal corticosteroid treatment reduces the seizure threshold during febrile illness in children born very preterm.

Because our results might be post hoc findings based on the small sample size, and other unknown confounding factors may exist, a long-term follow-up study of FS with a larger sample of children born very preterm is necessary to validate our results. The survival status was a potential common effect of corticosteroid use and FS. Because we included only survivors, we could have introduced selection bias that rendered spurious associations between the steroid use and FS. Nonetheless, this bias may have had only a minor effect on our finding because the mortality rate of FS is very rare.\textsuperscript{37} Regarding model selection, we considered that multiplicity testing might increase the false-positive rate in our study. However, our main finding remained significant after adjusting for type I errors. An experimental study of hyperthermia-induced seizures may delineate the neurobiologic mechanisms underlying increased seizure susceptibility after postnatal corticosteroid treatment.

**CONCLUSION**

The present study indicates that children born very preterm are susceptible to FS, and that the use of postnatal corticosteroids is associated with the FS risk in these children.

**ACKNOWLEDGMENTS**

We express our gratitude to the patients, their caretakers, and the clinical and laboratory staff from National Cheng Kung University Hospital. We also thank Ying-Chia Wu, Wen-Jung Chang, Ming-Yang Su, and Wen-Hao Yu for their valuable assistance.

**ABBREVIATIONS**

CI: confidence interval  
CRH: corticotropin-releasing hormone  
FS: febrile seizure  
OR: odds ratio

---

**FUNDING:** Supported by grants from National Cheng Kung University Hospital (NCKUH-10105002 and 10407014) and the Taiwan National Science Council (NSC 100-2314-B-006-045 MY2 and 103-2314-B-006-017-MY3; MOST 103-2314-B-038-062-MY3).

**POTENTIAL CONFLICT OF INTEREST:** The authors have indicated they have no potential conflicts of interest to disclose.

**REFERENCES**

7. Nelson KB, Ellenberg JH. Prenatal and perinatal antecedents of
33. McEwen BS, Magarinos AM. Stress and hippocampal plasticity: implications for the pathophysiology of affective disorders. Hum Psychopharmacol. 2001;16(S1):37–519
Postnatal Steroids and Febrile Seizure Susceptibility in Preterm Children
Yi-Fang Tu, Lan-Wan Wang, Shan-Tair Wang, Tsu-Fu Yeh and Chao-Ching Huang

Pediatrics 2016;137;
DOI: 10.1542/peds.2015-3404 originally published online March 24, 2016;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/137/4/e20153404