

THE PREVALENCE OF EPILEPSY AND SEIZURES IN SUBJECTS
WITH FETAL ALCOHOL SPECTRUM DISORDERS

By

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ABSTRACT

The Prevalence of Epilepsy and Seizures in Subjects with Fetal Alcohol Spectrum Disorders. MSc Thesis, Queen's University, Kingston, Ontario, Canada, May 2009.

OBJECTIVE: Fetal alcohol spectrum disorders (FASD) is the umbrella term that describes the range of adverse developmental outcomes that occur in offspring as a consequence of maternal drinking during pregnancy. FASD has been associated with a large number of co-morbidities, including neurological disorders such as epilepsy. Epilepsy occurs in 0.6% of the population in Canada. The aim of this study was to evaluate the prevalence of epilepsy or seizure disorders in people who have been diagnosed with Fetal Alcohol Syndrome (FAS), partial Fetal Alcohol Syndrome (pFAS) or Alcohol Related Neurodevelopmental Disorder (ARND). **METHODS:** A retrospective chart review was conducted on all active charts (N=1063) at St. Michael's Hospital (Toronto) and Glenrose Rehabilitation Hospital (Edmonton) FASD clinics. A total of 425 subjects between the ages of 2 to 49 were included in the analysis. The relationship between FASD diagnosis and other risk factors for co-occurrence of epilepsy and seizures (e.g. extent of exposure to alcohol and other drugs, type of birth, maternal history, and trauma) in subjects with FASD was also examined. Chi-square tests and multivariate multinomial logistic regression were used. **RESULTS:** Twenty-five (5.9%) individuals with FASD had a confirmed diagnosis of epilepsy, and 50 (11.8%) had at least one documented seizure episode, yielding an overall prevalence of 17.7% with a history of seizures in this population. Those with epilepsy or seizures were two times

(Odds Ratio=2.27, 95% Confidence Interval=1.14-4.51, $p<0.05$) more likely to have an unnatural birth and those with epilepsy were three times (OR=3.41, 95% CI 1.11-10.5, $p<0.05$) more likely to have had an unnatural type of birth (breech, caesarean, forceps or vacuum) than those subjects with no history of seizures. None of the other risk factors examined were associated with a greater prevalence of epilepsy or seizures in subjects with FASD. These results indicate a remarkably high prevalence of epilepsy/seizures in the FASD population of two specialized FASD clinics compared with the general population.

CO-AUTHORSHIP

The research described in this thesis was conducted by Stephanie Bell under the supervision of Dr. James Reynolds. The research question was conceived by Dr. James Reynolds and Dr. Peter Carlen. The study was designed by a collaborative team including: Dr. James Reynolds, Dr. Peter Carlen, Dr Brenda Stade, Dr. Paul Hwang and Stephanie Bell. Stephanie Bell reviewed the subject charts and collected all data from St Michael's Hospital. The data at Glenrose Rehabilitation Hospital was collected by Jennifer Lynn Benz and Maryam Soleimani under the supervision of Dr. Carmen Rasmussen. Dr. Peter Carlen and Dr. Paul Hwang reviewed all subject charts with evidence of seizures. Stephanie Bell tracked and coded the data from both sites. The data analysis was performed by Depeng Jiang and Stephanie Bell and it was interpreted by Dr. James Reynolds and Stephanie Bell. The first draft of the thesis was written by Stephanie Bell.

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TABLE OF CONTENTS

Title Page	i
Abstract	ii
Co-Authorship	iv
Acknowledgements	v
Table of Contents	vii
List of Tables	x
List of Abbreviations and Symbols	xi
Chapter 1: General Introduction	1
Chapter 2: Literature review	4
2.1 Fetal Alcohol Spectrum Disorders (FASD)	4
2.1.1 Drinking Patterns in Canada and the United States of America	4
2.1.2 Women at Risk for Drinking During Pregnancy	5
2.1.3 The Prevalence of FASD in Different Regions in Canada	7
2.1.4 Risk Factors for FASD	7
2.1.5 Diagnostic Guidelines for FASD	8
2.1.6 Proposed Mechanisms of Prenatal Ethanol-Induced Brain Injury	11
2.1.7 CNS Impairments in Individuals with FASD	13

2.2	Epilepsy	16
2.2.1	The Prevalence/Incidence of Epilepsy in Canada and the U.S.	16
2.2.2	Classification of Seizure Type	17
2.2.3	Age Specific Seizure Types and Common Causes	19
2.3	Risk Factors for Epilepsy in FASD	20
2.3.1	Family History and Genetics	21
2.3.2	Maternal Malnutrition	22
2.3.3	Drug Use during Pregnancy	23
2.3.4	Pregnancy, Labor, and Delivery Events	23
2.3.5	CNS Infection	25
2.3.6	Comorbidities	26
2.3.7	Congenital Malformations	27
2.3.8	Trauma and Stressful Life Events	28
2.3.9	Sleep and Seizures	29
	Chapter 3: Body of Thesis	31
3.1	Rationale and Hypothesis	31
3.2	Methods	31

3.3	Data Analysis	33
3.4	Results	34
Chapter 4: General Discussion and Conclusions		41
4.1	Overview of Main Findings and Interpretation	41
4.2	Cellular Mechanisms that may underlie the Increased Risk of Epilepsy/Seizures in FASD	43
4.3	The Impact of Additional Risk Factors for Epilepsy/Seizures in FASD	47
	4.3.1 Maternal Malnutrition and Risk of Seizures	47
	4.3.2 Alcohol and Drug use During Pregnancy	49
	4.3.3 Trauma and Seizures	50
	4.3.4 Sleep and Seizures	51
4.4	Strengths and Limitations	53
4.5	Clinical Implications & Future Studies	54
	Reference List	57
Appendices		
	Appendix A: data collection form	73

LIST OF TABLES

3.1	Demographic characteristics.	35
3.2	The prevalence of epilepsy and seizures in the study population.	36
3.3	Chi-square test results.	37
3.4	Multinomial logistic regression results.	39

LIST OF ABBREVIATIONS AND SYMBOLS

ADHD	Attention deficit hyperactivity disorder
BRFSS	Behavioral Risk Factor Surveillance System
CHS	Community Health Survey
CI	Confidence interval
CNS	Central nervous system
CT	Computed tomography
EEG	Electroencephalogram
FADU	Fetal Alcohol and Drug Unit
FAE	Fetal alcohol effects
FAS	Fetal alcohol syndrome
FASD	Fetal alcohol spectrum disorders
fl	Fluid
GABA	Gamma-aminobutyric acid
HPA	Hypothalamic-pituitary-adrenal
ILAE	International League Against Epilepsy
IOM	Institute of Medicine
MRI	Magnetic resonance imaging
NICU	Neonatal Intensive Care Unit
NMDA	N-methyl-D-aspartate
NPHS	National Population Health Survey
NSFG	National Survey of Family Growth
ODCD	Oppositional defiant conduct disorder
ODD	Oppositional defiant disorder
oz	Ounce
OR	Odds ratio
PCP	Phencyclidine
POS	Pediatric Outreach Service
PDD	Pervasive development disorder
PTSD	Post-traumatic stress disorder
pFAS	partial fetal alcohol syndrome
RAD	Reactive attachment disorder
SAS	Statistical Analysis Software
SCBU	Special Care Baby Unit
U.S.	United States of America
UK	United Kingdom
vs.	Versus

Chapter 1 GENERAL INTRODUCTION

The term fetal alcohol spectrum disorders (FASD), describes the range of adverse developmental outcomes that occur as a consequence of maternal drinking during pregnancy (Abel et al., 1998; 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). Children with FASD suffer from a large number of co-morbidities, 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 & 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 were conducted using relatively small sample sizes, and for the most part included only subjects with fetal alcohol syndrome (FAS). Collectively these studies indicate that between 3 to 21% of children with FASD also have epilepsy or a seizure disorder as a comorbidity. In a study by Olegard and colleagues (1979) 5 (10.4%) out of 52 children with FAS had convulsions. In 1981, Iosub reported that 3 out of 47 children (6.3%) with FAS also had convulsive disorder. Shortly thereafter, Majeski and colleagues (1982) studied the electroencephalogram (EEG) in 61 subjects with Alcohol Embryopathy. In this cohort, one fourth of the EEGs were abnormal, and 21% of the subjects suffered from convulsions. In 1987, Spohr and colleagues conducted a detailed follow-up study where children with FAS underwent pediatric, neurological and psychiatric assessment. In forty-five subjects, 44% showed abnormal EEG patterns, and 9% of these children had

epileptic seizures. In a more recent study O'Malley and Barr(1998) found dysrhythmias in the temporal lobe in 7 of 33(21%) subjects diagnosed with FAS, fetal alcohol effects (FAE) or combined FAE and fetal drug effects. FAE was previously used to describe individuals exhibiting CNS impairment but without the characteristic facial dysmorphology and growth restriction associated with FAS. All subjects had a complex partial seizure disorder. In summary, these studies suggest that there is a higher prevalence of seizures in children prenatally exposed to alcohol. However, these studies have left several important questions unanswered, since diagnoses were not consistently established (FASD, seizure type), and the relatively small sample sizes precluded examination of additional risk factors.

The FASD spectrum includes: FAS, pFAS and ARND. FAS is diagnosed when the characteristic pattern of facial dysmorphology, growth restriction and central nervous system (CNS) impairments are all present. pFAS is diagnosed when some of the characteristics facial features and/or growth restriction are present and there is evidence of CNS impairment. Those with ARND do not have the characteristic facial dysmorphology or growth restriction, but CNS impairments are present (Chudley et al., 2005).

There is 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. Furthermore, indirect complications may be linked to prenatal alcohol exposure, which also increase the risk of epilepsy. Such complications include: maternal malnutrition, other prenatal drug exposures, prematurity, type of birth

and/or birth 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 use and trauma.

Chapter 2 LITERATURE REVIEW

2.1 Fetal Alcohol Spectrum Disorders

2.1.1 Drinking Patterns in Canada & the United States of America (U.S.)

In Canada, awareness of the risks of drinking during pregnancy has improved and national intervention programs are fighting to make populations aware that “no amount is a safe amount” however binge drinking and drinking throughout pregnancy continues (Chudley et al., 2005). According to the *National Longitudinal Survey of Children and Youth* in Canada (1998-1999) 14.4% of women drank at some point during their pregnancy and 4.9% drank throughout pregnancy. Another three percent reported binge drinking during pregnancy.

In a recent U.S. survey, over half of women of childbearing age reported consuming alcohol in the past month and up to one in seven reported consuming five or more drinks on one drinking occasion at least once in the past month (Project CHOICES Research Group, 2002). The *Behavioral Risk Factor Surveillance System* (BRFSS) (Centers for Disease Control and Prevention, 1999) found that 12.3% of women of childbearing age binge drink. Using this rate and data from the National Survey of Family Growth (NSFG), (U.S. Department of Health and Human Services, 1997), it can be approximated that between 1% and 2% of non-pregnant, childbearing-aged women are fertile, sexually active, not using adequate contraception, and binge drinking. These women are therefore at risk for an alcohol-exposed pregnancy (Project CHOICES Research Group, 2002).

2.1.2 Women at Risk for Drinking During Pregnancy

There are specific groups of women who may be deemed “at risk” for an alcohol exposed pregnancy. Gladstone and colleagues (1997) performed a retrospective review of records in a Toronto outpatient counselling service that advises pregnant women about drugs, chemicals, radiation, infections during pregnancy and breast-feeding. Of the 3800 women seen in the clinic, 119 (3.1%) reported binge drinking during pregnancy and of the 19,991 women counselled by telephone, 153 (0.8%) reported binge drinking during pregnancy. Furthermore, 84% had binged fewer than 10 times during their pregnancy. A large majority (84%) of the women had a binge episode early in the first trimester, which may be defined as before 6 weeks gestation. When compared to a control group, the women who had engaged in binge drinking were significantly younger (mean 30.0 vs. 27.9 years), more likely to be single (12.2% vs. 54.6%), to be white (69.2% vs. 92.9%), to smoke (19.3% vs. 57.1%) and to use cocaine (1.1% vs. 11.0%), marijuana (3.0% vs. 19.3%) and/or other illicit drugs (0.7% vs. 9.2%) (Gladstone et al., 1997).

Project CHOICES Research Group performed a survey (2002) that was administered to 2672 English-speaking women aged 18 to 44 years from six settings, including an urban jail, a drug/alcohol treatment facility, a gynaecology clinic, two primary care clinics, and respondents to media solicitation. Among the women surveyed in this study, 70% reported a household income of <\$20,000, 68% had high school or equivalent education, and 62% were African American. Thirteen percent of women met the definition of “at risk” for an alcohol-exposed pregnancy. Recent drug use (odds ratio (OR)=3.1, 95% confidence interval (CI)=2.1–4.4), having smoked more than 100 cigarettes (OR=1.9, 95% CI=1.3–2.7), a history of inpatient treatment for drugs or

alcohol (OR=1.8, 95% CI=1.3–2.4) or inpatient mental health treatment (OR=1.6, 95% CI=1.1–2.3), having multiple sex partners (OR=1.7, 95% CI=1.2–2.2), and recent physical abuse (OR=1.5, 95% CI=1.1–2.0) were significantly correlated with being at risk. These factors were also associated with other conditions including poor prenatal care, drinking during pregnancy, and alcohol dependence.

Leonardson & Loudenburg (2003) found that women at a high risk for drinking during pregnancy reported partner use of alcohol/drugs (68.7%), memory impairment while drinking (53.2%), alcohol and/or drug use by other household members (50.6%), being a smoker (27.2%), feeling a need to cut down on drinking (22.8%), having been asked to drink less by friends and family (16.8%), and experience of sexual abuse (14.3%). They also found that high-risk groups were younger and had completed fewer years of education than low-risk groups. The high-risk group also had more abortions (0.19 vs. 0.11) and fewer children (.89 vs. 1.04) than the control group. Finally, sexual and physical abuse within the past year and physical abuse during pregnancy were significant risk factors for drinking during pregnancy (Leonardson & Loudenburg, 2003).

Women who have had a previous child with FAS are at an extremely high risk for drinking during subsequent pregnancies and are also at a high risk for maternal substance use. As indicated above, many studies reveal that significant predictors of drinking during pregnancy include: marital status (Bagheri et al., 1998; Kvigne et al., 1998), smoking (Bagheri et al. 1998; Kvigne et al., 1998; Serdula et al., 1991), physical and sexual abuse (Astley et al., 2000; Kvigne et al., 1998; Stratton et al., 1996), partner's use and/or drinking by the woman's mother (Astley et al., 2000; Kvigne et al., 1998; Stratton et al., 1996), individual psychological factors (Kvigne et al., 1998; Stratton et al., 1996), and

employment and economic factors (Astley et al., 2000; Kvigne et al., 1998; Stratton et al., 1996).

2.1.3 The Prevalence of FASD in Different Regions in Canada

In 2007, the Public Health Agency of Canada reported that FASD might affect as many as 1 in 100 children in Canada. Prevalence rates of FASD vary across Canada and more current studies are needed. Referrals to a diagnostic clinic in Saskatchewan indicated that the rate of FAS was 0.515 per 1000 between 1973 and 1977 (Habbick et al., 1996). In an isolated Aboriginal community in British Columbia, the prevalence of FASD was found to be as high as 190 per 1000 live births (Robinson et al., 1987). Asante and Nelms-Matzke (1985) estimated that the rate of FASD affected 46 per 1000 native Canadian children in the Yukon and 25 per 1000 in northern British Columbia. Many individuals with known prenatal alcohol exposure have not been assessed for a diagnosis of FASD; therefore prevalence statistics are very challenging to explore and may be greatly underestimated. More up to date studies on the prevalence of FASD in different regions in Canada are needed.

2.1.4 Risk Factors for FASD

There are a number of risk factors for having a child with FASD and the most important risk factors that have consistently been identified include: high blood-alcohol concentration, the timing of exposure during fetal development, the pattern of consumption (binge drinking) and the frequency of alcohol use (Jacobson & Jacobson 1994, 1999; Sood et al., 2001). In a study by Bingol et al. (1987) reduced access to

prenatal and postnatal care and services, inadequate nutrition and a poor developmental environment (e.g. stress, abuse, and neglect) were identified as risk factors for FAS.

In a 5-year follow-up study of birth mothers of children with FAS, Astley and colleagues (2000) found that these women came from diverse racial, educational and economic backgrounds. They often had untreated or under-treated mental health concerns, were socially isolated, were victims of abuse and had histories of severe childhood sexual abuse. Another study performed in 2001 by Sood and colleagues included women who reported alcohol consumption at conception of at least 0.5 oz of absolute alcohol per day and a random sample of lower level drinkers and abstainers. The average absolute alcohol intake was categorized into none, low (>0 but <0.3 fl oz of absolute alcohol/day), and moderate/heavy (>0.3 fl oz of absolute alcohol/day) drinking. Six years later, testing was done on 501 parent-children dyads. Low levels of alcohol use were reported in 63.8% and moderate/heavy use in 13% of pregnancies. Increasing prenatal alcohol exposure from low to heavy was associated with lower birth weight and gestational age, higher lead levels, higher maternal age, and lower education level, prenatal exposure to cocaine and smoking, custody changes, lower socioeconomic status, and paternal drinking and drug use at the time of pregnancy.

2.1.5 Diagnostic Guidelines for FASD

In 1968, Lemoine and colleagues recognized a variety of birth defects and developmental disabilities in offspring born to alcoholic parents. A specific pattern of birth defects following maternal alcohol exposure was described in the U.S by Jones and Smith (1973).

In the 1990s, the term “suspected fetal alcohol effects” (FAE) was created to describe the group of individuals with gestational alcohol exposure and not all the physical birth defects. These "effects" were further delineated by the U.S. Institute of Medicine (IOM), which published recommendations in 1996 for diagnosis of FASD in consultation with a panel of experts. In the late 1990s, Astley and Clarren created another diagnostic classification system: the 4-Digit Diagnostic Code developed using data from the Washington State Fetal Alcohol Syndrome Diagnostic and Prevention Network of clinics. In 2005, Chudley and colleagues published the Canadian Guidelines for Diagnosis. Currently, there is no standardized clinical definition of FASD. Rather, there are diagnostic guidelines that physicians and medical researchers are encouraged to follow.

The IOM (1996) provided guidelines for the diagnosis of FAS with and without a confirmed history of alcohol exposure, pFAS, alcohol-related birth defects (ARBD), and ARND. Under the IOM guidelines, FAS is characterized and diagnosed by: prenatal and postnatal growth deficiency (height or weight < 10th percentile when corrected for gestational age), a unique cluster of minor facial anomalies (short palpebral fissures, an elongated midface, a long and flattened philtrum, thin upper lip, and flattened maxilla) central nervous system damage (structural, neurological, and/or functional impairment) and gestational alcohol exposure. Central nervous system impairments include: neurological abnormality, developmental delay, behavioral dysfunction or deficit, intellectual impairment and/or structural abnormalities, such as microcephaly (head circumference below the 3rd percentile) or brain malformations found on imaging studies or autopsy. pFAS is characterized and diagnosed by: growth deficiency and/or facial

features of FAS, central nervous system damage (structural, neurological, and/or functional impairment) and gestational alcohol exposure. ARND is characterized and diagnosed by: central nervous system damage (structural, neurological, and/or functional impairment) and gestational alcohol exposure.

Astley and Clarren developed the 4-Digit Diagnostic Code in 1999. The 4-digits in the code reflect the magnitude of expression, or severity of the four key diagnostic features of FAS in the following order: growth deficiency, the FAS facial phenotype, central nervous system damage or dysfunction and gestational exposure to alcohol. The magnitude of expression of each feature is ranked independently on a 4-point Likert scale with one reflecting complete absence of the feature and four reflecting its extreme expression.

The names of the clinical diagnostic categories under the 4-digit diagnostic code are as follows. Sentinel physical findings refers to physical findings that are key diagnostic features of FAS including a cluster of minor facial anomalies (short palpebral fissures, thin upper lip and a smooth philtrum). Other physical findings (major or minor anomalies) may be detected instead of, or in addition to these sentinel findings suggesting alternate or additional conditions. Static encephalopathy refers to any physical abnormality in the brain. These can vary in magnitude from structural defects that are apparent on an image like a computed tomography (CT) scan to micro-cellular abnormalities that are confirmed with tissue samples or neurochemical analysis. The patient presents with cognitive and/or behavioral dysfunction accompanied by structural, neurologic, and/or psychometric measures, which strongly support the presence of structural brain abnormalities. The term does not define any specific pattern of structural

abnormality or cognitive/behavioral dysfunction. FAS is used to refer to patients who present with one of twelve 4-digit-diagnostic code combinations reflecting growth deficiency, the FAS facial phenotype and brain dysfunction. Atypical FAS is used with a small group of patients who have static encephalopathy, most of the sentinel physical findings of FAS, and evidence of alcohol exposure. Alcohol exposed, not exposed or unknown is used to reflect the exposure status of the fetus and it is reported independent of outcome and does not imply a causal association between exposure and outcome (Astley & Clarren, 2004).

The Canadian Guidelines for Diagnosis uses the 4-digit diagnostic code criteria and the IOM terminology (Chudley et al., 2005). In Canada, the diagnostic process generally consists of screening and referral, physical examination and differential diagnosis, neurobehavioural assessment, treatment and follow-up. The assessment process begins with recognition of the need for diagnosis and ends with implementation of appropriate recommendations. The multidisciplinary diagnostic team can be regional, geographic, or virtual and carry out the assessment using telemedicine.

The recommended core team may vary according to the environment, but should ideally consist of a: coordinator for case management (for example, a nurse or social worker), physician specifically trained in FASD diagnosis, psychologist, occupational therapist and speech-language pathologist (Chudley et al., 2005).

2.1.6 Proposed Mechanisms of Prenatal Ethanol-Induced Brain Injury

The extent to which ethanol impacts the developing central nervous system (CNS) depends on the stage of embryological development (Pratt, 1984; Riley & McGee, 2005).

At conception and during the first weeks of prenatal development, ethanol may act as a cytotoxic or mutagenic agent, leading to cell death or chromosomal aberrations. This is evident in embryonic tissue culture (Cook et al., 1990) and from the high rate of miscarriage in alcoholics (Olegard et al., 1979).

At four to 10 weeks after conception, ethanol may act as a cytotoxin, causing excessive cell death in the CNS and abnormalities in nerve cell migration from cell damage. This is seen in post-mortem studies of individuals with FAS (Clarren et al., 1978), which reveal abnormal migration leading to disorganization of tissue structure and severe cell loss, which in turn results in microcephaly. Also, the early shortening of the anterior cranial base due to an alcohol-induced deficiency in brain growth most likely accounts for the shape of the mid face in individuals with FAS (Kotch & Sulik, 1992).

From eight to 10 weeks of pregnancy onwards, ethanol can disorganize or delay cell migration and development (Pratt, 1984). Thus, if nerve cells are not in the right place at the right time, synapses will not be formed normally (Volk et al., 1981). In the third trimester, alcohol exposure has been associated with impairments in the: hippocampus, cerebellum, prefrontal cortex and other brain regions (Livy et al., 2001, 2003).

Ethanol disrupts neurotransmitter and neuroendocrine function in the CNS. The effect of ethanol on the hypothalamus leads to the suppression of growth hormone release (Thadani & Schanberg, 1979), which may account for the growth deficiency (including the brain) seen in those with FASD. Ethanol also increases maternal and fetal hypothalamic-pituitary-adrenal (HPA) activity, which can disrupt hormonal interactions between maternal and fetal systems. This will alter the development of fetal metabolic,

physiologic, and endocrine functions (Zhang et al., 2005). More recent research demonstrates that ethanol interferes with neurotransmitter mechanisms, which impairs synaptogenesis and induces neurons to die by apoptosis (Olney, 2004).

2.1.7 CNS Impairments in Individuals with FASD

Anatomical abnormalities in individuals with FASD may range from a reduction in brain volume to a decrease in cell numbers and neural connections (Chen et al., 2003; O'Hare et al., 2005). Researchers using autopsy and brain imaging have found a reduction and abnormalities in brain size and shape in individuals with FASD, especially in the basal ganglia, corpus callosum, cerebellum and hippocampus (Riley & McGee, 2005). This suggests that there is regional vulnerability within the brain affected by prenatal alcohol exposure (Guerri, 2002). Imaging studies have shown that structural abnormalities are common in children with FASD. These include anomalies of the corpus callosum, and decrease in the size of the anterior cerebellar vermis, basal ganglia and thalamus (Mattson & Riley, 1998; Riley et al., 2004; Roebuck et al., 1998; Sowell et al., 2002; Livy et al., 2001; Riikonen et al., 2005). Archibald and colleagues (2000) reported that white matter volume in children with prenatal alcohol exposure is significantly reduced compared to grey matter. Furthermore, within the cerebral cortex, the parietal lobes were significantly reduced in volume compared to the temporal and occipital lobes.

Post-mortem studies in children with prenatal alcohol exposure reveal that neurons are incorrectly located in the white matter, suggesting deficits in neuronal migration (Chen et al., 2003; Clarren et al., 1978). An absence of the corpus callosum, a decrease in the number of dendritic spines (Ferrer and Galofre, 1987) and abnormalities

in the thalamus, dentate gyrus and cerebellum have also been reported (Coulter et al., 1993).

Animal studies have helped us identify the affects of prenatal alcohol exposure on many brain regions. In the rat, numerous studies have demonstrated that heavy ethanol intake during the brain growth spurt and the early postnatal period (equivalent to the third trimester and early infancy in humans) significantly reduces the weight of the forebrain, brain stem and cerebellum (Chen et al., 1998). In 2004, Olney demonstrated that a single exposure of infant rats or mice to a high does of ethanol during synaptogenesis causes a massive neuro-apoptosis. More recently, one time exposure of ethanol to infant rodents was shown to generate acute neurodegeneration of Purkinje and other neuronal cells in the cerebellar cortex and cerebellar nuclei, in the nucleus pontis and in the inferior olivary complex (Dikranian et al., 2005).

Several studies have also shown that pathological effects are not just restricted to a reduction of neuronal cell numbers in the brain of animals exposed to ethanol *in utero* but may also include damage to the dendrites and a reduction of the number of connections in the substantia nigra, the cortex and the hippocampus (Chen et al., 2003). It is reasonable to hypothesize that in the human similar changes could be responsible for some of the cognitive difficulties displayed by children with FASD such as impaired learning, attention deficit and memory disabilities (Hausknecht et al., 2005).

Magnetic Resonance Imaging (MRI) studies have found reductions in the volume of the basal ganglia in children with FAS, pFAS, and ARND. These effects are more specific to the caudate nucleus, which is involved in higher cognitive and executive functions through the frontal lobe (Archibald et al., 2001). Furthermore, MRI studies

reveal abnormalities of the corpus callosum including: agenesis and thinning in the anterior and posterior regions (Riley et al., 1995; Sowell et al., 2001). Displacements of the splenium may be related to deficits in verbal learning observed in individuals with FASD (Sowell et al., 2001).

Studies also show a disproportionate reduction in cerebellar volume in those with FASD, particularly the cerebellar vermis (Archibald, 2001). The cerebellum is involved in motor skills (balance and coordination) and learning which is impaired in kids with FASD (Riley & McGee, 2005).

Behavioural and neuroanatomical deficits as a result of ethanol-induced injury to the hippocampus have also been reported (Berman & Hannigan, 2000). Wozniak et al. (2004) showed that binge-like exposure of infant mice to ethanol on a single postnatal day triggered apoptotic death of neurons in structures including the hippocampal circuit. In a MRI study, Riikonen et al. (1991) demonstrated that children with FAS had a smaller left hippocampal volume, than the right.

In summary, CNS dysfunction caused by prenatal alcohol exposure is variable and can present as deficits in memory, attention, motor skills, visual-spatial abilities and learning (Olson et al., 1998; Riley & McGee 2005). Individuals with FASD often exhibit deficits in executive functions thought to be mediated by the frontal lobe of the brain including: cognitive flexibility, planning, strategy use, verbal reasoning, inhibition, fluency, working memory and more abstract learning (Welsh et al., 1991).

2.2 Epilepsy

2.2.1 The Prevalence/Incidence of Epilepsy in Canada and the U.S.

The prevalence of epilepsy in Canada and the U.S. varies across studies; most report that five people per 1,000 have epilepsy (0.6%) (Cowan et al., 1989; Hauser et al., 1991; Cockerell et al., 1995; Sidenvall et al., 1996; Eriksson and Koivikko, 1997; Wallace et al., 1998; Kurtz et al., 1998). Currently, little information about the prevalence in different regions of Canada is available. In Ontario, the prevalence of epilepsy was found to be 5.8 per 1,000 (Wiebe et al., 1999) and in Manitoba, a study in children between birth and 15 years, identified a prevalence of 4.4 per 1,000 (Kozyrsky & Prasad, 2004).

More recently, Tellez-Zenteno et al. (2004) explored the point prevalence of self-reported epilepsy derived from two large, validated, general population health surveys in Canada [National Population Health Survey (NPHS) and the Community Health Survey (CHS)]. The age-adjusted point prevalence ranged from 3.0 to 7.1 per 1,000. In Ontario, the point prevalence was 5.0(NPHS) and 5.2(CHS) per 1,000, while in Alberta it was 4.4 (NPHS) and 5.7(CHS) per 1,000 people. In other provinces, the reported point prevalence of epilepsy ranged from 3.7 to 7.1 per 1,000. Self-reported epilepsy was more prevalent among those with the lowest income and educational level ($p < 0.001$) and there was no difference between genders.

The incidence of recurrent seizures is highest in the first year of life and declines thereafter throughout childhood and adolescence. Within the first year of life, rates are highest in the first month affecting 3.18 per 1,000 neonates (Sidenvall et al., 1993). The cumulative incidence rate of epilepsy by age 15 is approximately 0.8% (Hauser et al.,

1993). Most studies indicate slightly higher total rates in boys (Sidenvall et al., 1993; Hauser et al., 1993; Jallon et al., 1997; Kurtz et al., 1998); this difference in sex-specific rates varies by age. Before age five, incidence rates are about 30% to 60% higher in girls, while rates tend to be 10% to 20% higher in boys throughout later childhood and adolescence (Hauser et al., 1993; Annegers et al., 2000).

2.2.2 Classification of Seizure Type

The classification of seizure type is outlined by Shneker & Fountain, 2003. Epilepsy is classified by two distinctions: location of the lesion (localized or generalized) and known or suspected cause (idiopathic, symptomatic, or cryptogenic). Localized epilepsy is caused by focal disease, whereas generalized epilepsy is caused by disease that affects the entire cortex.

Idiopathic epilepsies are inherited and presumed to result from abnormalities of neurotransmission without associated structural deficits. Recent studies have demonstrated that most idiopathic epilepsies are due to genetically determined abnormalities of neurotransmission. Symptomatic epilepsies result from known structural diseases of a determined cause. Examples include malformation, tumor, and trauma, which are often identified using neuroimaging.

Cryptogenic epilepsy is presumed to have a structural basis, but there is no demonstrable structural disorder and the cause is unknown. Structural brain diseases that predispose someone to epilepsy include: congenital (heterotopias, cortical dysplasia), degenerative (Alzheimer disease, infectious meningitis, encephalitis, abscess, trauma, tumor) and vascular (vascular malformation, stroke, subarachnoid hemorrhage).

Generalized seizures are characterized by complete loss of consciousness at onset of the seizure, because the entire cortex is involved. Partial seizures are characterized by retention of consciousness, because they begin in a particular and limited brain region; partial seizures, however, can secondarily generalize.

Simple partial seizures are not associated with alteration of consciousness, because they begin in a small, discrete area of the brain. Only one neurologic modality is affected and resulting symptoms depend on the area where the seizure occurs. Complex partial seizures are associated with alteration but not loss of consciousness. The patient is awake and staring blankly, but is not responsive to external stimuli. Complex partial seizures can arise from any region of the brain, but most commonly arise in the temporal lobe, followed by the frontal lobe. These seizures are sometimes accompanied by automatism, for example, repetitive purposeless movements (lip smacking, chewing, swallowing, and gulping).

Some generalized seizures, for example myoclonic seizures, are so brief that it is difficult to determine whether there is any loss of consciousness. Generalized seizures are characterized by major motor symptoms (generalized tonic-clonic, tonic, clonic, and myoclonic seizures) or by lack of motor activity (absence, atypical absence, and atonic seizures).

Generalized tonic-clonic seizures begin with a tonic phase of whole-body stiffening, followed by a clonic phase of repetitive contractions. Tongue biting and urinary incontinence are common and these seizures last two to three minutes and are followed by a period of confusion or complete unresponsiveness for another few minutes. Primary generalized tonic-clonic seizures are generalized from the onset. Any type of

partial seizure, however, may secondarily generalize to a tonic-clonic seizure. Tonic seizures consist of the tonic phase of generalized tonic-clonic seizures, while clonic seizures consist only of the clonic phase. Myoclonic seizures are brief, lightning-like muscular jerks. The most common signs are bilateral hand or arm jerks, although these seizures can affect any body region. Absence seizures manifest as brief (1-10 s) episodes of staring and unresponsiveness. Atypical absence seizures are similar to absence seizures but they last longer and often include more motor involvement. Atypical absence seizures are often associated with other types of seizures in severe forms of epilepsy. Atonic seizures or “drop attacks” are manifested as sudden loss of muscle tone and falling or dropping to the floor unprotected. Finally, infantile spasms are manifested as forward flexions of the torso and extension of both arms. Types of seizures may be indicative of affected brain regions for the purpose of the current study. Specific areas of the brain such as the hippocampus that are targeted during particular trimesters are relevant to exposure and epileptic activity including diagnoses.

2.2.3 Age Specific Seizure Types and Common Causes

One-fifth of recently diagnosed children (Berg et al., 1999) and three-quarters (Waalder et al., 2000) of prevalent cases are reported to have experienced more than one type of seizure. Most studies find partial seizures to be slightly more common than generalized seizures (Murphy et al., 1995; Waalder et al., 2000), although this varies by age (Sidenvall et al., 1993; Hauser et al., 1996; Eriksson and Koivikko, 1997).

Generalized seizures have the highest incidence in the first year of life and decline thereafter. The incidence of absence seizures tends to peak in five to 10 year olds (Hauser

et al., 1993). Incidence rates for partial seizures increase slightly during early childhood and remain moderately constant throughout childhood and adolescence (Hauser et al., 1993). Among partial seizures, complex partial seizures are the most common and among generalized seizures, motor seizures (tonic, clonic, and tonic clonic) are most commonly diagnosed.

Approximately 55% to 75% of cases of epilepsy have no known cause (Nelson and Ellenberg, 1986; Cowan et al., 1989; Hauser et al., 1993; Eriksson and Koivikko, 1997; Berg et al., 1999a; Waaler et al., 2000). Therefore, only 25% to 45% of cases of epilepsy can be attributed to specific risk factors. The factors consistently associated with an increased risk of epilepsy in children include: congenital malformations and metabolic disorders, febrile seizures, seizures within the first 28 days of life (neonatal seizures), moderate to severe head trauma, CNS infections, and family history of afebrile or febrile seizures (ILAE, Commission, 2003).

2.3 Risk Factors for Epilepsy in FASD

There are a number of factors that increase the risk of epilepsy. More importantly, indirect complications linked to prenatal alcohol exposure may also increase the risk of epilepsy. The risk factors may be in the mother and/or child and there is little information available that addresses the question of whether these additional risk factors or prenatal alcohol exposure is an independent risk factor for epilepsy and spontaneous seizures.

2.3.1 Family History and Genetics

A positive family history of epilepsy has been associated with an increased risk in offspring. Recurrence of epilepsy in families should be compared to the baseline risk of epilepsy in the general population, which is approximately one percent by age 20. Studies conducted from 1937 to 1990 report risks ranging from 2.4 to 4.6% for offspring of epileptic parents with any kind of epilepsy (Nelson and Ellenberg, 1986; Annegers et al., 1996). Mothers with epilepsy have even higher rates of affected offspring (2.8–8.7%) compared to fathers with epilepsy (1.0–3.6%). Risk also increases with the number of relatives affected; for example, risk of epilepsy in siblings of individuals with epilepsy rises from approximately 3 to 8% if the parent also has epilepsy (Winawer et al., 2005).

A maternal history of epilepsy or febrile seizures has been shown to increase the odds of complex partial seizures (Rocca et al., 1987c) and generalized tonic-clonic seizures (Rocca et al., 1987a). A more recent study estimated the genetic and environmental factors of the etiology of epilepsy among 11,900 Danish twin pairs (Kjeldsen et al., 2001). The authors reported a concordance rate for epilepsy of .37 for monozygotic twins and .08 for dizygotic twins. Their analysis suggests that 70 to 88% of the risk of developing epilepsy can be attributed to genetic factors.

The current study collected information on family history of epilepsy, seizures, and other neurological disorders in the subject, the biological mother and father, maternal and paternal grandparents and siblings in order to determine whether epilepsy in the subject with FASD, may result from epilepsy in the family.

2.3.2 Maternal Malnutrition

Thiamine and other B vitamins play a critical role in Krebs cycle function. Deficiencies of these vitamins, either due to inadequate dietary intake or impaired absorption, will interfere with energy metabolism, and seizures are often one of the clinical signs (O'Brien, 1998). Several studies report that 30 to 80% of alcoholics become thiamine deficient because of poor diet, impaired absorption, vomiting, and direct inhibition of pyrophosphokinase (Butterworth et al., 1993; Ceccanti et al., 2005; Heap et al., 2002).

Gestation is a very important time of metabolic changes and increases in energy demands for the mother and the fetus. Severe undernutrition increases the risk of abortion, prematurity, intrauterine growth retardation and impaired fetal brain development (Baker et al., 1975; Gabr, 1987). In Western countries, the proportion of pregnant women with energy malnutrition was estimated to be 4% (Gabr, 1987). The effects of malnutrition can be detrimental, particularly during the brain growth spurt period, but also during early organizational processes such as neurogenesis, cell migration, and differentiation. Malnutrition can result in a variety of brain dysfunctions, with distributed brain pathology and a variety of developmental failures (Morgane et al., 1993).

The current study could not collect information on specific dietary patterns in the mother and child. In cases of severe malnutrition in the mother and/or baby, information was classified as a complication during pregnancy. Otherwise, prenatal care may be used as an indicator of dietary patterns in the mother.

2.3.3 Drug Use during Pregnancy

Leonardson & Loudenburg (2003) found that 60% of women who report drinking during pregnancy use other drugs as well. Furthermore, women who use alcohol during pregnancy are more likely to use cigarettes and/or drugs during pregnancy as well. However, if there is no maternal consumption of ethanol during pregnancy, there is no FASD in the offspring. The current study attempted to gather information on drug use in the mother during pregnancy including: type, frequency and amount. This way we could assess whether there was an increase in the risk of epilepsy among subjects born to women who used drugs and alcohol during pregnancy compared to those who solely use alcohol.

2.3.4. Pregnancy, Labor and Delivery Events

In previous studies of epilepsy and pregnancy factors, the greatest risks have been associated with bleeding in pregnancy (Degen, 1978; Ross et al., 1980; Sidenvall et al., 2001). In a study by Whitehead and colleagues (2006) children born between January 1986 and December 2000 in Nova Scotia, Canada were followed up to December 2001. There were 648 new cases of epilepsy diagnosed among 124,207 live births, for an overall rate of 63 per 100,000 person-years. Among the factors most frequently cited as being associated with childhood epilepsy were eclampsia/toxemia, bleeding in the prenatal period, infection, method of delivery, asphyxia, neonatal seizures, congenital anomalies, low Apgar score and preterm gestational age.

Sun and colleagues (2008) determined that children exposed to maternal cystitis, pyelonephritis, diarrhea, coughs, and/or vaginal yeast infection in prenatal life had an

increased risk of epilepsy. Coughs lasting >1 week were also associated with an increased risk for epilepsy only in the first year of life, as was vaginal yeast infection in children who were born preterm. Coyne et al. 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. Therefore, alcohol exposed babies may have a higher risk of complications in labor, delivery and birth events.

The current study gathered information on type of birth as well as birth complications, in order to determine whether the risk of epilepsy and seizures may be higher among those with an unnatural birth and/or those who encounter problems during labor compared to those with a normal, non-problematic birth.

Birth weight, prematurity, gestational age and Apgar scores have also been explored in previous studies. Nevo and colleagues (1995) found that prematurity, low birth weight and size for gestational age (both small and large for gestational age) were significant risk factors for epilepsy. Low birth weight and gestational age have been reported as possible risk factors in others studies (Van den Berg & Yerushalmy, 1969; Degen, 1978).

Sun and colleagues (2008) looked at the association between gestational age, birth weight, intrauterine growth, and epilepsy in a population-based cohort of 1.4 million

singletons born in Denmark between 1979 and 2002. A total of 14,334 inpatients and outpatients with epilepsy were registered in the Danish National Hospital. The study authors found that the incidence rates of epilepsy increased consistently with decreasing gestational age and birth weight. Sidenvall et al. (2001) also reported that the risk of an epileptic seizure was increased in children with gestational age <37 completed weeks (OR = 5.6, 95% CI=1.7–19). Finally, in a study by Coyne et al. (2008) there was a significant increase in the incidence of IUGR consistent with the diagnosis of FAS among cases. The birth weights of cases were on average 720 g lighter than those of controls. The majority of cases (56.1%) were born with low birth weights (1500–2499 g) compared to the controls (17.5%). Low birth weights were also strongly correlated to alcohol and smoking in both groups. The current study gathered information on birth weight, number of week's gestation, size for gestational age and Apgar score, to assess whether they increase the risk of developing epilepsy or seizures.

2.3.5 CNS Infection

CNS infection is reported as the cause of three to six percent (Hauser et al., 1993; Kurtz et al., 1998; Waaler et al., 2000) of cases of epilepsy. Those who survive the infection are three times more likely to develop subsequent unprovoked seizures (Annegers et al., 1988). The magnitude and duration of the increased risk of developing epilepsy following CNS infection varies depending on the type of infection (Annegers et al., 1996). After viral encephalitis, the individual is 26 times more likely to develop epilepsy and the risk remains for 15 years after the infection. The risk of unprovoked

recurrent seizures after bacterial meningitis is increased five fold and the risk remains for five years after the infection.

The current study attempted to gather information on CNS infections in the mother and child.

2.3.6 Comorbidities

Structural brain diseases that predispose an individual to epilepsy include: congenital (heterotopias, cortical dysplasia), degenerative (Alzheimer disease, infectious meningitis, encephalitis, abscess, trauma, tumor) and vascular (vascular malformation, stroke, subarachnoid hemorrhage). Therefore, comorbidities in individuals with FASD must be considered as a risk factor for the development of subsequent epilepsy. Head trauma will be considered as an independent risk factor in the analysis.

Common comorbidities in children with FASD include: attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), pervasive development disorder (PDD), post-traumatic stress disorder, anxiety, depression and substance abuse disorders (Fanny et al., 1998; Burd et al., 2003; Mills, 2006). In a study by Bhatara and colleagues (2006) the authors reviewed the charts of 2,231 youth referred for FASD. They found that 41% of participants had ADHD, 17% had a learning disorder and 16% had oppositional defiant/conduct disorder (ODD, ODCD).

2.3.7 Congenital Malformations

Investigators have also identified relationships between epilepsy and congenital anomalies although these associations are most often nonspecific (Chevrie et al., 1977;

Rantakallio & Wendt, 1986; Nelson & Ellenberg, 1986). In a study by Whitehead and colleagues (2006) children with major anomalies other than CNS anomalies were at risk of epilepsy and those with an anomaly of the CNS were at a much higher risk. As expected, abnormalities of the CNS, increased the risk of epilepsy, as did prenatal infections and neonatal metabolic disorders (Hauser et al., 1998; Rantakallio & Von Wendt, 1986; Nelson & Ellenberg, 1986; Browne & Holmes, 2001). In the study conducted by Sidenvall (2001), 5.2% of children among those with epilepsy, had a cerebral malformation and one-third were mentally disabled. There were two children among the cases and one in the control group with a congenital heart defect.

Most often, those with FASD experience ocular anomalies including: strabismus, microphthalmia, anomalies of the cornea and lens, coloboma of the iris and retina, tortuous retinal vessels, and hypoplastic optic disc and nerve. Craniofacial anomalies associated with FASD include: hypertelorism, ptosis, epicanthal fold, narrow or abnormal slanting of the palpebral fissures, microtia, stenosis of the ear canal, low set and/or posteriorly rotated ears, maxillary hypoplasia, micrognathia, retrognathia, dental malocclusions, missing and rotated teeth, crooked and crowded teeth, cleft lip, cleft palate, short or anteverted nose, flat nasal bridge, thin upper lip, flat philtrum, and high arched, narrow or banded palate (Church et al., 1997).

For the purpose of the current study, all congenital anomalies seen in this study population were recorded so that we were able to determine whether there were differences in the number and type of congenital anomalies between those with FASD, and those with FASD and a history of seizures.

2.3.8 Trauma and Stressful Life Events

Trauma is an important risk factor for epilepsy. It has been approximated, that the proportion of epilepsy attributed to trauma ranges from four to 10% (Cowan, 2002). A study by Annegers and colleagues (1995) revealed that the age-specific incidence of head trauma was trimodal: the first peak during the first year of life was associated with falls; the second peak among males aged 15 to 24 years was associated with recreational activities and motor vehicle injuries; and the third peak in the elderly was due to falls. Acute symptomatic seizures associated with head trauma were more common in males versus females at all ages. Children, if similarly injured, have higher risks of acute symptomatic seizures with similar traumatic brain injuries to adults.

Hauser and colleagues (1993) found that trauma is a more important contributor to remote symptomatic seizures among children older than five years than it is to younger children. In a more recent study in Rochester, Minnesota, the relative risk of epilepsy in people of all ages, was increased with moderate head trauma and largely increased in those with severe head injury (Annegers and Coan, 2000). Severe head trauma was defined as a documented brain contusion, intracranial hematoma, 24 hours or more of unconsciousness or posttraumatic amnesia; moderate head trauma was defined as skull fractures or head injuries sufficient to cause half an hour or more of unconsciousness or post-traumatic amnesia. These authors also found that the risk of developing epilepsy in the future, declines after the first year (post-injury) however the risk remains elevated for up to 10 years after the injury (Annegers & Coan, 2000).

Traumatic brain injury elicits epileptic seizures hours or days after the impact, yet the mechanisms on a cellular level are poorly understood. In most cases, post-traumatic

epilepsy manifests as temporal lobe epilepsy. Griesmer and Mautes (2007) found that morphologically closed head injury led to gradual, progressive neuronal degeneration in a particular cell type. They found a large increase in the frequency of spontaneous action potentials of CA1 but not CA3 hippocampal pyramidal cells after closed head injury. This may indicate that strong hyperexcitability, after closed head injury, is cell-specific and transient. These complex neuronal interactions need to be further explored and have pharmacological potential for treating post-traumatic epilepsy.

Mothers who consume alcohol during pregnancy, and their children, may experience a number of forms of trauma. Mothers' may be subject to traumatic events that increase the risk of negative consequences of their babies *in utero*, and many of their children continue to live in circumstances where trauma including neglect, physical and sexual abuse is common (Streissguth et al., 2004). Trauma in this population including falls, physical abuse, sexual abuse and number of moves between families must be carefully considered. Such incidences may increase the risk of epilepsy in this population. The following study collected information on head trauma, physical abuse, sexual abuse and number of moves in each subject.

2.3.9 Sleep and Seizures

Sleep disorders are not only common in those with epilepsy; they are common in those with FASD (Chudley et al., 2005; Steinhausen & Spohr, 1998). Mills and colleagues (2006) found that 64.2% of those with FASD experienced sleeping problems. Sleep deprivation has long been recognized as a precipitating factor for seizures. Currently, the effect of sleep deprivation on seizures has been well documented and most

researchers believe there is a specific activating effect of sleep deprivation on epileptiform discharges (Degen, 1980; Geller et al., 1969; Kilnger et al., 1991; Mattson et al., 1965; Molaie and Cruz, 1988; Pratt et al., 1968; Rowan et al. 1982; Tartara et al., 1980).

Sleep disorders in subjects with FASD were collected for the purpose of the current study. This way we could assess whether they were more common in those with epilepsy and seizures.

Chapter 3 BODY OF THESIS

3.1 Rationale and Hypothesis

There is a clear need to distinguish 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 seizure disorders in offspring exposed to alcohol during fetal life. The current study tested the hypotheses that: (1) individuals with FASD have a higher prevalence of epilepsy (>0.6%) than the general population in Canada; (2) epilepsy and/or seizures are not associated with a specific FASD diagnostic subgroup (ARND, pFAS, or FAS); and (3) a diagnosis of FASD is independent of other risk factors associated with epilepsy and seizures.

3.2 Methods

The following study was reviewed and approved by the research ethics boards of St. Michael's Hospital and Glenrose Rehabilitation Hospital. All active charts (n=1063) from the FASD clinics 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 of ARND, pFAS or FAS. Data was collected from patient charts at St. Michael's FASD clinic. The same researcher (Stephanie H. Bell) reviewed the charts at Glenrose Rehabilitation Hospital with two research assistants. After two days training, the research assistants performed the rest of the data collection. Once all information was collected, the lead researcher (S.H.B.) reviewed and

coded all the data. The following process ensured that data was collected in the same way.

Information regarding maternal drinking history was extracted including: pattern and magnitude of consumption, and type of beverage. If the patient had epilepsy or seizures, type, age of onset, frequency and treatment was recorded (when available). A pediatric (Paul A. Hwang, for subjects under 15) or adult (Peter L. Carlen, for subjects 15 and older) neurologist reviewed these patient records. They identified epilepsy and based it on classification in the International Classification of Diseases revision 10.

Information was also collected (when available) on family history, other comorbid conditions, congenital anomalies, prenatal drug exposure, prenatal care (whether the mother or family member reported any prenatal care), type of birth including complications, prematurity, size for gestational age, Apgar 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 (see Appendix A for data collection sheet).

Five hundred and fifty three subjects were excluded from St. Michael's data collection for reasons including: absence of a confirmed diagnosis within the FASD spectrum; lost to follow-up and insufficient chart information. Therefore, 266 subjects with a diagnosis of FASD were included in the data analysis. Those who obtain a diagnosis at St. Michael's FASD clinic are seen a minimum of two times in the clinic, once all information is collected (maternal drinking is confirmed, family history, neuropsychological testing, school records). They are seen by a nurse practitioner, a family physician who specializes in FASD and an administrative assistant. In the first

session the subjects are screened and a final assessment is performed where a diagnosis may be given.

At Glenrose Rehabilitation Hospital, 85 subjects were excluded from data collection due to absence of a confirmed diagnosis within the FASD spectrum. Therefore, 159 subjects with a diagnosis of FASD were included in the data analysis. This diagnostic clinic is also a two-day process; on the first day the child is assessed by a developmental pediatrician, psychologist and occupational therapist. On the second day further testing is done if needed and the team meets to present the data and look for evidence of organic brain damage in three different domains outlined in the 4-digit code and Canadian Guidelines (Astley & Clarren, 2004, Chudley et al., 2005). In total, 425 subjects from the two sites were included for the purpose of data analysis.

3.3 Data Analysis

The prevalence of FASD subjects with epilepsy and one or more seizure was determined. Chi-square analysis (Fisher's exact tests) was used to compare the prevalence of epilepsy and seizures among diagnostic subgroups (FAS, pFAS and ARND) and epilepsy or seizure subjects to those FASD subjects without a history of seizures. The chi-square test examines the general association between two variables without controlling for anything else. Multivariable multinomial logistic regression analysis was conducted to examine if other potential risk factors significantly increased or decreased the likelihood of epilepsy or spontaneous seizures in subjects with FASD. 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 p-values were two-tailed and p-values less than 0.05 were regarded as being significant.

Age and gender were adjusted for in the regression analysis. Insufficient information led to the exclusion of five risk factors in the regression analysis. Birth complications, Apgar score, sleep disorders and subject use of alcohol and drugs were excluded in the model 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 in order 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.

3.4 Results

A total of 425 subjects were included in the analysis. Demographic information on the study population is shown below.

Table 3.1: Demographic characteristics.

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

Table 3.2: The prevalence of epilepsy and seizures in the study population.

FASD Diagnosis	No Seizures	≥ 1 Seizure	Epilepsy	All Seizures
FAS, N (%)	12(80.0)	3(20.0)	0(0)	3(20.0)
pFAS, N (%)	61(85.9)	7(9.9)	3(4.2)	10(14.1)
ARND, N (%)	277(81.7)	40(11.8)	22(6.5)	62(18.23)
Overall, N (%)	350(82.3)	50(11.8)	25(5.9)	75(17.7)

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. The total sample with a history of seizures was 75 (17.7%). The chi-square test (Fisher's exact) indicated that there were no differences between FASD diagnosis and risk of epilepsy, or one or more seizure ($p=0.73$).

3.3: Chi-square test results.

	N	No (%)	Epilepsy (%)	≥ 1 Seizure (%)	p-value	All Seizures (%)	p-value
Family History of Epilepsy					.237		.178
Yes	20	75.0	10.0	15.0		25.0	
No	338	84.3	5.6	10.1		15.7	
Unknown	67	76.1	6.0	17.9		23.9	
Prenatal Drug Exposure					.160		.054
Yes	181	84.0	5.5	10.5		16.0	
No	140	86.4	3.6	10.0		13.6	
Unknown	104	75.0	9.6	15.4		25.0	
Prematurity					.648		.404
Yes	52	88.5	1.9	9.6		11.5	
No	237	82.7	5.9	11.4		17.3	
Unknown	136	80.2	7.4	12.5		19.9	
Size for Gestational Age					.615		.423
Appropriate	192	82.8	5.2	12.0		17.2	
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					.134		.035
Natural	197	83.8	5.1	11.2		16.2	
Other	77	72.7	10.4	16.9		27.3	
Unknown	151	86.1	4.6	9.3		13.9	
Prenatal Care					.239		.562
Yes	122	79.5	7.4	13.1		20.5	
No	77	84.4	9.1	6.5		15.6	

Unknown	226	83.6	4.0	12.4		16.4
Head Trauma					.409	.745
Yes	16	81.3	12.5	6.2		18.7
No	409	82.8	5.4	11.8		17.2
Physical Abuse					.596	.526
Yes	82	80.5	8.5	11.0		19.5
No	260	84.2	4.6	11.1		15.8
Unknown	83	79.5	7.2	13.3		20.5
Sexual Abuse					.581	.316
Yes	68	80.9	7.3	11.8		19.1
No	245	84.9	4.5	10.6		15.1
Unknown	112	78.6	8.0	13.4		21.4
Number of Moves					.583	.860
None	121	82.6	8.3	9.1		17.4
One or more	227	83.3	4.9	11.9		16.7
Unknown	77	80.5	5.2	14.3		19.5

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), $p < 0.05$. 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.

Table 3.4: Multinomial logistic regression results.

Risk Factor	Epilepsy		≥ 1 Seizure		All Seizures	
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Family History of Epilepsy (Yes vs. No)	2.00(0.43-9.39)	2.93(0.50-17.1)	1.68(0.46-6.09)	1.37(0.34-5.48)	1.79(0.63-5.14)	1.64(0.52-5.19)
Prenatal Drug Exposure (Yes vs. No)	1.59(0.53-4.78)	1.35(0.42-4.39)	1.08(0.52-2.24)	1.19(0.55-2.60)	1.22(0.65-2.27)	1.23(0.63-2.40)
Prematurity (Yes vs. No)	0.30(0.04-2.37)	0.21(0.02-2.27)	0.79(0.29-2.16)	0.70(0.23-2.20)	0.62(0.25-1.56)	0.57(0.20-1.60)
Size for Gestational Age (Large vs. Appropriate)	2.45(0.48-12.4)	4.06(0.70-22.7)	1.06(0.23-5.02)	0.95(0.18-5.03)	1.48(0.46-4.83)	1.57(0.44-5.54)
Size for Gestational Age (Small vs. Appropriate)	0.51(0.11-2.41)	0.88(0.16-4.87)	0.67(0.26-1.72)	0.63(0.22-1.79)	0.62(0.27-1.42)	0.69(0.28-1.73)
Type of Birth (Others vs. Natural)	2.36(0.89-6.27)	3.41(1.11-10.5)*	1.74(0.82-3.69)	1.96(0.87-4.40)	1.93(1.03-3.63)*	2.27(1.14-4.51)*
Prenatal Care (Yes vs. No)	0.86(0.31-2.43)	0.68(0.21-2.17)	2.14(0.75-6.14)	1.91(0.64-5.72)	1.40(0.66-2.97)	1.21(0.54-2.72)
Head Trauma (Yes vs. No)	2.26(0.48-10.6)	2.59(0.41-16.4)	0.54(0.07-4.23)	0.51(0.06-4.45)	1.10(0.31-3.96)	1.11(0.27-4.47)
Physical Abuse (Yes vs. No)	1.94(0.73-5.12)	2.10(0.55-8.06)	1.03(0.46-2.29)	0.76(0.28-2.08)	1.30(0.68-2.46)	1.05(0.46-2.39)
Sexual Abuse (Yes vs. No)	1.72(0.57-5.15)	1.11(0.27-4.62)	1.16(0.50-2.71)	1.11(0.40-3.11)	1.33(0.66-2.67)	1.15(0.48-2.72)
Number of Moves (more than 1 move vs. no move)	0.58(0.24-1.42)	0.51(0.19-1.38)	1.30(0.62-2.73)	1.27(0.58-2.80)	0.96(0.53-1.72)	0.93(0.49-1.74)
Congenital Malformations (Yes vs. No)	0.90(0.30-2.74)	0.56(0.15-2.07)	1.42(0.68-2.95)	1.29(0.58-2.87)	1.23(0.65-2.32)	1.07(0.52-2.20)

Note: 1. Age and gender were adjusted in the multivariate multinomial logistic regression. 2. Unknown categories were also included in the analysis, but not reported here. 3. * $p < .05$.

The multinomial logistic regression analysis showed that those with epilepsy were three times (OR=3.41, 95% 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. Furthermore, when all seizures were combined, those with epilepsy or seizures were two times (OR=2.27, 95% CI=1.14-4.51, $p < 0.05$) more likely to have an unnatural birth than those subjects without a history of seizures.

Chapter 4 GENERAL DISCUSSION AND CONCLUSIONS

4.1 Overview of Main Findings and Interpretation

The current study found a remarkably high prevalence of epilepsy and spontaneous seizures among 425 subjects with FASD at St. Michael's Hospital (Toronto) and Glenrose Rehabilitation Hospital (Edmonton), compared to the general population in Canada. The prevalence of epilepsy was 5.9% compared to the prevalence of 0.6% in the general population of Canada. Furthermore, 11.8% experienced one or more documented seizure episode. There were no differences in the prevalence of epilepsy or seizures among individuals with FAS, pFAS, or ARND.

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(s) for epilepsy that accompany maternal alcohol abuse. Subjects with a breech, cesarean, forceps or vacuum birth were three times more likely to have epilepsy and, two times more likely to have epilepsy or one or more seizure (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 (Lilienfield et al., 1959; Degen, 1978; Nelson & Ellenberg, 1986; Greenwood et al., 1998). In contrast, Chevie (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 (induced labor, labor ≥ 24 hours, fetal distress, breech, cesarean section, forceps, nuchal cord and "other"), assuming comparable consequences. Also, a study conducted by Sidenvall (2001) found that cesarean sections (OR = 18, 95% CI, 3.7–88) increased the risk of having epilepsy. In all emergency sections and in three of four of the elective cesarean sections in the cases reported, this procedure was performed as a consequence of adverse events occurring in the mother and/or fetus (Sidenvall, 2001).

In the current study, 12 subjects with epilepsy and two with seizures were born by cesarean section, five of which were reported as emergency cesarean sections. Emergency cesarean sections were performed due to adverse events occurring in the mother or fetus including: ruptured membrane and slow progression of labor, high maternal blood pressure, and fetal distress. 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 (these were not well defined, one baby required resuscitation); which might have contributed to neonatal hypoxic brain damage and subsequent seizures. 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; Ellenberg and Nelson, 1979; Nelson and Ellenberg, 1984; Deymeer & Leviton, 1985; Rocca et al., 1987).

Subjects with prenatal alcohol and other drug exposure were more likely to have epilepsy or seizures than those without prenatal drug exposure, 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 multi-drug 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, multi-drug users were also 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 during pregnancy and the elevated risk of seizures in offspring who were exposed to alcohol and other drugs in the prenatal period.

4.2 Cellular Mechanisms that may underlie the Increased Risk of Epilepsy/Seizures in FASD

In accordance with the results of the current study, prenatal alcohol exposure may act as an independent mechanism for developing subsequent seizures and seizure disorders in those with FASD.

One of the most epileptogenic regions of the brain is the hippocampus (Stringer & Lothman, 1992a), which is susceptible to neuronal loss (e.g. pyramidal cells) and disruptions in circuitry as a result of ethanol exposure (Bouilleret et al., 1999; Cavazos & Sutula, 1990; Germano et al., 1998). In the rat, there have been several reports that document vulnerability of the hippocampus to developmental exposure to ethanol during

the brain growth spurt, which occurs during the first week of postnatal life (Bonthius & West, 1990, 1991; West & Hamre, 1985).

Bonthius and colleagues (2001) showed that ethanol exposure during the brain growth spurt in the rat resulted in a permanent reduction in seizure threshold. Repeated exposure to high blood alcohol concentrations during early postnatal life depleted CA1 pyramidal cell neurons, and the severity of alcohol-induced CA1 pyramidal cell loss was correlated with a reduction in seizure threshold. Adult rat offspring exposed to a high dose of alcohol during early development exhibited a number of electrophysiological disturbances in the hippocampus. The time to onset and stimulus threshold for maximal activation of the dentate gyrus were both decreased in ethanol-exposed offspring, and the duration of the after discharge was increased. With induced seizures, spreading depression occurred more often and with fewer stimuli in the high-dose alcohol group. The series of repeated electrically-stimulated seizures induced rapid kindling in all treatment groups, but was enhanced in a dose-dependent manner in alcohol-exposed animals. Thus, alcohol exposure during the brain growth spurt in the rat (equivalent to third trimester exposure in the human) may alter hippocampal physiology, promoting epileptiform activity, enhancing kindling and facilitating spreading depression (Bonthius et al., 2001).

Ethanol targets GABA receptors (Nestoros, 1980; Suzdak et al., 1986) and repeated exposure can lead to long-term changes in the ordinary function of these receptors (Kang et al., 1998) and in the gene expression for GABA receptor subunits (Mahmoudi et al., 1997). Seyfried et al. (1986) and Shwartz et al. (1989) demonstrated

that animals with genetic defects of the GABA receptor have hyperexcitable neurons, which predispose them to seizures. Repeated exposure to ethanol may alter GABA receptor subunit composition specifically within the CA1 area of the hippocampus (Kang et al., 1998), leading to altered inhibitory synaptic function in this brain structure.

More recently, Gonzalez-Burgos et al. (2006) examined 30-day-old offspring of rats exposed to moderate levels of ethanol during gestation and lactation, and found a decreased volume of the hippocampal CA1 field as well as reductions in the number of spines from surviving CA1 pyramidal neurons. Further evidence is found in humans with hippocampal sclerosis, which is characterized by the loss of hippocampal pyramidal cell bodies, mostly those from the CA1 area (Kim 1990, Kuzniecky, 1999).

Withdrawal in the pregnant woman and her fetus, or newborn baby may also increase the risk of epilepsy and seizures in offspring. Twenty to 30% of children who have seizures in the newborn period will develop epilepsy (Ellenberg et al., 1984; Mizrahi, 1999), and three-quarters of these will have seizure onset within the first year of life (Ellenberg et al., 1984). In a 10-year prospective cohort study by Ronen and colleagues (2007) in 88 subjects with neonatal seizures, 17 (27%) developed epilepsy. The severity and timing of the pathologic process continue to be the major determinants for outcome.

The N-methyl-D-aspartate (NMDA) subtype of ionotropic glutamate receptors, which plays a crucial role during neuronal development, is activated excessively during withdrawal and may lead to neuronal cell death (Thomas & Riley, 1998). During abstinence, as alcohol is eliminated from the body, alcohol's inhibitory action decreases,

thus cells with elevated NMDA receptor levels experience rebound excitability.

Hyperexcitability may contribute to symptoms such as tremors, agitation and seizures. In the rat, pharmacological block of NMDA receptors selectively during ethanol withdrawal results in improved outcome in offspring (Thomas & Riley, 1998). Overactivation of NMDA receptors is associated with a cascade of intracellular events that may culminate in cell death or excitotoxicity. Excitotoxicity as a consequence of ethanol withdrawal has been reported to lead to cell loss in regions such as the cerebral cortex, hippocampus and striatum (Lovinger, 1993).

Studies by Bradford (1995) demonstrate an “up regulation” of NMDA receptor function both *in vivo* and *in vitro* as a consequence of chronic exposure to ethanol. Moreover, neuronal cell cultures chronically exposed to ethanol are also much more susceptible to glutamate-induced cell death. This demonstrates the role of the NMDA receptor in neuronal damage after chronic ethanol exposure and withdrawal in both animals and humans (Hoffman & Tabakoff, 1994). Withdrawal and hyperexcitation may interfere with the ability of the cell to maintain resting potential below the threshold (Davies, 2003). Cell death and tissue damage would result in rapid and acute leakage of glutamate to the extra cellular space, leading to hyperexcitation and seizures. Potassium channels may also be disrupted so that repolarization does not occur and action potentials are prolonged, again increasing excitability to the central nervous system (Davies, 2003). Particular seizure types resulting from withdrawal or ethanol ingestion during pregnancy may include complex partial seizures (Davies, 2003). In adults, complex partial seizures account for 40% of epilepsy as a result of neuronal cell death in the CA1 areas of

Ammon's Horn in the hippocampus (Davies, 2003). More in depth studies are needed to determine the exact type or types of seizures occurring in subjects who undergo neonatal ethanol withdrawal and who go on to develop epilepsy.

4.3 The Impact of Additional Risk Factors for Epilepsy/Seizures in FASD

There are a number of key factors that are evident in mothers and/or individuals with FASD that may greatly increase the risk of subsequent seizures. The following factors are described in more depth, although the current study may not have included them in the analysis.

4.3.1 Maternal Malnutrition and Risk of Seizures

In the current study, prenatal care was used as an indicator for maternal nutrition; however more detailed prospective studies are needed to measure and assess the implications of under nutrition. Nutrition may be a very important difference between an alcoholic and a non-alcoholic pregnant woman. In 1998 O'Brien obtained detailed information on seven mothers who were alcoholics. Dietary history was assessed and revealed that five of the seven mothers had moderate to severe deficiencies, either in protein or in calories, or both, during their pregnancies. Three admitted to consuming 25% or more of their daily caloric intake in the form of alcohol. The laboratory studies, which included tests for hemoglobin, red cell indices, total serum protein, albumin, and globulin, and the assay of various vitamins in blood or urine, did not indicate the presence of specific vitamin deficiencies, except in one mother, who had serum folate

less than 4 micrograms percent. One mother had slightly decreased serum albumin, whereas five mothers had increased globulin with normal albumin more consistent with liver changes of chronic alcoholism than with malnutrition. A more recent study done by Manari and colleagues (2003) using a cohort of United Kingdom (UK) alcohol abusers, revealed that the whole patient population had a low intake of one or more macro- and micro-nutrients compared to the dietary reference requirements. All patients had intakes of vitamin E and folate below UK recommended standards, while 85 to 95% of patients had low intakes of selenium and Vitamin D. Between 50% and 85% of all patients had intakes of calcium, zinc, Vitamins A, B₁, B₂, B₆ and C below UK recommended standards.

Ba and colleagues (1999) assessed the combined effects of a thiamine-deficient diet on newborns and alcohol exposure in pregnant and lactating rats. The nuclear size of hippocampal pyramidal cells in the CA3 field was significantly reduced compared to controls and the decrease was more severe in the thiamine deficient diet with ethanol exposure than the thiamine deficient diet alone. Furthermore, the administration of thiamine during developmental ethanol exposure partially restored the mean nuclear size of the CA3 cells in the hippocampus. The authors postulated the existence of common and separate mechanisms underlying the effects of alcohol intoxication and thiamine deficiency on cell death and cell atrophy in the brain. It has also been reported that maternal malnutrition and alcohol toxicity alter the morphology, distribution and the number of spines on the dendrites resulting in a reduced ability of the brain to adapt to

internal and external changes and impairment in its ability to create new connections in the global process of plasticity (Fiala et al., 2002).

Malnutrition leads to a decrease in myelin synthesis (Montanha-Rojas et al., 2005) and thus fewer nerve fibers become myelinated (Peeling & Smart, 1994). In the developing brain, poor diet can alter the distribution of the dendritic spines on neurons (Fiala et al., 2002). All of the above may increase the likelihood of seizures. Malnutrition may play a key role in increasing the risk of seizure disorder in individuals with prenatal alcohol exposure and it is likely, that if the child received poor nutrition *in utero*, they may not receive adequate dietary recommendations postnatally.

4.3.2 Alcohol and Drug Use during Pregnancy

A high proportion of mothers who consume alcohol during pregnancy may use a combination of drugs throughout pregnancy and it is very challenging to separate out the effects of individual agents. In the current study, those who used other drugs also tended to be heavy, frequent drinkers. Leonardson and Loudenburg (2003) found that 60% of women who report drinking during pregnancy use other drugs as well. In the study identified above, the most common drugs of abuse used by women during pregnancy included phencyclidine (PCP), marijuana and cocaine.

Sharpe and Velasquez (2008) administered a survey to 2672 women aged 18 to 44, in low-income settings in Florida, Virginia and Texas. Women who reported using more than one illicit drug, were compared to women who reported never using illicit drugs. Findings indicated that 75% of women reported using more than one illicit drug;

these women were more likely to report frequent drinking, binge drinking, and drinking during pregnancy compared to nonusers. Moreover, a greater proportion of drug users failed to use contraception compared with nonusers. These findings suggest that women who report ever using more than one illicit drug, are at a greater risk for having an alcohol-exposed pregnancy.

4.3.3 Trauma and Seizures

Many individuals in the current study experiences physical, abuse, sexual abuse and/or head trauma. Among the environmental circumstances frequently found in association with prenatal alcohol exposure, are early maternal death (Streissguth et al., 1991; May et al., 1983) living with an alcoholic parent, child abuse and neglect, (Russel et al., 1984; Werner, 1986) being removed from the home by authorities, experiencing foster care and other transient home placements, and being raised by adoptive families.

In 1999, Muhajarine and D'Arcy studied the prevalence and predictors of physical abuse in a sample of pregnant women in Saskatoon. Six hundred and five women receiving prenatal services through the Saskatoon District public health system between 1993 and 1994 were interviewed in the second trimester and 543 were interviewed again, late in the third trimester. Overall, 31 women (5.7%) reported experiencing physical abuse during pregnancy and 46 (8.5%) reported experiencing it within the 12 months preceding the second interview. Of these women, 63.3% reported that the abuser was her husband, boyfriend or ex-husband and aboriginal women were at greater risk than non-aboriginal women.

Streissguth and colleagues (2004) evaluated life circumstances in 415 patients enrolled in the Fetal Alcohol Follow-up Study of the University of Washington's Fetal Alcohol and Drug Unit (FADU). Among these individuals, 67% had been the victim of physical abuse, sexual abuse or domestic violence. Many individuals with FASD do not remain in the care of their biological parents; parents' substance abuse very often leads to the placement in one or more foster homes (Niccols 1994; Gessner et al., 1998). In Saskatchewan, 72% of people with FASD have resided in foster care for part of their life (Habbick et al., 1996). In the study by Streissguth and colleagues (2004), 80% were not raised by their biological mothers and their median percent of life in a stable/nurturing home was 75% of their lives and median years in each living situation was 2.7 years. In a more recent study by Mills and colleagues in Edmonton, Alberta (2006) 79% of children with an FASD were residing with a foster parent, and 27% lived in a group home. In the current study, there were no differences in head trauma, physical and/or sexual abuse found between those with a history of seizures and those with no history.

4.3.4 Sleep and Seizures

The current study was not able to obtain enough information on sleep disturbances to include this factor in the statistical analysis; although a higher prevalence of sleep disorders and more sleep problems may contribute to the increased risk of one or more seizures in the current study sample. Animal studies reveal that ethanol exposure during brain development can cause alterations in the circadian rhythm and its regulating system. Earnest and colleagues (2001) found that developmental alcohol exposure in the

rat may interfere with circadian clock function due to a shortened circadian sleep-wake cycle and changes in the release of certain brain chemicals. Sakata-Haga and Fukui (2007) looked at the effects of pre- or postnatal exposure to ethanol on the circadian rhythm in adulthood, by measuring deep body temperature and wheel running activity in rats. After a phase delay in the light/dark cycle, ethanol-exposed rats took longer than control rats to resynchronize to the new light/dark cycle. This suggests that pre- and postnatal ethanol exposure impairs the development of the circadian clock response to light cue. Such abnormal development of the circadian clock system might contribute to the neuropsychiatric symptoms seen in FASD. Further studies are needed to understand the long-term effects of ethanol on circadian rhythms.

Sleep deprivation may also have an activating effect on epileptiform activity in the brain. In subsequent studies, sleep was found to be necessary to define interictal epileptiform activity in 26.7% to 63.8% of patients in various reports (Mattson et al., 1965; Niedermeyer and Rocca, 1972; Dinner et al., 1984). Most of the evidence indicates that sleep deprivation causes marked activation of interictal epileptiform abnormalities. Some researchers however attribute the EEG activation after sleep deprivation to the presence of drowsiness and sleep in the tracing (Degen and Degen, 1991; Degen et al., 1987). Indicated above, disrupted sleep and sleep disorders are more common in individuals with FASD, potentially increasing the risk for spontaneous seizures.

4.4 Strengths and 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. However, during the writing of this thesis, the results of a large-scale epidemiological study that investigated the relationship between binge drinking and epilepsy/seizures were published (Sun et al., 2009). This study reported on over 80,000 singleton births followed for up to 8 years of age through the Danish National Hospital Register. The results of this study suggested that binge drinking during early gestation (11-16 weeks) was associated with a 3.15-fold increase in neonatal seizures, and a 1-81-fold increase in the risk for epilepsy (Sun et al., 2009).

Data collected from FASD patient charts included information obtained from birth records, physician reports, government reports and self-report intake forms. 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 although information bias cannot be completely eliminated. 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. Importantly, the main outcome variables were not subject to information bias, as information was collected after fetal alcohol exposure and was most often confirmed in physician assessments. Also, two neurologists extensively reviewed records of those with epilepsy. In order to classify those with a history of seizures however, more detailed work-ups are required.

We attempted to consider as many risk factors as possible (where information was available) for developing epilepsy in this FASD population. 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. This information was not available for the purpose of the current study. Birth complications (e.g., hypoxia), 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 consumption, and thus it is not certain whether the increased risk is associated with high alcohol consumption, other drug use, or the combination.

4.5 Clinical Implications and Future Studies

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 need to be evaluated to determine thresholds for alcohol exposure and potential critical periods of vulnerability. Epilepsy is frequently missed in routine clinical assessments, and untreated epilepsy can lead to increased or unrecognized cognitive deficits. After most complex partial, and all tonic-clonic seizures, memory is impaired. Patients complain of impaired recall for recently learned information, particularly details and names (Devinsky, 2004). Attention impairments are also recognized and interictal epileptiform activity can impair transient and sustained attention (Sherman et al., 2007; Dunn et al., 2003).

Many children who have a medical evaluation for epilepsy have a known history of prenatal alcohol exposure, but do not have the physical features of FAS. Furthermore, many of these individuals have no other predispositions to that of epilepsy, for example, family history or a head injury (Bonthius 2001). Therefore, it is very important for the physician to be aware of alcohol exposure *in utero*, when considering possible etiology and mechanisms of seizures.

Timing and pattern of maternal alcohol consumption during pregnancy are also very important in assessing the relationship between prenatal ethanol exposure and the development of epilepsy and types of epilepsy in the offspring. Behavioral and physiologic effects of alcohol during development depend on the timing of alcohol exposure, as well as the dose of ethanol consumed and reflect regional and cellular differences in vulnerability to alcohol neurotoxicity (Bonthius, 2001). Animal studies are necessary to explore these windows of vulnerability. Scientists also need to look at ethanol exposure as a factor independent of other drug exposures. Now that we are aware

of the much higher risk of epilepsy in people with FASD, future studies are needed to understand the brain mechanisms that link the effects of prenatal alcohol exposure and a reduced seizure threshold. Apart from controlled animal studies, a prospective analysis of subjects with FASD is needed. In this way, better information on seizure onset, type and duration will be available. Then, detailed workups with EEG and MRI may be performed. EEG results will give us an idea as to type of seizures and diagnosis of epilepsy, and MRI results will demonstrate structural brain damage that may indicate the affected brain region. Importantly, these results will guide patient care in terms of identification and treatment of seizures.

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Appendix A: data collection form.

Data Collection Sheet (from each patient chart)

Code Number:

Diagnosis: FAS, pFAS or ARND (circle)

1) Does the patient have seizures or epilepsy?

- i) Classification of epilepsy
- ii) Age of onset
- iii) Duration of the seizures
- iv) Treatment

Seizure Classification:

Partial Seizures

- a) Simple Partial
- b) Complex Partial

Generalized Seizures

- a) Primary
- b) Secondary

Absence
Tonic-clonic
Myoclonic
Atonic

Seizures (Not classified)

- a) Neonatal
- b) Febrile
- c) Myoclonic
- d) Infantile spasms
- e) Drug withdrawal seizures

2) What is the prior history of prenatal alcohol exposure (confirmed/unconfirmed)?

3) What is the pattern of prenatal exposure?

i) Number of days of alcohol consumption per week

ii) Type of alcohol consumed

Beer

Liquor

Wine

Other

iii) Average amount of alcohol used per drinking occasions

iv) Weeks of pregnancy in which alcohol consumed

In first trimester

In second trimester

In third trimester

4) Are there any other prenatal exposures, substances consumed?

Cocaine

Crack/cocaine

Marijuana

Ecstasy

Other

i) Number of Days per week

ii) Average amount of substance used each time

iii) Weeks of pregnancy in which substance was used

In first trimester

In second trimester

In third trimester

5) Does the subject have any other comorbid conditions (E.g. ADHD, ODD, PDD Fragile X, head injury, or other)?

6) Does the subject have any congenital malformations/anomalies?

7) Did the mother receive prenatal care?

8) What was the type of birth?

Normal
Breech
Forceps
Cesarean Section
Vacuum
Other

- 8) Where there any birth complications?
- 9) At how many weeks was the subject born? Were they premature?
- 10) What was the subject's size for gestational age (normal, SGA, LGA)?
- 11) What was their Apgar score (at 5 minutes and at 10 minutes)?
- 12) What is the family history? Is there a history of epilepsy?
- 13) What are the current/previous medications the child is/was taking?
- 14) Has the patient ever had an electroencephalogram (EEG)? What are the results, if available?

Normal
Abnormal (focal, generalised, epileptiform, not epileptiform)

- 15) Has the child or birth mother ever experienced any physical or sexual abuse?
- 16) Does the child have a sleep disorder or any sleep problems?
- 17) How many moves as the child endured (note: moves from one family to another family)?
- 18) Does the subject have drug or alcohol abuse problems?