Teratogenicity and Perinatal Outcomes Associated with Epilepsy and the Use of Antiepileptic Drugs

by

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ABSTRACT

Background and Objectives:

Epilepsy complicates 0.3 – 0.7% of all pregnancies in developed countries. There is a lack of consensus on appropriate antiepileptic drug (AED) regimens, folic acid supplementation, delivery management, and breastfeeding guidance. This thesis examines how women with epilepsy in British Columbia (BC) and throughout Canada are being managed to concurrently control seizures, decrease teratogenicity and optimize obstetric and perinatal outcomes.

Design and Methods:

Using BC linked administrative data, I examined utilization of AEDs, teratogenicity and small for gestational age (SGA) outcomes in infants exposed to newer generation AED monotherapy in utero. Using the Canadian Community Health Survey Cycle 3.1, I compared rates of preconceptual folic acid supplementation and breastfeeding among women with and without epilepsy. Using data from the BC Perinatal Data Registry, I compared rates and indications for induction of labour and cesarean section among women with and without epilepsy.

Results:

Our study on the BC population demonstrates no risk for both major malformations and SGA outcomes with newer generation AED monotherapy such as gabapentin, topiramate and lamotrigine. While pregabalin was not found to increase the risk for major malformations, it is possible that it does increase the risk for SGA outcomes. Newer

generation AEDs were less frequently prescribed during pregnancy than older generation AEDs.

Women with epilepsy in Canada were no more likely to supplement with folic acid and were significantly less likely to breastfeed when compared to women without epilepsy.

In BC, when compared to women without epilepsy, women with epilepsy were significantly more likely to deliver via cesarean section, induction of labour, assisted vaginal delivery, epidural or general anesthesia. Significant differences observed between women with and without epilepsy in the indications provided for cesarean section included breech, fetal malposition and "Other;" and "Maternal Condition" for those undergoing induction of labour.

Conclusion:

In women with epilepsy, pregnancy management is best implemented preconceptually. This includes planning for sufficient time to transition to the appropriate AED therapy, and to initiate folic acid supplementation. During preconceptual counselling, women with epilepsy of childbearing age should be apprised of delivery options and encouraged to attempt breastfeeding.

PREFACE

This statement is to certify that the work in this thesis was conceived, conducted and written by Kristi McIntosh.

Research described in this dissertation was approved by the University of British Columbia's Behavioural Research Ethics Board: UBC BREB Number: H11-00392 (Teratogenicity associated with the use of antiepileptic medications in utero in British Columbia), and H11-00630 (Delivery outcomes in pregnant women with epilepsy in British Columbia). "University of British Columbia's Policy #89: Research and other studies involving human subjects" states that ethics approval for Chapter 3 (Preconceptual counselling in women with epilepsy in Canada: the association between folic acid supplementation and breastfeeding) was not necessary.

Chapter 1 is based on work conducted by Kristi McIntosh (KM). KM was responsible for the conception of the literature review, writing the manuscript, and revising the manuscript. Dr. Patricia Janssen, Dr. Jan Friedman, Dr. Tim Oberlander and Dr. Bruce Carleton participated in editing the manuscript.

Chapter 2 is based on work conducted by Kristi McIntosh. KM was responsible for conception of the study, study design, conducting the data analysis, writing the manuscript, and revising the manuscript. Jaafar Aghajanian assisted with data management. Dr. Carleton, Dr. Friedman and Dr. Oberlander approved the study design, suggested some additional analysis, and edited the manuscript.

Chapter 3 is based on work conducted by Kristi McIntosh. KM was responsible for conception of the study, study design, conducting the data analysis, writing the manuscript,

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Chapter 5 is based on work conducted by Kristi McIntosh. KM was responsible for the conception of the conclusion, writing the manuscript, and revising the manuscript. Dr. Bruce Carleton participated in editing the manuscript.

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LIST OF ABBREVIATIONS

AAN……American Academy of Neurology
AED……antiepileptic drug
AES……American Epilepsy Society
BC PDR……British Columbia Perinatal Data Registry
BC……British Columbia
BMI……body mass index
CCHS……Canadian Community Health Survey
CI……confidence interval
cm……centimetre
CS……cesarean section
EURAP……International Registry of AEDs and Pregnancy
EUROCAT……European Concerted Action on Congenital Anomalies and Twins
GSK……GlaxoSmithKline
g……gram
ICD……International Classification of Disease
IQ……intelligent quotient
IUGR……intrauterine growth restriction
MBRN……Medical Birth Registry of Norway
mg……milligram
mmHg……millimeter of mercury
MSP……Medical Services Plan
NAAPR……North American AED Pregnancy Registry
NBDPS……National Birth Defects Prevention Study
NEAD…… Neurodevelopmental Effects of Antiepileptic Drugs Study
NICE……National Institute of Clinical Excellence
OR..... odds ratio
PCCF……Postal Code Conversion File
PR……prevalence ratio
PROM……pre-mature rupture of membranes
RR……relative risk
SAS……Statistical Analysis System
SECBDS……Slone Epidemiology Center Birth Defects Study
SES……socioeconomic status
SGA……small for gestational age
UBC……University of British Columbia
UK……United Kingdom
USA……United States of America

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Finally, I must thank my husband, Dr. Michael Parr who inspired me to go back to school, supported me every minute of those long and occasionally painful years and agreed that both sleep and a clean house were extremely overrated. I love you more than I can ever say.

DEDICATION

In memory of Autumn, Lisa, Ed and John.

To my kids; Sevi, Finn and Case.

"Life moves pretty fast. If you don't stop and look around once in a while, you could miss it."

Ferris Bueller's Day Off (1986)

CHAPTER 1: Review of the literature

Epilepsy is defined as "a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, psychological and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure."(1) Epilepsy is the most common maternal neurologic disorder requiring medical treatment during pregnancy.(2) In this chapter, I review the epidemiology of epilepsy in pregnancy, the teratogenicity of antiepileptic drugs (AEDs), growth restriction after exposure to AEDs, cognitive outcomes after both in utero and breastfeeding exposure to AEDs, preconceptual counselling for folic acid supplementation, management of pregnancy and labour, and rates of breastfeeding.

1.1 Epidemiology of epilepsy in pregnancy

It is estimated that fifty million individuals worldwide have epilepsy.(3) The prevalence of epilepsy in the general population has been reported to be between 5 and 10 cases per 1,000 persons (excluding febrile convulsions, single seizures and inactive epilepsy).(4-8) In a Canadian representative cross-sectional study using self-reported data from 130,822 individuals in 2005, the prevalence of epilepsy was 5.6 per 1,000 (95% confidence interval (CI), 5.2 – 6.0) among women.(7) It was most prevalent among those with less education, lower income levels, and a history of unemployment within the previous year.(7) In a recent (2010) systematic review and meta-analysis of studies from 31 developed countries and 34 developing countries, the median lifetime prevalence of epilepsy in both men and women was reported to be 15.4 per 1,000 (95% CI, 4.8 – 49.6) in rural areas and 10.3 per

1,000 (95% CI, 2.8 – 37.7) in urban areas of developing countries, and 5.8 per 1,000 (95% CI, 2.7 – 12.4) for rural and urban combined in developed countries.(5)

A recent review reported on incidence. In the most recent comprehensive systematic review and meta-analysis of 33 studies from 19 countries (2011),(9) the median incidence of epilepsy was reported to be 45.0 per 100,000 person-years for high-income countries and 81.7/100,000 person-years for low and middle come countries in both men and women.(9) In Denmark, a prospective cohort study of the entire population (5,491,652) between 1995 and 2002 reported the incidence of new cases of epilepsy to be 83.3 per 100,000 person-years at risk.(4) Incidence rates were higher in men than in women except for the ages 10—20 years.(4) By age 25, cumulative incidence for women was 1.96% (95% CI, 1.90-2.01%) and for men was 1.98% (95% CI, 1.93-2.03%).(4) For women of childbearing age, the incidence of epilepsy was reported to be between 45 and 75 per 100,000 person-years.(4)

During pregnancy, the prevalence of epilepsy has been found to be between 0.3 – 0.7% in developed countries.(10-12) The incidence of epilepsy during pregnancy has not been reported. For the majority (63.6%) of women with epilepsy, seizure control (assessed by measuring seizure frequency and severity and using the first trimester as a reference) remains unchanged during pregnancy.(13) EURAP (an International Registry of AEDs and Pregnancy developed by a consortium of researchers from 42 countries in Europe, Australia, Asia, South America and Africa) reported prospectively documented seizure control and treatment in 1,956 pregnancies among 1,882 women with epilepsy.(13) Among women with epilepsy, 58.3% were seizure-free throughout pregnancy.(13) Among

the remaining 41.7%, when comparing to the first trimester, 5.0% had no change in seizure frequency, 17.3% had an increase in seizure frequency, 15.9% had a decrease in seizure frequency and 3.1% had seizure frequency changing in opposite directions between the second and third trimesters compared to the first.(13)

1.2 Overview of treatment of epilepsy in pregnancy

1.2.1 Goal of therapy

Indications for AED therapy include epilepsy, mental health disorders, headache and neuropathic pain.(14, 15) In patients with epilepsy, the primary goal of AED therapy is to decrease the number and severity of seizures. The prevalence of antiepileptic therapy in pregnant women is 0.2 – 0.5%.(16) In Denmark and the USA, it is estimated that half of these AED prescriptions are used for treating epilepsy.(17) Secondary goals of AED therapy include improving concerns about quality of life that are related to the severity of the patient's epilepsy. Pregnant women with epilepsy require ongoing AED therapy to decrease the likelihood of adverse outcomes such as anoxia and injury to both themselves and the fetus from seizures.(18) The potential risk of accidental injury or anoxia to the mother and/or the fetus from maternal seizures after stopping AEDs may outweigh the potential risks to the fetus associated with in utero drug exposure.

Approximately 60–70% of all women experience seizure freedom with appropriate therapy, with more than 90% of that group experiencing seizure freedom as a result of monotherapy treatment.(19) AED treatment usually continues throughout pregnancy, utilizing the fewest possible drugs at the lowest doses necessary to maintain seizure

control. However, this may be challenging as pregnancy itself can significantly alter the pharmacokinetics of AEDs, necessitating increases in AED dose with higher levels of exposure for the fetus.(20)

Exposure to AEDs may have teratogenic effects on the fetus and adverse effects on the newborn, including iatrogenic preterm delivery, small-for-gestational-age (SGA) outcomes (< 10 percentile), and impaired cognitive development.(10, 18, 21-25) It is well established that treatment with most of the older-generation AEDs such as phenobarbital, phenytoin, carbamazepine, and valproate, may be teratogenic.(26) In the following section, I will review the literature, examining associations between major malformations and maternal therapy with newer generation AED (AEDs licensed since the early 1990s).

1.2.2 Teratogenesis: therapy vs. pathophysiology of epilepsy

A teratogenic effect is defined as any fetal adverse event caused by an exposure during pregnancy, whether or not the effect is apparent at birth.(27) Observational studies have not demonstrated an association between maternal epilepsy and either major or minor malformations in the absence of AED exposure.(25) However, epilepsy may have profound effects on maternal health, including maternal mortality.(28) In addition, generalized tonic-clonic seizures during pregnancy have been associated with poor postnatal cognitive development.(29, 30) When studying whether epilepsy alone or AEDs are associated with major malformations, it is important to consider that untreated women with epilepsy during pregnancy are likely different in aspects such as socioeconomic status (SES) and comorbidities when compared to treated women with epilepsy.(7, 31, 32) Some studies have used untreated women with epilepsy as a control group when investigating the

teratogenicity of AEDs, but this may not be ideal, as SES and comorbidities may independently alter the risk for malformations.

In a 2001 prospective cohort study, the association between epilepsy and major malformations was evaluated. Of 128,049 women giving birth at any of five hospitals in the Boston area in the USA between 1986 and 1993, three cohorts were observed: infants exposed to AEDs, infants not exposed to AEDs whose mothers had a history of seizures and infants not exposed to AEDs whose mothers had no history of seizures (control group).(25) Of those infants examined, the combined frequency of either major malformations, microcephaly, growth restriction, or minor abnormalities characteristic of AED exposure in utero was increased in 316 infants exposed to any AED when compared to the 508 control infants (22.8% vs. 8.5%; OR, 3.2; 95% CI, 1.3 – 5.0). Among the 98 infants born to unmedicated women with epilepsy, the frequency of such abnormalities was similar to that found in the control group (6.1 vs. 8.5%).(25) This study demonstrates that major or minor malformations in infants of mothers with epilepsy are associated with the use of anticonvulsant drugs during pregnancy, rather than with epilepsy itself.

To determine if epilepsy itself represents a teratogenic risk, a 2004 meta-analysis was conducted of all cohort and case-control studies reporting malformations rates in both exposed and unexposed children of mothers with epilepsy compared with that of children of women without epilepsy.(33) The risk for malformations in the unexposed children of women with epilepsy was similar to the risk for children of women without epilepsy (OR, 1.92; 95% CI 0.92 – 4.00). Furthermore, the children of exposed women with epilepsy had

a higher risk for malformations than unexposed children of women with epilepsy (OR, 3.26; 95% CI, 2.15 - -4.93).

1.2.3 Newer versus older generation antiepileptic drugs

The number of AED options has increased substantially in the last thirty years. Drugs introduced prior to 1971 are referred to as "older generation antiepileptic drugs." Valproic acid, the last older generation AED, was introduced in 1970 (Table 1.1). Treatment with any of the older generation AEDs in women with epilepsy has been associated with higher rates of major malformations compared to unmedicated women without epilepsy. Numerous studies have confirmed that the older generation AEDs (e.g., phenobarbital, phenytoin, carbamazepine and valproic acid) are associated with increased rates of birth defects, intrauterine growth restriction (IUGR) and cognitive delay.(27, 34-36) An increased risk of neural tube defects, hypospadias, oral clefts and cardiovascular malformations has been found among infants whose mothers were treated with valproic acid.(21, 36-38) Increased risk of autism has also been reported in infants exposed to valproic acid *in utero*.(39) Increased risk for oral clefts, cardiovascular defects and urogenital defects have been reported after maternal phenytoin therapy.(40, 41) Risks of cardiovascular malformations, oral clefts and urogenital defects are increased in among infants whose mothers were treated with phenobarbital.(21, 42) Increased risks of oral cleft, neural tube defects, hypospadias and cardiovascular defects have been seen in infants exposed prenatally to carbamazepine.(43, 44) Older generation AEDs have also been

associated with elevated risks for adverse events (e.g. weight gain, nausea, sedation, headache, dizziness).(45) This in turn may decrease compliance.

A number of AEDs have been licensed since the early 1990s: gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, topiramate, vigabatrin, zonisamide and others (Table 1.1). As a group, these AEDs are often referred to as "newer generation antiepileptic drugs." Prior to 1989, no new AEDs had been introduced since the 1970s (Table 1.1). With the exception of felbamate and lamotrigine, the newer generation of AEDs are better tolerated and have fewer drug interactions than the older generation AEDs.(45)

Table 1.1 - Older and Newer Generation Antiepileptic Drugs

Year of introduction of antiepileptic drug			Year of introduction of antiepileptic drug	
Phenobarbital	1912		Topiramate	1995
Phenytoin	1939		Tiagabine	1996
Primidone	1960		Levetiracetam	2000
Carbamazepine	1965		Pregabalin	2005
Valproic acid	1970		Zonisamide	2007
Vigabatrin	1989		Eslicarbazepine	2010
Oxcarbazepine	1990		Lacosamide	2010
Lamotrigine	1991		Clobazam	2011
Gabapentin	1994		Retigabine	2011
Felbamate	1994			

Adapted from Landmark and Patsalos, 2012, with permission.(46)

Newer generation AEDs have not been proven more effective than older AEDs at decreasing the severity and frequency of seizures, but many of the newer drugs have

beneficial pharmacokinetic or formulation properties.(47) These include therapeutically efficacious concentrations with more convenient dosing schedules for the patient, fewer adverse effects, and greater tolerability than older generation drugs.(48) In spite of the availability of the newer generation drugs, valproic acid and carbamazepine (both older generation drugs) continue to be prescribed.(49, 50) Both are less expensive than many of the newer generation AEDs, and valproic acid in particular is more effective for many patients at decreasing the frequency of seizures.(49) Furthermore, when seizures are well controlled by an older generation drug, patients and their physicians may be reluctant to change medications prior to or during pregnancy, as this transition can take several weeks and may result in more seizures. In addition, people with epilepsy are often required to discontinue driving while they alter their AED regimens.(51)

A 2009 study from the EURAP Study Group reviewed AED utilization in 38 countries.(50) Carbamazepine, an older generation AED, was the most commonly used AED in monotherapy and the most frequently included drug in polytherapy.(50) Geographical differences in the prevalence of newer generation AED treatment in pregnancy were recorded, ranging from 3.5% in India up to 75% in Denmark. This wide range may be due in part to a combination of lack of information for caregivers for treating women of childbearing age, country-specific patterns in healthcare (e.g. frequency of seeking care, preference of types of health care providers before and during pregnancy, availability of specialists), and increased cost and decreased availability of newer AEDs, but likely reflects the lack of an evidence-based consensus among physicians for treating pregnant women with epilepsy.(50)

1.2.4 Monotherapy vs. polytherapy

The risk of major malformations in infants exposed to AEDs in utero may differ depending on whether mothers with epilepsy are treated with monotherapy treatment or polytherapy treatment, in addition to the actual individual AED exposure. Approximately 50% of all epilepsy patients become seizure free within the first year of diagnosis on monotherapy, the gold standard of drug treatment for epilepsy (Figure 1.1). Of those remaining, 50% will require an alternative monotherapy or polytherapy to attempt to obtain seizure control.(19) Ultimately, 20 – 25% of all patients with epilepsy are treated with AED polytherapy.(47) However, only 5% of total epilepsy patients achieve seizure freedom with AED polytherapy.(19) Patients whose seizures cannot be controlled with monotherapy often cannot achieve seizure freedom with any drug therapy, despite treatment with polytherapy.

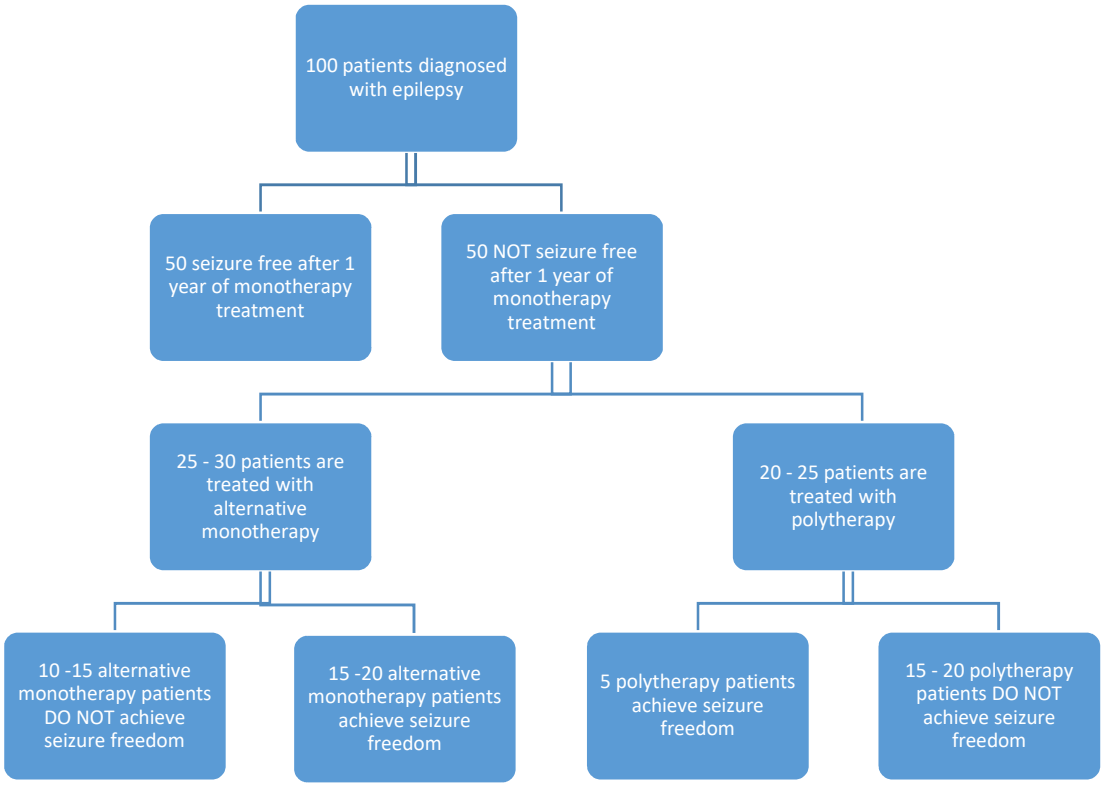

Figure 1.1 - The distribution of responses to monotherapy or polytherapy among 100 typical patients with epilepsy

As discussed in the previous section, comparing the risk for malformations in the infants of treated women with epilepsy in comparison to untreated women with epilepsy is complicated by other factors. In much the same way, comparing the risk for malformations in the infants of women with epilepsy on AED monotherapy to the infants of women with epilepsy on AED polytherapy is not ideal, as these women are likely to differ in terms of seizure control, total medication, adverse events, quality of life and comorbidities. Furthermore, there are over 200 two-drug combinations and more than 1000 triple

therapy combinations available. This makes it difficult to compare the relative malformation risks for exposure in utero to polytherapy versus exposure in utero to monotherapy (Table 1.2).(47) However, with polytherapy, it seems that prescribing AEDs with different mechanisms of action would be more likely to achieve seizure freedom than combining AEDs with similar pharmacological properties.(52) Furthermore, certain AEDs are also best used for different types of epilepsy and epileptic syndromes. In two analyses, the majority of patients controlled were on two AEDs (86.4% vs. 81.3%), with the commonest combination in both being valproic acid and lamotrigine. There is clinical evidence for possible synergism between these drugs.(53, 54)

Major malformations occur more (52) frequently in infants whose mothers were treated with AED polytherapy than in infants whose mothers received monotherapy.(11, 33, 37, 38, 55) An American 2008 meta-analysis of 59 studies including 65,533 pregnancies in women with epilepsy and 1,817,024 pregnancies (including healthy births, stillbirths, spontaneous abortions, elective abortions and perinatal deaths) in healthy women examined the incidence of major malformations associated with monotherapy and polytherapy AED regimens containing carbamazepine, lamotrigine, phenobarbital, phenytoin, and valproic acid.(18) Incidence rates of the total number of major malformations (an infant could have more than one malformation) were 2.28% (95% CI, 1.46 – 3.10%), 8.42% (95% CI, 6.73 – 10.11%) among infants of all women with epilepsy, 5.30% (95% CI, 3.51 – 7.09) among those exposed to monotherapy, and 9.84% (95% CI,7.82 – 11.87%) among those receiving polytherapy.(18) Polytherapy combinations involving valproic acid (an older generation drug) produced major malformation (total

events) incidence rates of 9.79% (95% CI, 7.57 – 12.02%) when two drugs were used and 25.00% (95% CI, 5.97 – 44.03%) when three or more drugs were used.(18)

1.2.5 Teratogenicity and therapy

1.2.5.1 Introduction to studies of teratogenicity

There are no randomized controlled trials of AED use during pregnancy and teratogenic outcomes, as studies to examine human teratogenic risks are considered unethical.(56) However, many observational studies have attempted to investigate the teratogenicity of AEDs over the past forty years and several designs have been employed.

Cohort studies are a common approach and can be retrospective or prospective. They may or may not be population-based. Population-based nationwide registries from the Scandinavian countries have been used to assess rates of malformation after exposure to different AEDs. Population-based registries may lack detail on maternal epilepsy diagnoses (e.g., type, severity and frequency of seizures) and other risk factors for major malformations, including family history, smoking history, alcohol intake, substance abuse and folic acid supplementation. Finally, in population-based registries, prescription information (e.g., drug doses, timing of exposures and whether or not a woman actually took the prescription or merely filled the prescription) may be lacking.

AEDs and pregnancy registries are a special type of cohort study which have been more recently employed.(57) To overcome some of the aforementioned limitations of population-based cohort studies, registries restricted to volunteers were initiated in the late 1990s for prospective data collection to obtain more detailed information.(14) Two

pharmaceutical companies created their own registries to study only their own product (lamotrigine or levetiracetam). Other independent voluntary registries recruited women taking any AEDs during pregnancy. The North American AED Pregnancy Registry (NAAPR) includes data on pregnant women taking AEDs from the USA and Canada. Pregnant women from the UK are enrolled in the United Kingdom Epilepsy and Pregnancy Register. More than forty countries worldwide participate in the International Registry of Antiepileptic Drugs and Pregnancy (EURAP), which also collects data on pregnant women taking AEDs. The EURAP collaboration also includes the Australian Pregnancy Register and the Kerala Registry of Epilepsy and Pregnancy in India, but these (21) registries analyse and report separately.(14) Each of these major registries has prospectively enrolled thousands of women taking AEDs during pregnancy and reported on the outcome of the pregnancies.(58) However, many of these pregnancy and epilepsy registries have different methodologies that can affect their results (Table 1.3). These include differing recruitment strategies, AED usage at time of conception, choice of control groups, exclusion criteria and period for diagnosing major malformations.

Compared to population based registries where information is most often gathered from coding used for billing purposes, data from vital statistics registries or pharmaceutical records, non-population-based registries, are more often subject to selection bias (generally, only a small subset of eligible individuals are included) or recall bias. In addition, non-population based registries may lack information regarding the background risk for malformations in the specific region from which they originate and may have difficulties recruiting appropriate controls. The generalizability of the observations may be a potential problem depending on how pregnancies were enrolled in registries.(59)

Information on cognitive outcomes and minor malformations is often not available from either population-based or non-population-based registries. Cognitive outcomes are not easily assessed until years after birth while minor malformations are often only diagnosed after detailed examination by a specialist. Finally, the quality of the outcome data (i.e. major malformations) in registries may depend on which specialist provides the data (e.g., neurologist, obstetrician, general practitioner or pediatrician).

Because individual specific types of malformations are rare, the estimates from cohort studies including pregnancy registries are calculated from few reported cases. For rare outcomes, such as these specific malformations, large population-based case–control studies are more appropriate.(14, 60) The associations between some specific malformations and exposure to lamotrigine, valproate and carbamazepine have been studied using the population-based European Surveillance of Congenital Anomalies (EUROCAT) database, which includes data on malformations in 14 European countries.(36, 44, 61)

Lastly, experiments using animal models are another type of study to evaluate teratogenicity and have allowed for careful assessment of the effects of AEDs in utero. Using these models can be advantageous as the timing, dose, exposure and biologic plausibility can be assessed on a uniform genetic background. However, care must be taken when considering which effects can be generalized to humans, as significant differences exist between species with regard to the timing of neurodevelopmental events. For these reasons, animal studies will be excluded from further consideration in this thesis.(62)

1.2.5.2 Cohort studies

The differences between various cohort studies including non-population based registries and population-based registries will next be discussed.

1.2.5.2.1 Non-population based registries

A prospective cohort study using data from the NAAPR reported outcomes from 7,370 pregnancies among women taking AEDs for any indication across the USA and Canada between 1997 and 2011. Approximately ten percent of pregnant women taking AEDs did so for indications other than epilepsy.(21) The primary exposure group included those women who started AED monotherapy after conception or stopped AED monotherapy before the end of the first trimester, but excludes those women switching between AEDs in the first trimester.

The main comparison group was 1,562 pregnant women exposed to lamotrigine, known to be low risk as an AED.(21, 49) The authors felt lamotrigine would minimize confounding by indication because most women in this comparison group would have had epilepsy and are consequently similar to the groups exposed to other AEDs in many ways. Two additional comparison groups were also used. These included 479 pregnant friends and relatives without epilepsy not on AEDs from across North America who were followed with the same methodology as those exposed and 206,224 infants born to women (with or without epilepsy) on no AEDs giving birth at Brigham and Women's Hospital in Boston. Pregnant women self-enrolled by calling a toll-free number after receiving a card from a caregiver while the mothers of the 206,224 infants at the hospital were included through medical record review. In North America, only a small percentage (number not stated) of

pregnancies of women with epilepsy on AEDs enroll in the registry. Women may enroll in the registry at any time during pregnancy.

The primary outcome was major malformations diagnosed before 12 completed weeks after birth, with the exception of the infants born to women at Brigham and Women's Hospital where the primary outcome was major malformation diagnosed within 5 days after birth. When comparing the rate of malformations in the exposure group and the hospital comparison group, malformations identified in the exposure group after 5 days of life had to be excluded, as the window for detecting malformations in the hospital group was only the first 5 days of life. With the exception of the hospital comparison group where outcomes were obtained through medical record review, there were two follow-up interviews completed by study staff at 7 months of pregnancy and 8–12 weeks after the date of delivery. The information obtained in the interview was supplemented with data from medical records when the patient consented to such access (consent is granted by about 70% of the enrolled women). Sixty percent of the women did not yet know if malformations complicated their pregnancy at time of enrolment. Medical records were reviewed for malformation outcomes by a teratologist who was blinded with respect to the mother's exposure status. Information on seizure type and frequency, maternal age, race, education, alcohol use, cigarette smoking, periconceptional folic acid supplementation, illicit drug use, chronic diseases (e.g., insulin-dependent diabetes), and calendar year were collected from the patient and her medical records. These potential confounders did not change the relative risks (RR), so crude RRs were presented in the main analysis.

Among infants who were exposed to valproic acid early in gestation, the risk of major malformations was found to be 9.3% (95% CI, 6.4 – 13.0%); for phenobarbital, 5.5% (95% CI, 2.8 – 9.7%); for topiramate, 4.2% (95% CI, 2.4 – 6.8%); for carbamazepine, 3.0% (95% CI, 2.1 – 4.2%); for phenytoin, 2.9% (95% CI, 1.5 – 5.0%); for levetiracetam, 2.4% (95% CI, 1.2 – 4.3%);; for oxcarbazepine, 2.2% (95% CI, 0.6 – 5.5%); for gabapentin, 0.7% (0.02–3.8); and for clonazepam, 3.1% (0.4 – 10.8%). In comparison, the risk of malformations in the infants exposed to lamotrigine was 2.0% (95% CI, 1.4 – 2.8%) and 1.1% (95% CI, 0.4–2.6%) in the unexposed hospital population. The AEDs with significantly elevated unadjusted RRs when compared to lamotrigine exposure included valproic acid (RR, 5.1; 95% CI, 3.0 – 8.5), phenobarbital (RR, 2.9; 95% CI, 1.4 – 5.8), and topiramate (RR, 2.2; 95% CI, 1.2 – 4.0) for topiramate. The authors also note that the prevalence of oral clefts for lamotrigine monotherapy-exposed infants was 0.45% (95% CI, 0.20 – 0.88%) compared to approximately 0.11% in the hospital-based comparison group, which was not a significantly increased risk. Furthermore, prevalence of oral clefts was determined to be 1.4% (95% CI, 0.51 – 3.1%) in the topiramate-exposed pregnancies, which is higher than in the study comparison group(21) or other reference populations.(16, 63)

Selection bias may be present due to voluntary enrollment. As women may enroll at any time during pregnancy, three groups emerge:

1. Women who enroll who have not yet completed prenatal screening (“purely prospective”).
2. Women who enroll with knowledge of their prenatal screening with evidence of malformations (“traditional prospective”).

3. Women who enroll with knowledge of their prenatal screening without evidence of malformations ("traditional prospective"). This group tends to be underrepresented and consequently, selection bias may occur.

Medical records were received for more than 70% of voluntarily enrolled mothers with 65% of neurologists or psychiatrists and 59% of pediatricians providing medical records. Much of the information was supplied by the patients after enrolment and potentially after knowledge of results from prenatal screening (e.g. amniocentesis, screening ultrasound, maternal serum screening), so there is a possibility of reporting bias. While concerns have been raised about both exposure and outcome data obtained from the patients, in a validation study there was a 99% agreement between the mother's verbal report and the doctors' records for the infants whose mothers had provided permission to obtain medical records.(21)

A prospective cohort study from the EURAP group that included 4,540 pregnant women with epilepsy between 1999 and 2010 reported a dose-dependent risk of major malformations from in utero exposure to monotherapy AEDs.(64) EURAP relies on enrollment through regional and national networks of collaborating physicians in more than 40 countries in Europe, Asia, Oceania, Australia and South America. Pregnant women cannot self-enroll. The ascertainment rate varies markedly between countries, ranging from a few percent up to 20–30%.

The study included women who were taking AEDs without a diagnosis of epilepsy. The proportion of pregnancies with AED exposure for indications other than epilepsy was approximately 2%. As with NAAPR, the comparison group was 1,280 women exposed to

lamotrigine. This study did not include unmedicated women with epilepsy or women without epilepsy as controls.(13)

EURAP applies strict criteria for prospective pregnancies, including only pregnancies enrolled before the malformation outcome is known. In addition, enrollment can occur no later than week 16 of gestation. In EURAP, data are reported by the referring healthcare provider on three occasions during pregnancy.

The primary outcome was the rate of major malformations diagnosed in the first year of life. Teratologists blinded to exposure status reviewed medical records to determine the presence of major malformations. Information on seizure type and frequency, folic acid supplementation, and variables examined as potential confounders (including parental education, smoking and alcohol) was obtained by the reporting physician on the same three occasions during pregnancy. Seizure information related to the woman's epilepsy is probably more reliable in EURAP compared to other studies, as the source in general is the treating neurologist (typically, an epileptologist). The exposure measurement was refined by categorization into three dose ranges (low, intermediate and high) for carbamazepine, lamotrigine or valproic acid and two dose ranges (high and low) for phenobarbital. Analysis of subcategories is important because it is often necessary during pregnancy to adjust drug doses to maintain seizure control, particularly for lamotrigine and oxcarbazepine, two drugs for which a decrease in plasma concentrations due to increases in maternal blood volume is most marked. The lowest rate of malformations was found in the low category of less than 300 mg per day of lamotrigine (2.0%; 95% CI, 1.2 – 3.2%), which was used as the control. The highest rate of malformations was found in the high

category of 1500 mg per day or greater of valproic acid (16.1%; OR, 16.1, 95% CI, 8.2 – 31.5). For valproic acid, the rate of malformations was 10.4% (OR, 5.8; CI, 3.3 – 10.1) in the middle category (greater than or equal to 700 mg per day, to less than 1500 mg per day) and 5.6% (OR, 2.8; 95% CI, 1.5 – 5.3) in the lowest category (less than 700 mg per day). The rate of malformations in the low category (less than 150 mg per day) of phenobarbital was 4.2% (OR, 2.5; 95% CI, 1.1 – 5.8) and 13.7% (OR, 8.2; 95% CI, 3.2 – 21.5) in the high category (greater than or equal to 150 mg per day). The rate of malformations in the lowest category (less than 400 mg per day) of carbamazepine was 3.4% (OR, 1.6; 95% CI, 0.6 – 4.5), 5.3% (OR, 2.5; 95% CI, 1.4 – 4.5) in the middle category (less than or equal to 400 mg per day, to greater than 1000 mg per day) and 8.7% (OR, 4.6; 95% CI, 2.3 – 9.3) in the highest category (greater than or equal to 1000 mg per day).(13)

Limitations from this EURAP study include a selection bias toward more severe epilepsy as subjects were enrolled by physicians who may only enroll patients they saw most frequently. Furthermore, women who are more likely to receive early prenatal screening (e.g. women of advanced maternal age) are less likely to be included in this study. Finally, EURAP lacks direct access to the patients to allow for clarification of missing or insufficient information from the reports previously filed by the referring physicians.

A 2006 prospective cohort study from the United Kingdom Epilepsy and Pregnancy Register that examined 4,414 infants born to women with epilepsy between 1996 and 2005 in the UK and Ireland investigated the rate of major malformations after exposure to various AEDs.(37) The comparison group was women with epilepsy on no AEDs. Compared to NAAPR and EURAP, this registry enrolled the highest proportion of eligible

pregnancies within its region of interest (an estimated 25 – 33% of eligible pregnancies). Approximately 50% of the pregnancies were enrolled through direct self-referral and the rest were enrolled through general practitioners, midwives, or other health care personnel. A standardized questionnaire was completed upon enrollment by the referring healthcare provider.

The UK registry includes pregnant women with epilepsy with or without ongoing monotherapy or polytherapy AED treatment after the first trimester. However, women who started an AED after conception were excluded. Women taking carbamazepine, valproic acid, lamotrigine, phenytoin, gabapentin, topiramate or levetiracetam were included. In the UK registry, subjects were only included if they were referred to the registry before the fetus had been screened for malformations.

The primary outcome was the rate of major malformations diagnosed in the first three months of life. This information was collected by sending a standardized questionnaire for completion to the patient's general practitioner and any others involved in the patient's care. Because the amount of information collected was kept to a minimum, assessing the role of all potential confounders was impossible but adjustment was made for maternal age, parity, family history of major malformation, folic acid supplementation and sex of the infant.

For individual AED analyses, carbamazepine was used as the comparator. Rates of major malformations by monotherapy drug exposures were as follows: carbamazepine, 2.2% (95% CI, 1.4 – 3.4%); valproic acid, 6.2% (OR, 2.78; 95% CI, 1.62 – 4.76); lamotrigine, 3.2% (OR, 1.44; 95% CI, 0.77 – 2.67); phenytoin, 3.7% (OR, 1.64; 95% CI, 0.48 – 5.62);

gabapentin, 3.2% (OR, 1.33; 95% CI, 0.17 – 10.20); topiramate, 7.1% (OR, 2.75; 95%, 0.62 – 12.20); and levetiracetam, 0.0% (95% CI, 0.0 – 14.9%). Compared to women with epilepsy on no AEDs (3.5%), the major malformation rate for monotherapy exposure was 3.7% (OR, 1.05; 95% CI, 0.50 – 2.19) and 6.0% (OR, 1.71; 95% CI, 0.79 – 3.69) for polytherapy exposures. The rate of major malformations in women with epilepsy on no AEDs was similar to that seen in lamotrigine and not significantly different from the rates in women with epilepsy treated with any of the other medications.

One strength of this study is that women enrolled in the UK registry were more likely to be representative of the UK epilepsy population as a whole due to the enrollment of 25 - 35% eligible pregnancies, but data are somewhat limited in detail compared to the two aforementioned registries. As with NAAPR, there is potential for reporting bias as some of the information is patient-reported; however, subjects did not have knowledge of results from prenatal screening.

In 2014, the Australian Pregnancy Register published a prospective cohort study of 1,572 pregnancies of both treated and untreated women with epilepsy aimed at determining the rate of major malformations after exposure to three newer AEDs (lamotrigine, levetiracetam and topiramate).(48, 65, 66) Of the 1,572 pregnancies exposed to AEDs throughout pregnancy, 1,141 pregnancies were exposed to AED monotherapy and 431 pregnancies were exposed to polytherapy. The comparison groups were:

1. Women with epilepsy treated with older generation AEDs
2. Women without epilepsy on AEDs

3. 153 women with epilepsy untreated with AEDs in the first half of their pregnancy

Enrollment was initiated by treating care providers the majority of the time or through self-referral by calling a toll-free number. The authors estimate that since 1999, 10% of the total population of women on AEDs have enrolled in the registry.(67) Women were enrolled in the first trimester regardless of prenatal investigations.

The primary outcome was the rate of major malformations diagnosed in the first year of life. The presence of these was determined by review of medical records by registry staff and verification by the treating physician. Women were also contacted over four telephone interviews conducted at enrollment, 7 months of pregnancy, delivery and 12 months after delivery. Information on family, medical, social, epilepsy and treatment history was obtained.

In 2007, the registry reported that 96.6% of the enrolled pregnancies were in women with epilepsy.(67) While it has been acknowledged in the literature that women with epilepsy who are on AEDs may differ significantly from women with epilepsy who are not taking AEDs,(11, 33) the Australian Pregnancy Registry found that these two groups were similar for many potentially confounding variables including seizure frequency and SES. Seizure frequency is a confounding variable because it is related to the severity of the patient's epilepsy, the amount of medication required to treat it, the resulting quality of life, and the number and severity of comorbidities.

Major malformations were seen in the infants of 3.3% of 153 untreated women with epilepsy. Crude analyses were presented in comparison to pregnancies not exposed to

AEDs. For those exposed to monotherapy AED treatment, the rates of major malformations among the infants were as follows: lamotrigine, 4.6% (RR, 1.40; 95% CI, 0.51 – 3.80); topiramate, 2.4% (RR, 0.73; 95% CI, 0.09 – 6.07), and levetiracetam, 2.4% (RR, 0.75; 95% CI, 0.15 – 3.76). In the older generation AEDs, the rates of major malformations were: phenytoin, 2.4% (RR, 1.49; 95% CI, 0.30 – 7.42), valproic acid, 13.8% (RR, 4.23; 95% CI, 1.69 – 10.57), and carbamazepine, 5.5% (RR, 1.68; 95% CI, 0.64 – 4.42). With monotherapy treatment, valproic acid was the only AED that had a significantly greater rate of malformations than that found in pregnancies not exposed to AEDs. For those exposed to polytherapy AED treatment, the rates of major malformations were as follows: lamotrigine, 5.5% (RR, 1.67; 95% CI, 0.61 – 4.59); topiramate, 14.1% (RR, 4.32; 95% CI, 1.57 – 11.05), and levetiracetam, 8.7% (RR, 2.25; 95% CI, 0.76 – 6.69). In the older generation AEDs, the rates of major malformations were: phenytoin, 8.6% (RR, 2.62; 95% CI, 0.66 – 10.46), valproic acid, 10.2% (RR, 3.11; 95% CI, 1.18 – 8.18), and carbamazepine, 6.7% (RR, 2.04; 95% CI, 0.73 – 5.74). The malformation rate associated with use of the newer AED topiramate polytherapy was significantly increased, as was the malformation rate associated with polytherapy that included valproic acid, an older AED. The authors acknowledge the small size of some of their sample groups and their comparator group that may limit the ability to detect even a 200% difference but found their results to be in keeping with previous studies.(16, 21, 63, 68, 69)

The authors felt that there was some selection bias towards urban, more educated and English-speaking women, which may result in a lack of generalizability. As with NAAPR, reporting bias is likely as some of the information was supplied by the patients after enrollment and after knowledge of results from prenatal screening.

Recent studies have begun to emerge on newer generation AEDs including topiramate, gabapentin and pregabalin. First trimester topiramate exposure has been associated with an increased risk for oral cleft in other studies.(70) In a 2014 multicenter retrospective cohort study, first trimester in utero topiramate exposure was associated with a moderate increase in birth prevalence of oral clefts compared to two difference reference groups: women formerly exposed to topiramate or other AEDs and infants of women with similar medical profiles that were not exposed to topiramate. Oral clefts were prevalent in 0.36% (7/1,945) of the topiramate cohort, 0.14% (20/13,512) of the formerly exposed cohort and 0.07% (9/13,614) of the similar medical profile cohort. The prevalence ratio (PR) for topiramate versus the formerly exposed was 2.5 (95% CI: 1.0 – 6.0) and for topiramate versus a similar medical profile was 5.4 (95% CI: 2.0 – 14.6).

A population-based study of case-control design using data from the Slone Epidemiology Center Birth Defects Study (SECBDS) from 1997 to 2009 and the National Birth Defects Prevention Study (NBDPS) 1997 to 2007 supported this finding.(71) The first-trimester use of topiramate monotherapy was compared to no AED use during the periconceptional period between the mothers of infants with cleft lip/palate and the mothers of controls. First-trimester topiramate monotherapy was associated with cleft lip/palate in the SECBDS (OR, 10.1; 95% CI, 1.1 - 129.2), in the NBDPS (OR, 3.6; 95% CI, 0.7 - 20.0) and in the pooled data (OR, 5.4; 95% CI, 1.5 - 20.1).

However, not all recent studies have agreed with these findings. A 2012 American retrospective study using pharmacy and data and medical claims evaluated the risk of oral clefts and major malformations in infants born to 870 women exposed to topiramate in

their first trimester of pregnancy compared with 3615 women who used other AEDs or those with other disease states in which topiramate may be used.(72) The comparison groups included infants not exposed to topiramate born to women with migraine without epilepsy (n = 26,865), women with epilepsy (n = 2,607), women with diabetes mellitus (n = 13,062), and 99,761 randomly sampled women. For topiramate use compared to other AEDs, the risk of oral clefts was 0.23% vs. 0.17% (RR, 1.39; 95% CI, 0.28 - 6.85), and the risk for major malformations was 4.33% vs. 3.21% (RR, 1.33; 95% CI, 0.92 – 1.90). Unlike some previous studies,(21, 63) this study suggested no significant association between topiramate exposure during pregnancy and the risk of oral cleft or major malformations, nor did it suggest an increase in risk in comparison to other AEDS or disease states such as migraine, epilepsy or diabetes. However, small numbers of events limit the strength of inferences.

Similarly, studies on the effects of gabapentin and pregabalin have shown inconclusive findings. In 2016, a European multicenter prospective study reported an increased rate of major malformations (9.6%; OR, 3.7; 95% CI, 1.5 – 8.6) after first trimester exposure to pregabalin (164 exposed pregnancies and 656 controls).(73) Exclusion criteria included exposure to any major teratogen. Maternal characteristics (age, smoking and alcohol use, medical and obstetric information) were collected. Pregnancy outcomes for other factors including prematurity, gestational age at birth, and birth weight were similar in both the exposed and control groups. However, that study was limited by the lack of a control group of women treated for similar conditions and the small sample size when limited to patients strictly on pregabalin monotherapy during the first trimester.

A Canadian prospective study from 2013 reported that gabapentin does not appear to increase the risk for major malformations but may increase the risk for low birth weight ($p = 0.033$) and preterm birth ($p = 0.019$).(74) Sample size was not large enough to make a definitive conclusion. However, there was no difference in the rate of SGA outcomes in this cohort. While this study was the largest prospective study thus far with 223 exposed cases and 223 unexposed, again, there was no comparator group treated with other AEDs.

The use of many newer generation AEDs has increased in the last decade.(50) Assessing their safety is of paramount of importance. More studies are needed to determine the risk for major malformations in topiramate, gabapentin and pregabalin. Despite the increased safety profile for lamotrigine, some studies have demonstrated a more pronounced decrease in plasma drug levels during pregnancy than that observed with other AEDs.(75, 76) Such a decrease may result in seizure recurrence or frequency increase resulting in more frequent dose adjustments.(13, 76) More research into the rate of malformations following exposure to unusually high doses of lamotrigine may be required. While oxcarbazepine is used in parts of Scandinavia (16, 50) and studies there have been conducted to investigate the risk for malformations, more North American studies are needed. Furthermore, additional studies of increased power are needed to determine the risk for malformations in levetiracetam.

1.2.5.2.2 Population-based studies

A recent (2011) population-based cohort study of 837,795 infants born between 1996 and 2008 in Denmark investigated the relationship between in utero exposure to newer generation AEDs during the first trimester of gestation and the likelihood of major

malformations diagnosed in the first year of life.(16) This was one of the largest analytic cohort studies to date reporting the rate of malformations in infants whose mothers had been treated newer generation AEDs. The study used records from the Medical Birth Registry, which was established in 1978 and contains records on all Danish births. Consequently, recall and selection bias are likely to be minimal in this study as data were obtained during pregnancy from all participants representing the entire Danish population.

Rates of major malformations among 1,532 exposures to lamotrigine, oxcarbazepine, topiramate, gabapentin or levetiracetam at any time during the first trimester were compared to 836,263 infants of women with or without epilepsy not exposed to newer generation AEDs in the first trimester. Exclusions included genetic disorders and birth defects with known causes (e.g. fetal alcohol syndrome). Potential confounders were documented, including maternal epilepsy diagnosed before the second trimester, filled prescriptions for older generation AEDs, other maternal comorbidities, SES information, maternal parity, smoking and history of malformations in siblings. Odds ratios (ORs) were adjusted for use of older generation AEDs during the first trimester and diagnosis of epilepsy before the second trimester.

Malformations were reported using International Classification of Diseases (ICD) codes on all inpatients and outpatients from the National Patient Registry. Concurrent maternal use of older generation AEDS during the first trimester and maternal epilepsy before the second trimester were the only covariates that were found to be confounding.

Of the 1,532 infants exposed to lamotrigine, oxcarbazepine, topiramate, gabapentin, or levetiracetam during the first trimester, 3.2% were diagnosed with a major malformation

compared with 2.4% of infants whose mothers were not exposed to any AED at all (adjusted OR of 1.0; 95% CI, 0.7 - 1.4). Major malformations were discovered in 38 (3.7%) of 1,019 infants exposed to lamotrigine during the first trimester (OR, 1.2; 95% CI, 0.8 - 1.7); in 11 (2.8%) of 393 infants exposed to oxcarbazepine (OR, 0.9; 95% CI, 0.5 - 1.6); and in 5 (4.6%) of 108 infants exposed to topiramate (OR, 1.4; 95% CI, 0.6 - 3.6). No infants exposed to levetiracetam (n = 58) were diagnosed with major malformations. Only 1 (1.7%) infant exposed to gabapentin (n = 59) was diagnosed with a major malformation.

A population-based cohort study (2009) of infants born to 2,861 women with epilepsy and 369,267 women without epilepsy from the compulsory Medical Birth Registry of Norway (MBRN) between 1999 and 2005 compared the rate of malformations among infants born to women in either group.(77) The MBRN is a population-based registry from Norway of all deliveries at 12 or more weeks of gestation that includes information on maternal health both before and during pregnancy, perinatal outcomes, information on maternal epilepsy, use of AEDs, and folic acid supplementation.

The data collected on malformations in the infants included major malformations, minor malformations and chromosomal disorders diagnosed within the first year of life. Information on demographic data, smoking during pregnancy, SES and parity were collected, but information on seizure activity or AED dosage was not. Results were adjusted for maternal age, parity, and smoking.

An increased risk for major malformations was only seen among the infants of women who were treated with valproic acid monotherapy (5.6%; OR, 2.3; 95% CI, 1.3 – 4.2) or valproic acid polytherapy (6.1%; OR, 2.5; 95% CI, 1.2 – 5.1) but not with lamotrigine monotherapy

(3.2%; OR, 1.2; 95% CI, 0.6 – 2.5) or carbamazepine monotherapy (2.5%; OR, 1.1; 95% CI, 0.6 – 1.9) compared to unexposed women without epilepsy (2.5%). The number of women taking newer generation AEDs other than lamotrigine was insufficiently powered for drawing conclusions. This is one of the few studies to collect information on genetic and minor abnormalities, which are excluded from most studies.

A population-based cohort study used Finland's National Medical Birth Registry to compare the rates of malformations among 1,411 infants born to women with epilepsy taking AEDs and 939 infants born to women with epilepsy who discontinued use of their AEDs before pregnancy.(11) Finnish women with epilepsy were identified using the nation-wide pharmaceutical reimbursement system, which requires a medical certificate issued by a board-certified specialist. The 6,535 women in this cohort gave birth to 2,350 children between 1991 and 2000.

Medical records were used to abstract information on any AED use during the first trimester and pregnancy outcomes, including malformations documented using ICD coding at discharge from the maternity unit. Information on maternal demographics, previous pregnancies, deliveries and stillbirths was also collected and analysed as potential confounders. Crude ORs were presented, as adjusted ORs were similar.

Results from exposure to valproic acid, lamotrigine and carbamazepine monotherapy were reported in addition to different combinations of polytherapy. The risk of malformations was significantly increased in the infants of mothers who took valproic acid as monotherapy (10.7%; OR, 4.18; 95% CI, 2.31 - 7.57) or valproic acid as part of polytherapy (9.2%; OR, 3.54; 95% CI, 1.42 - 8.11) compared to infants born to untreated women with

epilepsy. An increased rate of malformations was not associated with maternal treatment with carbamazepine, oxcarbazepine, phenytoin monotherapy or phenytoin polytherapy without valproic acid.

A strength of this study was the inclusion of an analysis of infants born to women with epilepsy who had discontinued their AEDs prior to pregnancy. Limitations included a lack of available information for folic acid supplementation and SES. Malformations were only identified at birth, so those diagnosed later would not be reported. Finally, the authors could not always distinguish between major and minor malformations when reviewing records, as the coding information was at times imprecise. Despite the inclusion of minor abnormalities, the prevalence of malformations in the infants of patients with epilepsy not taking AEDs (277/10,000) was comparable to previous studies of the general population in Finland. These limitations could have resulted in differential misclassification.

A 2004 Swedish population-based cohort study of 582,656 infants born between 1995 and 2001 reported the rate of major malformations in 1,398 infants exposed in utero to AEDs.(38) The comparison group included infants of women not on AED therapy (with or without epilepsy). Mothers who had reported the use of AEDs were identified and the medical records of their infants were analysed for the presence of malformations using ICD coding in the Medical Birth Registry, the Swedish Register of Congenital Malformations and information from the Hospital Discharge Registry.

Exposure was defined as AED monotherapy or polytherapy usage during "early pregnancy" (not further defined in this study). While the emphasis of this study was on valproic acid

and carbamazepine, some data were also reported for newer generation AEDs, including lamotrigine, topiramate and gabapentin.

The two categories of malformations presented were "total" and "severe." "Severe" malformations excluded the following conditions: preauricular tag, patent ductus arteriosus in preterm infant, congenital laryngeal stridor, undescended testicle, hip dislocation, pes calcaneovalgus, unspecified foot deformity, facial asymmetry and naevus. ORs were adjusted for year of birth, maternal age, parity and smoking in early pregnancy.

Total malformations were increased in 35 (13.1%) of 268 infants exposed prenatally to valproic acid monotherapy compared with 46 (6.5%) of 703 infants exposed to carbamazepine monotherapy (adjusted OR, 2.51; 95% CI, 1.43 – 4.68), but were not significantly increased when compared to the 5 of 90 (5.6%) infants exposed to lamotrigine (unadjusted OR, 2.55; 95% CI, 0.97 – 6.73). No malformations were found in the 4 infants exposed in utero to oxcarbazepine, 18 exposed to gabapentin or 1 exposed to topiramate.

The risk of bias is decreased in this study due to the multiple sources for reporting from the various registries. No information on the diagnosis of epilepsy, potential confounders or drug dosage in the two groups was presented.

1.2.5.3 Observational studies

In 2008, a follow-up prospective observational study of 203 pregnancies from 2004-2007 from the UK registry analysed the rate of major malformations after first trimester exposure to topiramate.(63) A comparator group was not used in this study. Major malformations were observed in 4.8% (95% CI, 1.7 – 13.3%) of monotherapy exposures

and in 11.2% (95% CI, 6.7 – 18.2) of polytherapy exposures. Oral clefts occurred in 2.2% (95% CI, 0.9 – 5.6%) of those infants exposed to polytherapy including topiramate in utero, while hypospadias occurred in 5.1% (95% CI, 0.2 – 10.1%) of the male infants exposed in utero to polytherapy including topiramate. The authors reported that in the UK, oral clefts occur in 1 in 500 (0.20%) live births and hypospadias occurs in 1 in 300 (0.33%) male births.(78, 79) Co-administration of valproic acid with topiramate was associated with the highest rates of major malformations (36.4%; 95% CI, 15.2 – 64.6% for the two AEDs; 23.8%; 95% CI, 10.6 – 45.1% for three or more AEDs) compared to topiramate polytherapy not including valproic acid (8.4%; 95% CI, 4.3% - 15.8%).

Another follow-up prospective observational study of 671 pregnancies from 2000 – 2011 from the UK registry reported the rate of major malformations after first trimester exposure to levetiracetam.(69) A comparator group was not used for this study. Of these, 304 were monotherapy exposures while 367 were polytherapy exposures. Two major malformations were found in the monotherapy group (0.70%, 95% CI, 0.19 – 2.51%), while 19 were found in the polytherapy group (6.47%, 95% CI, 4.31 – 9.60%) with rates of 1.77% (95% CI, 0.49 – 6.22%) when levetiracetam was given with lamotrigine, 6.90% (95% CI, 1.91 - 21.96%) when levetiracetam was given with valproic acid and 9.38% (95% CI, 4.37 – 18.98%) when levetiracetam was given with carbamazepine. While monotherapy exposure had malformation rates significantly lower than that of polytherapy exposures, there was no significant difference between the different combinations of polytherapy exposures.

The International Lamotrigine Pregnancy Registry published an industry-sponsored prospective clinical series enrolling pregnant women on lamotrigine from 1992-2010 with or without epilepsy and reporting the rate of major malformations.(80) Comparisons were made with rates of major malformations detected in the first week of life from other population cohorts in the published literature.(81, 82) However, such comparisons may not be suitable for several reasons such as differences in data collection, recruitment, inclusion/exclusion criteria, classification of outcomes, and study design that could result in biased risk differences. Furthermore, the comparison groups may not be suitable for comparison due to geographic and population differences.

Enrollment by their healthcare provider was voluntary from anywhere in the world via phone, facsimile or mail. It is difficult to estimate the amount of duplicate enrollment of pregnancies with other registries due to the lack of personal identifiers across datasets, but it is suspected that this does occur. The timing of enrollment varied; however, early in pregnancy was encouraged.

Healthcare workers reported prenatal lamotrigine exposure, including both lamotrigine monotherapy and polytherapy in which lamotrigine was a component. Information collected from caregivers included use of AEDs, maternal demographics, pregnancy details, prenatal testing results and history of epilepsy. Shortly after the expected date of delivery, the healthcare provider who originally enrolled the patient was contacted by registry staff to obtain pregnancy outcome details. How likely the healthcare provider was to know if the infant had a malformation probably varied, depending on the provider's role in the care

of the patient. Twice a year, a scientific advisory committee met to review the collected data for the presence of major malformations or spontaneous pregnancy loss.

Major malformations were observed among 1,558 infants with first trimester monotherapy exposure (2.2%; 95% CI, 1.6 – 3.1%). While no unexposed comparison group was available, the rate of major malformations was significantly increased in 150 babies with lamotrigine/valproic acid polytherapy exposures (10.7%; 95% CI, 6.4 – 17.0%) compared to 430 infants exposed to lamotrigine polytherapy without valproic acid (2.8%; 95% CI, 1.5 – 5.0%). Of the 16 infants (10.7%) with major malformations who were exposed to lamotrigine polytherapy during the first trimester, 4 had an orofacial cleft defects. While a dose-dependent increase in risks for major malformations for lamotrigine had previously been reported by the UK epilepsy and Pregnancy Registry,(37) this was not observed with higher lamotrigine doses in this study. However, there were few exposures (44/1,558) above 600mg per day. A lamotrigine dose-dependent relationship has not been documented in studies subsequent to the UK study.(16, 21, 64)

There were several limitations to this study. While enrollment early in pregnancy was encouraged, over 40% of pregnancies exposed to lamotrigine monotherapy during the first trimester were enrolled after 16 weeks gestation, which could result in a non-representative sample. This registry also encountered a high loss to follow-up rate (28.7%), possibly in the mothers of those infants without abnormal outcomes. This may contribute to differential reporting. Finally, the limited follow-up of infants after birth may also decrease the number of malformations reported due to that fact that some malformations (e.g. cardiac malformations) are not obvious at birth.

In closing, a need to assess the teratogenicity of newer generation AEDs for the clinical management of women with epilepsy of childbearing age remains as most newer generation AEDs have not been adequately studied. While epilepsy and pregnancy registries have been established to obtain such information, many early studies have lacked power or sufficiently sound methodology to demonstrate the true teratogenic potential in newer generation AEDs. While studying the teratogenicity of newer generation AEDs, the role of confounders such as smoking continues to require attention as does choosing appropriate comparators. Therefore, the differing methodology of registries must be considered when comparing the results of various studies.

Finally, research is needed to evaluate whether newer generation AEDs are associated with a specific pattern of malformations and timing of exposure, in addition to a dose-dependent response. Consequently, drug-level monitoring during pregnancy will be important in future studies. More research into plausible mechanisms will be needed and separate studies into long-term outcomes including neurodevelopmental deficits will also be required.(14)

Table 1.2 - Absolute rate of major malformations with individual AEDs as monotherapy published in nine pregnancy registries

Registry	Study	Rate of major malformations with individual AEDs as monotherapy								
		CBZ	GBN	LTG	LEV	OXC	PHB	PHT	TPM	VPA
NAAPR	Hernandez(21)	3.0% (1,033)	0.7% (145)	2.0% (1,562)	2.4% (450)	2.2% (182)	5.5% (199)	2.9% (416)	4.2% (359)	9.3% (323)
EURAP	Tomson(64)	5.6% (1,402)		2.9% (1,280)	1.6% (126)	3.3% (184)	7.4% (217)	6% (103)	6.8% (73)	9.8% (1,010)
UK Pregnancy Registry	Morrow(37) Hunt(63) Mawhinney(69)	2.2% (927)	3.2% (32)	3.2% (684)	0.7% (304)			3.7% (82)	4.8% (203)	6.2% (715)
Australian Pregnancy Registry	Vajda(67) Vajda(65)	6.3% (301)	0% (11)	5.2% (231)	0% (22)			2.9% (35)	3.2% (31)	16.3% (215)
Danish Registry	Molgaard(16)		1.7% (59)	3.7% (1,019)	0% (58)	2.8% (393)			4.6% (108)	
Birth Registry of Norway	Veiby(77)	2.5% (439)		3.2% (237)						5.6% (215)
Finland National Birth Registry	Artama(11)	2.7% (805)				1.0% (100)				10.7% (263)
Swedish Medical Birth Registry	Wide(38)	3.9% (703)	0% (18)	4.4% (90)			14% (7)	6.7% (103)		9.7% (268)

AED = antiepileptic drug; CBZ = carbamazepine; EURAP = International Registry of Antiepileptic Drugs and Pregnancy; GBN = gabapentin; GSK = GlaxoSmithKline; LEV = levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; PHB = phenobarbital; PHT = phenytoin; TPM = topiramate; VPA = valproic acid

Modified from Girard, E., 2014.(83)

Table 1.3 – Summary of methodological issues in AED and pregnancy registries

	NAAPR(21)	EURAP(64)	UK Pregnancy Registry(37)	Australian Pregnancy Registry(48)	GSK Lamotrigine Registry(80)	Danish Registry(16)	Birth Registry of Northway(77)	Finland National Birth Registry(11)	Swedish Medical Birth Registry(38)
Enrolled pregnancies for publication	7,370	4,540	4,414	1,572	1,558	837,795	372,128	2,350	584,054
Study Design	Prospective Cohort	Prospective Cohort	Prospective Cohort	Prospective/ retrospective Cohort	Prospective observational	Prospective Cohort	Prospective Cohort	Prospective Cohort	Prospective Cohort
Criteria for prospective	”Pure” prospective enrolled before results from prenatal screening	Enrolled before outcome is known (prenatal screening) and before week 16	Enrollment before outcome is known	Prospectively enrolled before screening results known	“Early in pregnancy was encouraged”	All included.	All included.	All included.	All included.
Comparator	1. Pregnant women exposed to lamotrigine 2. External comparison group (hospital group) 3. Internal unexposed control group (friends/ family)	Internal comparison between different AED treatments (or no treatment)	Internal comparison between different AED groups and untreated epilepsy	1. Untreated women with epilepsy 2. AEDs for nonepilepsy 3. Internal comparison between different AEDs	Published literature	Women with or without epilepsy not exposed to AEDs in the first trimester	Women without epilepsy not exposed to AEDs	Women with epilepsy untreated in the first trimester	Women with or without epilepsy not exposed to AEDs
Methods for enrollment	USA and Canada self-enrollment by the pregnant women	International (42 countries) Through network of reporting physicians	UK through physicians, nurses and patient self-enrollment	Australia (contributes to EURAP) self-enrollment by eligible women	Anywhere in the world by healthcare provider	Records from Medical Birth Registry	Records from Medical Birth Registry of Norway	Records from nation-wide pharmaceutical reimbursement system	Records from Swedish Medical Birth Registry
Inclusion criteria	Women taking AEDs for any reason during pregnancy	Pregnancies with AED exposure at time of conception	Women with epilepsy with/without AEDs 1st trimester	Women with epilepsy with/without AED 1st trimester	Lamotrigine exposure	All births	Women with epilepsy exposed/ not exposed to AEDs	Women with epilepsy on AEDs during the first trimester	AED usage “early in pregnancy”
Exclusion criteria	-	Change in AED 1st trimester. Outcome unclassifiable	Prenatal tests with abnormality before referral. Change in AED in 1st trimester	-	Pregnancy is no longer ongoing or birth defect has been detected.	-	-	-	-
AEDs exposure and drug levels	AED dose, regimen and brand Levels not systematically done	AED dose, regimen Levels not recorded	AED dose, regimen Levels not recorded	AED dose, regimen Levels not recorded	AED dose, regimen	AED dose, regimen	AEDs only Levels/ dose/ regimen not recorded	AED dose, regimen Levels not recorded	AEDs Levels/ dose/ regimen not recorded
Data collection and methods for follow-up	3 contacts. Telephone interviews with subjects, supplemented by medical records in 60%	4 – 5 contacts, mainly personal visits with reporting physician supplemented by medical records	2 contacts with patient’s physician	4 telephone interviews with patient supplemented by contact with physician	One contact with health care provider	Medical records	Medical records	Medical records	Medical records
Diagnosis of epilepsy	Self report, medical records from neurologist or enrollee	Patient’s physician	Patient’s physician	Patient’s physician	N/a	National Patient Registry and the Registry of Medicinal Product Statistics	Medical Birth Registry of Norway	Medical certificate issued by board-certified neurologist when AEDs are started	N/a

	NAAPR(21)	EURAP(64)	UK Pregnancy Registry(37)	Australian Pregnancy Registry(48)	GSK Lamotrigine Registry(80)	Danish Registry(16)	Birth Registry of Northway(77)	Finland National Birth Registry(11)	Swedish Medical Birth Registry(38)
Birth outcome Exclusion criteria	Genetic/ chromosomal, minor anomalies, positional deformities	Genetic/ chromosomal abnormalities analyzed separately	Genetic/ chromosomal abnormalities analyzed separately	Genetic/ chromosomal abnormalities analyzed separately	Stillbirth or elective termination. All spontaneous losses. Genetic/ Chromosomal defects.	Genetic/ chromosomal abnormalities analyzed separately. Birth defects with known causes. Minor abnormalities	-	-	Preauricular tag, patent ductus arteriosus in preterm infant, congenital laryngeal stridor, undescended testicle, hip dislocation, pes calcaneovalgus, unspecified foot deformity, facial asymmetry and naevus
Assessment	Review of medical records by blinded teratologist, direct communication with mother/ physician when needed.	Central classification by blinded teratologists based on reports from physicians	Abnormal outcomes classified by one clinical geneticist based on medical records	Based on review of medical records by	Healthcare provider	Review of medical record registry	Review of medical record registry	Review of medical record registry	Review of medical record registry
Time window of assessment	Malformation detected at two time points: 1. Within 5 days of life; 2. At postpartum call at 8 – 12 weeks of age.	Within 12 weeks after birth	Within 3 months after birth	Within 12 months of birth	Shortly after date of delivery	First year of life	First year of life	Prior to maternity unit discharge	"By the examining paediatrician at the routine examination"
Classification of outcome	Major malformations as determined by expert review	Major malformations according to EUROCAT criteria	Major malformations according to EUROCAT criteria	Major malformations (birth defects as defined by Victorian Birth Register	Major congenital malformation as classified by scientific advisory committee	Major malformations by ICD and EUROCAT criteria	ICD, MBRN classification system (including minor and chromosomal) causing significant impairment and/or operative intervention	Main categories of malformations as defined by ICD	"Severe" malformation by ICD and Swedish Register of Congenital Malformations

Modified from Tomson et al., 2010, with permission.(58)

1.2.6 In utero exposure to antiepileptic drugs and fetal growth restriction

In utero exposure to AEDs may decrease the rate of fetal growth, resulting in small for gestational age (SGA) infants (birth weight less than 10th percentile) and decreased head circumference or microcephaly at birth.(14) Infants who have suffered growth restriction in utero are known to have an increased risk of neonatal complications, including higher infant mortality.(84) Particular attention has been paid to the possibility of reduced head circumference and microcephaly because this could be associated with neurodevelopmental deficits. SGA outcomes, decreased head circumference and microcephaly have been observed in infants born to women with epilepsy on AEDs, but many of these studies involved older generation drugs.(12, 85) Limited information is available on the contribution of individual newer generation AEDs to SGA outcomes, decreased head circumference or microcephaly.(85, 86)

In a (2014) cohort study from the Medical Birth Registry of Norway, the risks of fetal growth restriction in 2,600 infants exposed *in utero* to newer or older AEDS were investigated.(23) Comparisons were made to 771, 412 unexposed infants of women without epilepsy. Odds ratios were adjusted for maternal and paternal age, educational level, child's birth order, single mother status, periconceptional folate supplementation, chronic maternal disease other than epilepsy and maternal smoking habits. After adjustment, the overall risk of SGA outcomes was increased in infants exposed to AEDs (10.7%; OR, 1.17; 95% CI, 1.03 - 1.33) and significantly increased for topiramate exposure (25.0%; OR 3.29; 95 % CI 1.70 – 6.39) compared to unexposed infants (8.9%). The overall risk of head circumference less than 10th percentile was increased in infants prenatally

exposed to AEDs (10.8%; OR, 1.24; 95% CI, 1.09 - 1.40) compared to unexposed infants (8.7%). The overall risk of head circumference less than 2.5 percentile was increased in infants exposed *in utero* to AEDs (3.4%; OR, 1.39; 95% CI, 1.12 - 1.72) and significantly increased for those exposed to topiramate (14.9%; OR 7.21; 95 % CI 3.23 – 16.1) compared to unexposed infants (2.4%).

In the 3,773 infants of women with untreated epilepsy, a slightly increased rate of SGA outcomes (10.3%; adjusted OR 1.15; 95 % CI 1.03 – 1.27) was found compared to the unexposed infants of mothers without epilepsy (8.9%). However, the rate of head circumference less than 10th percentile was identical to the unexposed infants.

A cohort study from 2009 using the Swedish Medical Birth Registry reported the influence of AED exposure on head circumference in over 900,000 infants born between 1995 and 2005.(87) After adjustment for year of birth, maternal age, parity, smoking, and body mass index, the most significant reductions of mean head circumference were seen with maternal carbamazepine or valproic acid treatment and corresponded to reductions of 0.2 – 0.4 cm. However, increased rates of microcephaly, defined as birth-weight adjusted head circumference smaller than two standard deviations below the expected mean, were not seen in infants exposed in utero to valproic acid or carbamazepine. No differences were observed in measurements of mean head circumference or rates of microcephaly when unexposed infants were compared to infants prenatally exposed to phenytoin, clonazepam, and lamotrigine or gabapentin monotherapy. Polytherapy did increase the rate of microcephaly as defined above (OR, 2.85; 95% CI, 1.74-4.78) when compared to those not exposed to AEDs (2.6%).

Not all studies have found this association. A 2011 Canadian population-based cohort study (Kulaga et al.) conducted by the Quebec Pregnancy Registry found no significant difference in rates of SGA outcomes among infants born to 171 women with epilepsy not using AED drugs, 19 women on AED monotherapy and 42 women on AED polytherapy between 1998 and 2003.(88) However, the number of infants enrolled in this study is insufficient to detect even a two hundred percent increase in the prevalence of SGA. Head circumference was not investigated. Results were not compared to women without epilepsy.

As with malformations, assessing the contribution of newer generation AEDs to SGA outcomes and decreased head circumference remains critical. With the exception of some early findings regarding the association between topiramate in utero exposure and SGA outcomes, very little is known about newer generation AED exposure in utero and fetal growth in infants. SGA outcomes and decreased head circumference may be associated with epilepsy, exposure to AEDs, seizures, genetic factors, SES or lifestyle choices such as smoking in women with epilepsy.(85) Studies to date have not been able to quantify the contributions of each of these factors. In addition, identifying the best control for measuring differences in SGA outcomes after in utero AED exposure has not been established. As with teratology research, investigations are needed to evaluate whether SGA outcomes are associated with a certain timing of exposure, in addition to a dose-dependent response.

1.2.7 Cognitive outcomes associated with antiepileptic drug therapy

Children of women with epilepsy are also at increased risk for neurodevelopmental deficits, particularly impaired cognitive development. Studies to date have implicated AEDs, seizures during pregnancy, heredity and socioeconomic status as possible causal factors.(89)

The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) Study (a descriptive prospective study from epilepsy centres in the USA and the UK) compared the cognitive effects of fetal exposure to four different AEDs. There were 309 children enrolled between 1999 and 2004, and evaluations were conducted at ages 3 years,(35) 4.5 years(90) and 6 years.(91) A control group of unexposed children was not included.

Pregnant women with epilepsy taking AED monotherapy (carbamazepine, lamotrigine, phenytoin or valproic acid) were studied. Exclusion criteria included mothers with intelligence quotient (IQ) scores below 70, or mothers with certain health problems (e.g., syphilis, HIV, progressive cerebral disease, other major diseases), exposure to major teratogenic agents others than AEDs, poor AED compliance or prior drug use (not specified) in the past year. Information collected included maternal IQ, demographics, SES, seizure type and frequency, folic acid supplementation, AEDs, AED compliance, alcohol intake, smoking, use of other drugs, abnormalities or complications in prior pregnancies, whether the pregnancy was planned, gestational age of the infant, weight at birth and breastfeeding status. Cognitive assessors were blinded to the drug exposure of the mother.

Significantly lower IQ scores were found in three-year-old children who had been exposed in utero to valproic acid compared to those children exposed to any other AED.(35, 92)

After adjustment for maternal IQ, standardized AED dose in the mother, age of mother at delivery, seizure type, gestational age of the neonate at delivery and preconceptual folic acid supplementation, the mean IQ was 101 (95% CI, 98 - 104) for children exposed in utero to lamotrigine, 99 (95% CI, 94 – 104) for those exposed to phenytoin, 98 (95% CI, 95 – 102) for those exposed to carbamazepine, and 92 (95% CI, 88 – 97) for those exposed to valproic acid. A dose-dependent relationship between maternal valproic acid use during pregnancy and her child's IQ was noted.

These findings persisted to 4.5 years of age.(90) The mean IQ after adjustment at age 4.5 years was 106 (95% CI, 102 – 109) for those exposed in utero to carbamazepine, 106 (95% CI, 102 – 109) for those exposed to lamotrigine, 105 (95% CI, 102 - 109) for those exposed to phenytoin, and 96 (95% CI, 91 – 100) for those exposed to valproic acid. The occurrence of marked intellectual impairment (IQ less than 70) was found to decrease between ages 3 years and 4.5 years in lamotrigine, phenytoin and carbamazepine exposed children but not for children whose mothers took valproic acid. Verbal abilities were found to be impaired compared to nonverbal skills in all four groups studied. Furthermore, maternal IQ correlated with children's IQ (as expected), except for those children with in utero exposure to valproic acid. In the children exposed to valproic acid in utero, the study found IQs significantly lower than those of the mother.

In the follow-up study when the children were approximately six years of age, IQ was associated with that found at younger ages but had improved with age for children exposed in utero to any of the drugs studied. IQ at age 6 provides a stable measure of intelligence and is associated with both adult IQ and school performance.(91) Right-handedness was less frequently seen in the children in this study overall compared to a normative sample of

187 unexposed children (86% vs. 93%; p=0.0404), especially in the valproic acid (79%, p=0.0089) and lamotrigine groups (83%; p=0.0287). The exposed children in this study had decreased verbal abilities compared to non-verbal abilities overall. The verbal and non-verbal indices were equal in the normative sample, but verbal abilities were significantly lower than non-verbal abilities for children whose mothers had taken lamotrigine (p=0.028) or valproate (p=0.0063) during pregnancy. The authors concluded that in utero valproic acid exposure has dose-dependent associations with several cognitive abilities (reduced IQ, verbal, non-verbal, memory and executive function) at 6 years of age.

A prospective, observational study of women with epilepsy and their children was conducted through the Australian Pregnancy Register for Women With Epilepsy and Allied Disorders.(93) Researchers looked at the language skills of 102 school-aged children exposed prenatally to either newer or older generation AEDs. Subjects were enrolled between 2007 and 2009, and the study compared their scores to published normative data. With regards to mean language scores, more children exposed to valproic acid monotherapy or polytherapy had scores significantly below normal than would be expected in the general population. In contrast, the scores of children whose mothers had been treated with carbamazepine or lamotrigine monotherapy or to polytherapy without valproic acid were not significantly different from those in the general population. Interestingly, valproic acid usage as early as first trimester resulted in a decrease in language scores among the children.

Studies so far suggest that in utero valproic acid and AED polytherapy exposure (especially with valproic acid) pose a dose-dependent risk for impaired cognitive development.(30, 35,

90, 91, 93) Consideration must be given to the possibility of such cognitive deficits when deciding on treatment during pregnancy. Such effects are not apparent for several years and may require detailed testing to diagnose. Studies of newer generation AEDs are limited. As with teratogenicity and fetal growth restriction, more studies of the cognitive effects of newer generation AEDs are required with attention given to appropriate methodology, timing of exposure, and dose-dependent responses.

1.3 Preconceptual counselling with antiepileptic drug therapy

The primary goal in the treatment of epilepsy during pregnancy is to gain the best possible control of seizures with the fewest adverse effects on the mother and infant. With half of pregnancies in women with and without epilepsy in the UK and USA reported as unplanned,(94-96) preconceptual counselling is of the utmost importance. For women taking AEDs, changing medication regimens to one thought to be safer during pregnancy may take weeks or months. Slow transitions are necessary to avoid certain adverse events such as rash associated with rapid-titration and concomitant use of lamotrigine and valproic acid.(97) Therefore, pregnancy management is best implemented preconceptually, which includes planning the timing of pregnancy in order to choose the appropriate AED therapy during pregnancy, to have sufficient time to transition medication, and to initiate folic acid supplementation. Furthermore, as different AEDs have varying rates of penetration into breast milk, breastfeeding intentions should also be discussed early in pregnancy as this may affect the choice of AED treatment postnatally.

1.3.1 Preconceptual folic acid supplementation

Insufficient folic acid can interfere with the biosynthesis of purines and pyrimidines and decrease the metabolism of amino acids such as homocysteine, methionine, histidine, glycine and serine.(98) Insufficient maternal folic acid intake or low serum folate levels have been associated with pregnancy complications like repeated spontaneous abortion and IUGR, as well as with increased rates of neural tube defects, heart defects, and cleft lip and palate in the infant.(40, 99) Maternal folic acid (folate) supplementation early in pregnancy has been shown to reduce the frequency of neural tube defects in infants.(100)

The mechanism by which AEDs cause increased rates of malformations in pregnant women is largely unknown,(101) but some AEDs, such as valproic acid, carbamazepine, phenobarbital, phenytoin and primidone (all older generation AEDs), change folic acid metabolism and decrease blood levels of folic acid as the plasma levels of these drugs increase.(40) There are two main ways that AEDs cause low plasma levels of folic acid: reduction of folate intestinal absorption (phenytoin, carbamazepine, phenobarbital and primidone) or action as an antimetabolite (valproic acid).

As previously mentioned, 50% of all births are unplanned,(94-96) and since many women discover they are pregnant after neural tube development in the embryo, folic acid supplementation is recommended continuously through the child-bearing years for all women with epilepsy by the American Epilepsy Society (AES), the American Academy of Neurology (AAN) and the National Institute of Clinical Excellence (NICE).(102, 103) However, the higher risk of major malformations in women with epilepsy appears to be multifactorial and is explained, in large part, by mechanisms other than those related to

folic acid metabolism.(101) The recommendation for preconceptual high dose folic acid supplementation remains controversial, as it has not been proven to decrease the higher rate of birth defects in women with epilepsy on AEDs.(102) In Canada, women at moderate or high risk for a neural tube defect (including those exposed to teratogenic medications such as AEDs) are advised to maintain a diet of folate-rich foods and take a daily oral supplement with 4.0 mg folic acid beginning at least 3 months before conception and continuing through a gestational age of 12 weeks.(104) In addition, preconceptual high dose folic acid supplementation of 4 mg or 5 mg continues to be recommended by many caregivers as it is felt at the very least to have no detrimental effects in women with epilepsy on AEDs..(101, 102)

A prospective single-centre Finnish study of 970 pregnancies and 979 infants of women with epilepsy (regardless of their AED intake) reported a significant association between maternal serum folic acid concentrations less than 4.4 nmol/L measured after the first trimester and malformations in the infants of women with epilepsy on any AED (18.2%; adjusted OR, 5.8; 95% CI, 1.3–27) compared to those with higher levels of folic acid concentration.(55)

Other studies have not found any association between folic acid supplementation in women taking AEDs and the frequency of major malformations in the infants. The effectiveness of preconceptual folic acid supplementation was examined in a 2009 prospective study in the UK (Morrow et al.) by comparing the rate of major malformations in the infants of women with epilepsy on AED monotherapy, AED polytherapy or no AED treatment. Of the women on AED monotherapy, 34.7% were treated with carbamazepine,

31.8% were being treated with lamotrigine and 26.4% were treated with valproic acid. In 1,935 infants whose mothers took preconceptual folic acid supplements in various doses, 76 major malformations (3.9%; 95% CI, 3.1 - 4.9%) were observed. Among the infants of 2,375 women who did not start taking folic acid supplements until later in the pregnancy or who did not supplement at all, there were only 53 major malformations (2.2%; 95% CI 1.7 - 2.9%). These results may be explained by something other than folic acid supplementation alone.

A 2013 prospective study (Campbell et al.) of 1,526 pregnancies in Scottish women with epilepsy found that different rates of preconceptual folic acid supplementation existed by socioeconomic quintiles (56.8% vs. 14.0%; RR, 4.1; 95% CI 3.1 – 5.2), but there was no associated difference in the rate of major malformations when the lowest and highest socioeconomic quintiles were compared (4.4% compared to 4.7%, p = 0.84).(105)

These studies suggest that periconceptional folic acid supplementation may not reduce the rate of malformations among the offspring of women with epilepsy treated with AEDs. This contrasts with findings in studies of women without epilepsy who took folic acid.(101, 106, 107) The higher risk of major malformations among the infants of women with epilepsy may be explained by mechanisms other than those related to folic acid metabolism.

Many women with epilepsy do not regularly take folic acid supplements.(105) In the previously mentioned 2009 UK study (Morrow et al.): 51.4% of patients on monotherapy preconceptually supplemented with any dose of folic acid, compared to only 15.0% of patients with polytherapy exposures.(101) In the 2013 Scottish study (Campbell et al.),

only 41.3% of women with epilepsy received folic acid supplements preconceptually.(105) In 2009, a population-based study from Norway reported that 31.6% of women with epilepsy taking AEDs preconceptually supplemented with folic acid compared to 9.6% of the general population.(10) Rates of preconceptual supplementation have not been reported in women with epilepsy in Canada.

Regardless of whether folic acid is effective at decreasing the increased rate of malformations in women with epilepsy on AEDs, the question as to whether women with epilepsy supplement preconceptually with folic acid remains of importance because preconceptual folic acid supplementation serves as a marker for intent to conceive and indicates who has received preconceptual counselling in women of child-bearing age.(108) Furthermore, as epilepsy is more prevalent among those with less education and lower income levels,(7) it is important to examine whether women with epilepsy of childbearing age are being counselled appropriately preconceptually. In closing, there is a need for continuous and repetitive preconceptual counselling for women with epilepsy of childbearing age. This includes planning the timing of pregnancy in order to choose the appropriate AED for use before, during and after pregnancy, having sufficient time to transition medications, and to initiate folic acid supplementation.

1.4 Management of pregnancy and labour

In several international studies, women with epilepsy have been reported to have up to twice the rate of both induction of labour and cesarean section in the absence of other comorbidities.(24, 77, 109, 110) Obstetricians may attempt to shorten gestation by induction of labour or cesarean section delivery in women with epilepsy.(110)

1.4.1 Obstetric complications

A population-based study investigated the pregnancy outcome of mothers with and without epilepsy by comparing all singleton pregnancies between the years 1988 and 2002 in a tertiary medical center in Israel.(111) During this timeframe, 139,168 singleton deliveries occurred of which 220 (0.2%) were born to mothers with epilepsy. The only notable difference in maternal outcomes between the groups was gestational diabetes mellitus (9.1% vs. 5.5%; OR, 1.7; 95th CI, 1.1 – 2.7). However, a higher rate of congenital malformations was noted among infants born to mothers with epilepsy (7.7% vs. 3.8%; OR, 2.1; 95% CI, 1.3–3.4). Finally, an increased rate of cesarean section deliveries was discovered among women with epilepsy (17.3% vs. 11.6%; adjusted OR, 1.5; 95% CI, 1.1 – 2.3).

Two Norwegian studies were conducted using data from 1999-2005 to investigate if the increased rates of labour induction and cesarean section among women with epilepsy were associated with the diagnosis of epilepsy, the obstetric complications associated with epilepsy, the use of AEDs during pregnancy, or all three factors.(10, 77, 109) The first, a retrospective population-based study (Borthen et al.) utilizing the Medical Birth Registry of Norway (MBRN), investigated whether 2,805 pregnant women with epilepsy had a greater likelihood of complications during pregnancy than 362,302 women without epilepsy.(10) The effects of AED use were also explored; however, results from individual AEDs were not reported. Main outcomes included pre-eclampsia, gestational hypertension, eclampsia, vaginal bleeding and prematurity. Adjustments were made for maternal age, smoking, maternal education and diabetes. Women with epilepsy (independent of AED treatment) were more likely to be diagnosed with strictly defined pre-eclampsia (5.7%; OR, 1.3; 95%

CI, 1.1 – 1.5) and deliver before 34 weeks of gestation (4.0%; OR, 1.2; 95% CI, 1.0 – 1.5) when compared to women without epilepsy.

Women with epilepsy who took AEDs during pregnancy were more likely to develop pre-eclampsia (6.5%; OR, 1.5; 95% CI, 1.2 – 2.0), gestational hypertension (2.8%; OR, 1.5; 95% CI, 1.0 – 2.2), or vaginal bleeding late in pregnancy (1.5%; OR, 1.9; 95% CI 1.1 – 3.2), or to deliver before 34 weeks of gestation (4.9%; OR, 1.6; 95% CI, 1.2 – 2.1) than women without epilepsy who did not take AEDs. These increased rates of gestational hypertension and vaginal bleeding late in pregnancy were not seen in women with epilepsy who did not take AEDs during pregnancy.

In a 2010 follow-up study of the same sample, Borthen et al. found elevated risks of labour induction (15.8%; OR, 1.3; 95% CI, 1.1–1.4) and cesarean section delivery (19.1%; OR, 1.4; 95% CI, 1.3–1.6) among 2,805 pregnant women with epilepsy (with or without AED treatment) compared to 365,107 women without epilepsy.(109) Even higher risks were observed in women with epilepsy who took AEDs during pregnancy (induction: 19.5%; OR, 1.6, 95% CI, 1.4–1.9 and cesarean section: 21.1%; OR, 1.6; 95% CI, 1.4–1.9). Only a mildly increased likelihood of cesarean section delivery was found among women with epilepsy on no medication (18.1%; OR, 1.3; 95% CI, 1.2-1.5) compared to women without epilepsy (14.3%)

In a retrospective hospital-based 2011 study, Borthen et al. reported on complications during pregnancy and delivery in 205 women with epilepsy from 1999-2006 that were also included in the previous studies and compared them to a control group of women without epilepsy matched for age and parity.(24) Induction of labour occurred in 21.0% of

deliveries in women with epilepsy, compared to 11.2% in women without epilepsy (OR, 1.8; 95% CI, 1.0 – 3.2). Cesarean section delivery was performed in 24.9% of all women with epilepsy and 12.7% of women without epilepsy (OR, 1.8; 95% CI, 1.0 – 3.1) after adjustment for maternal education, smoking, body mass index (BMI), medical conditions, diabetes, parity, maternal age, previous cesarean section delivery, pre-eclampsia and vaginal bleeding. However, after adjustment for preterm birth, women with epilepsy had no increased risk of overall cesarean section delivery (OR, 1.7; 95% CI, 1.0 – 3.0, p=0.065). The most frequent indications in the epilepsy group included fetal asphyxia (19.5%), epilepsy (11.8%) and failed induction (9.8%). However, increased risks of pregnancy complications were not observed among the women with epilepsy and no AED use compared to the women without epilepsy.

In conclusion, studies have found that women with epilepsy on AEDs are more likely to deliver by induction of labour or cesarean section. While pregnancy complications such as gestational hypertension, pre-eclampsia, vaginal bleeding and premature delivery have been documented in some studies of women with epilepsy, such complications may not be associated with the disorder itself but rather a result of the use of AEDs or of increased attention and more frequent visits to specialist caregivers due to having a diagnosis of epilepsy.(24)

An association between high serum folate and a reduced risk of pre-eclampsia has recently been demonstrated.(112, 113) Carbamazepine, phenytoin and lamotrigine are known to be folic acid antagonists that could predispose to placental microvascular disease.(24)

Research investigating the role of newer generation AEDs in proteinuria, hypertension and placental circulation is required.

1.4.2 Obstetrical interventions for seizure control

Having epilepsy is not itself an indication for obstetrical interventions such as induction of labour and cesarean section delivery.(24, 114) Such interventions are unlikely to be necessitated by the occurrence of seizures during labour because the prevalence of seizures in labour is low in women with pre-existing epilepsy (as discussed below).(13, 24, 56) An increased frequency of seizures late in pregnancy may sometimes warrant induction of labour or cesarean section delivery, but the decision to resort to a cesarean section to prevent seizures may be due to unwarranted caution.(110) Eclamptic seizures have been estimated to occur with an incidence of 5.7 per 10,000 deliveries in Canada (115) and may necessitate cesarean section delivery. However, it is unclear to what extent women with epilepsy are predisposed to having eclampsia, due to the rarity of both.

While no population-based studies have examined seizure control during pregnancy in women with epilepsy, some of the pregnancy registries that rely on voluntary recruitment have studied this. In 2006, EURAP reported prospectively documented seizure control and treatment in 1,956 pregnancies of 1,882 women with epilepsy.(13) Seizures occurred during delivery in 60 pregnancies (3.5%) and were more commonly encountered in both treated and untreated women who had had seizures during pregnancy than in women who did not seize during pregnancy (OR, 4.8; 95% CI, 2.3 -10.0).

These findings have been replicated. A retrospective, hospital-based Norwegian study reported on complications during pregnancy and delivery in 205 women with epilepsy from 1999-2006 and compared them to a control group of women without epilepsy matched for age and parity.(24) Women with epilepsy were more likely to have an "acute" cesarean section compared to the control group (17.1%; OR, 1.9; 1.0 - 3.6), but were no more likely to have a planned cesarean section (7.8%; OR, 1.4, 95% CI, 0.6 – 3.4). Three women (1.5%) experienced seizures during labour, two of whom were delivered by cesarean section.

More research is required to replicate results showing differences in pregnancy complications in women with epilepsy compared to women without epilepsy, and to see if such differences are due to epilepsy or obstetrical indications such as pre-eclampsia or hypertension arising from the use of various AEDs. In addition, the differences in the mode of delivery between women with epilepsy and women without epilepsy need to be understood better.

1.5 Antiepileptic drugs in breast milk

Different AEDs have varying kinetics and extent of penetration and residence into breast milk due to a variety of factors related to both the nature of the drug molecule and maternal metabolism. Some drugs (primidone, levetiracetam, gabapentin, lamotrigine and topiramate) transfer more readily into breast milk than others (valproic acid, carbamazepine, phenytoin and phenobarbital) due to minimal protein binding, low molecular weight, high lipophilicity, cationic molecules and high oral bioavailability of the drug to the mother or to the baby (via breast milk) of the drug or its metabolites.(102, 116,

117) Overall, the level of exposure to AEDs through breast milk is much lower than that occurring in utero.(116) In utero exposure to AEDs varies by drug, transfer mechanisms, placental metabolism, and other properties cited above. While overall the exposure corresponds to maternal plasma concentrations, yet there is little correlation between infant plasma concentrations after breastfeeding and maternal plasma concentrations.(116, 117) There have been very few studies of AEDs via breast milk. It has proven difficult to isolate the adverse effects of ingested exposure because most of the children were also previously exposed to AEDs in utero, and the studies have power or other methodological limitations.(90, 92, 102)

The implications of AED therapy while breastfeeding on cognitive outcomes were investigated in a study of children at three years of age.(92) As part of the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) cohort study, pregnant women with epilepsy who were taking a single AED (carbamazepine, lamotrigine, phenytoin or valproic acid) were enrolled prospectively between 1999 and 2004 through epilepsy centres in the USA or UK.(92) Of the 199 children studied, 42% were breastfed (44% for carbamazepine, 46% for lamotrigine, 42% for phenytoin and 32% for valproic acid). Mean adjusted intelligence quotient (IQ) scores for those who were breastfed (median time breastfeeding across all AEDs was 6 months with a range 3–24 months) and whose mothers were concurrently taking AEDs versus those who were not breastfed were: 103 (95% CI, 97-108) vs. 98 (95% CI, 93-103) for carbamazepine; 104 (95% CI, 97-110) vs. 104 (95% CI, 98-110) for lamotrigine; 91 (95% CI, 84-98) vs. 99 (95% CI, 93-105) for phenytoin; and 93 (95% CI, 82-105) vs. 90 (95% CI, 83-98) for valproic acid. Thus, this investigation did not show any significant adverse effect on cognitive outcomes from AED

exposure via breast milk for children who were also exposed in utero to four of the more common AEDs.

A prospective cohort study from Norway (Veiby et al.) that included the children of 78,744 mothers between 1999 and 2009 provided detailed information on motor skills, social skills, language and behaviour in their children at 6 months, 18 months and 36 months of age.(118) Continuous breastfeeding was defined as daily breastfeeding for a minimum of 6 months, while discontinued breastfeeding was defined as breastfeeding for less than 6 months or not at all. Groups compared included 77,770 women without epilepsy, 276 women with epilepsy on no AEDs and 223 women with epilepsy being treated with one or more AEDs (including lamotrigine monotherapy, carbamazepine monotherapy, valproic acid monotherapy or polytherapy). Using a standardised questionnaire issued to the mothers, researchers found that significantly more infants of women with epilepsy exposed to AEDs in utero had clinically relevant impaired fine motor skills at 6 months of age (11.5%; OR, 2.1; 95% CI, 1.3-3.2) compared to unexposed infants of women without epilepsy (4.8%). Use of polytherapy AEDs was associated with adverse outcomes for both fine motor skills (25.0%; OR, 4.3; 95% CI, 2.0-9.1) and social skills (22.5%; OR, 2.6; 95% CI, 1.2-5.5) compared to unexposed infants of women without epilepsy (4.5% and 10.2% respectively). However, among infants exposed to AEDs in utero, continuous breastfeeding was associated with less impaired development of these two skills at ages 6 and 18 months compared with children with no breastfeeding or breastfeeding for less than 6 months. Regardless of breastfeeding status during the first year, in utero AED exposure was associated with adverse outcomes at 36 months when compared to those not exposed to AEDs in utero (Figure 1.2). The authors reported that continuous breastfeeding during the

first year occurred less frequently among women using AEDs, particularly with lamotrigine monotherapy and polytherapy, compared to women with epilepsy who did not use AEDs during pregnancy or to the reference population.

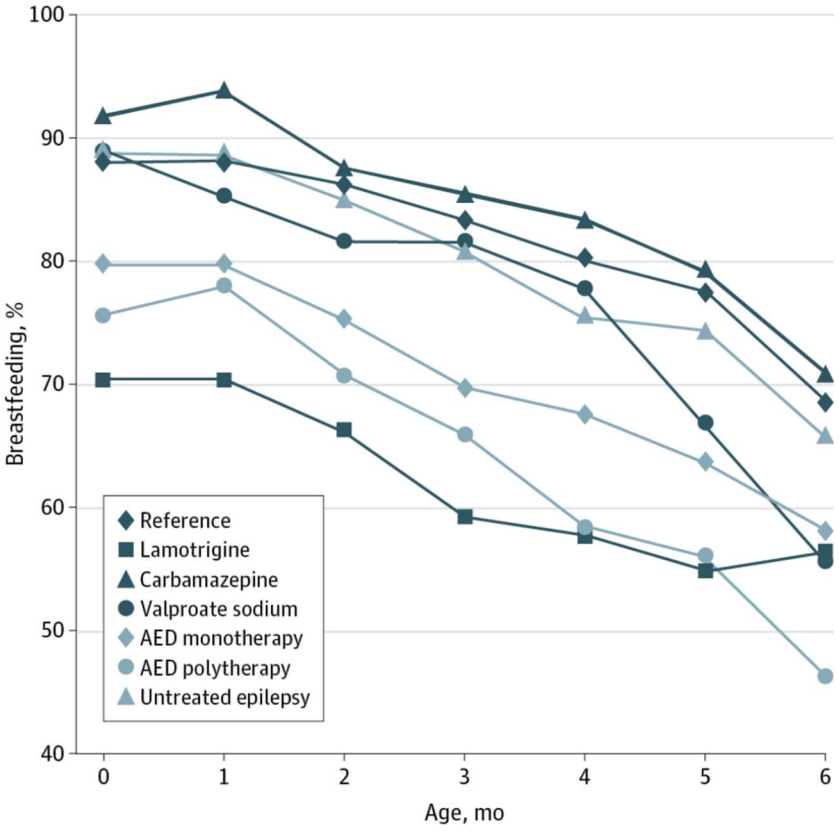

Figure 1.2 - Exclusive or Mixed Breastfeeding at Ages 0 to 6 Months: Frequency of breastfeeding in epilepsy groups and the reference group at 0 to 6 months after delivery. AED indicates antiepileptic drug. With permission. From Veiby et al., 2013.(118)

This may indicate that AEDs are erroneously regarded by patients, midwives and physicians as a contraindication for breastfeeding. The authors concluded that women should be encouraged to breastfeed their children despite AED treatment.(118)

Published USA and UK clinical guidelines recommend that women be counselled to breastfeed (102, 114) but women with epilepsy report receiving conflicting advice on

whether or not they can breastfeed.(118) Canadian guidelines for breastfeeding in women with epilepsy are lacking.

1.6 Summary

There remains a lack of literature on the management of newer generation AEDs in women with epilepsy before, during and after pregnancy. Existing evidence concerning the risk of malformations and adverse perinatal outcomes among infants exposed in utero to both newer and older generation AEDs is derived from both population-based and non-hospital based registries. Methodological differences in classification of exposure, control groups, study populations and windows of outcome assessment have presented challenges in comparing study results. While the registries differ substantially in their methodologies, they can also be viewed as complementary.

1.6.1 Strengths and limitations of existing literature

Population-based studies have several major advantages. Large study populations may provide sufficient statistical power to find significant differences in rare outcomes, and there is low potential for selection and reporting bias. Results are generalisable to similar populations and include varying degrees of detailed data on AED exposure, maternal epilepsy diagnoses, maternal adverse events including maternal age, maternal comorbidities, perinatal outcomes (such as gestational age, birth weight and length and mode of delivery), and presence of malformations in the newborn. However, many population-based studies are not able to obtain more detailed AED information such as AED blood levels, dosage and actual dates of treatment (i.e., not merely the date that the

prescription was filled), and other possible confounders, including detailed folic acid supplementation information, illicit drug use, prenatal care, level of education, income, previous obstetric history, body mass index and breastfeeding intentions.

Non-population based studies that include hospital studies and voluntary registries may lack complete information about the covariates listed above. They are also predisposed to selection and recall bias. Women who enroll prospectively without knowledge of fetal screening outcomes would selectively decrease the number of older women or other women predisposed for giving birth to infants with malformations (who would have been more likely to have early gestational screening). In North America and Australia, non-population based registries are also more likely to select for more educated, urban and English-speaking women.

In both population and non-population based studies, control groups should be similar in as many ways possible to the groups under study. However, sometimes there is a difference in the severity of epilepsy between the two groups, as well as associated differences in socioeconomic status, total medication, adverse events, quality of life and comorbidities, all of which may increase the risk for malformations and undermine the utility of the comparison. This very serious problem invalidates most of the statistical comparisons and power calculations done by these registries.

Finally, data quality may be a study limitation in both population-based and non-population-based studies. Sometimes the origin of the outcome data (e.g., neurologist, obstetrician, general practitioner, pediatrician, study participant) is problematic, or the

window of outcome detection may be inadequate (not all malformations are detected immediately at birth).

1.6.2 Research gaps

More studies are needed on fetal malformation rates among the children of women treated during pregnancy with newer generation AEDs. Few studies are sufficiently powered to provide meaningful data on newer generation drugs and associated teratogenicity, SGA outcomes and perinatal outcomes. Furthermore, no information is available regarding specific malformations and individual newer generation AEDs. With the exception of lamotrigine, almost no information on possible associations between newer generation AEDs and cognitive outcomes is available. In addition, no attention has been given to biologic plausibility between newer generation AEDs and both malformations and SGA outcomes as evidenced by the timing of exposure and a dose-dependent response. Older generation AEDs continue to be prescribed despite their established record of teratogenicity and early evidence of decreased rates of teratogenicity from newer generation AEDs. The reasons for this trend are unclear, but there may be an association with the number of patients that have been counselled preconceptually regarding AED treatment in pregnancy.

Preconceptional counselling may encourage women with epilepsy who are contemplating pregnancy to switch to an AED that is safer for the embryo/fetus and begin taking a high-dose folic acid supplement before becoming pregnant. While research on maternal folic acid supplementation has not definitively shown a reduction in the rate of infant malformations associated with AED exposure, in the absence of evidence of harm from high

dose supplemental folic acid, many caregivers recommend that women with epilepsy begin taking high dose folic acid prior to conception. It is important to determine how many patients adhere to this recommendation as a measure of whether women with epilepsy are receiving adequate preconceptual counselling. As with high dose folic acid supplementation, the frequency of breastfeeding in women with epilepsy may be associated with the number of women with epilepsy who have been counselled appropriately preconceptually. Despite the varying transfer of AEDs into breastmilk, published USA and UK clinical guidelines recommend that women be counselled to breastfeed. More research is required to investigate the frequency of breastfeeding, particularly among those on newer generation AEDs and the factors that may inhibit women with epilepsy from breastfeeding their babies.

Increased rates of cesarean section and induction of labour have been documented among women with epilepsy, particularly among those on AEDs. In the absence of obstetrical complications, having epilepsy is not itself an indication for induction of labour or cesarean section delivery. However, an increase in seizure frequency may necessitate induction of labour. In addition, increased risks for pre-eclampsia and hypertension have been documented and an association with AEDs has been postulated. More research is required to investigate whether newer generation AEDs are associated with gestational hypertension and pre-eclampsia and ultimately an increased risk for cesarean section and induction.

1.6.3 Purpose of the current thesis research

This thesis capitalizes on an opportunity to utilize the population-based data in BC. The purpose of the current thesis research is to examine how women with epilepsy in BC and other parts of Canada are being managed to concurrently control seizures, decrease teratogenicity and optimize obstetric and perinatal outcomes. To achieve this, there are nine important dimensions of patient management that can be examined.

1. To compare rates of use of newer generation AEDs among pregnant women with epilepsy with rates of use of older generation AEDs and no use of AEDs;
2. To compare the rates of major malformations among infants exposed to newer generation AED monotherapy in utero versus the rates in infants not exposed;
3. To compare rates of major malformations among infants exposed to other newer generation AED monotherapy in utero versus the rates in infants exposed to lamotrigine monotherapy in utero;
4. To compare rates of SGA outcomes among infants exposed to newer generation AED monotherapy in utero versus infants not exposed to AEDs;
5. To compare rates of SGA outcomes among infants exposed to other newer generation AED monotherapy in utero versus infants exposed to lamotrigine monotherapy in utero;
6. To compare rates of preconceptual folic acid supplementation among women with epilepsy versus those without epilepsy (regardless of AED regimen);
7. To compare rates of breastfeeding among women with epilepsy versus those without epilepsy (regardless of AED regimen).

8. To determine if preconceptual folic acid supplementation predicts breastfeeding in women with epilepsy (regardless of AED regimen);
9. To compare rates and indications for induction of labour and cesarean section delivery among women with epilepsy versus those without epilepsy (regardless of AED regimen).

CHAPTER 2: Utilization, teratogenicity and SGA outcomes associated with use of AEDs during pregnancy in British Columbia

2.1 Introduction

The prevalence of AED therapy in pregnant women is 0.2 – 0.5%.(16) In Denmark and the USA, it is estimated that half of these prescriptions are used for treating epilepsy. Other indications for AED therapy include mental health disorders, headache and neuropathic pain.(14, 15, 17) Pregnant women with epilepsy require ongoing AED therapy to decrease the likelihood of seizures and related maternal and fetal adverse outcomes associated with seizures.(18) However, the risk of fetal adverse outcomes from AED therapy is also a concern. While an association between epilepsy itself and malformations has not been demonstrated using observational studies to date, the rate of major malformations among infants of women with epilepsy treated with AEDs has been reported to be higher than the rate among infants of untreated women with epilepsy.(11, 25, 33, 119)

In addition to this increased risk of malformations, in utero exposure to older AEDs (those licensed prior to 1971) is also associated with cognitive deficits, fetal growth restriction resulting in SGA outcomes (birth weight less than 10th percentile), decreased head circumference and microcephaly at birth.(14, 35, 36) While newer generation AEDs licensed since the early 1990s have not been proven more effective at decreasing the severity and frequency of seizures, many of these newer drugs have beneficial pharmacokinetic properties or formulations which result in more convenient dosing schedules for the patient, fewer adverse effects, greater tolerability and possibly less

teratogenicity than the older generation drugs.(48) However, older generation AEDs may have a higher rate of reported adverse reactions because they have been more widely and longitudinally studied.

Major malformations occur more frequently in AED polytherapy than in monotherapy. Incidence rates of the total number of major malformations were nearly twice as high among infants exposed to polytherapy (9.84%; 95% CI, 7.82 – 11.87%) when compared to infants exposed to monotherapy (5.30%; 95% CI, 3.51 – 7.09) in a large meta-analysis.(18) Polytherapy combinations involving valproic acid (an older generation drug) produce the highest rates of major malformations.(11, 18, 33, 37, 38, 55) Polytherapy combinations involving valproic acid produced major malformation (total events) incidence rates of 9.79% (95% CI, 7.57 – 12.02%) when two drugs were used and 25.00% (95% CI, 5.97 – 44.03%) when three or more drugs were used.(18)

The teratogenicity of newer AEDs during pregnancy is not well documented.(16, 21, 37, 49) While the teratogenicity of lamotrigine therapy has been described in the most detail,(16, 21, 35, 49, 80, 120) fewer data are available for other newer generation AEDs such as levetiracetam, topiramate, gabapentin and oxcarbazepine (Table 2.1). Even less is known about the effect of newer generation AEDs on cognitive and SGA outcomes.

Table 2.1 – Teratogenic findings in newer generation AEDs

Newer Generation AED	Monotherapy -specific malformations	Effects on Intelligence and Learning Skills	Effect on Birth Weight
Lamotrigine	Increased risk for cleft lip and palate or cleft palate alone; absolute risk between 0.1 and 0.4%.	No apparent effect on IQ or learning skills. More data needed on children over age 6.	No increased frequency of SGA outcomes.
Topiramate	Two- to threefold increase in risk for malformations overall, largely due to an increased risk for cleft lip with or without cleft palate.	No information available on effect on IQ or learning skills.	Suggestions of increased risk of low birth weight and SGA outcomes.
Gabapentin	Data available not sufficient to determine whether this exposure is harmful to fetus or not.	Data available not sufficient to determine whether this exposure is harmful to fetus or not.	Data available not sufficient to determine whether this exposure is harmful to fetus or not.
Levetiracetam	Data available not sufficient to determine whether this exposure is harmful to fetus or not.	Data available not sufficient to determine whether this exposure is harmful to fetus or not.	Data available not sufficient to determine whether this exposure is harmful to fetus or not.
Oxcarbazepine	Data available not sufficient to determine whether this exposure is harmful to fetus or not.	Data available not sufficient to determine whether this exposure is harmful to fetus or not.	Data available not sufficient to determine whether this exposure is harmful to fetus or not.

Adapted from Holmes and Hernandez, 2012.(49)

Pregnancy and epilepsy registries investigating perinatal outcomes and the teratogenicity of the newer generation AEDs employ different methodologies that can affect their results and make it hard to compare studies. These include different recruitment strategies, AED usage status at time of conception, choice of control groups, exclusion criteria and time frame for diagnosis of major malformations.(58)

In this chapter, my objectives are:

1. To compare rates of use of newer generation AEDs, older generation AEDs and no use of AEDs among pregnant women with epilepsy;
2. To compare rates of major malformations among infants of women with epilepsy exposed to newer generation AED monotherapy, infants not exposed to AEDs

born to women with epilepsy, and infants not exposed to AEDs born to women without epilepsy;

3. To compare rates of major malformations among infants of women with epilepsy exposed to newer generation AED monotherapy, infants exposed to lamotrigine born to both women with and without epilepsy, and infants of women without epilepsy not exposed to AEDs;
4. To compare rates of SGA outcomes among infants of women with epilepsy exposed to newer generation AED monotherapy, infants exposed specifically to lamotrigine born to both women with and without epilepsy, and infants of women without epilepsy not exposed to AEDs.

2.2 Methods

This study was approved by the University of British Columbia (UBC) Behavioural Research Ethics Board and Population Data BC on the basis of the methods described below.

2.2.1 Study design and data set compilation

This population-based cohort study used several administrative databases [Medical Services Plan (MSP), PharmaNet, BC Perinatal Data Registry, BC Vital Statistics Births] housed at Population Data BC, a multi-university data and education resource.(121-124) All inferences, opinions, and conclusions drawn in this dissertation are those of the author, and do not reflect the opinions or policies of the Data Steward(s). All women who gave birth in a BC hospital between 1 January 2000 and 31 December 2010 and their infants were identified using the provincial administrative database, BC Vital Statistics Births. This database includes all births registered by the attending provider in the province of BC. From this population, mothers taking AEDs during pregnancy were identified using data

from PharmaNet. PharmaNet is an online system that captures all drug prescriptions and medical supplies dispensed and picked up by the patient from pharmacies in BC. It does not include medications administered or dispensed and used in hospital. Mothers were identified as having epilepsy or convulsions using ICD-9 (International Classification of Diseases, Ninth Revision) coding from the Medical Services Payment (MSP) information file. This file contains data on medically necessary services provided by fee-for-service practitioners to individuals covered by the Medical Services Plan, BC's universal insurance program. Maternal characteristics and conditions [including maternal mental health conditions identified at delivery and classified using ICD-9 coding: 290 – 319 and International Statistical Classification of Diseases and Related Health Problems Tenth Revision, Canada (ICD-10-CA) coding: F00 – F99] were then reviewed using the BC Perinatal Database Registry (PDR). The BC PDR contains provincial coverage of deliveries and births in any acute care facility or at home with a registered provider (approximately 99% of total births), throughout the province of BC. Full provincial coverage gradually increased over time with full coverage available since 1 April 2000. By obtaining the admission weight from the BC PDR, the presence of SGA outcomes were then calculated using growth distributions from the standard population-based birth charts in use in BC.(125) Comparisons were made to infants of women without epilepsy not receiving AEDs (used when reporting maternal characteristics and when reporting major malformations and SGA outcomes) and the infants of women with or without epilepsy on lamotrigine (when reporting major malformations and SGA outcomes).

2.2.2 Hypotheses

A. The rates of major malformations are not associated with in utero newer generation AED monotherapy (or odds ratio equal to one);
B. The rates of SGA outcomes are not associated with in utero newer generation AED monotherapy (or odds ratio equal to one).

In order to test the above hypotheses, I performed the following cohort study using the linked, administrative data from prescription, birth record, billing and perinatal databases described above.

2.2.3 Exposures of interest

All mothers who delivered in BC between 2000 and 2010 were included in our study, resulting in a study sample of 437,215. Date of conception was derived by subtracting the gestational age in weeks as determined in order by either early ultrasound if available, last known menstrual period if cycles are regular, or, pediatric examination at birth, from the date of birth of the infant.

Epilepsy was defined using ICD-9 codes for epilepsy (345) or convulsions (780.3). Mothers were determined to have epilepsy if they had either of the appropriate ICD-9 codes from the MSP information file any time in the year before the date of birth of the infant.

2.2.3.1 Inclusion criteria

Mothers were identified as taking AED monotherapy during pregnancy if they picked up a prescription for AED monotherapy (carbamazepine, lamotrigine, clobazam, clonazepam,

gabapentin/ pregabalin, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate, and valproic acid) from a BC pharmacy to be taken for any length of time during the first trimester (13 weeks) of their pregnancy (the period in which structural defects are most likely to be caused(14)). It was not necessary for the mothers to be taking AED monotherapy at the time of conception as we were not analyzing pregnancy outcome by dose at conception.

2.2.3.2 Exclusion criteria

Mothers taking AED polytherapy were excluded from the study. Mothers who changed AED prescriptions during the first trimester were also excluded. Using PharmaNet, we determined if the subject was on two AEDs concurrently or consecutively in the first thirteen weeks of pregnancy by reviewing the date the prescription was picked up from the pharmacy.

2.2.4 Outcomes of interest

2.2.4.1 Ascertainment of outcomes

Primary outcomes of interest included major malformations and SGA outcomes. Major malformations were determined using ICD-9 codes for malformations (codes: 740.0 to 759.9). Certain malformations (743.6, 744.1, 744.2–744.4, 744.8, 744.9, 747.0, 747.5, 750.0, 752.4, 752.5, 754.6, 755.0, 755.1, 757.2–757.6, 757.8, 757.9, 758.4) were classified as minor (126) and excluded. Codes for ventricular septal defects (745.4) and atrial septal defects (745.5) were included, as were chromosomal abnormalities. Major malformations

were deemed present if the infant had at least two of the same ICD-9 codes for major malformations from the MSP information file in the infant's first year of life.

SGA outcomes were derived from comparison of birthweight to population-based charts that are in current use in BC.(125) The population charts used were stratified on sex and gestational age at birth by week but not by ethnic background. An infant was considered SGA if her or his birth weight was below the tenth percentile for gestational age.

Finally, per BC PDR guidelines, perinatal data with cell size between 1 and 4 must not be published as such.

2.2.5 Statistical analysis

We used SAS statistical software version 9.4 (SAS Institute Inc., Cary, North Carolina) to perform descriptive statistics and logistic regression.

Our main outcome measures were major malformations and SGA outcomes. The date that the prescription was picked up by the patient was considered to be the date of exposure. The main exposure period of interest was the first trimester of pregnancy. The primary reference groups were women without epilepsy not receiving AEDs (used when reporting maternal characteristics and when reporting major malformations and SGA outcomes) and women with or without epilepsy on lamotrigine (when reporting major malformations and SGA outcomes). We specifically identified this drug as the reference AED for comparison for normalizing other AED data analysis as lamotrigine is frequently prescribed to women with epilepsy and psychiatric disorders and is felt to minimize confounding by indication or severity.(21, 49) In addition, it is known not to be associated with a high risk of

malformations in general. Women who are prescribed an AED have characteristics and associated comorbidities that may confound results if they are simply compared to women who are not prescribed AEDs.(127)

2.2.5.1 Analysis of potential confounders

To eliminate bias caused by different rates of maternal characteristics and conditions known to increase the major malformations, the BC PDR was interrogated for these potential confounders. The maternal characteristics examined included maternal age, smoking during pregnancy, and parity. The maternal conditions controlled for were mental health disorders, all hypertensive disorders, pre-existing or gestational diabetes, proteinuria (mother had proteinuria > 1g/litre), preterm delivery (less than 37 weeks gestational age), and a history of major congenital anomalies in a prior pregnancy. Analysis using income quintiles generated using PCCF+ software packages, weight gain during pregnancy and BMI were not possible due to the high frequency of missing data for those parameters.(128, 129)

The selection of confounders was based on a change in the odds ratio (OR) estimate as the criterion for inclusion in the final model. Using the maternal characteristics and conditions listed above, the potential confounders were individually included in separate models with AED monotherapy and selected for the final adjusted regression models if they changed the ORs by 10% or more.

2.3 Results

From 1 January 2000 to 31 December 2010, 437,215 pregnancies were analysed. Of those, 1,849 were AED-exposed women without epilepsy, 211 were AED-exposed women with epilepsy, 349 were unexposed women with epilepsy and 434,806 were unexposed women without epilepsy (control group).

2.3.1 Maternal demographic characteristics

Maternal characteristics and conditions are tabulated in Table 2.2. Key differences in maternal characteristics emerged between exposure groups (Table 2.3).

Compared to mothers without epilepsy not taking AEDs, mothers without epilepsy taking AED monotherapy were less likely to be nulliparous, more likely to be current smokers and much more likely to have mental health issues. They were also more likely to have hypertension during pregnancy (defined as a blood pressure reading greater than or equal to 140/90 mmHg), more likely to have any diabetes during pregnancy, more likely to have proteinuria during pregnancy and more likely to have premature infants.

Compared to mothers without epilepsy not taking AEDs, mothers with epilepsy not taking AED monotherapy were more likely to be nulliparous, more likely to be current smokers and more likely to have mental health issues. They were also more likely to have hypertension during pregnancy (as described above), more likely to have any diabetes during pregnancy, more likely to have proteinuria during pregnancy and more likely to have premature infants.

Compared to mothers without epilepsy not taking AEDs, mothers with epilepsy taking AED monotherapy were more likely to be current smokers and more likely to have mental health issues. They were also more likely to have hypertension during pregnancy (as described above), more likely to have proteinuria during pregnancy and more likely to have premature infants.

Table 2.2 – Characteristics of study participants

	No Epilepsy n (%)		Epilepsy n (%)	
	No AED (reference) (n=434806)	AED* (n=1849)	No AED (n=349)	AED* (n=211)
Parity				
Nulliparous	200961 (46.2)	715 (38.7)	198 (56.7)	85 (40.3)
Multiparous	233845 (53.8)	1134 (61.3)	151 (43.3)	126 (59.7)
Smoking				
Current	45528 (10.5)	514 (27.8)	59 (16.7)	32 (15.2)
Not current	389278 (89.5)	1335 (72.2)	290 (83.1)	179 (84.8)
Mother's age at birth				
< 20	15459 (3.6)	56 (3.0)	19 (5.4)	8 (3.8)
20 – 24	63928 (14.7)	254 (13.7)	74 (21.2)	26 (12.3)
25 – 29	121900 (28.0)	536 (29.0)	97 (27.8)	54 (25.6)
30 – 34	140170 (32.2)	523 (28.3)	100 (28.7)	65 (30.8)
35 – 39	76963 (17.7)	369 (20.0)	47 (13.5)	45 (21.3)
40 – 44	15573 (3.6)	105 (5.7)	12 (3.4)	13 (6.2)
>45	813 (0.2)	6 (0.3)	0 (0.0)	0 (0.0)
Maternal mental health disorders				
Yes	7333 (1.7)	316 (17.1)	33 (9.5)	17 (8.1)
No	427473 (98.3)	1533 (82.9)	316 (90.5)	194 (91.9)
Hypertensive disorders				
Yes	10605 (2.4)	70 (3.8)	25 (7.2)	10 (4.7)
No	424201 (97.6)	1779 (96.2)	324 (92.8)	201 (95.3)
Diabetes				
Yes	1817 (0.4)	24 (1.3)	5 (1.4)	0 (0.0)
No	432989 (99.6)	1825 (98.7)	344 (98.6)	211 (100.0)
Proteinuria				
Yes	5536 (1.3)	36 (2.0)	13 (3.7)	9 (4.3)
No	429270 (98.7)	1813 (98.1)	336 (96.3)	202 (95.7)

	No Epilepsy n (%)		Epilepsy n (%)	
	No AED (reference) (n=434806)	AED* (n=1849)	No AED (n=349)	AED* (n=211)
Past pregnancy with major malformations				
Yes	3276 (0.8)	14 (0.8)	7 (2.0)	<5 (2.3)
No	431530 (99.3)	1835 (99.2)	342 (98.0)	208 (98.6)
Preterm (< 37 weeks)				
Yes	39529 (9.1)	270 (14.6)	55 (15.8)	34 (16.1)
No	395277 (90.9)	1579 (85.4)	294 (84.2)	177 (83.9)

* - AED monotherapy only

Table 2.3 – Summary of maternal characteristics

Reference: No epilepsy, no AEDs	No epilepsy, AEDs OR (95th CI)	Epilepsy, no AEDs OR (95th CI)	Epilepsy, AEDs OR (95th CI)
Multiparous	0.73 (0.67 - 0.81)	1.53 (2.05 - 4.64)**	0.79 (0.60 - 1.03)
Current smoking	1.53 (1.05 - 2.23)**	1.74 (1.31 - 2.30)**	3.29 (2.97 - 3.64)**
Mental health	12.02 (10.62 - 13.59)**	6.09 (4.25 - 8.7)**	5.11 (3.11 - 8.39)**
Hypertension	1.57 (1.24 - 2.00)**	3.09 (2.05 - 4.64)**	1.99 (1.05 - 3.76)**
Diabetes	3.13 (2.09 – 4.70)**	3.46 (1.43 – 8.38)**	- *
Proteinuria	1.54 (1.11 – 2.14)**	3.00 (1.72-5.22)**	3.45 (1.77-6.74)**
Prematurity	1.71 (1.50-1.95)**	1.87 (1.40-2.50)**	1.92 (1.33-2.77)**

* - unestimable;

** - significant

The prevalence of epilepsy in pregnant women was 0.14%. Key differences in AED utilization were encountered (Table 2.4). Of the 436,801 mothers without epilepsy, 434,806 (99.5%) were not prescribed AED monotherapy while 1,849 (0.4%) were prescribed AED monotherapy. Of this 0.4%, 475 (25.8%) were on newer generation AED monotherapy and 1,367 (74.2%) were on older generation AED monotherapy. Gabapentin was the most commonly prescribed newer generation AED during the first trimester (34.7%).

Of the 625 mothers with epilepsy, 349 (55.8%) were not prescribed AEDs, 211 (33.8%) were prescribed AED monotherapy and 65 (10.4%) were prescribed AED polytherapy. Of

the 33.8% prescribed monotherapy, 35 (16.6%) were on newer generation AED monotherapy and 176 (83.4%) were on older generation AED monotherapy. Lamotrigine was the most commonly prescribed newer generation AED during the first trimester (19.9%).

Table 2.4 - AED usage in pregnancy

	No epilepsy n (%)	Epilepsy n (%)
Total	436801 (99.9)	625 (0.14)
No AED	434806 (99.5)	349 (55.8)
AED Polytherapy	146 (0.0)	65 (10.4)
AED Monotherapy	1849 (0.4)	211 (33.8)
Newer AEDs	475 (25.8)	35 (16.6)
Gabapentin and pregabalin	256	2
Topiramate	136	10
Lamotrigine	78	21
Levetiracetam	4	1
Oxcarbazepine	1	1
Older AEDs	1367 (74.2)	176 (3.4)

2.3.2 Major malformations

Compared with no exposure, gabapentin monotherapy significantly increased the risk for major malformations (unadjusted OR, 1.63; 95% CI, 1.01 - 2.63), as did phenytoin (unadjusted OR, 2.44; 95% CI, 1.17 - 5.09) (Table 2.5). However, when compared with exposure to lamotrigine, gabapentin monotherapy did not increase the risk for major malformations. No potential confounders were identified so only the crude results are presented.

Table 2.5 – AEDs and major malformation

			Compared to unexposed	Compared to lamotrigine
	Women (n)	Major Malformations (n (%))	Unadjusted OR (95th CI)	Unadjusted OR (95th CI)
Unexposed	434,806	21,176 (4.9)	1.0	-
Exposed**	2060	138 (6.7)	1.40 (1.18 - 1.67)	0.94 (0.43 – 2.07)
Lamotrigine	99	7 (7.1)	1.49 (0.69 - 3.20)	1.0
Carbamazepine	334	22 (6.6)	1.38 (0.89 - 2.12)	0.93 (0.38 - 2.24)
Clobazam	8	0 (0.0)	*	*
Clonazepam	860	54 (6.3)	1.31 (0.99 - 1.73)	0.88 (0.39 - 2.00)
Gabapentin**	234	18 (7.7)	1.63 (1.01 – 2.63)	1.10 (0.44 – 2.71)
Pregabalin	25	2 (8.0)	1.70 (0.40 – 7.20)	1.14 (0.22 – 5.87)
Levetiracetam	5	0 (0.0)	*	*
Oxcarbazepine	2	0 (0.0)	*	*
Phenobarbital	21	3 (14.3)	3.26 (0.96 – 11.05)	2.19 (0.52 – 9.28)
Phenytoin**	72	8 (11.1)	2.44 (1.17 - 5.09)	1.64 (0.57 - 4.76)
Topiramate	146	5 (3.4)	0.69 (0.28 - 1.69)	0.47 (0.14 - 1.51)
Valproic	254	19 (7.5)	1.58 (0.99 -0.52)	1.06 (0.43 - 2.61)

* - unestimatable
** - significant

2.3.3 SGA outcomes

Compared with no exposure, both gabapentin monotherapy (unadjusted OR, 2.56; 95% CI, 1.71 – 3.82) and pregabalin monotherapy exposures (unadjusted OR, 3.72; 1.28 – 10.83)

increased the risk for SGA outcomes (Table 2.6). When compared with exposure to lamotrigine, these associations persisted in both the former (unadjusted OR, 3.10; 95% CI, 1.05 – 9.10) and the latter (unadjusted OR, 4.52; 1.05 – 19.56). However, with gabapentin monotherapy exposure only, this association did not persist after adjustment for smoking (adjusted OR, 2.86; 95% CI, 0.97 – 8.42).

Table 2.6 – AEDs and SGA outcomes

			Compared to unexposed	**Compared to lamotrigine**	**Compared to lamotrigine**
	Women (n)	SGA Outcomes (n (%))	Unadjusted OR (95th CI)	Unadjusted OR (95th CI)	Adjusted OR (95th CI)[a]
Unexposed	435,155	29,661 (6.8)	1.0	-	
Exposed**	2053	166 (8.1)	1.20 (1.03 - 1.41)	2.09 (0.76 – 5.75)	
Lamotrigine	99	4 (4.0)	0.57 (0.21 - 1.57)	1.0	1.0
Carbamazepine	334	24 (7.2)	1.02 (0.68 - 1.55)	1.84 (0.62 – 5.43)	1.84 (0.62 – 5.45)
Clobazam	8	1 (12.5)	*	*	*
Clonazepam	860	68 (7.9)	1.17 (0.92 - 1.50)	2.04 (0.73 - 5.72)	1.88 (0.67 – 5.27)
Gabapentin**	234	27 (11.5)	2.56 (1.71 – 3.82)	3.10 (1.05 – 9.10)	2.86 (0.97 – 8.42)
Pregabalin**	25	4 (16.0)	3.72 (1.28 – 10.83)	4.52 (1.05 - 19.56)	4.88 (1.12 – 21.19)
Levetiracetam	5	0 (0)	*	*	*
Oxcarbazepine	2	0 (0)	*	*	*
Phenobarbital	21	2 (9.5)	2.06 (0.48 – 8.83)	2.50 (0.43–14.64)	1.93 (0.33 – 11.41)
Phenytoin	72	7 (9.7)	1.47 (0.67 - 3.21)	2.56 (0.72 – 9.1)	2.34 (0.66 – 8.35)
Topiramate	146	9 (6.1)	0.90 (0.46 - 1.76)	1.56 (0.47 - 5.21)	1.46 (0.44 – 4.89)
Valproic	254	20 (7.9)	1.17 (0.74-- 1.84)	2.03 (0.68 - 6.10)	1.87 (0.62 – 5.63)

* - unestimatable;
** - significant;
[a] - adjusted for current smoking

2.4 Discussion

2.4.1 AED utilization

The use of newer generation AEDs continues to increase in pregnant women and safety surveillance remains essential.(50) However, of the 2,060 pregnant women taking AED monotherapy in our study, use of older generation AEDs was more prevalent, especially among women with epilepsy (83.4%). Carbamazepine monotherapy was the most commonly prescribed AED in monotherapy (16.1%), followed by valproic acid (12.3%). Gabapentin was the most commonly used newer generation AED in monotherapy among 1849 women without epilepsy (13.8%), while lamotrigine was the most commonly used newer generation AED in monotherapy among 211 women with epilepsy (10.0%).

Of interest in our study was the high number of women with epilepsy in BC who were not treated with any AED at all during pregnancy (55.8%). Differences in prescribing practices within Canada may be due to geographical differences for available specialists. In BC, lamotrigine was used in 10.0% of all monotherapies during pregnancy in 211 women with epilepsy. In a 2009 study from the EURAP study group (an international registry of AEDs and pregnancy that consists of more than forty countries worldwide), regional differences in treatment were well documented.(50) For women with epilepsy, the highest exposure to lamotrigine during pregnancy was 57.7% in Demark, with high rates of exposure also recorded in the Czech Republic (48.4%) and Germany (40.2%) and much lower rates of exposure from Australia (19.1%), Austria (15.1%), Spain (13.6%) and Italy (3.2%).(50) The reasons for these disparities are unclear.

2.4.2 Major malformations

The overall prevalence of major malformations was 4.9% in the infants of women not exposed to AEDs without epilepsy. While the numbers in our study are small, the risk of major malformations associated with first trimester AED monotherapy in utero exposure ranged from 3.4% for topiramate to 14.3% for phenobarbital. In our study, when compared to unexposed women without epilepsy, both gabapentin monotherapy (7.7%; unadjusted OR, 1.63; 95% CI, 1.01 – 2.63) and phenytoin monotherapy (11.1%; unadjusted OR, 2.44; 95% CI, 1.17 - 5.09) during the first trimester were associated with major malformations in comparison to infants of untreated women.

Lamotrigine monotherapy in utero exposure was then used as a reference as previous studies have concluded that lamotrigine is a relatively safe, effective newer generation AED.(21, 37, 49, 64) Its use as a comparator may minimize confounding by indication due to cancellation of effects from characteristics such as socioeconomic status and comorbidities in both groups.(16, 21) When compared to lamotrigine monotherapy exposure (7.1%), gabapentin monotherapy exposure (OR, 1.10; 95% CI, 0.44 – 2.71) and phenytoin monotherapy (OR, 1.64; 95% CI, 0.57 - 4.76) exposure were not associated with major malformations.

Maternal conditions and characteristics including maternal age, parity, current smoking, mental health conditions, all hypertension, all diabetes, proteinuria, prior history of malformations in a sibling and preterm delivery (less than 37 weeks gestational age) were not found to be confounders. This lack of effect from confounders has been previously

encountered in other studies which may relate to insufficient numbers in subgroups which also may be true here.(11, 16, 37)

A European multicenter prospective study also reported a higher rate of major malformations (9.6%; OR, 3.7; 95% CI, 1.5 – 8.6) after first trimester exposure to pregabalin (164 exposed pregnancies and 656 controls).(73) Pregnancy outcomes for other factors including prematurity, gestational age at birth, and birth weight were similar in both the exposed and control groups. However, that study was limited by the lack of a control group of women treated for similar conditions and the small sample size when limited to patients strictly on pregabalin monotherapy during the first trimester.

It is well documented that older generation AEDs are associated with an increase in major malformations, yet they continue to be prescribed.(18, 50) Valproic acid is still prescribed to pregnant women because of its effectiveness in treating idiopathic generalized epilepsy despite its well-established teratogenicity.(21, 64, 130) However, we did not see an increased risk for major malformations from exposure to either valproic acid monotherapy or carbamazepine monotherapy when compared to lamotrigine monotherapy (OR, 1.06; 95% CI, 0.43 - 2.61, and OR, 0.93; 95% CI, 0.38 - 2.24; respectively). This may reflect the shift in practice toward a decreased dosage during pregnancy due to established dose-dependent risks for those that continue to be treated with older generation drugs (64) or it may simply reflect the robustness of our data.

2.4.3 SGA outcomes

Less attention has been given to an association between in utero exposure to newer generation AED monotherapy and SGA outcomes. In our study, the risk of SGA outcomes associated with first trimester AED monotherapy exposure ranged from 4.0% for lamotrigine to 16.0% for pregabalin. Both gabapentin monotherapy exposure (11.5%; OR, 2.56; 95% CI, 1.71 – 3.82) and pregabalin monotherapy exposure (16.0%; OR, 3.72; 95% CI, 1.28 – 10.83) during the first trimester were associated with higher SGA outcomes when compared to unexposed women without epilepsy (who had a 6.8% background risk of SGA outcomes).

The use of lamotrigine exposure as a comparison group for SGA outcomes has not been previously studied. Assuming lamotrigine exposure is a suitable reference as with major malformations, these associations did persist when compared to lamotrigine (4.0% SGA outcomes) for both gabapentin monotherapy exposure (OR, 3.10; 95% CI, 1.05 – 9.10) and pregabalin monotherapy exposure (OR, 4.52; 95% CI, 1.05 19.56). After adjustment for smoking, the association between SGA outcomes and gabapentin monotherapy exposure during the first trimester did not persist, but the association remained for pregabalin monotherapy, albeit with a very wide confidence interval (OR, 4.88; 95% CI, 1.12 – 21.19). No other conditions or characteristics besides smoking were identified as confounders, including mental health diagnoses. It is not clear if the effect of smoking is due to comorbidities associated with smoking or a specific interaction between smoking and AED drug metabolism.

A Canadian prospective study reported that gabapentin does not appear to increase the risk for major malformations but may increase the risk for low birth weight (p = 0.033) and preterm birth (p = 0.019).(74) However, there was no difference in the rate of SGA outcomes. While this study was the largest prospective study thus far with 223 exposed cases and 223 unexposed, again, there was no comparator group treated with other AEDs.

2.4.4 Strengths

There were several strengths to our study. Using linked administrative data allowed for a province-wide cohort study over a period of 10 years. Information on filled prescriptions was obtained through a province-wide prescription drug registry, which increases the completeness and accuracy of drug exposure data. Other strengths included ascertainment of major malformations using two ICD-9 diagnoses and a 1-year follow-up window after birth. As with population-based studies, we were able to include a large number of potential confounders and enrollment was involuntary. Unlike many of the previously described studies, we had both a control group of women who were treated with lamotrigine for similar conditions (who likely possessed many similar characteristics) and an unexposed control group of women without epilepsy.

2.4.5 Limitations

Limitations included those inherent to administrative, population-based studies. We were unable to investigate epilepsy severity, seizure frequency, folic acid and other maternal comorbidities as this data was unavailable. We were also unable to analyse income quintiles as a proxy of SES status, weight gain during pregnancy, and BMI due to the

inconsistent availability of data in these categories. We did not collect information on dosage nor did we analyse the amount of exposure time that women were treated with AEDs. We also did not have access to information on other medications taken. What other non-AED medications pregnant women were taking was unclear and it was likely that many infants were exposed to other drugs, as epilepsy is associated with an increased risk for many other comorbidities such as mental health issues, migraine, upper gastrointestinal tract disorders, urinary incontinence and chronic fatigue for which women with epilepsy could be taking other medications.(31, 32, 131) However, we compensate for this by comparing to appropriate controls, such as women taking lamotrigine who possess similar disease severity, socioeconomic status and comorbidities as the groups exposed to other AEDs.(21)

When using filled prescriptions as a proxy for exposure, noncompliance and discontinuation may overestimate exposure, which will bias the results toward no effect. However, for women filling AED prescriptions for epilepsy and some psychiatric disorders, discontinuing treatment during pregnancy is less likely because of the increased likelihood of the occurrence of seizures or psychiatric disorders.(16) For pregnant women with other indications (such as restless legs, migraine or neuropathic pain), incentives to continue use of their AEDs may depend on the severity of their disorders.(16)

Epilepsy diagnoses were obtained if mothers had the appropriate ICD-9 codes from the MSP information file any time in the year before the date of birth of the infant. It is not clear how accurately this identifies women with epilepsy, as it is possible that a woman with epilepsy does not receive an ICD-9 code for epilepsy or seizures each time she visits

her doctor. This could be possible if her seizure disorder is well controlled and she receives prescriptions while seeing her primary care physician for other issues.

It was also not possible to include information on therapeutic or spontaneous abortions in our study, as this information was not available in the dataset to which we had access. Both will bias an association between AED use during pregnancy and a major malformation toward null if the major malformation increases the likelihood of either an induced or spontaneous abortion.(16)

Codes for malformations in medical records systems are often unreliable. Furthermore, in our study, codes for ventricular septal defects, atrial septal defects and chromosomal abnormalities were included as major malformation outcomes. This may partially explain our slightly elevated background risk of 4.9% compared to other population-based studies which observed background risks of 1% - 3%. (16, 21, 25, 77) Furthermore, it has been determined that the rate of major malformations identified increases between two and twelve months in those exposed to AEDs.(14) Such an increase also extends to those who are not exposed to AEDs. In addition, our study did not analyse specific major malformations (e.g. neural tube defects, hypospadias, oral clefts and cardiovascular malformations) or categorize malformations by organ system due to a small number of total major malformations in our sample, nor did we use ethnicity-specific growth distributions for SGA outcomes.

We do not have information regarding AED exposure for the second and third trimesters. Exposures during these two trimesters could further affect growth restriction to varying

degrees.(23) However, it is quite possible that if a women was on AEDs during the first trimester that her treatment would continue throughout pregnancy.

Finally, despite being a population-based study, the size of the dataset available for BC meant that it was inadequately powered to detect a significantly increased risk for major malformations for some AEDs above the background malformation risk of 4.9% or SGA outcome risk of 6.8%. Properly powered analyses of clobazam, levetiracetam and oxcarbazepine were not possible due to the limited number of cases.

2.5 Conclusion

As with previous studies from other jurisdictions, our study on the BC population demonstrates that newer generation AEDs such as gabapentin, topiramate and lamotrigine do not significantly increase the risk for malformations and SGA outcomes. While pregabalin was not found to increase the risk for major malformations, it is possible that it does increase the risk for SGA outcomes. We are unable to determine the teratogenicity and rate of SGA outcomes for levetiracetam and oxcarbazepine due to an insufficient number of exposures in our study and analysis of all types of exposure would benefit from further study with a larger sample. The role of smoking in those treated with AED monotherapy also warrants attention. Finally, the lack of consensus regarding AED management during pregnancy as evidenced by prescribing patterns of AEDs in BC compared to other regions is worth further investigation.

CHAPTER 3: Preconceptual counselling in women with epilepsy in Canada: the association between folic acid supplementation and breastfeeding

3.1 Background

Epilepsy is the most common maternal neurologic disorder requiring medical treatment during pregnancy(2) and complicates 0.3 – 0.7% of all pregnancies in developed countries(10-12). Epilepsy occurs in 0.5 - 1.0% of the non-pregnant population of women of childbearing age.(5-8, 132) Women with epilepsy are at increased risk for poor pregnancy outcomes.(77, 133) Low education and low income are also associated with epilepsy.(7, 134, 135)

In women with epilepsy, the primary goal of AED therapy is to decrease or eliminate the number and severity of seizures. However, exposure to several AEDs during pregnancy may have teratogenic effects on the fetus and impair childhood cognitive development. Because of the risk for malformations such as neural tube defects, folic acid supplementation is recommended for all women with epilepsy,(102, 114) although uncertainty remains as to whether it is beneficial in reducing the increased risk of malformations after AED exposure in utero.(101, 102)

Breastfeeding is recommended by the American Epilepsy Society (AES), the American Academy of Neurology (AAN) and the National Institute of Clinical Excellence (NICE) for infants of both untreated and treated women with epilepsy.(102, 114) Given these considerations, pregnancy counselling best occurs preconceptually and should include discussion of the timing of pregnancy, appropriate AED therapy during pregnancy,

initiation of folic acid supplementation and breastfeeding options (which may affect the choice of AED treatment postnatally).

The question of what proportion of women with epilepsy supplement preconceptually with folic acid remains important despite a lack of evidence of its effectiveness at reducing malformations (101, 105) because preconceptual folic acid supplementation may serve as a marker of intent to conceive and more importantly may also indicate whether women of child-bearing age in population-based studies have received preconceptual counselling.(108) It may also provide indirect evidence as to whether AED treatment stimulates an adverse outcome pathway or acts along an adverse outcome pathway that is folic acid sensitive.

Furthermore, as epilepsy is more prevalent among those with less education and lower income levels,(7) it is important to examine whether all women with epilepsy of childbearing age are being counselled appropriately. We also investigated whether preconceptual counselling and subsequent folic acid supplementation predict breastfeeding behaviour in both women with and without epilepsy.

The Canadian Community Health Survey (CCHS cycle 3.1) is a cross-sectional survey that collects information related to health status, health care utilization and health determinants for the Canadian population.(136) Using data from the CCHS, we examined whether women (with or without epilepsy) who had given birth in the last 5 years had taken folic acid supplements before they found out they were pregnant and if they had breastfed (or attempted to breastfeed) their infants after adjusting for age, partner status and measures of socioeconomic status. Furthermore, we investigated if preconceptual folic

acid supplementation was associated with breastfeeding in women with or without epilepsy.

3.1.1. Objectives

In this chapter, my primary objectives are:

1. To compare rates of preconceptual folic acid supplementation among pregnant women with or without epilepsy;
2. To compare rates of breastfeeding among pregnant women with or without epilepsy;
3. To compare the strength of association between preconceptual folic acid supplementation and breastfeeding in women with or without epilepsy.

My secondary objectives are:

1. To compare the length of breastfeeding (less than six months vs. greater than six months) in women with or without epilepsy;
2. To compare the rates of various reasons provided by women (with or without epilepsy) for not breastfeeding.

3.2 Methods

The CCHS is an ongoing cross-sectional survey conducted by Statistics Canada that collects information on health status, health care utilization, and determinants of health. Statistics Canada uses several strategies to encourage participation, including letters of introduction and brochures mailed to each household, flexible scheduling and several attempts to reach the subject if there is no initial response. Interviewers with a wide range of language competencies including English, French, Spanish, Portuguese, Italian, Chinese, Punjabi, and

Inuktitut, among others, are used when needed. A national response rate of over 80% is achieved after data collection concludes using a cluster sampling strategy.

3.2.1 Study design

We performed a cross-sectional analysis using data from the CCHS, Cycle 3.1 (CCHS 3.1) (n=132,221). Data were self-reported and collected between January 2005 and December 2005 in person or over the telephone. CCHS 3.1 was the most recent CCHS survey from which data on both pregnancy and self-reported epilepsy are available.(137) The data are publicly available: consequently the data clause (Item 1.3.1) of the "University of British Columbia's Policy #89: Research and other studies involving human subjects" states that ethics approval for this study is not necessary.

3.2.2 Exposures

The independent variable of interest was "Do you have epilepsy?" Individuals who did not provide yes or no answers (e.g., "don't know", refusal or not stated) to this question were excluded.

3.2.3 Outcomes

The primary outcomes were preconceptional folic acid intake and breastfeeding. Preconceptual folic acid intake was measured by the question, "Did you take a vitamin supplement containing folic acid before your (last) pregnancy, that is, before you found out that you were pregnant?" and breastfeeding was measured by the question, "Did you breastfeed or try to breastfeed your baby, even if only for a short time?" Responses were

limited to "yes" or "no." Covariates included age (20 – 34 or 35 – 44 years), education of respondent (high school graduation or less, or more than high school graduation), partner status (living alone or with a partner) and level of income as determined by the number of bedrooms (2 or fewer bedrooms, or more than 2 bedrooms). Number of bedrooms, a measure of socioeconomic status, was assessed because it was less likely to have missing responses (3,845 responses were unstated out of 132,221) compared to the total household income variable (19,863 responses were unstated out of 132,221). Again, individuals who did not provide yes or no answers (e.g., "don't know", refusal or not stated) to the questions of interest were excluded from our sample. Only one mother with epilepsy was eliminated from the study due to non-response to the folic acid, breastfeeding or socioeconomic status (SES) questions.

3.2.4 Participants

For this study, we included data from women between the ages of 20 and 44 years who reported giving birth in the last 5 years (Figure 3.1).

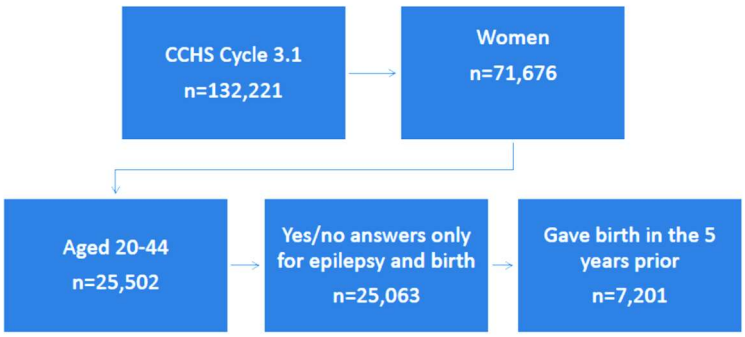

Figure 3.1 - The selection process of study participants

3.2.5 Sample size

With a sample size of 31 women with epilepsy and 6984 women without epilepsy, we had 8.4% power to determine > 5% difference in rate of folic acid intake (55.5% for the non-epilepsy group; 51.6% for the epilepsy group) with an alpha error set at 0.05 (2-sided). To achieve 80% power for this question, 194,993 women with epilepsy would be required. Our population of 31 women with epilepsy is only able to detect > 20% difference in rate of folic acid intake (55.5% for the non-epilepsy group; < 35.5% for the epilepsy group). Next, with a sample size of 31 women with epilepsy and 7040 women without epilepsy, we had 86% power to determine > 18% difference in the rate of breastfeeding (84.9% for the non-epilepsy group vs. 67.7% for the epilepsy group) with an alpha error set at 0.05 (2-sided). Data were analyzed using SAS Version 9.3. Due to the small size of this study population, analyses were not weighted.

3.2.6 Statistical analysis

The statistical significance of the association between epilepsy and our primary outcomes were tested under the null hypotheses:

1. The rate of preconceptual folic acid supplementation is not associated with epilepsy (or odds ratio equal to one);
2. The rate of breastfeeding is not associated with epilepsy (or odds ratio equal to one);
3. There is no association between the rate of preconceptual folic acid supplementation (or odds ratio equal to one) and the rate of breastfeeding in women with and without epilepsy (or odds ratio equal to one).

We examined bivariate associations between epilepsy and both preconceptual folic acid intake and breastfeeding using logistic regression models. Our outcomes were modeled using multivariate logistic regression with epilepsy as the independent variable and preconceptual folic acid intake or breastfeeding as the dependent variable, and in the final model, of folic acid as the independent variable and breastfeeding as the dependent variable, stratified by epilepsy. The selection of potential confounders was based on a 10% change in the odds ratio (OR) estimate as the criterion for inclusion in the final model. Potential confounders in the final model included respondent education level (>high school vs. ≤ high school), number of bedrooms in one's home, age category (35 years and over vs. under 35 years), and partner status (living with partner or alone).

3.3 Results

In the CCHS, 7,201 (28.7%) of 25,063 females between the ages of 20 and 44 gave birth in the previous five years. Of those women, 32 (0.4%) women described themselves as having epilepsy, while 7,169 (99.6%) did not (Table 3.1). Women with epilepsy did not differ from those without epilepsy with respect to age or number of bedrooms in the home. Women with epilepsy were less likely to be living with a partner (married or common law) and were less likely to have more than a high school education.

Table 3.1 - Distribution of study variables in women that gave birth in the last 5 years

	Epilepsy			
	Yes (n=32)		No (n=7,169)	
	n	(%)	n	(%)
Current age				
20 - 34 years	25	(78.1)	5099	(71.1)
35 - 44 years	7	(21.9)	2070	(28.9)
Partner status *				
Living with partner	20	(62.5)	5742	(80.3)
Alone	12	(37.5)	1407	(19.7)
Education category *				
≤ high school	16	(50.0)	1768	(25.0)
> high school	16	(50.0)	5307	(75.0)
# of bedrooms category				
≤ 2 bedrooms	6	(18.8)	1629	(23.1)
≥3 bedrooms	26	(81.2)	5429	(76.9)
Preconceptual folic acid intake				
Yes	16	(51.6)	3879	(55.5)
No	15	(48.4)	3105	(44.5)
Breastfeeding*				
Yes	21	(67.7)	5978	(84.9)
No	10	(32.3)	1062	(15.1)

*- $P < 0.05$

The relationship between preconceptual folic acid intake and epilepsy was next explored (Table 3.2). The association between preconceptual folic acid supplementation and epilepsy was confounded by partner status and education, but not by age, nor by the socioeconomic measure of number of bedrooms. In the final model, after adjustment for partner status and education, the odds of women with epilepsy supplementing with folic acid were similar to those of women without epilepsy.

The number of women with epilepsy who breastfed was next analyzed (Table 3.2). The relationship between breastfeeding and epilepsy was confounded by education, but not by age, partner status or number of bedrooms. After adjustment for education, the odds of

breastfeeding was decreased for women with epilepsy compared to women without epilepsy.

Table 3.2 – Preconceptual folic acid supplementation and breastfeeding in women with vs. without epilepsy

	Unadjusted Preconceptual folic acid intake OR (95% CI)	Adjusted* Preconceptual folic acid intake OR (95% CI)	Unadjusted Breastfeeding OR (95% CI)	Adjusted** Breastfeeding OR (95% CI)
Epilepsy Yes vs. No	0.86 (0.42, 1.73)	1.21 (0.58, 2.53)	0.37 (0.18, 0.79)	0.45 (0.21, 0.97)

* - adjusted for the following categories: education (>high school, ≤ high school); partner status (partner status, with partner, alone)

** - adjusted for the following category: education (>high school, ≤ high school)

Women with epilepsy who breastfed (Table 3.3) were as likely as women without epilepsy to breastfeed for longer than 6 months.

Table 3.3 - Length of breastfeeding in women that gave birth in the last 5 years

Length of breastfeeding	Epilepsy			
	Yes (n=16)		No (n=5,113)	
	n	(%)	n	(%)
Less than or equal to 6 months (%)	9	(56.3)	3,113	(60.9)
Greater than 6 months (%)	7	(43.7)	2,000	(39.1)

* - $P < 0.05$

The distribution of reasons for not breastfeeding, including caesarean section, bottle feeding and other, were similar in the two groups (Table 3.4). However statistical comparisons could not be done due to the small sample size. The most frequent response occurred in the "other" category in both groups.

Table 3.4 - Reasons for not breastfeeding in women that gave birth in the last 5 years

	Epilepsy			
	Yes (n=10)		No (n=1,072)	
	n	(%)	n	(%)
Reason did not breastfeed (%)				
Bottle feeding easier	2	(20.0)	197	(18.4)
Formula as good	0	0	26	(2.4)
Breastfeeding is unappealing/disgusting	1	(10.0)	165	(15.4)
Father/partner didn't want me to	0	0	4	(0.4)
Return to work/school early	0	0	36	(3.4)
C-section, medical condition, etc.	2	(20.0)	138	(12.9)
Wanted to drink alcohol or smoke	0	0	32	(3.0)
Other	5	(50.0)	474	(44.2)

Finally, the relationship between breastfeeding and preconceptual folic acid supplementation was explored in women with (Table 3.5) and without epilepsy (Table 3.6). Of those with epilepsy, preconceptually supplementing with folic acid was not associated with breastfeeding after adjustment for partner status (Table 3.7) however, this is likely due to insufficient power. Of those without epilepsy, women supplementing preconceptually with folic acid were more likely to breastfeed (Table 3.7). These relationships were not confounded by education, age or number of bedrooms.

Table 3.5 - Preconceptual folic acid supplementation by breastfeeding in women with epilepsy

	Breastfeeding			
	Yes		No	
	n	(%)	n	(%)
Preconceptual folic acid supplementation*				
Yes	11	(55.0)	4	(40.0)
No	9	(45.0)	6	(60.0)

* - P < 0.0

Table 3.6 - Preconceptual folic acid supplementation by breastfeeding in women without epilepsy

	Breastfeeding			
	Yes		No	
	n	(%)	n	(%)
Preconceptual folic acid supplementation*				
Yes	3454	(58.1)	430	(40.6)
No	2490	(41.9)	628	(59.4)

* - P < 0.05

Table 3.7 - Adjusted logistic regression model for preconceptual folic acid supplementation by breastfeeding in women with and without epilepsy

	Adjusted breastfeeding OR (95% CI)	
	Women with epilepsy*	Women without epilepsy
Preconceptual folic acid supplementation Yes vs. No	2.9 (0.47, 18.2)	1.87 (1.63, 2.11)

* - adjusted for the following category: partner status (partner status, with partner, alone)

3.4 Discussion

Prepregnancy planning in women with epilepsy includes review of AED treatment and preparation of the patient to ensure optimal maternal health while minimizing risk factors to the infant such as malformations and cognitive deficits. In addition to AED management, this includes preconceptual counselling regarding folic acid supplementation and an informed discussion of the safety and benefits of breastfeeding.

3.4.1 Preconceptual folic acid supplementation

Our results suggest that, in Canada, mothers with epilepsy who have had children in the last 5 years were as likely as mothers without epilepsy to take preconceptual folic acid, after adjustment for education and partner status (Table 3.2). However, it is possible that epilepsy is associated with preconceptual folic acid supplementation but may only be demonstrated with a larger sample. Nevertheless, we found both groups often did not take

folic acid, which is similar to results found in prior Canadian studies of mothers without epilepsy.(138) Approximately 50% of pregnancies in women in the United Kingdom and United States are unplanned.(94-96) This may partly explain why women with and without epilepsy do not preconceptually supplement with folic acid. Furthermore, as our study shows that women with epilepsy were significantly less likely to be living with a partner than women without epilepsy (Table 3.1), this *may* also indicate that pregnancies were unplanned and consequentially preconceptual folic acid supplementation was not occurring.

Lower levels of education, as found in both this (Table 3.1) and prior studies,(7) may also explain why some women with epilepsy do not supplement with folic acid. Socioeconomic status represented by education and income has been shown to impact the counselling of women with epilepsy of childbearing age in socialized health care systems such as those found in Scotland and Sweden.(105, 139) A 2013 prospective study of 1,526 pregnancies in Scottish women with epilepsy reported that increased rates of preconceptual folic acid supplementation were associated with higher socioeconomic quintiles.(105) In a 2010 retrospective study of 26,124 Swedish epilepsy patients, sociodemographic differences in care among epilepsy patients were reported. Being female, young, highly educated, having high incomes, and residing in a larger city meant being more often treated by a neurologist than by other specialists.

Reasons why women without epilepsy do not preconceptually supplement with folic acid may also include lack of fear of malformation risks (such as neural tube defects) in their infants from exposure in utero to medications such as those used by women with epilepsy,

in addition to unplanned pregnancies. However, we were unable to investigate these possibilities.

3.4.2 Breastfeeding

There is little correlation between infant plasma concentrations after breastfeeding and maternal plasma concentrations.(116, 117) However, there have been very few studies of AEDs via breast milk as it been difficult to isolate the adverse effects of ingested exposure because most of the children were also previously exposed to AEDs in utero, in addition to power or other methodological limitations.(90, 92, 102) Disparities in counselling women with epilepsy may extend to discussions surrounding breastfeeding intentions. Despite recommendations supporting breastfeeding for women with epilepsy, we found that women with epilepsy were less likely to breastfeed than women without epilepsy after adjustment for education (Table 3.2). Because some women with epilepsy did not breastfeed, it was not clear if their decreased socioeconomic status prevented them from doing so (perhaps they had to return to work earlier than those of higher income and were unable to breastfeed). However, we did find women with epilepsy were as likely to breastfeed for more than 6 months as women without epilepsy (Table 3.3). For those who did not breastfeed, the distribution of reasons appeared similar although a statistical analysis was not possible due to a limited sample (Table 3.4). Furthermore, it was not clear if women with epilepsy were not counselled to breastfeed or were reluctant to do so.
In a population-based study from Norway of 78,744 pregnant mothers from 1999-2000 investigating the effects of breastfeeding and AEDs on motor skills, social skills, language and behaviour in their young children,(118) the authors reported that continuous

breastfeeding during the first year occurred less frequently among women using AEDs, particularly with lamotrigine monotherapy, compared to those with epilepsy not using AEDs and the reference population. However, lamotrigine has been reported to be prescribed more frequently by specialists and to women compared to men.(139) This may indicate that AEDs are regarded by patients, midwives, and physicians as a contraindication for breastfeeding.

It is important to examine whether women with epilepsy of childbearing age are being counselled appropriately to supplement with folic acid preconceptually and encouraged to breastfeed when possible, especially as epilepsy is more prevalent among those with less education and lower income levels. Prior studies have documented that insufficient preconception counselling received by many women with epilepsy results in uninformed decision-making about pregnancy.(140) Women without epilepsy who preconceptually supplement with folic acid supplementation are significantly more likely to breastfeed than women who do not supplement. However, in women with epilepsy, we found no such association. This is possibly due to our small sample size. Regardless, epilepsy caregivers should be educated about the safety of breastfeeding in women with epilepsy. Women with epilepsy should be encouraged to breastfeed during preconceptual counselling.

3.4.3 Strengths

This survey represented 98% of the Canadian population, allowing for valid inferences regarding women with and without epilepsy. While women may not be certain of their epilepsy diagnoses, only one participant in this dataset reported being unsure of her

epilepsy diagnosis. Validation of epilepsy self-report compares more favourably than for other chronic conditions.(141)

3.4.4 Limitations

Our study has several limitations. The CCHS 3.1 is a cross-sectional study of self-reported data. Consequently, it may be prone to recall bias. Furthermore, women may be uncertain of their folic acid supplementation status. Secondly, we did not have data on the duration or dosage of preconceptual folic acid supplementation or AED treatment. Thirdly, it is important to mention that this survey does not examine populations on Reserves, Canadian Forces Bases, and some remote areas in Quebec and Ontario. Finally, most importantly, our study was insufficiently powered to study the association between epilepsy and folic acid supplementation. While a larger sample may find more robust results, in order to achieve adequate power using a cohort design, the study would need to be exceedingly large. Future research could be designed as a case-control study using mothers with epilepsy and randomly selected non-epilepsy participants from the community to address this issue.

3.5 Conclusion

Our results suggest that despite the predisposition for major malformations, after adjustment for education and partner status, women with epilepsy are just as likely as women without epilepsy to supplement preconceptually with folic acid. Secondly, despite practice recommendations, after adjustment for education, women with epilepsy are less likely to breastfeed. Socioeconomic status plays an important role in the rate of preconceptual folic acid supplementation and rate of breastfeeding. The role of increasing

access to education and preconceptual counselling should be studied to understand how best to concurrently increase preconceptual folic acid supplementation and breastfeeding rates in women with epilepsy. In conclusion, in women without epilepsy, preconceptual folic acid supplementation is associated with breastfeeding. In women with epilepsy, it is not clear if preconceptual folic acid supplementation is associated with breastfeeding as our study was insufficiently powered to determine this. A number of factors including partner status, and possible additional factors not able to be analyzed in this dataset (e.g. fear on the part of the mother, or caution on the part of their physician, of exposure to AEDs through breast milk) may affect this relationship.

CHAPTER 4: Delivery outcomes in women with epilepsy in British Columbia

4.1 Introduction

Epilepsy, defined as an enduring predisposition to generate epileptic seizures, (1) is the most common maternal neurologic disorder requiring medical treatment during pregnancy.(2) Epilepsy occurs at a rate of 0.3 – 0.7% among pregnant women in developed countries, (10-12) compared to 0.5 - 1.0% in the non-pregnant population of women of childbearing age.(5-8, 132) Pregnant women with epilepsy require ongoing AED therapy to decrease the likelihood of seizures and various related maternal and fetal adverse outcomes associated with seizures.(18) While most women with epilepsy have uneventful gestational periods, they have nevertheless been considered to be high-risk pregnancies. In addition to the increased risk of malformations in the infant, recent studies have demonstrated, for example, increased risks of gestational hypertension,(142, 143) pre-eclampsia,(10, 142) and bleeding in pregnancy,(10) particularly among those using AEDs.(10) However, not all studies have replicated these findings.(12, 111) Similarly, several studies have reported up to twice the rate of both induction of labour and cesarean section in women with epilepsy in the absence of other comorbidities.(24, 77, 109, 110, 144) However, while such delivery outcomes have been investigated, very few studies have reported the indications for induction of labour and cesarean section, and whether they are consistent with the complications found in the aforementioned studies. Nor have any studies investigated rates of various types of assisted vaginal delivery or rates of various anesthetics during delivery in women with epilepsy compared to women without. There are no known contraindications to vaginal delivery among women with epilepsy.

Using data from the British Columbia Perinatal Data Registry (BC PDR), we examined the rates of cesarean section, vaginal delivery, induction of labour, and assisted vaginal delivery among women with and without epilepsy.(122) Furthermore, we explored the indications for these various deliveries. Finally, we investigated rates of various types of anesthesia (e.g., epidural, general) during delivery.

The primary objectives of this chapter are:

1. To compare rates of cesarean section, induction of delivery, and assisted vaginal delivery among women with and without epilepsy;
2. To compare indications for both cesarean section and induction of labour among women with and without epilepsy.

The secondary objectives of this chapter are:

1. To compare rates of various pregnancy complications among women with and without epilepsy;
2. To compare both rates of epidural anesthesia and rates of general anesthesia among women with and without epilepsy.

4.2 Methods

This study was approved by both the University of British Columbia (UBC) Behavioural Research Ethics Board on the basis of the methods described below. All inferences, opinions, and conclusions drawn in this publication are those of the authors and do not reflect the opinions or policies of BC Perinatal Data Registry.

4.2.1 Study design and data set compilation

This population-based cross-sectional study used an administrative database from the BC PDR which includes information on approximately 99% of all births in the province.(122) The registry collects information on maternal, fetal, and newborn characteristics from the antepartum, intrapartum, and postpartum periods for approximately 45,000 births per year. Validation studies confirm that it is an accurate and comprehensive source of perinatal information.(145)

Via the BC PDR, a sample of 1,090 pregnancies in women who gave birth between 1 January 2000 and 31 December 2010 was gathered: a randomly-generated sample of 545 pregnancies in women identified as not having epilepsy at labour admission were compared to 545 pregnancies in women identified as having epilepsy or convulsions at labour admission using ICD-9 (International Classification of Diseases, Ninth Revision) or ICD-10-CA (International Statistical Classification of Diseases and Related Health Problems Tenth Revision, Canada) at the delivery episode of care. Maternal characteristics and conditions were abstracted from obstetrical and neonatal medical records by hospital and health authority staff into the BC PDR. Date of conception was derived by subtracting the gestational age in weeks as determined (in order of preference) by early ultrasound if available, last known menstrual period if cycles are regular, or pediatric examination at birth.

Income quintiles were reviewed as an estimate of socioeconomic status (SES). These were generated using PCCF+ software packages developed by Russell Wilkins of Statistics Canada to automatically assign neighbourhood income quintiles/deciles to BC patients

based on the first three characters and digits of the postal code of patient residence.(128, 129)

4.2.2 Hypotheses

A. The rates of various modes of delivery (cesarean section, induction of labour, assisted delivery) are not associated with epilepsy (or odds ratio equal to one).
B. The rates of indications for both cesarean section and induction of labour are not associated with epilepsy (or odds ratio equal to one).

To test the above hypotheses, I performed the following cross-sectional study using the perinatal database described above.

4.2.3 Exposures of interest

Mothers either with or without epilepsy who delivered in British Columbia between 1 January 2000 and 31 December 2010 were included in our study, resulting in a study sample of 1,090.

Epilepsy was defined using ICD-9 codes for epilepsy (345) or convulsions (780.3), or ICD-10-CA codes for epilepsy (G40) or convulsions (R56). Mothers were determined to have epilepsy if they fell under either of the aforementioned ICD-9 or ICD-10-CA codes at the time of the delivery episode of care.

4.2.3.1 Inclusion criteria

We included all pregnancies of women coded with epilepsy or convulsions at the delivery episode of care and an equal number of women not coded as having epilepsy or convulsions. Women with more than one infant were included in our sample. Only women who delivered in hospital were included in our sample.

4.2.3.2 Exclusion criteria

In recent years, North American women have become less likely to plan vaginal birth after having previously had cesarean section delivery.(146) Therefore, women who delivered by cesarean section previously were excluded from our study. In addition, women who were pregnant with multiples were not included as they are more likely to deliver by cesarean section.(146)

4.2.4 Outcomes of interest

4.2.4.1 Ascertainment of outcomes

As with maternal characteristics and conditions, delivery outcomes (vaginal delivery, cesarean section delivery, assisted delivery) and indications (as labelled by the BC PDR) were abstracted from maternal medical records by hospital and health authority staff before being compiled into the BC PDR. Assisted vaginal delivery was further refined into the following categories: forceps alone, forceps and vacuum, or vacuum alone. Cesarean section delivery indications included: breech, malposition/malpresentation, active herpes, maternal request, dystocia, non-reassuring fetal heart rate, abruptio placenta, placenta previa and "other". Induction of labour indications included: post estimated date of

delivery (post dates), diabetes, premature rupture of membranes (PROM), fetal compromise, maternal condition, logistics, fetal demise, hypertension and "other".

4.2.5 Statistical analysis

We used SAS statistical software version 9.4 (SAS Institute Inc., Cary, North Carolina) to perform descriptive statistics and logistic regression. Our main outcome measures were delivery outcomes (cesarean section delivery, vaginal delivery including assisted delivery, induction of labour) and indications. Crude and adjusted RRs and ORs were calculated for the previously mentioned delivery outcomes. The primary reference group included randomly selected women not coded as having epilepsy or convulsions. For cesarean section delivery and induction of labour indications, statistical comparisons of proportions for each indication were separately carried out between women with and without epilepsy using $\chi 2$ tests with a p-value cut-off of < 0.05. Finally, per BC PDR guidelines, data with cell size between 1 and 4 must not be published as such.

4.2.5.1 Sample size

With a sample size of 545 pregnancies of women with epilepsy and 545 pregnancies of women without epilepsy, we had 99% power to determine <12% difference in rate of cesarean section delivery (19.3% for the non-epilepsy group; 30.8% for the epilepsy group) with an alpha error set at 0.05 (2-sided). With a sample size of 377 women with epilepsy and 440 women without epilepsy who did not have cesarean section deliveries, we had 85% power to determine <10% difference in rate of induction of delivery (31.3%

for the non-epilepsy group; 21.8% for the epilepsy group) with an alpha error set at 0.05 (2-sided).

4.2.5.2 Analysis of potential confounders

The BC PDR was reviewed for potential confounders to eliminate bias caused by different rates of maternal characteristics and conditions known to be associated with higher rates of certain modes of delivery (cesarean section delivery, induction of labour and assisted delivery). The maternal characteristics examined included: maternal age, body mass index (BMI), smoking during pregnancy, income quintiles and parity. The maternal conditions controlled for were all hypertensive disorders, pre-existing or gestational diabetes, proteinuria, intrauterine growth restriction (IUGR), preterm delivery (less than 37 weeks gestational age), and post dates. An analysis of weight gain during pregnancy was not possible due to the high frequency of missing data for those parameters.

The selection of confounders was based on a change in the odds ratio (OR) estimate as the criterion for inclusion in the final model. Using the maternal characteristics and conditions listed above, the potential confounders were individually included in separate models with delivery outcomes and selected for the final adjusted regression models if they changed the ORs by 10% or more. Information regarding AED treatment for epilepsy was unavailable and could not be explored as a potential confounder.

4.3 Results

From 1 January 2000 to 31 December 2010, 1,090 pregnancies were analysed. Of those, 545 were to women with epilepsy while 545 were to women without epilepsy (the control

group). Key differences in maternal characteristics and conditions are tabulated in Table 4.1. Significant differences between women with and without epilepsy included parity and smoking status. Women with epilepsy were significantly more likely to be nulliparous and current smokers when compared to women without epilepsy (Table 4.1).

Table 4.1 - Characteristics of mothers with or without epilepsy

	Epilepsy			
	Yes		No	
	n	(%)	n	(%)
Current age				
< 30 years	299	(54.9)	273	(50.1)
≥ 30 years	246	(45.1)	272	(49.9)
Parity *				
Nulliparous	321	(58.9)	281	(51.6)
Multiparous	224	(41.1)	264	(48.4)
Smoker*				
Current	92	(16.9)	55	(10.1)
Past, never or unknown	453	(83.1)	490	(89.9)
Income quintiles				
1 (lowest)	140	(25.7)	133	(24.4)
2	119	(21.8)	113	(20.7)
3	108	(19.8)	99	(18.2)
4	87	(16.0)	116	(21.3)
5 (highest)	86	(15.8)	79	(14.5)
9 (missing)	5	(0.9)	5	(0.9)

* - $P < 0.05$

Women with epilepsy were significantly more likely to experience a cesarean section delivery compared to women without epilepsy (Tables 4.2 and 4.4). Induction of labour was also more likely to occur in women with epilepsy compared to women without epilepsy (Tables 4.2 and 4.4). Similarly, women with epilepsy were more likely to have assisted vaginal deliveries, to receive epidural anesthesia (Tables 4.2 and 4.4) and to receive a general anesthetic during cesarean section delivery (before adjustment for preterm delivery and proteinuria) (Table 4.4).

Table 4.2 – Delivery outcomes of women with and without epilepsy

	Epilepsy			
Delivery outcome	**Yes**		**No**	
	n	**(%)**	**n**	**(%)**
Cesarean section delivery * (yes vs. no)	**545**		**545**	
Yes	168	(30.8)	105	(19.3)
Primary elective Cesarean section	40	(7.3)	18	(3.3)
Primary emergent Cesarean section	128	(23.5)	87	(16.0)
No	377	(69.2)	440	(80.7)
Induction of labour *	**377**		**440**	
Yes	118	(31.3)	96	(21.8)
No	259	(68.7)	344	(78.2)
Assisted vaginal delivery * (yes vs. no)	**377**		**440**	
Yes	81	(21.5)	49	(11.1)
Forceps assisted Breech delivery	<5	(<1.3)	0	(0.0)
Forceps assisted vaginal delivery	32	(8.5)	18	(4.1)
Vacuum assisted vaginal delivery	40	(10.6)	29	(6.6)
Forceps and vacuum assisted vaginal delivery	8	(2.1)	<5	(<1.1)
No	296	(78.5)	391	(88.9)
Epidural* (all births)	**545**		**545**	
Yes	201	(36.9)	151	(27.7)
No	344	(63.1)	394	(72.3)
General* (CS only)	**168**		**105**	
Yes	21	(12.5)	<5	(<4.8)
No	147	(87.5)	101	(96.2)

* - $P < 0.05$

Women with epilepsy were more likely to have hypertension, proteinuria, and deliver prematurely (less than 37 weeks gestation), especially among those within the 33 – 36 gestational week period (Table 4.3).

In women with epilepsy compared to women without epilepsy who had cesarean section deliveries, significant differences in the frequency of indications included being less likely to require cesarean section delivery due to breech or malposition/malpresentation and more likely to require cesarean section due to "Other" (Table 4.3). "Other" was also the

most frequently encountered indication in women with epilepsy. Upon further investigation, however, there were no significant differences in pregnancy complications between the mothers with and without epilepsy that had "Other" listed (Appendix C). The most common indication in women with epilepsy who experienced induction of labour was "Maternal condition" which was also the only indication that differed in frequency significantly when compared to women without epilepsy (Table 4.3).

Table 4.3 – Pregnancy complications and delivery indications in women with and without epilepsy

		Epilepsy		No epilepsy	
		n	(%)	n	(%)
Pregnancy complications (yes vs. no)					
	Hypertensive disorders*	34	(6.2)	15	(2.8)
	All diabetes	59	(10.8)	46	(8.4)
	Proteinuria (>+1)*	24	(4.4)	<5	(<0.9)
	Preterm (< 37 weeks)*	85	(15.6)	41	(7.5)
	Detailed Preterm				
	< 22 weeks	<5	(<0.9)	0	(0.0)
	22 – 27 weeks	11	(2.0)	0	(0.0)
	28 – 32 weeks	14	(2.6)	8	(1.5)
	33 – 36 weeks *	57	(10.5)	32	(5.9)
	Missing	<5	(<0.9)	<5	(<0.9)
	Post dates	66	(12.1)	81	(14.9)
Delivery Indication (yes vs. no)					
C-section					
	Breech*	18	(10.7)	21	(20.0)
	Malposition/malpresentation*	10	(6.0)	14	(13.3)
	Active herpes	<5	(<3.0)	<5	(<4.8)
	Maternal request	6	(3.6)	<5	(<4.8)
	Dystocia/CPD	40	(23.8)	27	(25.7)
	Non-reassuring fetal heart rate	33	(19.6)	29	(27.6)
	Abruptio placenta	<5	(<3.0)	<5	(<4.8)
	Placenta previa	5	(3.0)	<5	(<4.8)
	Other	53	(31.6)	8	(7.6)
	Total	168	(100.0)	105	(100)
Induction					
	Post-dates	29	(24.6)	30	(31.3)
	Diabetes	<5	(<4.2)	<5	(<5.2)
	PROM	17	(14.4)	24	(25.0)
	Fetal compromise	11	(9.3)	12	(12.5)
	Maternal condition*	43	(36.4)	19	(19.8)
	Logistics	0	(0.0)	<5	(<5.2)
	Fetal demise	<5	(<4.2)	0	(0.0)
	Hypertension	6	(5.1)	<5	(<5.2)
	Other	6	(5.1)	<5	(<5.2)
	Total	118	(100.0)	96	(100.0)

* - $P < 0.05$

Table 4.4 – Odds ratios of delivery outcomes in women with and without epilepsy

	Delivery outcomes in women with vs. women without epilepsy		
	Relative risk (95% CI)	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Cesarean section delivery *	1.60 (1.29 - 1.98)	1.87 (1.41 - 2.47)	-
General anesthetic (CS delivery only),**	3.28 (1.16 - 9.29)	3.61 (1.20 - 10.82)	2.65 (0.85 - 8.3)
Received epidural (vaginal delivery)*	1.33 (1.12 - 1.58)	1.89 (1.39 - 2.56)	-
Assisted vaginal delivery ***	1.92 (1.39 - 2.68)	2.18 (1.49 - 3.21)	1.83 (1.23 - 2.74)
Induction of labour *	1.43 (1.14 - 1.81)	1.63 (1.19 - 2.24)	-

* - < 10% difference in OR after adjustment for potential confounders
** - adjusted for preterm delivery and proteinuria
*** - adjusted for epidural

4.4 Discussion

As stated above, women with epilepsy were significantly more likely to be nulliparous and current smokers when compared to women without epilepsy (Table 4.1). Furthermore, women with epilepsy were significantly more likely to have hypertension, proteinuria, or to deliver prematurely (Table 4.3). Our results replicated findings from previous studies.(10, 77, 133, 142)

While these complications have been documented in some studies of women with epilepsy, complications such as hypertension and proteinuria may not be associated with the disorder itself, but rather as result of the use of AEDs,(112, 113) or of increased attention from and more frequent visits to specialist caregivers due to having a diagnosis of epilepsy.(24)

4.4.1 Cesarean section delivery

Women with epilepsy were significantly more likely to require a cesarean section delivery compared to women without epilepsy (Table 4.4). The overall rate of cesarean section deliveries was 30.8% in women with epilepsy compared to 19.3% in women without epilepsy. A recent report from the Canadian Institute of Health Information indicates that BC had the second highest primary cesarean section delivery rate in Canada for 2010-2011 (22.9%; 95% CI, 22.4 – 23.3) which has been increasing slowly over the past decade.(147) In our study, when compared to women without epilepsy, women with epilepsy were more likely (unadjusted OR, 1.87; 95% CI, 1.41 - 2.47) to deliver by cesarean section. Our lower rate in the control group may reflect the fact that we have excluded pregnancies of multiples and those who had previously delivered by cesarean section. Maternal conditions and characteristics including maternal age, parity, current smoking, income quintiles, hypertension, diabetes, proteinuria, and preterm delivery (less than 37 weeks gestational age) were not found to be confounders. Significant differences in indications for cesarean section delivery between women with and without epilepsy included breech, fetal malposition and "Other" (Table 4.4). It is not clear why women with epilepsy are less likely to have breech and malposition listed as the primary indication for cesarean section, however, it could simply be because "Other" was felt to be the primary indication. However, it is unclear what indications "Other" actually represents.

Women with epilepsy were significantly less likely to require cesarean section delivery due to breech or malposition/malpresentation when compared to women without epilepsy. The reason for this is unclear. Women with epilepsy were also significantly more likely to require cesarean section due to "Other" (also the most frequently encountered indication).

Therefore, we conducted an analysis in all women with or without epilepsy who delivered by cesarean section with a delivery indication of "Other" to see if there were any other significant differences in pregnancy complications (Appendix C). The distribution of pregnancy complications was similar among the two "Other" groups although the non-epilepsy group was of small size. This may suggest that "Other" represents indications, possibly including epilepsy or an increase in seizure frequency, not captured in our study that could best be accomplished through chart review.

4.4.2 Induction of delivery

Induction of labour also occurred significantly more often in women with epilepsy compared to women without epilepsy (Table 4.4). The overall rate of induction of labour was 31.3% in women with epilepsy compared to 21.5% in women without epilepsy (unadjusted OR, 1.63; 95% CI; 1.19 - 2.24). Again, the previously listed covariates did not prove to be confounders and the unadjusted ORs are presented. The only significantly different and most frequently listed indication for induction of labour in women with epilepsy was "Maternal Condition." While it is possible that "Maternal Condition" refers to epilepsy or an increase in seizure frequency, it is not possible to draw that conclusion without chart review. Having epilepsy is not itself an indication for either induction of labour or cesarean section delivery.(24, 114, 148) An increased frequency of seizures late in pregnancy may sometimes warrant induction of labour, but the decision to resort to a cesarean section in particular to prevent seizures may be unnecessary and due to unwarranted caution.(110)

4.4.3 Assisted vaginal deliveries

Among those who had vaginal deliveries, assisted deliveries occurred significantly more often in women with epilepsy compared to women without epilepsy (Table 4.4). The overall rate of assisted deliveries was 21.5% in women with epilepsy compared to 11.1% in women without epilepsy (adjusted OR, 1.83; 95% CI, 1.23 - 2.74). Having had an epidural was the only covariate that confounded this association. Of note in that regard is the fact that women with epilepsy were more likely to have had an epidural when compared to women without epilepsy (36.9% vs. 27.7%; OR, 1.89; 1.39 - 2.56). The administration of epidural anesthesia to women with epilepsy may be performed with an intention to minimize pain and sleep deprivation in order to decrease seizure risk factors. Consequently, increased rates of administering epidural anesthesia may also increase the rates of more painful assisted deliveries.

4.4.4 General anesthetic

In our study, we found that general anesthetic was administered significantly more often in women with epilepsy compared to women without epilepsy (Table 4.4). The overall rate of administration of general anesthetic was 12.5% in women with epilepsy compared to <4.8% in women without epilepsy (unadjusted OR, 3.61; 95% CI, 1.20 – 10.82). After adjustment for preterm delivery and proteinuria, this association no longer remained significant (OR, 2.65; 95% CI, 0.85 - 8.3). However, the question remains as to whether preterm delivery and proteinuria warrant the administration of general anesthetic. Furthermore, in order to maintain general anesthesia, volatile anesthetics may be used, of which some are known to provoke seizure activity.(149)

4.4.5 Limitations

Our study is not without those limitations common to administrative datasets. We were unable to investigate AEDs, epilepsy severity or type, seizure frequency, and other maternal comorbidities or medications, as these data were unavailable. Epilepsy diagnoses were obtained only if mothers had the appropriate ICD-9 or ICD-10-CA codes for the delivery of care. It is not clear how accurately this identifies all women with epilepsy. It is possible that a woman with epilepsy may not be coded as such if her epilepsy is mild, well controlled, or she does not take AEDs. In that situation, she could be classified as a woman without epilepsy and this would consequently make it more difficult to find a significant difference between the two groups of women. Therefore, any positive association between epilepsy and the various modes of delivery would only strengthen if the subject had not been misclassified as not having epilepsy.

4.5 Conclusion

Epilepsy alone is not an indication for cesarean section delivery or induction of labour. However, more frequent seizures during pregnancy may precipitate induction of labour. A review of the literature suggests that less than 2% of women with epilepsy experience a seizure during labour.(24, 148) This would not necessitate an almost two-fold increase in the rate of cesarean section delivery. Thus, we suggest that both the health care provider's knowledge of and attitude towards epilepsy play a role in decision making regarding the mode of delivery.(110) Health care providers and patients alike need to be counselled and encouraged to pursue normal birth in the absence of other complications. The increased rates of cesarean section delivery, induction of labour, assisted vaginal delivery and general

anesthesia in women with epilepsy, and the relationship, if any, to AEDs deserve further study.

CHAPTER 5: Conclusion

5.1 Summary and contributions

In pregnant women with epilepsy, a notable lack of consensus on appropriate drug regimens, folic acid supplementation, delivery management, and breastfeeding guidance remains. The objective of this thesis was to examine how women with epilepsy in BC and Canada are being managed to concurrently control seizures, decrease teratogenicity and optimize obstetric and perinatal outcomes.

5.1.1 Utilization, teratogenicity and SGA outcomes associated with use of AEDs during pregnancy in BC

There remains a lack of literature on the management of newer generation AEDs in women with epilepsy before, during and after pregnancy. Methodological differences in classification of exposure, control groups, study populations and windows of outcome assessment have presented challenges in comparing study results.

There is still a need to assess the teratogenicity of newer generation AEDs for the clinical management of women with epilepsy of childbearing age, as most newer generation AEDs have not been adequately studied. While epilepsy and pregnancy registries have been established to obtain such information, many early studies have lacked power or sufficiently sound methodology to demonstrate the true teratogenic potential of newer generation AEDs. To address this, we drew from a population of over 437,000 pregnant women and analysed several potential confounders. In addition, we compared infants exposed to newer generation AEDs to both unexposed infants and infants exposed to

lamotrigine in utero. We also applied this methodology to our analysis of SGA outcomes. Finally, we extended the diagnosis of malformations up to one year after birth to account for those malformations that may not be obvious at birth.

Our study on the BC population demonstrates decreased risks for both major malformations and SGA outcomes with the use of newer generation AEDs such as gabapentin, topiramate and lamotrigine. It is possible that pregabalin does increase the risk for SGA outcomes although it was not found to increase the risk for major malformations. We are unable to determine the teratogenicity of levetiracetam and oxcarbazepine due to an insufficient number of exposures in our study.

5.1.2 Preconceptual counselling in women with epilepsy in Canada: the association between folic acid supplementation and breastfeeding

While research on maternal folic acid supplementation has not definitively shown a reduction in the rate of infant malformations associated with AED exposure, in the absence of evidence of harm from high dose supplemental folic acid, many caregivers recommend that women with epilepsy begin taking high dose folic acid prior to conception. In addition, while Canadian guidelines are lacking, published USA and UK clinical guidelines recommend that women be counselled to breastfeed,(102, 114) but women with epilepsy report receiving conflicting advice on whether or not they can breastfeed.(118) As with high dose folic acid supplementation, the frequency of breastfeeding in women with epilepsy may be associated with the number of women with epilepsy who have been counselled appropriately preconceptually. While it would be preferable for even more women with epilepsy to supplement with folic acid because of the risks for this group in

particular, our results suggest that after adjustment for education and partner status, women with epilepsy are only as likely as women without epilepsy to supplement preconceptually with folic acid. Secondly, despite practice recommendations, after adjustment for education, women with epilepsy are less likely to breastfeed. Finally, for women without epilepsy, preconceptual folic acid supplementation was associated with breastfeeding. However, we were unable to prove such an association in women with epilepsy, likely due to insufficient power. Nevertheless, preconceptual counselling should be used to discuss choosing the appropriate AED therapy for pregnancy, initiating folic acid supplementation and breastfeeding intentions as this may affect the choice of AED treatment postnatally.

5.1.3 Delivery outcomes in women with epilepsy in BC

In our study, we found that women with epilepsy were significantly more likely to be nulliparous and current smokers when compared to women without epilepsy. Furthermore, we were able to replicate findings from past studies as women with epilepsy were significantly more likely to have hypertension, proteinuria, or to deliver prematurely.(10, 77, 133, 142) In addition, we found that in women with epilepsy compared to women without, the rates of cesarean section delivery, induction of labour, assisted vaginal delivery and general anesthesia were increased.

Women with epilepsy who had cesarean section deliveries were compared to women without epilepsy who had cesarean section deliveries. The indications for cesarean section delivery were significantly different between the two groups. Women without epilepsy were more likely to require cesarean section delivery due to breech or

malposition/malpresentation, while the delivery records of women with epilepsy revealed that "Other" was the most frequently encountered indication for cesarean section. Upon further investigation, however, there were no significant differences in pregnancy complications between the mothers with and without epilepsy that had “Other” listed. Therefore, it is possible that “Other” may represent having epilepsy or an increase in seizure frequency but this study was unable to confirm that without chart review. The most common indication in women with epilepsy who experienced induction of labour was “Maternal condition” which was also the only indication that differed in frequency significantly when compared to women without epilepsy. Again, this may also refer to epilepsy or an increase in seizures as discussed above.

5.2 Strengths and limitations

5.2.1 Strengths

Epilepsy is a rare disease, and very few pregnant women are treated with AEDs. Due to both of these factors, the population we draw from to adequately answer our questions must be provincial or national in scope. Furthermore, as with most population-based studies, we were able to include a large number of potential confounders. Finally, enrollment was involuntary or in the case of the CCHS 3.1 study, random, consequently reducing selection bias.

5.2.2 Limitations

Despite being population-based, some studies within my thesis were inadequately powered. Other limitations in my thesis included those inherent to administrative,

population-based studies. Properly powered analyses examining the teratogenicity of clobazam, levetiracetam and oxcarbazepine were not possible due to the limited number of cases. Because of our sample size, our study did not analyse specific major malformations (e.g. neural tube defects, hypospadias, oral clefts and cardiovascular malformations) or categorize malformations by organ system, nor did we use ethnicity-specific growth distributions for SGA outcomes. In addition, we were unable to detect any differences in preconceptual folic acid supplementation and epilepsy status which could be attributed to our small sample of women with epilepsy who gave birth in the last five years.

Another problem in all three chapters was the certainty we had regarding our exposure status of epilepsy. In chapter 2, epilepsy diagnoses were obtained if mothers had the appropriate ICD-9 codes from the MSP information file at any time in the year before the date of birth of the infant. As previously discussed, it is not clear how accurately this identifies women with epilepsy, as it is possible that a woman with epilepsy does not receive an ICD-9 code for epilepsy or seizures each time she visits her doctor. In chapter 3, the CCHS 3.1 is a cross-sectional study of self-reported data and participants in this study may not be aware of their epilepsy status. In chapter 4, epilepsy diagnoses were obtained only if mothers had the appropriate ICD-9 or ICD-10-CA codes for the delivery of care. It is possible that a woman with epilepsy may not be coded as such if her epilepsy is mild, well controlled, or she does not take AEDs.

Uncertainty extended to confirming some outcomes. Coding for major malformations in medical records systems is often unreliable. To overcome this in our chapter 2 study, a baby needed to receive ICD-9 coding for a major malformation two or more times in the span of a year. However, it is unclear if this allows for the inclusion of too many major

malformations or too few. In chapter 3, it was possible that women may be uncertain of their folic acid supplementation status. Folic acid may be taken as part of a prenatal vitamin or by itself. Furthermore, we did not have information regarding the duration at which women supplemented with folic acid or at what dose.

Several important covariates were frequently unavailable throughout this dissertation that could have been beneficial. We were unable to investigate epilepsy severity, seizure frequency, and other maternal comorbidities. We were also unable to analyse certain covariates due to missing data such as income quintiles as a proxy of SES status (in chapter 2), weight gain during pregnancy, and BMI due to the inconsistent availability of data in these categories. When AED treatment information was available, we did not collect information on dosage nor did we analyse the amount of exposure time that women were treated with AEDs. We also did not have access to information on other medications taken. However, we compensate for this by comparing to appropriate controls, such as women taking lamotrigine who possess similar disease severity, SES and comorbidities as the groups exposed to other AEDs.(21)

It would have been of particular interest in having additional information on AED treatment for chapters 3 and 4. It is very possible that AED status may contribute to whether or not a woman chooses to both supplement with folic acid and breastfeed. Secondly, the role of AED exposure in the development of pregnancy complications and their subsequent impact on the mode of delivery would be important to explore. Unfortunately, information on AED treatment was not available for those two studies.

5.3 Recommendations

This dissertation demonstrates that evidence-based guidelines need to be established and implemented regarding pregnancy management for women with epilepsy. This is apparent because:

1. The majority of women with epilepsy do not take newer generation AEDs during pregnancy.
2. An inadequate number of women supplement with folic acid preconceptually.
3. Women with epilepsy are less likely to breastfeed than women without epilepsy.
4. Women with epilepsy are almost two times as likely to deliver by cesarean section or induction as women without epilepsy. The indications for which are unclear.

Caregivers must be educated regarding AED management, folic acid initiation and supplementation, delivery options and the safety of breastfeeding. Patients need to be counselled as early as possible to make informed decisions and to be able to implement necessary changes such as initiating folic acid supplementation and transitioning to a new AED preconceptually. Furthermore, as women may not want to transition from an established teratogenic AED that has given them seizure freedom, these discussions are best discussed upon diagnosis in women of child-bearing age so safer AEDs may be attempted first. Breastfeeding is encouraged in women with epilepsy and should also be discussed prior to pregnancy as some women may want to be counselled about which AEDs transfer into breastmilk. Modes of delivery are also important to discuss with women with epilepsy. During delivery, emphasis on pain management and reducing sleep deprivation are important to decrease the risk for seizures, but previous studies have demonstrated no

justification from the rare occurrence of seizures in labour for an almost two-fold increase in the rate of cesarean section delivery. (24, 148)

5.4 Future studies

Future studies should attempt to replicate the association between pregabalin and/or gabapentin and SGA outcomes. Furthermore, the mechanism by which smoking affects this association deserves attention. It is unclear if the effect from smoking is due to associated comorbidities or a specific interaction between smoking and AED drug metabolism.

Older generation AEDs continue to be prescribed despite their established record of teratogenicity and early evidence of decreased rates of teratogenicity from newer generation AEDs. More research is needed to investigate why women continue to take older generation AEDs during pregnancy. It is not clear if this is because they are unwilling to transition to a less teratogenic medication during pregnancy due to successful treatment from older generation AEDS, or if either the patient or the caregiver are not educated about safer alternatives during pregnancy.

In addition, research is needed to evaluate whether newer generation AEDs are associated with a specific pattern of malformations and timing of exposure, and, with the exception of lamotrigine, to a dose-dependent response.(16, 21, 64) More research into plausible mechanisms will be needed and separate studies into long-term outcomes including neurodevelopmental deficits will also be required.(14)

More research is required to investigate inadequate rates of supplementation with folic acid and decreased frequency of breastfeeding in women with epilepsy, particularly among

those on newer generation AEDs. With respect to folic acid, it is unclear if this is due to a lack of preconceptual counselling or a lack of action taken by the patient (whether due to a lack of concern regarding malformations or as a consequence of unplanned pregnancies). With breastfeeding, it is unclear if breastfeeding is discouraged by the caregiver or if the patient is reluctant to breastfeed while being treated with AEDs. The role of increasing access to education and preconceptual counselling should be studied to understand how best to concurrently increase preconceptual folic acid supplementation and breastfeeding rates in women with epilepsy.

More research is required to replicate results showing differences in pregnancy complications in women with epilepsy compared to women without epilepsy, and to see if such differences are due to epilepsy or obstetrical indications such as pre-eclampsia or hypertension arising from the use of various AEDs. In addition, these differences need to be further examined to see if they contribute to subsequent differences in modes of delivery between women with epilepsy and women without epilepsy.

Finally, epilepsy is a rare disease that is prevalent in 0.3 – 0.7% of all pregnancies in developed countries(10-12) while AED therapy is prevalent in 0.2 – 0.5% of pregnant women.(16) Future research could be designed as a case-control study using mothers with epilepsy and randomly selected non-epilepsy participants from the community to address this issue. Carleton et al. described the development of an active surveillance system to identify and report adverse drug reactions (ADRs) in Canada's children's hospitals.(150) This model included the goal of identifying genetic biomarkers of drug risk for ADRs in children. Such a model applied to the infants exposed to AEDs born to women with and

without epilepsy could help to address specific AED safety concerns in otherwise rare exposures.

5.5 Conclusion

The best possible control of seizures with the fewest adverse effects on the mother and infant is the primary goal in the treatment of epilepsy during pregnancy. To achieve this, pregnancy management is best implemented preconceptually. This includes planning for sufficient time in order to transition to the appropriate AED therapy, and to initiate folic acid supplementation. Furthermore, during preconceptual counselling, women with epilepsy of childbearing age should be apprised of delivery options and encouraged to attempt breastfeeding.

REFERENCES

1. Fisher RS. Commentary: Operational Definition of Epilepsy survey. Epilepsia. 2014 Nov;55(11):1688.
2. Pennell PB. Using current evidence in selecting antiepileptic drugs for use during pregnancy. Epilepsy Curr. 2005 Mar-Apr;5(2):45-51.
3. Banerjee PN, Filippi D, Allen Hauser W. The descriptive epidemiology of epilepsy—A review. Epilepsy Research. 2009;85(1):31-45.
4. Christensen J, Vestergaard M, Pedersen MG, Pedersen CB, Olsen J, Sidenius P. Incidence and prevalence of epilepsy in Denmark. Epilepsy Research. 2007;76(1):60-5.
5. Ngugi AK, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Estimation of the burden of active and life-time epilepsy: a meta-analytic approach. Epilepsia. 2010 May;51(5):883-90.
6. Forsgren L, Beghi E, Oun A, Sillanpaa M. The epidemiology of epilepsy in Europe - a systematic review. Eur J Neurol. 2005 Apr;12(4):245-53.
7. Tellez-Zenteno JF, Pondal-Sordo M, Matijevic S, Wiebe S. National and regional prevalence of self-reported epilepsy in Canada. Epilepsia. 2004 Dec;45(12):1623-9.
8. Kobau R, Zahran H, Thurman DJ, Zack MM, Henry TR, Schachter SC, et al. Epilepsy surveillance among adults--19 States, Behavioral Risk Factor Surveillance System, 2005. MMWR Surveill Summ. 2008 Aug 8;57(6):1-20.
9. Ngugi AK, Kariuki SM, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Incidence of epilepsy: a systematic review and meta-analysis. Neurology. 2011 Sep 6;77(10):1005-12.
10. Borthen I, Eide MG, Veiby G, Daltveit AK, Gilhus NE. Complications during pregnancy in women with epilepsy: population-based cohort study. BJOG: An International Journal of Obstetrics & Gynaecology. 2009;116(13):1736-42.
11. Artama M, Isojarvi JI, Raitanen J, Auvinen A. Birth rate among patients with epilepsy: a nationwide population-based cohort study in Finland. Am J Epidemiol. 2004 Jun 1;159(11):1057-63.

12. Viinikainen K, Heinonen S, Eriksson K, Kalviainen R. Community-based, prospective, controlled study of obstetric and neonatal outcome of 179 pregnancies in women with epilepsy. Epilepsia. 2006 Jan;47(1):186-92.
13. Seizure control and treatment in pregnancy: Observations from the EURAP Epilepsy Pregnancy Registry. Neurology. 2006;66(3):354-60.
14. Tomson T, Battino D. Teratogenic effects of antiepileptic drugs. Lancet Neurol. 2012 Sep;11(9):803-13.
15. McDonagh M, Peterson K, Lee N, Thakurta S. Drug Class Review: Antiepileptic Drugs for Indications Other Than Epilepsy: Final Report Update 2 Portland, Oregon: Oregon Health & Science University2008 Oct Report Update 2.
16. Molgaard-Nielsen D, Hviid A. Newer-generation antiepileptic drugs and the risk of major birth defects. JAMA. 2011 May 18;305(19):1996-2002.
17. Meador KJ, Zupanc ML. Neurodevelopmental outcomes of children born to mothers with epilepsy. Cleve Clin J Med. 2004 Feb;71 Suppl 2:S38-41.
18. Meador K, Reynolds MW, Crean S, Fahrbach K, Probst C. Pregnancy outcomes in women with epilepsy: A systematic review and meta-analysis of published pregnancy registries and cohorts. Epilepsy Research. 2008;81(1):1-13.
19. Stephen LJ, Brodie MJ. Antiepileptic drug monotherapy versus polytherapy: pursuing seizure freedom and tolerability in adults. Curr Opin Neurol. 2012 Apr;25(2):164-72.
20. Tomson T, Landmark CJ, Battino D. Antiepileptic drug treatment in pregnancy: changes in drug disposition and their clinical implications. Epilepsia. 2013 Mar;54(3):405-14.
21. Hernandez-Diaz S, Smith CR, Shen A, Mittendorf R, Hauser WA, Yerby M, et al. Comparative safety of antiepileptic drugs during pregnancy. Neurology. 2012 May 22;78(21):1692-9.
22. Meador KJ, Baker GA, Browning N, Cohen MJ, Clayton-Smith J, Kalayjian LA, et al. Foetal antiepileptic drug exposure and verbal versus non-verbal abilities at three years of age. Brain. 2011;134(2):396-404.
23. Veiby G, Daltveit AK, Engelsen BA, Gilhus NE. Fetal growth restriction and birth defects with newer and older antiepileptic drugs during pregnancy. J Neurol. 2014 Mar;261(3):579-88.

24. Borthen I, Eide MG, Daltveit AK, Gilhus NE. Obstetric outcome in women with epilepsy: a hospital-based, retrospective study. BJOG: An International Journal of Obstetrics & Gynaecology. 2011;118(8):956-65.
25. Holmes LB, Harvey EA, Coull BA, Huntington KB, Khoshbin S, Hayes AM, et al. The teratogenicity of anticonvulsant drugs. N Engl J Med. 2001 Apr 12;344(15):1132-8.
26. Tomson T, Battino D. Teratogenicity of antiepileptic drugs: state of the art. Curr Opin Neurol. 2005 Apr;18(2):135-40.
27. Holmes LB. The teratogenicity of anticonvulsant drugs: a progress report. J Med Genet. 2002 Apr;39(4):245-7.
28. Cantwell R, Clutton-Brock T, Cooper G, Dawson A, Drife J, Garrod D, et al. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. BJOG. 2011 Mar;118 Suppl 1:1-203.
29. Adab N, Kini U, Vinten J, Ayres J, Baker G, Clayton-Smith J, et al. The longer term outcome of children born to mothers with epilepsy. J Neurol Neurosurg Psychiatry. 2004 Nov;75(11):1575-83.
30. Cummings C, Stewart M, Stevenson M, Morrow J, Nelson J. Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. Arch Dis Child. 2011 Jul;96(7):643-7.
31. Tellez-Zenteno JF, Matijevic S, Wiebe S. Somatic comorbidity of epilepsy in the general population in Canada. Epilepsia. 2005 Dec;46(12):1955-62.
32. Tellez-Zenteno JF, Patten SB, Jette N, Williams J, Wiebe S. Psychiatric comorbidity in epilepsy: a population-based analysis. Epilepsia. 2007 Dec;48(12):2336-44.
33. Fried S, Kozer E, Nulman I, Einarson TR, Koren G. Malformation rates in children of women with untreated epilepsy: a meta-analysis. Drug Saf. 2004;27(3):197-202.
34. Tomson T, Battino D. Pharmacokinetics and therapeutic drug monitoring of newer antiepileptic drugs during pregnancy and the puerperium. Clin Pharmacokinet. 2007;46(3):209-19.
35. Meador KJ, Baker GA, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. N Engl J Med. 2009 Apr 16;360(16):1597-605.

36. Jentink J, Loane MA, Dolk H, Barisic I, Garne E, Morris JK, et al. Valproic acid monotherapy in pregnancy and major congenital malformations. N Engl J Med. 2010 Jun 10;362(23):2185-93.
37. Morrow J, Russell A, Guthrie E, Parsons L, Robertson I, Waddell R, et al. Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. J Neurol Neurosurg Psychiatry. 2006 Feb;77(2):193-8.
38. Wide K, Winbladh B, Kallen B. Major malformations in infants exposed to antiepileptic drugs in utero, with emphasis on carbamazepine and valproic acid: a nation-wide, population-based register study. Acta Paediatr. 2004 Feb;93(2):174-6.
39. Christensen J, Gronborg TK, Sorensen MJ, Schendel D, Parner ET, Pedersen LH, et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. JAMA. 2013 Apr 24;309(16):1696-703.
40. Dansky LV, Rosenblatt DS, Andermann E. Mechanisms of teratogenesis: folic acid and antiepileptic therapy. Neurology. 1992 Apr;42(4 Suppl 5):32-42.
41. Czeizel AE, Bod M, Halasz P. Evaluation of anticonvulsant drugs during pregnancy in a population-based Hungarian study. Eur J Epidemiol. 1992 Jan;8(1):122-7.
42. Nakane Y, Okuma T, Takahashi R, Sato Y, Wada T, Sato T, et al. Multi-institutional study on the teratogenicity and fetal toxicity of antiepileptic drugs: a report of a collaborative study group in Japan. Epilepsia. 1980 Dec;21(6):663-80.
43. Kallen AJ. Maternal carbamazepine and infant spina bifida. Reprod Toxicol. 1994 May-Jun;8(3):203-5.
44. Jentink J, Dolk H, Loane MA, Morris JK, Wellesley D, Garne E, et al. Intrauterine exposure to carbamazepine and specific congenital malformations: systematic review and case-control study. BMJ. 2010;341:c6581.
45. Hung OL, Shih RD. Antiepileptic drugs: the old and the new. Emerg Med Clin North Am. 2011 Feb;29(1):141-50.
46. Johannessen Landmark C, Patsalos PN. Drug interactions involving the new second- and third-generation antiepileptic drugs. Expert Rev Neurother. 2010 Jan;10(1):119-40.
47. Stephen LJ, Forsyth M, Kelly K, Brodie MJ. Antiepileptic drug combinations--have newer agents altered clinical outcomes? Epilepsy Res. 2012 Feb;98(2-3):194-8.

48. Vajda FJ, O'Brien TJ, Lander CM, Graham J, Eadie MJ. The teratogenicity of the newer antiepileptic drugs - an update. Acta Neurol Scand. 2014 Oct;130(4):234-8.
49. Holmes LB, Hernandez-Diaz S. Newer anticonvulsants: lamotrigine, topiramate and gabapentin. Birth Defects Res A Clin Mol Teratol. 2012 Aug;94(8):599-606.
50. Utilization of antiepileptic drugs during pregnancy: comparative patterns in 38 countries based on data from the EURAP registry. Epilepsia. 2009 Oct;50(10):2305-9.
51. Drazkowski J. An overview of epilepsy and driving. Epilepsia. 2007;48 Suppl 9:10-2.
52. Brodie MJ, Covanis A, Gil-Nagel A, Lerche H, Perucca E, Sills GJ, et al. Antiepileptic drug therapy: does mechanism of action matter? Epilepsy Behav. 2011 Aug;21(4):331-41.
53. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000 Feb 03;342(5):314-9.
54. Brodie MJ. Antiepileptic drug therapy the story so far. Seizure. 2010 Dec;19(10):650-5.
55. Kaaja E, Kaaja R, Hiilesmaa V. Major malformations in offspring of women with epilepsy. Neurology. 2003 Feb 25;60(4):575-9.
56. Mawhinney E, Morrow J. Managing epilepsy in pregnancy. Expert Review of Obstetrics & Gynecology. 2011;6(6):667-80.
57. Tomson T. Commentary: Valproate in the treatment of epilepsy in women and girls: The need for recommendations. Epilepsia. 2015 Jul;56(7):1004-5.
58. Tomson T, Battino D, Craig J, Hernandez-Diaz S, Holmes LB, Lindhout D, et al. Pregnancy registries: differences, similarities, and possible harmonization. Epilepsia. 2010 May;51(5):909-15.
59. Tomson T, Battino D. Teratogenic effects of antiepileptic drugs. Seizure. 2008;17(2):166-71.
60. Mitchell AA. Systematic identification of drugs that cause birth defects--a new opportunity. N Engl J Med. 2003 Dec 25;349(26):2556-9.
61. Dolk H, Jentink J, Loane M, Morris J, de Jong-van den Berg LT. Does lamotrigine use in pregnancy increase orofacial cleft risk relative to other malformations? Neurology. 2008 Sep 2;71(10):714-22.
62. Bath KG, Scharfman HE. Impact of early life exposure to antiepileptic drugs on neurobehavioral outcomes based on laboratory animal and clinical research. Epilepsy Behav. 2013 Mar;26(3):427-39.

63. Hunt S, Russell A, Smithson WH, Parsons L, Robertson I, Waddell R, et al. Topiramate in pregnancy: preliminary experience from the UK Epilepsy and Pregnancy Register. Neurology. 2008 Jul 22;71(4):272-6.
64. Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Sabers A, et al. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. Lancet Neurol. 2011 Jul;10(7):609-17.
65. Vajda FJ, Graham J, Roten A, Lander CM, O'Brien TJ, Eadie M. Teratogenicity of the newer antiepileptic drugs--the Australian experience. J Clin Neurosci. 2012 Jan;19(1):57-9.
66. Vajda FJ. The Australian Pregnancy Register of Anti-epileptic Drugs: 10 years of progress. J Clin Neurosci. 2010 Dec;17(12):1485-8.
67. Vajda FJ, Hitchcock A, Graham J, O'Brien T, Lander C, Eadie M. The Australian Register of Antiepileptic Drugs in Pregnancy: the first 1002 pregnancies. Aust N Z J Obstet Gynaecol. 2007 Dec;47(6):468-74.
68. Vajda FJ, O'Brien TJ, Graham J, Lander CM, Eadie MJ. Associations between particular types of fetal malformation and antiepileptic drug exposure in utero. Acta Neurol Scand. 2013 Oct;128(4):228-34.
69. Mawhinney E, Craig J, Morrow J, Russell A, Smithson WH, Parsons L, et al. Levetiracetam in pregnancy: results from the UK and Ireland epilepsy and pregnancy registers. Neurology. 2013 Jan 22;80(4):400-5.
70. Mines D, Tennis P, Curkendall SM, Li DK, Peterson C, Andrews EB, et al. Topiramate use in pregnancy and the birth prevalence of oral clefts. Pharmacoepidemiol Drug Saf. 2014 Oct;23(10):1017-25.
71. Margulis AV, Mitchell AA, Gilboa SM, Werler MM, Mittleman MA, Glynn RJ, et al. Use of topiramate in pregnancy and risk of oral clefts. Am J Obstet Gynecol. 2012 Nov;207(5):405 e1-7.
72. Green MW, Seeger JD, Peterson C, Bhattacharyya A. Utilization of topiramate during pregnancy and risk of birth defects. Headache. 2012 Jul-Aug;52(7):1070-84.
73. Winterfeld U, Merlob P, Baud D, Rousson V, Panchaud A, Rothuizen LE, et al. Pregnancy outcome following maternal exposure to pregabalin may call for concern. Neurology. 2016 Jun 14;86(24):2251-7.

74. Fujii H, Goel A, Bernard N, Pistelli A, Yates LM, Stephens S, et al. Pregnancy outcomes following gabapentin use: results of a prospective comparative cohort study. Neurology. 2013 Apr 23;80(17):1565-70.
75. Pennell PB, Newport DJ, Stowe ZN, Helmers SL, Montgomery JQ, Henry TR. The impact of pregnancy and childbirth on the metabolism of lamotrigine. Neurology. 2004 Jan 27;62(2):292-5.
76. de Haan GJ, Edelbroek P, Segers J, Engelsman M, Lindhout D, Devile-Notschaele M, et al. Gestation-induced changes in lamotrigine pharmacokinetics: a monotherapy study. Neurology. 2004 Aug 10;63(3):571-3.
77. Veiby G, Daltveit AK, Engelsen BA, Gilhus NE. Pregnancy, delivery, and outcome for the child in maternal epilepsy. Epilepsia. 2009;50(9):2130-9.
78. Abdullah NA, Pearce MS, Parker L, Wilkinson JR, Jaffray B, McNally RJ. Birth prevalence of cryptorchidism and hypospadias in northern England, 1993-2000. Arch Dis Child. 2007 Jul;92(7):576-9.
79. Harper PS. Practical Genetic Counselling. 6th edition ed. London: Arnold; 2004.
80. Cunnington MC, Weil JG, Messenheimer JA, Ferber S, Yerby M, Tennis P. Final results from 18 years of the International Lamotrigine Pregnancy Registry. Neurology. 2011 May 24;76(21):1817-23.
81. Correa A, Cragan JD, Kucik JE, Alverson CJ, Gilboa SM, Balakrishnan R, et al. Reporting birth defects surveillance data 1968-2003. Birth Defects Res A Clin Mol Teratol. 2007 Feb;79(2):65-186.
82. Nelson K, Holmes LB. Malformations due to presumed spontaneous mutations in newborn infants. N Engl J Med. 1989 Jan 5;320(1):19-23.
83. Girard EE. Preconception counseling for women with epilepsy. In: Bui E KA, editor. Women with epilepsy a practical management handbook. Cambridge, United Kingdom: Cambridge University Press; 2014. p. 145.
84. Clausson B, Cnattingius S, Axelsson O. Outcomes of post-term births: the role of fetal growth restriction and malformations. Obstet Gynecol. 1999 Nov;94(5 Pt 1):758-62.
85. Hvas CL, Henriksen TB, Ostergaard JR, Dam M. Epilepsy and pregnancy: effect of antiepileptic drugs and lifestyle on birthweight. BJOG. 2000 Jul;107(7):896-902.

86. Ashwal S, Michelson D, Plawner L, Dobyns WB. Practice parameter: Evaluation of the child with microcephaly (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 2009 Sep 15;73(11):887-97.
87. Almgren M, Kallen B, Lavebratt C. Population-based study of antiepileptic drug exposure in utero--influence on head circumference in newborns. Seizure. 2009 Dec;18(10):672-5.
88. Kulaga S, Sheehy O, Zargarzadeh AH, Moussally K, Bérard A. Antiepileptic drug use during pregnancy: Perinatal outcomes. Seizure. 2011;20(9):667-72.
89. Meador KJ, Penovich P, Baker GA, Pennell PB, Bromfield E, Pack A, et al. Antiepileptic drug use in women of childbearing age. Epilepsy Behav. 2009 Jul;15(3):339-43.
90. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, et al. Effects of fetal antiepileptic drug exposure: outcomes at age 4.5 years. Neurology. 2012 Apr 17;78(16):1207-14.
91. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol. 2013 Mar;12(3):244-52.
92. Meador KJ, Baker GA, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, et al. Effects of breastfeeding in children of women taking antiepileptic drugs. Neurology. 2010 Nov 30;75(22):1954-60.
93. Nadebaum C, Anderson VA, Vajda F, Reutens DC, Barton S, Wood AG. Language skills of school-aged children prenatally exposed to antiepileptic drugs. Neurology. 2011;76(8):719-26.
94. Fairgrieve SD, Jackson M, Jonas P, Walshaw D, White K, Montgomery TL, et al. Population based, prospective study of the care of women with epilepsy in pregnancy. BMJ. 2000 Sep 16;321(7262):674-5.
95. Davis AR, Pack AM, Kritzer J, Yoon A, Camus A. Reproductive history, sexual behavior and use of contraception in women with epilepsy. Contraception. 2008 Jun;77(6):405-9.
96. Finer LB, Henshaw SK. Disparities in rates of unintended pregnancy in the United States, 1994 and 2001. Perspect Sex Reprod Health. 2006 Jun;38(2):90-6.

97. Hirsch LJ, Weintraub DB, Buchsbaum R, Spencer HT, Straka T, Hager M, et al. Predictors of Lamotrigine-associated rash. Epilepsia. 2006 Feb;47(2):318-22.
98. Goh YI, Koren G. Folic acid in pregnancy and fetal outcomes. J Obstet Gynaecol. 2008 Jan;28(1):3-13.
99. Pittschieler S, Brezinka C, Jahn B, Trinka E, Unterberger I, Dobesberger J, et al. Spontaneous abortion and the prophylactic effect of folic acid supplementation in epileptic women undergoing antiepileptic therapy. Journal of Neurology. 2008;255(12):1926-31.
100. De Wals P, Tairou F, Van Allen MI, Uh SH, Lowry RB, Sibbald B, et al. Reduction in neural-tube defects after folic acid fortification in Canada. N Engl J Med. 2007 Jul 12;357(2):135-42.
101. Morrow JI, Hunt SJ, Russell AJ, Smithson WH, Parsons L, Robertson I, et al. Folic acid use and major congenital malformations in offspring of women with epilepsy: a prospective study from the UK Epilepsy and Pregnancy Register. Journal of Neurology, Neurosurgery & Psychiatry. 2009;80(5):506-11.
102. Harden CL, Pennell PB, Koppel BS, Hovinga CA, Gidal B, Meador KJ, et al. Management issues for women with epilepsy-Focus on pregnancy (an evidence-based review): III. Vitamin K, folic acid, blood levels, and breast-feeding. Epilepsia. 2009;50(5):1247-55.
103. Rothgang H, Niebuhr D, Wasem J, Gress S. [The National Institute for Clinical Excellence (NICE)]. Gesundheitswesen. 2004 May;66(5):303-10.
104. Wilson RD, Audibert F, Brock JA, Carroll J, Cartier L, Gagnon A, et al. Pre-conception Folic Acid and Multivitamin Supplementation for the Primary and Secondary Prevention of Neural Tube Defects and Other Folic Acid-Sensitive Congenital Anomalies. J Obstet Gynaecol Can. 2015 Jun;37(6):534-52.
105. Campbell E, Hunt S, Kinney MO, Guthrie E, Smithson WH, Parsons L, et al. The effect of socioeconomic status on treatment and pregnancy outcomes in women with epilepsy in Scotland. Epilepsy Behav. 2013 Sep;28(3):354-7.
106. Werler MM, Shapiro S, Mitchell AA. Periconceptional folic acid exposure and risk of occurrent neural tube defects. JAMA. 1993 Mar 10;269(10):1257-61.

107. Shaw GM, Schaffer D, Velie EM, Morland K, Harris JA. Periconceptional vitamin use, dietary folate, and the occurrence of neural tube defects. Epidemiology. 1995 May;6(3):219-26.
108. Sabers A. Influences on seizure activity in pregnant women with epilepsy. Epilepsy & Behavior. 2009;15(2):230-4.
109. Borthen I, Eide MG, Daltveit AK, Gilhus NE. Delivery outcome of women with epilepsy:a population-based cohort study. BJOG: An International Journal of Obstetrics & Gynaecology. 2010;117(12):1537-43.
110. Robinson JN, Cleary-Goldman J. Management of epilepsy and pregnancy: an obstetrical perspective. Int Rev Neurobiol. 2008;83:273-82.
111. Katz O, Levy A, Wiznitzer A, Sheiner E. Pregnancy and perinatal outcome in epileptic women: a population-based study. J Matern Fetal Neonatal Med. 2006 Jan;19(1):21-5.
112. Wen SW, Chen XK, Rodger M, White RR, Yang Q, Smith GN, et al. Folic acid supplementation in early second trimester and the risk of preeclampsia. Am J Obstet Gynecol. 2008 Jan;198(1):45 e1-7.
113. Catov JM, Nohr EA, Bodnar LM, Knudson VK, Olsen SF, Olsen J. Association of periconceptional multivitamin use with reduced risk of preeclampsia among normal-weight women in the Danish National Birth Cohort. Am J Epidemiol. 2009 Jun 1;169(11):1304-11.
114. National Institute for Health and Care Excellence. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. 2012 [updated November 2013; cited 2014 December 19].
115. Liu S, Joseph KS, Bartholomew S, Fahey J, Lee L, Allen AC, et al. Temporal trends and regional variations in severe maternal morbidity in Canada, 2003 to 2007. J Obstet Gynaecol Can. 2010 Sep;32(9):847-55.
116. Pennell PB, Gidal BE, Sabers A, Gordon J, Perucca E. Pharmacology of antiepileptic drugs during pregnancy and lactation. Epilepsy & Behavior. 2007;11(3):263-9.
117. Burakgazi E, Pollard J, Harden C. The effect of pregnancy on seizure control and antiepileptic drugs in women with epilepsy. Rev Neurol Dis. 2011;8(1-2):16-22.

118. Veiby G, Engelsen BA, Gilhus NE. Early child development and exposure to antiepileptic drugs prenatally and through breastfeeding: a prospective cohort study on children of women with epilepsy. JAMA Neurol. 2013 Nov;70(11):1367-74.
119. Dansky LV, Finnell RH. Parental epilepsy, anticonvulsant drugs, and reproductive outcome: epidemiologic and experimental findings spanning three decades; 2: Human studies. Reprod Toxicol. 1991;5(4):301-35.
120. Holmes LB, Baldwin EJ, Smith CR, Habecker E, Glassman L, Wong SL, et al. Increased frequency of isolated cleft palate in infants exposed to lamotrigine during pregnancy. Neurology. 2008 May 27;70(22 Pt 2):2152-8.
121. British Columbia Ministry of Health. Medical Services Plan (MSP) Payment Information File. V2. Population Data BC; 2011 [cited 2016 November 26]; Available from: http://www.popdata.bc.ca/data.
122. Perinatal Services BC. British Columbia Perinatal Data Registry. Population Data BC 2011 [cited 2016 November 26]; Available from: http://www.perinatalservicesbc.ca/health-professionals/data-surveillance/perinatal-data-registry.
123. BC Vital Statisics. Vital Statistics Births. V2. Population Data BC; 2011 [cited 2016 November 26]; Available from: http://www.popdata.bc.ca/data.
124. British Columbia Ministry of Health. PharmaNet. V2.: Population Data BC; 2011 [cited 2016 November 26]; Available from: http://www.popdata.bc.ca/data.
125. Kierans W, Kramer M, Wilkins R. Charting birth outcome in British Columbia: determinants of optimal health and ultimate risk: an expansion and update: British Columbia Ministry of Health, Division of Vital Statistics2003.
126. Berard A, Ramos E, Rey E, Blais L, St-Andre M, Oraichi D. First trimester exposure to paroxetine and risk of cardiac malformations in infants: the importance of dosage. Birth Defects Res B Dev Reprod Toxicol. 2007 Feb;80(1):18-27.
127. Salas M, Hofman A, Stricker BH. Confounding by indication: an example of variation in the use of epidemiologic terminology. Am J Epidemiol. 1999 Jun 1;149(11):981-3.
128. Statistics Canada. Postal Code Conversion File (PCCF) Reference Guide. Statistics Canada Catalogue.

129. Wilkins R. PCCF+ Version 5E User's Guide. Automated Geographic Coding Based on the Statistics Canada Postal Code Conversion Files, Including Postal Codes throughout March 2009. Ottawa: Health Analysis Division; 2009.
130. Campbell E, Kennedy F, Russell A, Smithson WH, Parsons L, Morrison PJ, et al. Malformation risks of antiepileptic drug monotherapies in pregnancy: updated results from the UK and Ireland Epilepsy and Pregnancy Registers. J Neurol Neurosurg Psychiatry. 2014 Sep;85(9):1029-34.
131. Fuller-Thomson E, Brennenstuhl S. The association between depression and epilepsy in a nationally representative sample. Epilepsia. 2009;50(5):1051-8.
132. Christensen J, Vestergaard M, Pedersen MG, Pedersen CB, Olsen J, Sidenius P. Incidence and prevalence of epilepsy in Denmark. Epilepsy Res. 2007 Aug;76(1):60-5.
133. Borthen I, Gilhus NE. Maternal epilepsy and adverse pregnancy outcomes. Expert Review of Obstetrics & Gynecology. 2010;5(3):347-55.
134. Wallace H, Shorvon S, Tallis R. Age-specific incidence and prevalence rates of treated epilepsy in an unselected population of 2,052,922 and age-specific fertility rates of women with epilepsy. Lancet. 1998 Dec 19-26;352(9145):1970-3.
135. Sukumaran SC, Sarma PS, Thomas SV. Polytherapy increases the risk of infertility in women with epilepsy. Neurology. 2010 Oct 12;75(15):1351-5.
136. Statistics Canada. Canadian Community Health Survery2005.
137. Ng D. Personal Email Communication. In: McIntosh K, editor.2013.
138. Koren G, Goh YI, Klieger C. Folic acid: the right dose. Can Fam Physician. 2008 Nov;54(11):1545-7.
139. Mattsson P, Tomson T, Eriksson O, Brannstrom L, Weitoft GR. Sociodemographic differences in antiepileptic drug prescriptions to adult epilepsy patients. Neurology. 2010 Jan 26;74(4):295-301.
140. McGrath A, Sharpe L, Lah S, Parratt K. Pregnancy-related knowledge and information needs of women with epilepsy: a systematic review. Epilepsy Behav. 2014 Feb;31:246-55.
141. Brooks. Validation of self-reported epilepsy for purposes of community surveillance.
142. Thomas SV, Sindhu K, Ajaykumar B, Devi PBS, Sujamol J. Maternal and obstetric outcome of women with epilepsy. Seizure. 2009;18(3):163-6.

143. Richmond JR, Krishnamoorthy P, Andermann E, Benjamin A. Epilepsy and pregnancy: an obstetric perspective. Am J Obstet Gynecol. 2004 Feb;190(2):371-9.
144. Viale L, Allotey J, Cheong-See F, Arroyo-Manzano D, McCorry D, Bagary M, et al. Epilepsy in pregnancy and reproductive outcomes: a systematic review and meta-analysis. Lancet. 2015 Nov 7;386(10006):1845-52.
145. Frosst G, Hutcheon J, Joseph KS, Kinniburgh B, Johnson C, Lee L. Validating the British Columbia Perinatal Data Registry: a chart re-abstraction study. BMC Pregnancy Childbirth. 2015 May 27;15:123.
146. Roberts RG, Deutchman M, King VJ, Fryer GE, Miyoshi TJ. Changing policies on vaginal birth after cesarean: impact on access. Birth. 2007 Dec;34(4):316-22.
147. Canadian Institute for Health Information. Childbirth Indicators by Place of Residence. 2016 [cited 2016 November 26]; Available from: https://apps.cihi.ca/mstrapp/asp/Main.aspx?Server=apmstrextprd_i&project=Quick+Stats&uid=pce_pub_en&pwd=&evt=2048001&visualizationMode=0&documentID=029DB170438205AEBCC75B8673CCE822.
148. Sveberg L, Svalheim S, Tauboll E. The impact of seizures on pregnancy and delivery. Seizure. 2015 May;28:35-8.
149. Zahir F, Waters JH. Obstetrical anesthesia and the pregnant epileptic patient. In: B ui EK, A., editor. Women with epilepsy a practical management handbook. Cambridge, United Kingdom: Cambridge University Press; 2014. p. 210.
150. Carleton B, Poole R, Smith M, Leeder J, Ghannadan R, Ross C, et al. Adverse drug reaction active surveillance: developing a national network in Canada's children's hospitals. Pharmacoepidemiol Drug Saf. 2009 Aug;18(8):713-21.

APPENDICES

Appendix A – Drugs and major malformations

			Compared to unexposed	Compared to lamotrigine								
	Women (n)	Major malformations (n (%))	Unadjusted OR (95th CI)	Unadjusted OR (95th CI)	Adjusted OR[a] (95th CI)	Adjusted OR[b] (95th CI)	Adjusted OR[c] (95th CI)	Adjusted OR[d] (95th CI)	Adjusted OR[e] (95th CI)	Adjusted OR[f] (95th CI)	Adjusted OR[g] (95th CI)	Adjusted OR[h] (95th CI)
Unexposed	434,806	21,176 (4.9)	1.0	-								
Exposed	2060	138 (6.7)	1.40 (1.18 - 1.67)	0.93 (0.38 - 2.24)								
Lamotrigine	99	7 (7.1)	1.49 (0.69 - 3.20)	1.0	1.0	1.0	1.0	1.0	1.0	1.0		1.0
Carbamazepine	334	22 (6.6)	1.38 (0.89 - 2.12)	0.93 (0.38 - 2.24)	0.92 (0.38 – 2.22)	0.93 (0.38 – 2.24)	0.98 (0.40 – 2.37)	0.93 (0.39 – 2.25)	0.93 (0.38 – 2.24)	0.93 (0.38 – 2.24)	0.92 (0.38 – 2.21)	0.93 (0.38 – 2.25)
Clobazam	8	0 (0.0)	*	*	*	*	*	*	*	*	*	*
Clonazepam	860	54 (6.3)	1.31 (0.99 - 1.73)	0.88 (0.39 - 2.00)	0.87 (0.39 – 1.98)	0.83 (0.37 – 1.89)	0.85 (0.37 – 1.92)	0.89 (0.39 – 2.00)	0.88 (0.39 – 1.99)	0.88 (0.39 – 1.99)	0.87 (0.38 – 1.96)	0.84 (0.37 – 1.90)
Gabapentin	234	18 (7.7)	1.63 (1.01 – 2.63)	1.10 (0.44 – 2.71)	1.09 (0.44 – 2.69)	1.04 (0.42 – 2.57)	1.10 (0.45 – 2.73)	1.09 (0.44 – 2.70)	1.10 (0.44 – 2.71)	1.09 (0.44 – 2.71)	1.09 (0.44 – 2.69)	1.05 (0.42 – 2.60)
Pregabalin	25	2 (8.0)	1.70 (0.40 – 7.20)	1.14 (0.22 – 5.87)	1.13 (0.22 – 5.83)	1.19 (0.23 – 6.14)	1.19 (0.23 – 6.15)	1.13 (0.22 – 5.82)	1.14 (0.22 – 5.87)	1.14 (0.22 – 5.84)	1.14 (0.22 – 5.87)	1.19 (0.23 – 6.10)
Levetiracetam	5	0 (0.0)	*	*	*	*	*	*	*	*	*	*
Oxcarbazepine	2	0 (0.0)	*	*	*	*	*	*	*	*	*	*
Phenobarbital	21	3 (14.3)	3.26 (0.96 – 11.05)	2.19 (0.52 – 9.28)	2.17 (0.51 – 9.19)	1.85 (0.43 – 7.93)	2.13 (0.50 – 9.07)	2.16 (0.51 – 9.17)	2.19 (0.52 – 9.28)	2.18 (0.51 – 9.24)	2.19 (0.52 – 9.28)	2.06 (0.48 – 8.76)
Phenytoin	72	8 (11.1)	2.44 (1.17 - 5.09)	1.64 (0.57 - 4.76)	1.63 (0.56 – 4.72)	1.55 (0.53 – 4.50)	1.65 (0.57 – 4.79(	1.64 (0.57 – 4.75)	1.64 (0.57 – 4.76)	1.64 (0.57 – 4.76)	1.60 (0.55 – 4.65)	1.54 (0.53 – 4.46)
Topiramate	146	5 (3.4)	0.69 (0.28 - 1.69)	0.47 (0.14 - 1.51)	0.47 (0.14 – 1.51)	0.45 (0.14 – 1.45)	0.45 (0.14 – 1.47)	0.47 (0.14 – 1.51)	0.47 (0.14 – 1.51)	0.47 (0.14 – 1.51)	0.47 (0.14 – 1.51)	0.43 (0.13 – 1.40)
Valproic	254	19 (7.5)	1.58 (0.99 -0.52)	1.06 (0.43 - 2.61)	1.05 (0.43 – 2.60)	1.01 (1.07 – 2.12)	1.02 (0.41 – 2.50)	1.07 (0.44 – 2.63)	1.06 (0.43 – 2.61)	1.06 (0.43 – 2.61)	1.02 (0.42 – 2.52)	1.03 (0.42 – 2.53)

* - unestimatable, [a] – adjusted for parity, [b] – adjusted for current smoking, [c] – adjusted for mental health, [d] - adjusted for all hypertension, [e] – adjusted for all diabetes, [f] – adjusted for proteinuria, [g] – adjusted for prior history of malformations; [h] – adjusted for prematurity

Appendix B – Drugs and SGA outcomes

			Compared to unexposed	Compared to lamotrigine								
	Women (n)	SGA Outcomes (n (%))	Unadjusted OR (95th CI)	Unadjusted OR (95th CI)	Adjusted OR[a] (95th CI)	Adjusted OR[b] (95th CI)	Adjusted OR[c] (95th CI)	Adjusted OR[d] (95th CI)	Adjusted OR[e] (95th CI)	Adjusted OR[f] (95th CI)	Adjusted OR[g] (95th CI)	Adjusted OR[h] (95th CI)
Unexposed	435,155	29,661 (6.8)	1.0	-								
Exposed	2053	166 (8.1)	1.20 (1.03 - 1.41)	2.09 (0.76 – 5.75)								
Lamotrigine	99	4 (4.0)	0.57 (0.21 - 1.57)	1.0	1.0	1.0	1.0	1.0	1.0	1.0		1.0
Carbamazepine	334	24 (7.2)	1.02 (0.68 - 1.55)	1.84 (0.62 – 5.43)	1.97 (0.67 – 5.84)	1.84 (0.62 – 5.45)	1.89 (0.64 – 5.59)	1.83 (0.59 – 5.67)	1.83 (0.62 – 5.39)	1.85 (0.63 – 5.47)	1.85 (0.63 – 5.47)	1.84 (0.62 – 5.43)
Clobazam	8	1 (12.5)	*	*	*	*	*	*	*	*	*	*
Clonazepam	860	68 (7.9)	1.17 (0.92 - 1.50)	2.04 (0.73 - 5.72)	2.18 (o.78 – 6.11)	1.88 (0.67 – 5.27)	2.00 (0.71 – 5.61)	2.06 (0.73 – 5.76)	2.02 (0.72 – 5.66)	2.07 (0.74 – 5.82)	2.06 (0.74 – 5.77)	2.08 (0.74 – 5.85)
Gabapentin	234	27 (11.5)	2.56 (1.71 – 3.82)	3.10 (1.05 – 9.10)	3.29 (1.17 – 9.67)	2.86 (0.97 – 8.42)	3.11 (1.05 – 9.14)	3.09 (1.05 – 9.07)	3.05 (1.04 – 8.96)	3.14 (1.07 – 9.24)	3.11 (1.06 – 9.15)	3.16 (1.07 – 9.28)
Pregabalin	25	4 (16.0)	3.72 (1.28 – 10.83)	4.52 (1.05 19.56)	4.78 (1.10 – 20.72)	4.88 (1.12 – 21.19)	4.63 (1.07 – 20.02)	4.47 (1.03 – 19.36)	4.52 (1.05 – 19.56)	4.70 (1.09 – 20.35)	4.52 (1.05 – 19.56)	4.46 (1.03 – 19.3)
Levetiracetam	5	0 (0)	*	*	*	*	*	*	*	*	*	*
Oxcarbazepine	2	0 (0)	*	*	*	*	*	*	*	*	*	*
Phenobarbital	21	2 (9.5)	2.06 (0.48 – 8.83)	2.50 (0.43–14.64)	2.70 (0.46 – 15.88)	1.93 (0.33 – 11.41)	2.46 (0.42 – 14.43)	2.45 (0.42 – 14.38)	2.50 (0.43 – 14.64)	2.60 (0.44 – 15.22)	2.50 (0.43 – 14.64)	2.57 (0.44 - 15.10)
Phenytoin	72	7 (9.7)	1.47 (0.67 - 3.21)	2.56 (0.72 – 9.1)	2.75 (0.77 – 9.80)	2.34 (0.66 – 8.35)	2.56 (0.72 – 9.11)	2.55 (0.72 – 9.08)	2.56 (0.72 – 9.09)	2.57 (0.72 – 9.16)	2.60 (0.73 – 9.24)	2.64 (0.74 – 9.38)
Topiramate	146	9 (6.1)	0.90 (0.46 - 1.76)	1.56 (0.47 - 5.21)	1.59 (0.48 – 5.	1.46 (0.44 – 4.89)	1.54 (0.46 – 5.14)	1.56 (0.47 – 5.22)	1.54 (0.46 – 5.13)	1.57 (0.47 – 5.24)	1.56 (0.47 – 5.21)	1.61 (0.48 – 5.40)
Valproic	254	20 (7.9)	1.17 (2.74-- 1.84)	2.03 (1.68 - 6.10)	2.14 (0.71 – 6.44)	1.87 (0.62 – 5.63)	1.99 (0.66 – 5.98)	2.05 (0.68 – 6.16)	2.02 (0.67 – 6.08)	2.05 (0.68 – 6.16)	2.07 (0.69 – 6.23)	2.06 (0.69 – 6.19)

*- unestimatable, [a] – adjusted for parity, [b] – adjusted for current smoking, [c] – adjusted for mental health, [d] - adjusted for all hypertension, [e] – adjusted for all diabetes, [f] – adjusted for proteinuria, [g] – adjusted for prior history of malformations; [h] – adjusted for prematurity

Appendix C – Select maternal characteristics and pregnancy complications in women delivering by Cesarean section and coded as "other" for delivery indication

Delivery Indication					
		Epilepsy			**No epilepsy**
		n	**(%)**	**n**	**(%)**
Cesarean section "Other"		**53**	**(31.6)**	**8**	**(7.6)**
	Nullip	41	(77.4)	6	(75.0)
	Past/Current Smoker	10	(18.9)	0	(0)
	BMI <30	48	(90.6)	6	(75.0)
	Mother age >30	29	(54.7)	<5	(<62.5%)
	Hypertensive disorders	8	(15.1)	<5	(<62.5%)
	Diabetes	8	(15.1)	0	(0)
	Proteinuria (>+1)	8	(15.1)	0	(0)
	IUGR	7	(13.2)	0	(0)
	Post dates	5	(9.4)	0	(0)

*- $P < 0.05$