

# The Remarkably High Prevalence of Epilepsy and Seizure History in Fetal Alcohol Spectrum Disorders

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**Background:** Fetal alcohol spectrum disorder (FASD) is the umbrella term that describes the range of adverse developmental outcomes that may occur in the offspring of mothers who drink alcohol during pregnancy. FASD is associated with several comorbidities including epilepsy. The objective of the study was to evaluate the prevalence of epilepsy or a history of seizures in subjects with FASD and the contribution of relevant risk factors.

**Methods:** A retrospective chart review was conducted on all active charts ( $N = 1063$ ) at two FASD clinics. After exclusion of subjects without a confirmed diagnosis, a total of 425 subjects between the ages of 2–49 were included in the analysis. The relationships between FASD diagnosis and other risk factors for co-occurrence of epilepsy or a seizure disorder (e.g., extent of exposure to alcohol and other drugs, type of birth, and trauma) were examined using chi-square and multivariate multinomial logistic regression.

**Results:** Twenty-five (5.9%) individuals in the study population had a confirmed diagnosis of epilepsy, and 50 (11.8%) had at least one documented seizure episode, yielding an overall prevalence of 17.7% in this population. Importantly, a history of epilepsy or seizures was not different across the three diagnostic subgroups. In those subjects with available maternal drinking histories, first trimester exposure or drinking throughout all three trimesters were the predominant forms of fetal exposure. None of the other risk factors were associated with a greater prevalence of epilepsy or seizures.

**Conclusions:** There is a remarkably high prevalence of epilepsy/seizures in the FASD population.

**Key Words:** Fetal Alcohol Spectrum Disorders, Epilepsy, Seizures.

FETAL ALCOHOL SPECTRUM disorder (FASD) describes the range of adverse developmental outcomes that occur as a consequence of maternal drinking during pregnancy (Chudley et al., 2005; Sokol et al., 2003). This group of disorders may affect as many as 1 in 100 children in Canada (Public Health Agency of Canada, 2007), although a recent review of epidemiological studies indicated that prevalence

rates for FASD are usually underestimated and may be as high as 3–5% (May et al., 2009). Children with FASD suffer from a large number of comorbidities and may present with a range of neurological deficits including problems with learning, attention, memory, sensory-motor skills, executive function, and epilepsy. Epilepsy is a disorder characterized by spontaneous recurrence of unprovoked seizures (Shneker and Fountain, 2003), affecting 0.6% of the general population and with an incidence of 0.5% per annum (Tellez-Zenteno et al., 2004).

Previous studies that examined seizures and epilepsy among those with FASD comprised relatively small sample sizes, and for the most part included only subjects with fetal alcohol syndrome (FAS). Collectively, these studies indicated that between 3 and 21% of children with FAS also have epilepsy or a seizure disorder as a comorbidity (Iosub et al., 1981; Majewski and Goecke, 1982; O'Malley and Barr, 1998; Olegard et al., 1979; Spohr and Steinhausen, 1987). While these studies suggest that there is a higher incidence of seizures in children prenatally exposed to alcohol, they have left several important questions unanswered, because diagnoses were not clearly established (i.e., seizure type), and the relatively small sample sizes precluded examination of additional risk factors and other diagnostic subgroups included under the FASD umbrella.

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There is a significant overlap in the brain structures that suffer neuropathological and functional deficits in response to chronic prenatal alcohol exposure and those that are associated with the genesis and/or spread of epileptiform activity in the brain, including the hippocampus (Ba et al., 1999; Bonthius et al., 2001a,b). Furthermore, indirect complications may be linked to prenatal alcohol exposure, which also increase the risk of epilepsy. These include maternal malnutrition, other prenatal drug exposures, prematurity, type of birth and complications, increased exposure to infection, and deficient prenatal care. Social experiences and other incidents involving the mother and/or child may also adversely affect the child's health including sleep problems, drug and alcohol abuse, and trauma. Thus, there is a clear need to determine whether prenatal alcohol exposure puts people at an increased risk of epilepsy and seizures, whether there are specific types of seizure disorders that are linked to prenatal alcohol exposure, and whether additional maternal and/or fetal factors influence the risk of seizures disorders in offspring exposed to alcohol during fetal life. The current study tested the hypotheses that: (i) individuals with FASD have a high prevalence of epilepsy and/or seizures; (ii) epilepsy and/or seizures are not associated with a specific diagnostic subgroup; and (iii) a history of prenatal alcohol exposure is independent of other risk factors associated with epilepsy and seizures in individuals with FASD.

## MATERIALS AND METHODS

All active charts ( $n = 1063$ ) from the FASD clinics located at St. Michael's Hospital in Toronto, Ontario and Glenrose Rehabilitation Hospital in Edmonton, Alberta were reviewed. Information was gathered on subjects who had a confirmed diagnosis within the FASD spectrum. Both of these clinics follow the Canadian Guidelines for diagnosis, which identifies three diagnostic subgroups within FASD; fetal alcohol syndrome (FAS), partial FAS, and Alcohol-Related Neurodevelopmental Disorder (ARND) (Chudley et al., 2005). The criteria for diagnosis of FAS include evidence of prenatal and/or postnatal growth restriction, a characteristic triad of craniofacial dysmorphologies, impairment in three or more central nervous system (CNS) domains, and confirmed or suspected maternal alcohol consumption. The criteria for a diagnosis of pFAS include the presence of any two of the craniofacial features, impairment in three or more CNS domains, and confirmed maternal alcohol consumption. Finally, the criteria for the diagnosis of ARND include impairment in three or more CNS domains and confirmed maternal alcohol consumption. Information regarding maternal drinking history was extracted including: pattern and magnitude of consumption and type of beverage. If the patient had a diagnosis of epilepsy (clear history and anticonvulsant treatment) or a history of seizures documented in the chart, then type, age of onset, frequency, and treatment were recorded (when available). A pediatric (PAH, for subjects under 14 and younger) or adult (PLC, for subjects 15 and older) neurologist reviewed all of these patient records. Seizures were classified according to intake forms that asked the subject or caregiver about seizure history and reports from the primary care physician at the clinic. EEG data was not available for this study. The following definitions were used for the different seizure types as could be best assessed from the chart reviews: generalized seizures, characterized by generalized body convulsive activity with loss of consciousness; partial seizures, simple seizures with motor, sensory, autonomic, or psychic symptoms without impaired consciousness; complex partial, or

absence seizures are those seizures with impaired consciousness with or without partial seizure characteristics; febrile seizures are characteristically generalized seizures in infants associated with a high fever.

Information was also collected (when available) on family history, other comorbid conditions, congenital anomalies, prenatal alcohol intake and drug exposure history, prenatal care, type of birth including complications, prematurity, size for gestational age, APGAR (Appearance, Pulse, Grimace, Activity, Respiration) score, head trauma, physical abuse, sexual abuse, number of moves as a child (between families) or before seizure onset, sleep disorders, and subject use of alcohol and drugs.

Six hundred and eight subjects were excluded from data collection for reasons including: absence of a confirmed diagnosis within the FASD spectrum, lost to follow-up, and insufficient chart information. Therefore, 425 subjects with a diagnosis within the FASD spectrum were included in the data analysis.

## Data Analysis

Seizure type(s) were classified when possible by a pediatric or adult neurologist. Chi-square (Fisher's exact) tests were used to compare patients with epilepsy or seizure to those subjects with FASD with no history of seizures. Multinomial logistic regression analysis was conducted to examine whether other potential risk factors significantly increased or decreased the likelihood of epilepsy or spontaneous seizures. This type of analysis is used to examine the effect of predictors on outcome (adjusted associations). Statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC). All analyses were two-tailed, and  $p$  values  $>0.05$  were regarded as being significant.

Age and gender were adjusted for in the regression analysis. Birth complications, Apgar score, sleep disorders, and subject use of alcohol and drugs were excluded in the regression analysis because of zero cell frequency. For example, zero cell frequency occurred when none of the subjects with epilepsy had a reported "Yes" to the question concerning sleep disorders. Thus, for that particular category, one of the cells would report no instances or 0%, and therefore no meaningful analysis could be conducted. Unknown variables were included in the analysis to increase statistical power to detect the significance of predictors. These variables were included as a special category (dummy variable) in the regression analysis. They could not be excluded as this made the estimates inaccurate and thus not statistically valid.

## RESULTS

A total of 425 subjects were included in the analysis. Demographic information on the study population is shown in Table 1. Subjects included in the study ranged in age from 2 to 49 years old. Approximately equal numbers of subjects were  $\leq 14$  vs.  $\geq 15$  years old, and the proportion of men to women was 60:40. Individual subjects with an FASD also frequently had a history of one or more additional comorbid disorders; the most frequently reported comorbidity was Attention Deficit Hyperactivity Disorder (ADHD) (Table 1).

Of the 425 subjects included in the analysis, 86 (20%) had a diagnosis of FAS or pFAS, and the remaining 339 (80%) had a diagnosis of ARND (Table 2). These proportions are consistent with epidemiological reports on the prevalence of FAS versus all cases of FASD (May et al., 2009). Twenty-five subjects (5.9%) with FASD were found to have a confirmed diagnosis of epilepsy, and another 50 subjects (11.8%) had one or more documented seizure episodes, and the total sample with

**Table 1.** Demographic Characteristics

Characteristics	Subjects ( <i>n</i> = 425)
Age	
Mean (SD)	15.2(7.6)
Range Toronto	2–49
Edmonton	6–22
Age group	
2–14	219(51.5%)
15+	206(48.5%)
Gender, <i>n</i> (%)	
Male	254(59.8%)
Female	171(40.2%)
Comorbidities	276(64.9%)
ADHD	200(47.1%)
ODD	42(9.9%)
Autism	8(1.9%)
Depression	25(5.9%)
PTSD	17(4%)
ROD	17(4%)

ADHD, attention deficit hyperactivity disorder; ODD, oppositional defiant disorder; PTSD, post-traumatic stress disorder; ROD, reactive attachment disorder.

**Table 2.** The Prevalence of Epilepsy and Seizures in the FASD Population

FASD diagnosis	No seizures	≥1 seizure episode(s)	Epilepsy	All seizures
FAS, <i>N</i> (%)	12 (80.0)	3 (20.0)	0 (0)	3 (20.0)
pFAS, <i>N</i> (%)	61 (85.9)	7 (9.9)	3 (4.2)	10 (14.1)
ARND, <i>N</i> (%)	277 (81.7)	40 (11.8)	22 (6.5)	62 (18.23)
Overall, <i>N</i> (%)	350 (82.3)	<b>50 (11.8)</b>	<b>25 (5.9)</b>	<b>75 (17.7)</b>

Bold font indicates the total number of subjects with one or more seizures, epilepsy, or all seizures in those with FASD.

ARND, alcohol-related neurodevelopmental disorder; FAS, fetal alcohol syndrome; pFAS, partial fetal alcohol syndrome.

**Table 3.** Maternal Drinking Patterns in Epilepsy and Seizure Subjects

Trimester of alcohol exposure	Epilepsy	≥1 Seizure episode(s)
1st	5	8
2nd	0	1
3rd	0	0
1st and 2nd	0	2
1st and 3rd	1	0
All 3 trimesters	5	14

Information available for 36/75 subjects.

a history of seizures was 75 (17.7%) (Table 2). The chi-square test (Fisher's exact) indicated that there were no differences between FASD diagnosis and risk of epilepsy, or one or more seizures ( $p = 0.73$ ). Where available, maternal drinking history was also analyzed. There was a predominance of at least first trimester maternal drinking (5 mothers of those with epilepsy and 8 mothers of those with one or more seizure episodes) or drinking throughout all three trimesters (5 mothers of those with epilepsy and 14 mothers of those with one or more seizure episodes), in subjects with epilepsy or seizures (Table 3). Where possible, seizure types(s) were classified (Table 4), revealing the range of generalized and focal epilep-

**Table 4.** Classification of Seizures (number of subjects per category)

Classification	Epilepsy	≥1 Seizure episode(s)
Generalized	8	2
Partial	3	2
Complex partial or absence	9	22
Febrile	0	4
Unclassified	5	20
Total	25	50

sies, with the most common diagnosis being complex partial or absence seizures (31/75). Further classification was not possible.

The chi-square test revealed that those subjects who did not have a natural birth (breech, cesarean, forceps, or vacuum) were more likely to have epilepsy or seizures (all seizures),  $p < 0.05$  (Table 5). In addition, a history of prenatal drug exposure approached significance ( $p = 0.054$ ) for those with epilepsy or seizures (all seizures). No other risk factors examined had a significant effect on the risk of epilepsy or seizures.

The multinomial logistic regression showed that those with epilepsy were three times (OR = 3.41, CI 1.11–10.5,  $p < 0.05$ ) more likely to have an unnatural type of birth (breech, caesarean, forceps, or vacuum) than those with no history of seizures (Table 6). Furthermore, when all seizures were combined, those with epilepsy or seizures were two times (OR = 2.27, CI = 1.14–4.51,  $p < 0.05$ ) more likely to have an unnatural birth than those subjects with a history of seizures (Table 6). No other risk factor examined was found to be associated with a higher frequency of epilepsy and/or seizures (Table 6).

## DISCUSSION

The current study found a remarkably high prevalence of epilepsy (5.9%) and seizure history (11.8%) among 425 subjects with diagnosed FASD. This is very high, as epilepsy is reported to affect 0.6% of the general population (Tellez-Zenteno et al., 2004). There were no differences in the prevalence of epilepsy or seizures between individuals with FAS, pFAS, or ARND. Subjects were more likely to have epilepsy or a history of seizures, if exposure to alcohol occurred in the first trimester, or all three trimesters.

As is the case in the general epileptic population, the commonest seizure type deduced from the chart review was designated as complex partial or absence. Complex partial seizures imply a focal onset, whereas absence seizures can be associated with primary generalized epilepsy or a form of complex partial seizure. This chart review study, usually without EEG findings, did not permit more detailed classification. Similarly, those seizures designated as generalized could not be differentiated into primary or secondarily generalized types.

An important question that the current study attempted to address was whether epileptic disorders in children with FASD can be attributed directly to the neuroteratogenic effects of alcohol or to some other risk factor or factors for epilepsy that accompany maternal alcohol abuse. Subjects

**Table 5.** Chi Square Test Results

	N	No Seizures (%)	Epilepsy (%)	≥1 Seizure Episode(s) (%)	p-value	All seizures (%)	p-value
Family history of epilepsy							
Yes	20	75.0	10.0	15.0	0.237	25.0	0.178
No	338	84.3	5.6	10.1		15.7	
Unknown	67	76.1	6.0	17.9		23.9	
Prenatal drug exposure							
Yes	181	84.0	5.5	10.5	0.160	16.0	<b>0.054</b>
No	140	86.4	3.6	10.0		13.6	
Unknown	104	75.0	9.6	15.4		25.0	
Prematurity							
Yes	52	88.5	1.9	9.6	0.648	11.5	0.404
No	237	82.7	5.9	11.4		17.3	
Unknown	136	80.2	7.4	12.5		19.9	
Size for gestational age							
Appropriate	192	82.8	5.2	12.0	0.615	17.2	0.423
Small	70	88.6	2.9	8.6		11.4	
Large	17	76.5	11.8	11.8		23.5	
Unknown	146	80.1	7.5	12.3		19.9	
Type of birth							
Natural	197	83.8	5.1	11.2	0.134	16.2	<b>0.035</b>
Other	77	72.7	10.4	16.9		27.3	
Unknown	151	86.1	4.6	9.3		13.9	
Prenatal care							
Yes	122	79.5	7.4	13.1	0.239	20.5	0.562
No	77	84.4	9.1	6.5		15.6	
Unknown	226	83.6	4.0	12.4		16.4	
Head trauma							
Yes	16	81.3	12.5	6.2	0.409	18.7	0.745
No	409	82.8	5.4	11.8		17.2	
Physical abuse							
Yes	82	80.5	8.5	11.0	0.596	19.5	0.526
No	260	84.2	4.6	11.1		15.8	
Unknown	83	79.5	7.2	13.3		20.5	
Sexual abuse							
Yes	68	80.9	7.3	11.8	0.581	19.1	0.316
No	245	84.9	4.5	10.6		15.1	
Unknown	112	78.6	8.0	13.4		21.4	
Number of moves							
None	121	82.6	8.3	9.1	0.583	17.4	0.860
One or more	227	83.3	4.9	11.9		16.7	
Unknown	77	80.5	5.2	14.3		19.5	

A history of prenatal drug exposure approached significance ( $p = .054$ ). Those subjects who did not have a natural birth were more likely to have epilepsy or seizures ( $p < .05$ ).

**Table 6.** Multivariate Multinomial Logistic Regression Results

	Epilepsy OR (95% CI)	≥1 Seizure episode(s) OR (95% CI)	All seizures OR (95% CI)
Family history of epilepsy (yes vs. no)	2.93 (0.50–17.1)	1.37 (0.34–5.48)	1.64 (0.52–5.19)
Prenatal drug exposure (yes vs. no)	1.35 (0.42–4.39)	1.19 (0.55–2.60)	1.23 (0.63–2.40)
Prematurity (yes vs. no)	0.21 (0.02–2.27)	0.70 (0.23–2.20)	0.57 (0.20–1.60)
Size for gestational age (large vs. appropriate)	4.06 (0.70–22.7)	0.95 (0.18–5.03)	1.57 (0.44–5.54)
Size for gestational age (small vs. appropriate)	0.88 (0.16–4.87)	0.63 (0.22–1.79)	0.69 (0.28–1.73)
Type of birth (others vs. nature)	<b>3.41 (1.11–10.5)**</b>	1.96 (0.87–4.40)	<b>2.27 (1.14–4.51)**</b>
Prenatal care (yes vs. no)	0.68 (0.21–2.17)	1.91 (0.64–5.72)	1.21 (0.54–2.72)
Head trauma (yes vs. no)	2.59 (0.41–16.4)	0.51 (0.06–4.45)	1.11 (0.27–4.47)
Physical abuse (yes vs. no)	2.10 (0.55–8.06)	0.76 (0.28–2.08)	1.05 (0.46–2.39)
Sexual abuse (yes vs. no)	1.11 (0.27–4.62)	1.11 (0.40–3.11)	1.15 (0.48–2.72)
Number of moves (more than 1 moves vs. no move)	0.51 (0.19–1.38)	1.27 (0.58–2.80)	0.93 (0.49–1.74)
Congenital malformations (yes vs. no)	0.56 (0.15–2.07)	1.29 (0.58–2.87)	1.07 (0.52–2.20)

Those with epilepsy were three times (OR = 3.41, CI = 1.11–10.5,  $p < 0.05$ ) more likely to have an unnatural type of birth than those with no history of seizures. Those with seizures and epilepsy were two times (OR = 2.27, CI = 1.14–4.51,  $p < 0.05$ ) more likely to have an unnatural birth than those with no history of seizures. Age and gender are also adjusted in the multivariate multinomial logistic regression. Unknown categories are also included in the analysis, but not reported here. \*\*\*\* $p < 0.001$ ; \*\*\* $p < 0.01$ ; \*\* $p < 0.05$ ; \* $p < 0.10$ .

with a breech, cesarean, forceps, or vacuum birth were three times more likely to have epilepsy and two times more likely to have epilepsy and one or more seizures (all seizures) than

those with a normal vaginal birth. Most studies that have looked at labor and delivery events have not found an increased risk in the development of childhood epilepsy

(Degen, 1978; Greenwood et al., 1998; Lilienfeld and Pasamanick, 1954; Nelson and Ellenberg, 1986). In contrast, Chevrie and Aicardi (1977) reported that abnormal delivery was a significant risk factor when children with epilepsy diagnosed in the first year after birth were compared to children with febrile convulsions and with occasional epileptic seizures. However, this study grouped several labor and delivery events together, assuming comparable consequences. A study conducted by Sidenvall and colleagues (2001) found that cesarean sections (OR = 18, 95% CI, 3.7–88) increased the risk of having epilepsy. In the majority of caesarean sections, this procedure was performed as a consequence of adverse events occurring in the mother and/or fetus (Sidenvall et al., 2001). In the current study, 12 subjects with epilepsy and two with a seizure history were born by cesarean section, five of which were reported as emergency cesarean sections. Emergency cesarean sections were performed because of adverse events occurring in the mother or fetus including: a ruptured membrane and slow progression of labor, high maternal blood pressure, and breathing difficulties in the infant. Furthermore, in subjects with seizures, three individuals were born by forceps delivery, one by vacuum delivery, and three in breech position. Among those subjects with epilepsy or seizures and a birth other than natural, four had respiratory problems.

Coyne and colleagues (2008) reviewed pregnancy records of women whose infants were subsequently diagnosed with FAS by the Pediatric Outreach Service (POS) of the Cairns Base Hospital in Queensland, Australia. Among the delivery complications, incidences of fetal distress were significantly increased in case mothers. There was a highly significant difference between the two groups in rates of admission to special care baby unit (SCBU) or to the neonatal intensive care unit (NICU). Thirty-four cases (62.7%) were admitted to SCBU and two (3.4%) to NICU, compared to 17 (27.1%) controls admitted to SCBU. Moreover, in a study of over 900 women entering prenatal care in the United States, maternal problem drinking was significantly correlated to a higher incidence of birth complications (Flynn et al., 2009), including preterm rupture of membranes, fewer weeks of gestation, decreased APGAR scores, and decreased birthweight. Thus, maternal alcohol consumption would appear to be a significant risk factor for a number of complications in labor, delivery, and birth events.

Most studies that have examined various perinatal factors, especially those related to "birth asphyxia," have failed to find any significant associations increasing the risk of epilepsy (Degen, 1978; Deymeer and Leviton, 1985; Greenwood et al., 1998; Lilienfeld and Pasamanick, 1954; Nelson and Ellenberg, 1984, 1986; Rocca et al., 1987a,b,c). Furthermore, abnormal electrical activity is likely to occur prior to birth and acute events in labour are not likely to contribute (Sokol et al., 2003). However, fetal alcohol exposure could sensitize the neonatal brain to the damaging effects of perinatal complications.

Subjects with prenatal drug exposure were more likely to have epilepsy or seizures than those without prenatal drug exposures, although there was no longer an effect when other

risk factors were controlled for in the regression analysis. There was a high frequency of heavy drinkers among multidrug users. Most of these women drank heavily (5 or more drinks) regularly, throughout pregnancy. Nine women reported drinking five or more drinks (5–15 drinks) two or more days a week. All but two of these women drank throughout pregnancy. Two other women reported drinking one or more drinks (1–4) four to seven days a week. Evidently, and perhaps not surprisingly, multidrug users were the heaviest drinkers in this study population, and therefore the children of these mothers had the highest levels of alcohol exposure during prenatal life. This question requires more extensive study, to determine the true cause–effect relationship between multiple drug use and the elevated risk of seizures in subjects who were also exposed to alcohol and other drugs.

Recently, the results of a large-scale epidemiological study, examining the impact of prenatal alcohol exposure as a risk factor for epilepsy, showed that exposure to binge drinking during the eleventh to sixteenth gestational weeks led to a 3.15 fold increase in neonatal seizures and a 1.81 fold increase in the risk of epilepsy (Sun et al., 2009).

## LIMITATIONS

Although the results of the current study indicate a higher prevalence of epilepsy and seizures in the two specialized FASD clinics, these results cannot be directly compared to epilepsy and/or seizure prevalence in the general population. Children who receive a diagnosis of FAS, pFAS, or ARND have demonstrable CNS dysfunction in at least three domains (Chudley et al., 2005). Thus, these children can be considered to be among those that have been most affected by prenatal alcohol exposure. The current study, therefore, could not address the question of whether prenatal alcohol exposure per se, in the absence of an FASD diagnosis, increases the risk for epilepsy and/or seizures. All information was sought from physician, hospital, and government documents; however, when information was not available, self-report forms were considered. Most information could be verified through cross-examination of other documents. There were a number of unknown variables for subjects; they had to be included as a special category in the analysis, which may have impacted the overall results. Two neurologists extensively reviewed records of those with epilepsy. To properly classify those with a history of seizures, however, more detailed work-ups including EEGs and brain imaging are required, preferably in a controlled, prospective study.

Some factors need to be further explored. For example, diet in the mother pre and postnatally, as well as diet in the newborn infant, may increase the risk for epilepsy. Birth complications, Apgar score, sleep problems in the subject, and alcohol and drug use could not be evaluated in the current study, as detailed information on these parameters was often not included in the individual patient charts. Finally, many mothers consumed other drugs during pregnancy. Many of these mothers had the highest self-reports of alcohol con-

sumption, and thus it is not certain whether the increased risk is associated with high alcohol consumption, other drug use, or the combination.

## CONCLUSIONS AND FUTURE DIRECTIONS

The high prevalence of epilepsy and seizures in children and adults with FASD requires much more intensive study to address a number of critical questions. The timing of alcohol exposure during pregnancy and the pattern of maternal drinking, and the relative risk for epilepsy and seizures needs to be evaluated to determine thresholds for exposure and potential critical periods of vulnerability. Behavioral and physiologic effects of alcohol exposure during development depend on the timing of exposure and reflect regional and cellular differences in vulnerability to alcohol injury (Bonthius et al., 2001a,b). Epilepsy is frequently missed in routine clinical assessments, and untreated epilepsy can lead to increased or unrecognized cognitive deficits. Long-term consequences of epilepsy may include problems in attention and memory as well as the risk of unattended and dangerous seizures (Devinsky, 2004; Dunn et al., 2003; Sherman et al., 2007). Many children who have a medical evaluation for epilepsy have a known history of prenatal alcohol exposure and no other predispositions to epilepsy, but do not have the physical features of FASD. Therefore, it is very important for the physician to be aware of alcohol exposure in utero, when considering possible etiology and mechanisms of seizures.

Future studies are needed to understand the brain mechanisms that link the effects of prenatal alcohol exposure and a reduced seizure threshold. A prospective analysis of subjects with FASD is needed to obtain more accurate information on seizure onset, type, and duration. EEG results could provide important information as to type of seizures and diagnosis of epilepsy, and MRI results could identify structural brain damage in the affected brain region. Importantly, these results will heighten physicians' and other caregivers' awareness of this under recognized and important risk factor for epilepsy.

## REFERENCES

- Ba A, Seri BV, Aka KJ, Glin L, Tako A (1999) Comparative effects of developmental thiamine deficiencies and ethanol exposure on the morphometry of the CA3 pyramidal cells. *Neurobehav Toxicol Teratol* 21:579–586.
- Bonhithus DJ, Pantazis NJ, Karacay B, Bonhithus NE, Taggard DA, Lothman EW (2001a) Alcohol exposure during the brain growth spurt promotes hippocampal seizures, kindling, and spreading depression. *Alcohol Clin Exp Res* 25(5):734–745.
- Bonhithus D, Woodhouse J, Bonhithus N, Taggard D, Lothman E (2001b) Reduced seizure threshold and hippocampal cell loss in rats exposed to alcohol during the brain growth spurt. *Alcohol Clin Exp Res* 25(1):70–82.
- Chevrie JJ, Aicardi J (1977) Convulsive disorders in the first year of life: etiological factors. *Epilepsia* 18:489–497.
- Chudley A, Conry J, Cook J, Loock C, Rosales T, LeBlanc N (2005) Fetal alcohol spectrum disorder: Canadian guidelines for diagnosis. *CMAJ* 172(5):S2–S21.
- Coyne KL, de Costa CM, Heazlewood RJ, Newman C (2008) Pregnancy characteristics of women giving birth to children with fetal alcohol syndrome in Far North Queensland. *Aust N Z J Obstet Gynaecol* 47:240–247.
- Degen R (1978) Epilepsy in children: an etiological study based on their obstetrical records. *J Neurol* 217:145–158.
- Devinsky O (2004) Therapy for Neurobehavioral Disorders in Epilepsy. *Epilepsia* 45(2):34–40.
- Deymeier F, Leviton A (1985) Perinatal factors and seizure disorders: an epidemiologic review. *Epilepsia* 26:287–298.
- Dunn DW, Austin JK, Harezlak J, Ambrosius WT (2003) ADHD and epilepsy in childhood. *Dev Med Child Neurol* 45:50–54.
- Flynn H, Berman D, Marcus S (2009) The relationship between obstetrical outcomes and alcohol use in they year prior to pregnancy. *J Psychosomatic Obstetrics & Gynecology* 30:255–261.
- Greenwood R, Golding J, Ross E, Verity C (1998) Prenatal and perinatal convulsions and afebrile seizures: data from a national cohort study. *Paediatr Perinat Epidemiol* 12(1):76–95.
- Iosub S, Fuchs M, Bingol N, Gromisch DS (1981) Fetal alcohol syndrome revisited. *Pediatrics* 68:475–497.
- Lilienfeld AM, Pasamanick B (1954) Association of maternal and fetal factors with the development of epilepsy. I. Abnormalities in the prenatal and parnatal periods. *J Am Med Assoc* 155:719–724.
- Majewski F, Goecke T (1982) Alcohol embryopathy: Studies in Germany, in Abel. *Fetal Alcohol Syndr* 2:65–88.
- May PA, Gossage JP, Kalberg WO, Robinson LK, Buckley D, Manning M, Hoyme HE (2009) Prevalence and epidemiologic characteristics of FASD from various research methods with an emphasis on recent in-school studies. *Developmental Disabilities Research Reviews* 15:176–192.
- Nelson KB, Ellenberg JH (1984) Obstetric complications as risk factors for cerebral palsy or seizure disorders. *JAMA* 251:1843–1848.
- Nelson KB, Ellenberg JH (1986) Antecedents of seizure disorders in early childhood. *Am J Dis Child* 140:1053–1061.
- Olegard R, Sabel K, Aronsson M, Sandin B, Johansson PS, Carlsson C, Kyllerman M, Iversen K, Hrbek A (1979) Effects on the child of alcohol abuse during pregnancy: retrospective and prospective studies. *Acta Paediatrica* 68(S275):112–121.
- O'Malley K, Barr H (1998) Fetal Alcohol syndrome and seizure disorder. *Can J Psychol* 43:1051.
- Public Health Agency of Canada. Fetal Alcohol Spectrum Disorder. Available at: [http://www.phac-aspc.gc.ca/fasd-etcaf/faq\\_e.html#1](http://www.phac-aspc.gc.ca/fasd-etcaf/faq_e.html#1).
- Rocca WA, Sharbrough FW, Hauser WA (1987a) Risk factors for generalized tonic-clonic seizures: a population-based case-control study in Rochester, Minnesota. *Neurology* 37:1315–1322.
- Rocca WA, Sharbrough FW, Hauser WA (1987b) Risk factors for absence seizures: a population-based case-control study in Rochester, Minnesota. *Neurology* 37(8):1309–1314.
- Rocca WA, Sharbrough FW, Hauser WA (1987c) Risk factors for complex partial seizures: a population-based case-control study. *Ann Neurol* 21:22–31.
- Sherman E, Slick D, Connolly M, Eyrl K (2007) ADHD, Neurological Correlated and Health-related Quality of Life in Severe Pediatric Epilepsy. *Epilepsia* 48(6):1083–1091.
- Shneker BF, Fountain NB (2003) Epilepsy Dis Mon 49(7):426–478.
- Sidenvall R, Heijbel J, Blomquist HK, Nystrom L, Forsgren L (2001) An incident case-control study of first unprovoked afebrile seizures in children: a population-based study of pre- and perinatal risk factors. *Epilepsia* 42:1261–1265.
- Sokol R, Delaney-Black V, Nordstrom B (2003) Fetal Alcohol Spectrum Disorder. *JAMA* 290:2996–2999.
- Spohr H, Steinhausen H (1987) Follow-up studies of children with fetal alcohol syndrome. *Neuropediatrics* 18:13–17.
- Sun Y, Strandberg-Larsen K, Vestergaard M, Christensen J, Nybo Andersen AM, Grønbaek M, Olsen J (2009) Binge drinking during pregnancy and risk of seizures in childhood: a study based on the Danish National Birth Cohort. *Am J Epidemiology* 169(3):313–322.
- Tellez-Zenteno J, Pondal-Sordo M, Matijvic S, Wib S (2004) National and Regional Prevalence of Self-reported Epilepsy in Canada. *Epilepsia* 45(12):1623–1629.