Use of Antiseizure Medications During Pregnancy and Adverse Neonatal outcomes

by

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Thesis Abstract

Background: Epilepsy during pregnancy can lead to various adverse health outcomes in both pregnant people and infants. Furthermore, in-utero exposure to antiseizure medications (ASMs), employed in the management of epilepsy, is also associated with an increased risk of adverse birth outcomes. With the exponential increase in the use of ASMs over the last few decades, it is crucial to understand the safety of in-utero exposure to ASMs. In this thesis we aimed to evaluate the safety of ASMs in all pregnant people, pregnant people with epilepsy (PPWE) and pregnant people without epilepsy (PPWOE), using both evidence synthesis methods and real-world data.

Methods: First, we conducted a systematic review and meta-analysis to evaluate the risk of adverse birth weight outcomes due to in-utero exposure to ASMs in the published literature from inception to March 23rd, 2022. (Chapter 2: Protocol & Chapter 3: Report). Second, we conducted two population-based cohort studies utilizing the administrative databases in Manitoba to study the safety of in-utero exposure to ASMs and gabapentin in pregnancy. We included all pregnant people in Manitoba between 1998-2021. In study 1 (Chapter 4: ASMs) we evaluated the ASMs safety and in study 2 (Chapter 5: gabapentin) we evaluated gabapentin safety among all pregnant people, PPWE and PPWOE.

Results: In the systematic review, we found a significant association between in-utero exposure to all ASMs in pregnant people and small for gestational age (SGA), with relative risk (RR) 1.33 (95% CI 1.18 to 1.50, I^2 74%), low birth weight (LBW) RR 1.54 (95% CI 1.33 to 1.77, I^2 67%), and decreased birth weight with a mean difference (MD) of -118.87 (95% CI -161.03 to -76.71, I^2

42%) g compared to unexposed pregnant people. We found similar results among PPWE when compared to unexposed pregnant people, but they did not reach statistical significance. In our cohort study, among all pregnant people exposed to ASMs we found a significant increased risk of SGA (adjusted odds ratio [aOR] 1.16, 95% CI 1.04-1.30), LBW (aOR 1.66, 95% CI 1.47-1.88), preterm birth (aOR 1.56, 95% CI 1.41-1.73), neonatal intensive care unit (NICU) admissions (aOR 1.91, 95% CI 1.74-2.10), and length of hospital stay (LOS) infant (aOR 1.68, 95% CI 1.56-1.82) when compared with unexposed pregnant people. We found similar results among PPWOE when compared with unexposed PPWOE. For gabapentin exposure, among all pregnant people we found a significant increased risk of LBW (aOR 1.95, 95% CI 1.58-2.41), preterm birth (aOR 1.68, 95% CI 1.39-2.03), NICU admissions (aOR 2.04, 95% CI 1.71-2.42), pregnant peoples LOS (aOR 1.33, 95% CI 1.15-1.54), infant LOS (aOR 2.09, 95% CI 1.81-2.41) compared to unexposed pregnant people. We found similar results among exposed PPWOE when compared with unexposed PPWOE.

Conclusions: Both the choice of ASM use and the underlying condition (epilepsy) contribute to an elevated adverse risk during pregnancy. With the increased risk of adverse neonatal outcomes associated with in-utero exposure to ASMs, including gabapentin, clinicians should carefully assess the risk-benefit ratio before prescribing these medications. Moreover, the use of gabapentin requires caution among pregnant people.

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Dedication

To my cherished sister Sharanya Lavu, my foremost confidante in this world

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Abbreviations

1.	ASM: Antiseizure Medication
2.	ADME: Absorption, Distribution, Metabolism, and Excretion
3.	AED: Anti-epileptic drug
4.	aOR: Adjusted Odds Ratio
5.	aRR: Adjusted Risk Ratio
6.	ATC: Anatomical Therapeutic Chemical
7.	BW: Birth Weight
8.	CAN-EMIG: The Canadian Epilepsy and Mother-Infant health Group
9.	CBZ: Carbamazepine
10.	CI: Confidence Interval
11.	CINAHL: Cumulative Index of Nursing and Allied Health Literature
12.	Cm: Centimeters
13.	CVD: Cardiovascular Diseases
14.	DAG: Directed Acyclic Graphs
15.	EEG: Electroencephalogram
16.	FGR: Fetal Growth Restriction
17.	GA: Gestational Age
18.	GEE: Generalized Estimating Equations
19.	HBW: High Birth Weight
20.	HC: Head Circumference
21.	HDPS: High Dimensional Propensity Scores
22.	ILAE: International League Against Epilepsy
23.	IPA: International Pharmaceutical Abstracts
24.	IUGR: Intrauterine Growth Restriction
25.	IVH: Intraventricular Hemorrhage
26.	LBW: Low Birth Weight
27.	LGA: Large for Gestational Age

28.	LGT: Lamotrigine
29.	LOS: Length of hospital stay
30.	MCHP: Manitoba Centre for Health Policy
31.	MD: Mean Difference
32.	Mesh: Subject Headings
33.	MOA: Mechanism of Action
34.	NEAD: Neurodevelopmental Effects of Anti-epileptic Drugs
35.	NICU: Neonatal Intensive Care Unit
36.	NRDS: Neonatal Respiratory Distress Syndrome
37.	OR: Odds Ratios
38.	PHIN: Personal Health Identification Numbers
39.	PHT: Phenytoin
40.	PPWE: Pregnant People with Epilepsy
41.	PPWOE: Pregnant People without Epilepsy
42.	PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
43.	PVL: Periventricular Leukomalacia
44.	RLS: Restless Leg Syndrome
45.	Rob 2: The Cochrane Risk-Of-Bias Tool for Randomized Trials
46.	RR: Risk Ration
47.	SD: Standard Deviation
48.	SE: Standard Error
49.	SES: Socio Economic Status
50.	SGA: Small for Gestational Age
51.	STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
52.	SUDEP: Sudden Unexpected Death in Epilepsy
53.	VPA: Valproic Acid
54.	WWE: Women with Epilepsy
55.	WWOE: Women Without Epilepsy

Preface

This thesis is formatted as a sandwich thesis. Chapters 2, 3, 4, 5, are connected by an overview at the beginning of each chapter to connect each manuscript to overall thesis objectives. Each chapter presents original research that has been published or prepared for publication in peer-reviewed journals. All studies were conceptualized and executed by Alekhya Lavu, with contributions from her thesis advisors and advisory committee: Dr. Sherif Eltonsy (primary advisor), Dr. Silvia Alessi-Severini (co-advisor), Dr. Jamison Falk (committee member), and Dr. Chelsea Ruth (committee member). Alekhya Lavu is the guarantor and fully responsible for the integrity of the manuscripts, accuracy of analysis and interpretation. All co-authors contributed to study conceptualization, review, and interpretation of results. All manuscripts have been revised according to feedback from all co-authors, and final approval from co-authors was obtained prior to publication.

The thesis includes seven chapters: An Introductory chapter, four manuscripts which are published or prepared for publication in peer-reviewed journals, additional results chapter and a concluding chapter. The manuscripts generated from this thesis are:

- **Chapter 2:** Alekhya Lavu, Christine Vaccaro, Walid Shouman, Silvia Alessi Severini & Sherif Eltonsy. Anti-epileptic drug exposure during pregnancy and neonatal birth weight outcomes: protocol for a systematic review and meta-analysis. **Status:** Published in Syst Rev 10, 159 (2021). https://doi.org/10.1186/s13643-021-01711-8
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- **Chapter 4:** Antiseizure Medication Use During Pregnancy and Adverse Neonatal Birth Outcomes: Population-Based Cohort Study.
- **Chapter 5:** Gabapentin Use During Pregnancy and Adverse Neonatal Birth Outcomes: A Population-Based Cohort Study.

Chapter 1: Introduction, Rationale and Literature Review

1.1. Disease History

Epilepsy is a neurological disorder characterized by a disturbance of electric activity in the brain.[1] In medieval times, seizures due to epilepsy were either associated with magic, gods, or demons.[2] Hippocrates was the first scientist to provide a detailed scientific address regarding epilepsy.[3] Hippocrates said, "*This disease is, in my opinion no more divine than any other; it has the same nature as other diseases, and the cause that gives rise to individual diseases.*[3] *It is also curable, no less than other illnesses, unless by long lapse of time it be so ingrained as to be more powerful than the remedies that are applied.*"[3] With the dominance of mythical beliefs during medieval times, patients with epilepsy were considered witches or possessed.[4] The beliefs turned to scientific reasoning during the Renaissance period (14th-17th century).[4] John Hughlings Jackson, considered the father of modern neurology was the first scientist to believe that seizures were due to the brain's chemical changes.[5,6] Bromide was the first medication used to treat seizures it was discovered spontaneously by Sir Charles Locock in 1857.[7]

When Sir. Locock came across a report in the British and Foreign Medical Review suggesting that potassium bromide might lead to reversible impotence in males, it piqued his interest in investigating the potential therapeutic effects of this medication.[7] He hypothesized that bromide could be effective in treating seizures believed to be caused by hypersexual urges, as well as seizures experienced by females during menstrual cycle, which later became known as catamenial epilepsy resulting from hormonal fluctuations.[7] This fortuitous discovery positioned bromide as the first antiseizure medication (ASM) to be utilized, maintaining its use until 1912

when it was replaced by phenobarbital.[7–9] Since then multiple medications have been introduced to treat epilepsy.

1.2. Epilepsy definition and classification

According to International League Against Epilepsy (ILAE), epilepsy is defined by any of the following conditions *"At least two unprovoked (or reflex) seizures occurring >24 h apart or one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years or diagnosis of an epilepsy syndrome."*[10]

In general, a seizure can occur due to excessive cortical neuron discharge leading to changes in electrical activity measured by electroencephalogram (EEG).[11] Epilepsy can be caused by various medical conditions, genetics or injury.[12] Epilepsy etiology can be classified into 6 categories including genetic (e.g., childhood-onset epilepsy), structural (e.g., stroke or traumatic brain injury), infectious (e.g., neurocysticercosis), metabolic (e.g., lafora disease), and unknown.[12] Epilepsy can be classified according to different seizure types, which may vary in severity, appearance, cause, and management.[13]

Focal seizures: previously known as partial seizures originate from one brain hemisphere.[11,14,15] In focal seizures, patients retain awareness of the environment and themselves, including external stimuli.[11,14] Focal seizures can further be subclassified into having motor symptoms (clonic, myoclonic and automatisms symptoms), non-motor symptoms (autonomic and

sensory), complex symptoms (a mixture of motor and non-motor symptoms) and secondary generalized seizures (starts as focal but progresses to bilateral seizures).[11,14] (**Table 1.1**. **Seizure Generalized onset seizures** originate bilaterally and are symmetrical without local onset which include absence, tonic, clonic, tonic-clonic and myoclonic seizures.[11,14] Absence seizure is a non-motor seizure characterized by absent stare.[11,14] Tonic seizures are characterized by stiffening muscles, and clonic seizures are characterized by jerking or twitching.[11] Tonic-clonic seizures, also known as the "grand mal" seizures, are those during which the patients lose consciousness, followed by muscle stiffness and brief periods of rigidity and clonic movements.[11,14] Myoclonic seizures occur with brief, jerking spasms of a muscle or muscle group.[11,14] Status epilepticus is defined as a seizure lasting more than 5 minutes with continuous electrographic and/or clinical seizures or subsequent seizures without any recovery time.[11,16] Seizures with symptoms that cannot be classified are considered **unclassified seizures**.[11] (**Table 1.1**. **Seizure Classification**)

Classification)

Table 1.1. Seizure Classification

	Types of seizures
1	Partial/focal seizures (seizures originate locally)
A	Simple 1. With motor symptoms 2. With special sensory or somatosensory symptoms 3. With psychological symptoms
B	Complex 1. Simple partial-onset followed by impairment of consciousness—with or without automatisms 2. Impaired consciousness at the onset—with or without automatisms
C	Secondarily generalized

2	Generalized onset seizures A. Absence B. Myoclonic C. Clonic D. Tonic E. Tonic-clonic including status epilepticus F. Atonic G. Infantile spasms
3	Unclassified seizures
Adapted from Dipiro Pharmacotherapy Handbook, chapter 74; 2023.[12,48]	

1.3. Epidemiology

1.3.1. Epilepsy in general population

Globally epilepsy is the fourth most common neurological disease preceded by stroke, migraine, and Alzheimer's disease.[11] Almost 50 million people worldwide are affected by epilepsy.[17] In 2013-2014 approximately 300,000 Canadians were living with epilepsy.[18] Health Canada recently reported that the prevalence of epilepsy in Canada is around 0.27% in 2021 and is projected to be around 0.24% by 2031.[18,19]

Epilepsy imposes a significant economic burden on both the patients and health care institutions.[20] A systematic review and meta-analysis by Thompson et al reported that in 2019 direct healthcare costs per person due to epilepsy was $10,659 USD in Canada.[20] The average annual costs per person with epilepsy range between $204 USD to $11,432 USD for low and high income countries respectively.[20] The estimated cost of epilepsy globally based on the average costs per person is around 113.27 billion USD per year.[20] In addition to the economic burden, people with epilepsy and their families face psychological, physical and social consequences which prove to be a significant issue.[17,21,22]

1.3.2. Epilepsy in pregnant people

The prevalence of epilepsy has been estimated at 0.3–1% among pregnant people.[23] Approximately 3700 pregnant people in Canada suffer from epilepsy every year.[23] Epilepsy is often associated with major clinical challenges during pregnancy.[24] Obstetric complications such as premature delivery, preeclampsia, gestational hypertension, induced labour, cesarean delivery, and postpartum hemorrhage are more frequent among pregnant people with epilepsy (PPWE) than pregnant people without epilepsy (PPWOE).[25–31] Additionally, PPWE are susceptible to a tenfold increase in mortality risk compared to PPWOE.[32]

1.4. Physiological changes and beliefs among pregnant people

During pregnancy changes in sex hormonal (progesterone and estrogen) levels are observed.[33] Estrogen is associated with an increase in seizures, whereas progesterone has been associated with an antiseizure effect.[33] Therefore, sex hormone changes during pregnancy can affect seizure threshold.[34] Approximately 25-30% of pregnant people experience increased seizures during pregnancy.[35]

Epidemiological evidence suggests that PPWE have fewer infants than PPWOE.[36] Some reasons contributing to lower infant numbers in PPWE include a) **Pregnant peoples decision** to not have offspring due to rational or irrational beliefs about pregnancy complications and passing down epilepsy to the infant through genetics.[37,38] b) **Hormone imbalance:** compared to healthy people, epileptic people of childbearing age are prone to a higher risk of menstrual disorders (e.g., polycystic ovarian syndrome) due to hormonal dysfunction.[39] The reason behind this imbalance is not fully understood.[39] However, it has been related to central neuronal network

disturbance due to seizures that affect hormonal function resulting in decreased fertility among epileptic patients of childbearing age.[39] c) **Antiseizure medications (ASM)**: ASMs have been reported to interfere with the endocrine system, affecting the hormonal balance resulting in a higher risk of infertility among PPWE.[33] d) **Premature menopause:** PPWE who experience high seizure frequency have higher chances of premature menopause, therefore making it difficult to get pregnant at older ages.[33,39–41]

Effect of seizures on pregnant people

Seizures themselves are associated with various adverse birth outcomes such as malformations, and preterm birth, impacting the health of pregnant people and infants.[42] (**Table 1.2.** Immediate seizure-related complications in pregnancy). A meta-analysis by Viale et al reported an significant increase in the risk of preterm birth (OR 1.16 (95% CI 1.01-1.34) and fetal growth restriction (OR 1.26 (95% CI 1.20-1.33), and an non-significant increase in the risk of NICU admissions (OR 2.06 (95% CI 0.97-4.37) and perinatal death (OR 1.83 (95% CI 0.79-4.25) in PPWE compared with PPWOE.[43] Therefore it is essential to prevent seizures during pregnancy to avoid complications.[44]

Table 1.2. Immediate impact of seizures on pregnant people and infant

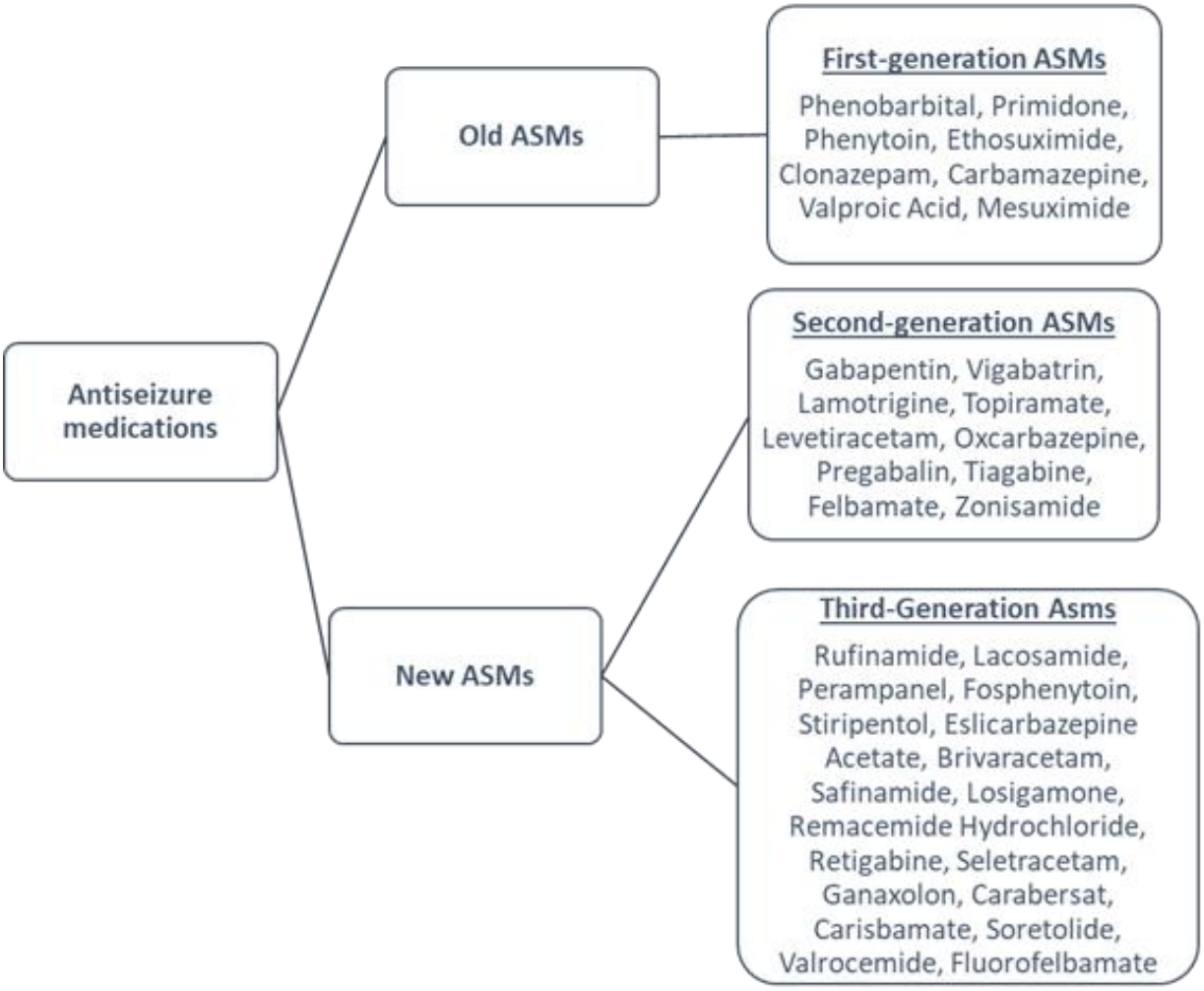
Epilepsy and seizure type	Effect on pregnant people and infant
Tonic-clonic seizures	• Sudden loss of consciousness can lead to injury. • Fetal hypoxia. • Sudden unexpected death in epilepsy (SUDEP).[45]
Absence seizures	• Brief loss of awareness leads to trauma in pregnant people and infants. • Worsening absence seizure leads to a tonic-clonic seizure.
Juvenile myoclonic seizures	• Sudden jerks lead to trauma in pregnant people and infant.
Focal seizures	• Sudden loss of consciousness leads to trauma in pregnant people and infants. • Fetal hypoxia • SUDEP
Adapted and modified from the first edition of epilepsy in pregnancy (green-top guidelines) published by the Royal College of Obstetricians and Gynecologists.[42]	

1.5. Treatment

1.5.1. Antiseizure medication classification

Bromide is the first known antiseizure medication, used in 1857.[7] In 1912, phenobarbital's antiepileptic properties were found serendipitously.[46] ASMs can be broadly classified into two classes, 1) old-generation ASMs which include first-generation ASMs and 2) new-generation ASMs which include the second-generation and third-generation ASMs.[46] First-generation ASMs include medications used till the 1970s, including phenobarbital, primidone, phenytoin, ethosuximide, clonazepam, carbamazepine, valproic acid, and mesuximide.[46]

Figure 1.1: **ASM drugs classification based on generation.**



Second-generation ASMs were introduced around the 1990s which include gabapentin, vigabatrin, lamotrigine, topiramate, levetiracetam, oxcarbazepine, pregabalin, tiagabine, felbamate, zonisamide.[46] Third-generation ASMs include newer ASMs such as rufinamide, lacosamide, perampanel, fosphenytoin, stiripentol, eslicarbazepine acetate, brivaracetam, safinamide, losigamone, remacemide hydrochloride, retigabine, seletracetam, ganaxolon, carabersat, carisbamate, , valrocemide, fluorofelbamate.[46] (**Figure 1.1.** ASMs classification based on generation).

1.5.2. Antiseizure medication mechanism of action

General MOA of ASMs

The exact mechanisms of action (MOA) of ASMs have not yet been established with most ASMs having multiple MOAs (**Table 1.3.**).[47] Some of the notable MOAs include modification of sodium and calcium ion channel kinetics, modulation of excitatory neurotransmission by antagonizing or decreasing aspartate and glutamate and increasing central nervous system GABA by the augmentation of inhibitory neurotransmission.[11,48]

Table 1.3. Antiseizure medication MOA Classification

Mechanism of Action	First Generation	Second Generation	Third Generation
Na channel	Carbamazepine [48,49] Phenytoin[48,49] Valproic acid[48,49]	Felbamate[48,49] Lamotrigine[48,49] Oxcarbazepine[48,49] Topiramate[48,49] Zonisamide[48,49]	Brivaracetam [50,51] Eslicarbazepine a[52] Fluorofelbamat[50] Fosphenytoin[50,52] Lacosamide[49,50] Remacemide hydrochloride[50] Rufinamide[48,49,51] Safinamide[52]
Ca channel	Phenobarbital[49] Phenyotin[49] Valproic acid[48,49]	Ethosuximide[48,49] Gabapentin[48,49] Lamotrigine[48,49] Oxcarbazepine[49] Topiramate[48,49] Zonisamide[48]	Pregabalin[48–50,52] Safinamide[50,52] Selectracetam[50]
GABA enhancers	Barbiturates[48] Benzodiazepines[48,49] Carbamazepine[49] Phenobarbital[49] Valproic acid[48,49]	Felbamate[48] Gabapentin[49] Tiagabine[49] Topiramate[48,49] Vigabatrin[48,49]	Ganaxolon[50,52] Pregabalin[49] Retigabine[48,52] Stiripentol[48,50–52]
Glutamate antagonists	Carbamazepine[49] Phenobarbital[49]	Felbamate[49] Oxcarbazepine[49] Topiramate[49]	
Carbonic anhydrase inhibitors		Topiramate[49] Zonisamide[49]	
Potassium channel blockade		Oxcarbazepine[48] Topiramate[48]	
Potassium channel activation			Retigabine[48,50,52]
NMDA receptor blockade		Felbamate[48]	Fluorofelbamat[50] Lacosamide[50]
AMPA receptor blockade		Topiramate[48]	Perampanel[50,51]
Na channel blockade (slow inactivation)			Lacosamide[48,51,52]

1.5.3. Treatment guidelines

The focus of epilepsy treatment is to control seizures while being attentive to various comorbidities and adverse effects of ASMs.[11]

Treatment guidelines in general population

The first step of treatment is to diagnose the seizure type and frequency.[11] Then ASM is chosen based on seizure type, classification, comorbidities, and side effects.[11] Monotherapy is the first choice of therapy.[11] If the seizures are controlled and the patient remains seizure free for 2 years, stooping ASM treatment should be considered.[11] If the seizures are not controlled with one ASMs, adjustments are made either by increasing the dose or polytherapy until seizure control is achieved.[11] (**Figure 1.2**)

Treatment guidelines in pregnancy

Epilepsy treatment in pregnant people is complicated due to several aspects. Treating seizures with ASMs can result in various adverse outcomes in infants.[27–31] In-utero exposure to topiramate is associated with oral cleft, phenobarbital exposure is associated with cardiac malformation, and valproic acid (valproate) is associated with spina bifida, hypospadias, autism spectrum disorder, lower IQ and adverse birth weight outcomes.[49,50] There is scarce evidence on the fetal safety of oxcarbazepine, gabapentin, and zonisamide. In pregnancy, lamotrigine, carbamazepine, and levetiracetam are associated with the least perinatal risk.[49,50]

Meanwhile, seizures during pregnancy are associated with adverse outcomes in both pregnant people and infants, resulting in adverse health outcomes, trauma, or death.[51] Therefore, treating seizures even with the possibility of adverse outcomes is necessary.[51]

Treating seizures with ASMs with the best seizure control and the least risk of adverse outcomes is the best choice during pregnancy.[51]

1.5.4. Treatment strategies according to clinical practice and guidelines around the world

Almost 30% of pregnancies in Canada are unplanned, and some ASMs reduce the efficacy of some contraceptives.[52–54] Therefore pre-pregnancy counselling for all people of childbearing age is recommended.[54,55] Counseling regarding seizure control, duration, and remission must be given in addition to medication use.[54,55] For planned pregnancies, if on valproate, it must be discontinued before conception.[50,56] Moreover, with an indication for the specific seizure type, the lowest dose of the lowest-risk ASM must be the first line of treatment.[50,57] When the first line of treatment does not control the seizures, an alternate high-dose, low-risk ASM or a combination of two low-risk ASMs should be considered.[58] Overall, valproic acid and polytherapy are considered high-risk worldwide.[49,50,59–62] Topiramate, gabapentin, zonisamide, phenytoin, and carbamazepine are considered to be of probable risk.[49,50,63] Lamotrigine and levetiracetam are considered to have a better safety profile.[14,49,50,59–62] New-generation ASMs risk in pregnant people is not yet established.[14,49,50,59–62] (**Table 1.4.** Pharmacological treatment recommendations according to guidelines worldwide)

Table 1.4. Pharmacological treatment recommendations in pregnancy according to different guidelines.

Country	**High established risk**	**Probable risk**	**Lowest risk**	**Unknown risk**	**Supplemental Rx**
Canada[49]	• Topiramate • Phenobarbital • Valproic acid	• Oxcarbazepine • Gabapentin • Zonisamide	• Lamotrigine • Carbamazepine • Phenytoin • Levetiracetam		• Folic Acid
Canada[50]	• Valproate and Valproic Acid • Polytherapy	• Topiramate	• Lamotrigine • Levetiracetam		• Folic Acid • Vitamin K
Australia[63]	• Sodium valproate • Polypharmacy	• Topiramate • Carbamazepine • Phenytoin	• Phenobarbital • Primidone • Lamotrigine	• Gabapentin • Levetiracetam • Vigabatrin	• Folic acid • Vitamin K
India[59]	• Polytherapy (*Valproate* + lamotrigine) • Valproate		• Monotherapy • Lamotrigine		
UK[42]	• Sodium valproate • Polytherapy		• Lowest effective dose of ASM • Carbamazepine • Lamotrigine	• Levetiracetam • Phenytoin	• Folic acid • Vitamin K
UK[60]	• Valproate • Polytherapy		• The lowest effective dose of ASM • Monotherapy		• Folic acid • Vitamin K
USA[64]	• Valproic acid • Polytherapy	• Phenytoin • Carbamazepine • Phenobarbital	• Primidone	• Lamotrigine • New-generation ASM	
Rx: Prescription, UK: United Kingdom, USA: United States of America.					

1.5.5. Physiological changes during pregnancy and effects on ASMs

During pregnancy, there are physiological changes in the absorption, distribution, metabolism, and excretion (ADME) of ASMs.[61] These changes may affect the frequencies of seizures and concentration of ASM exposure in-utero.[61] In early pregnancy malaise and vomiting can lead to impaired absorption of ASMs.[65] Also during pregnancy, there is an increase in blood volume , water retention and fat storage which leads to an increase in the volume of ASMs distribution resulting in a decrease in serum concentration of ASMs.[65] These changes vary among different ASMs.[65]

There are also changes in metabolism during pregnancy.[66,67] Due to enzyme induction, a decrease in the serum concentration of the drug is observed, but this shows high variability among individuals.[56,68,69] An increase in renal blood flow and glomerulus filtration is observed in pregnancy in the first and second trimester which decreases in the third trimester.[66,67] These changes affect the serum concentration of drugs in pregnancy, particularly for those whose main route of elimination is renal such as gabapentin, levetiracetam, pregabalin, and vigabatrin.[66]

1.6. Antiseizure medications utilization

1.6.1. ASMs utilization in the general population

The number of ASMs has increased substantially in the last thirty years.[27] In Manitoba, Leong et al. reported a decrease in the use of old-generation ASMs and an increase in new-generation ASMs among people with epilepsy between 1998 to 2013.[70] Among non-epilepsy prescriptions,

there was a drastic increase in the use of new-generation ASMs with a moderate decrease in old-generation ASMs.[70] Carbamazepine is the most used medication among people with epilepsy, followed by valproic acid, lamotrigine, topiramate and gabapentin.[70] Among people without epilepsy, there has been a drastic increase in the use of gabapentin compared with other medications.[70] Similar trends have been observed among different populations around the world.[44,71,72]

1.6.2. ASMs utilization in pregnancy

In Manitoba, Shouman et al. reported an increase in the use of new-generation ASMs and a decrease in old-generation ASMs among pregnant people between 1997 and 2019.[73] Among PPWE, carbamazepine, lamotrigine, levetiracetam, gabapentin, and phenytoin are the most used medications.[73] Whereas clonazepam, gabapentin, topiramate, and lamotrigine are the most used ASMs among PPWOE.[73] A drastic increase in the use of gabapentin was observed among PPWOE.[73]

1.6.3. Impact of COVID-19 on prescription medication utilization

The COVID-19 pandemic has impacted the lives of patients with chronic diseases.[74,75] Physician activity in Canada decreased by approximately 30-40% in April 2020 compared to 2019, and more than 25% of Canadians reported that an appointment for healthcare services was cancelled, rescheduled, or delayed.[76] The preventive measures to contain COVID-19 have affected the living conditions of chronic disease patients resulting in reduced physical activity, changes in diet, change in medical care, and availability of supplies.[77,78] Lavu et al. reported

small but significant changes in the incident and prevalent use of ASM prescriptions in Manitoba with the introduction of public health measures during COVID-19.[79]

1.7. Safety of ASMs in pregnancy

1.7.1. Mechanism for adverse effects of ASMs

Currently, a large body of evidence shows that infants exposed to ASMs in-utero have an increased risk of malformations.[30,80,81] The theorized mechanisms behind ASM teratogenicity include folate deficiency, hypoxia, reoxygenation, apoptosis, genetic susceptibility, or reactive intermediates.[82–84] Fetal growth restriction, which includes adverse growth outcomes, has been related mostly to folate deficiency as it plays a major role in fetal metabolism during development.[83,84] In one study, increased fetal weight and length in mice pups were observed when ASMs were co-administered with folic acid.[83] More recently, it has been hypothesized that several ASMs including trimethadione, carbamazepine, and phenytoin can lead to embryonic cardiac arrhythmia during the developmental period.[82,84] Cardiac arrhythmia results in embryonic hypoxia followed by reoxygenation and generation of reactive oxygen species, which can lead to tissue damage.[82] Altered expression of placental heterodimeric transporters due to ASMs has also been linked to delays in fetal development.[85] Further studies are needed to determine the mechanism by which ASMs can lead to growth restriction.[86]

1.7.2. Effect of adverse outcomes on short- and long-term neonatal health

Exposure to ASMs in-utero is associated with an increased risk of adverse perinatal and neurodevelopmental outcomes, including major congenital malformations, intrauterine growth

restrictions and various birth weight outcomes.[27–31] Adverse birth outcomes including small for gestational age (SGA), Low birth weight (LBW), preterm birth and neonatal intensive care unit (NICU) admissions substantially impact short- and long-term health outcomes in infants.[87–89] SGA is associated with short-term outcomes which include stillbirth, impaired thermoregulation and hypoglycemia and long-term outcomes which include impaired neurodevelopment, cardiovascular diseases and diabetes in adulthood.[90] Neonatal resuscitation was associated with increased short-term complications including hypoxic-ischemic encephalopathy.[91]

1.8. Literature review on ASMs safety in pregnancy

Kulaga et al. conducted a cohort study using the Quebec Pregnancy Registry.[92] This is the only available study in Canada examining the safety of ASMs in pregnancy.[92] They included 349 pregnant people with epilepsy between 1998 to 2003.[92] SGA was reported in 20 (18%) PPWE on ASM monotherapy and 5 (11.9%) PPWE on polytherapy, whereas 1 (5.3%) non-ASM exposed pregnant person had SGA infant.[92] Conversely, LBW was more frequent among non-exposed pregnant people (11 (10.5%)) than compared to exposed pregnant people (3 (7.8%)).[92] Preterm birth was reported in 11 (10%) PPWE on monotherapy, 4 (9.5%) PPWE in polytherapy and 3 (15.8%) unexposed pregnant people.[92]

Kilic et al. conducted a cohort study using the Danish Medical Birth Registry between 1997 and 2008, to study 2928 infants who have been exposed to ASMs during pregnancy.[30] The study reported a significantly increased risk of SGA among all exposed pregnant people (adjusted risk ratio (aRR) 1.21 (95% CI 1.10-1.34)) compared to unexposed pregnant people, and PPWE (aRR

1.19 (95% CI 1.02–1.37)) compared to unexposed PPWE and PPWOE (aRR 1.21 (95% CI 1.01–1.45)) compared to the unexposed PPWOE.[30] Similar increase LBW risk was observed among all exposed pregnant people (aRR 1.40 (95% CI 1.22–1.60)) compared to unexposed pregnant people and exposed PPWE (aRR 1.32 (95% CI 1.06–1.63)) compared to unexposed PPWE and exposed PPWOE (aRR 1.61 (95% CI 1.28–2.02)) compared to unexposed PPWOE.[30] They also observed a significant increased risk of preterm birth among all exposed pregnant people (aRR 1.32 (95% CI 1.16-1.50)) compared to unexposed pregnant people, and exposed PPWOE (aRR 1.56 (95% CI 1.27-1.93)) compared to unexposed PPWOE and no association was observed among exposed PPWE (aRR 1 (95% CI 0.82-1.21)) when compared with unexposed PPWE.[30] The risk of SGA was highest among the topiramate group followed by oxcarbazepine, valproic acid, clonazepam, carbamazepine and lamotrigine.[30] Lamotrigine had a lower risk of adverse outcomes among all ASMs.[30]

In 2009 Veiby et al. studied 2,861 PPWE deliveries using the Medical Birth Registry of Norway between 1999–2005.[23] Exposed PPWE reported an increased risk of preterm births (aOR 1.3 (95% CI 1.1-1.6) and neonatal care unit transfers (aOR 1.7 (95% CI 1.5-2.1)) compared with non-epilepsy births.[23] PPWE on polytherapy reported an increased risk of preterm birth (aOR 2.3 (95% CI 1.5-3.6) and neonatal care unit transfers (aOR 2.6 (95% CI 1.7-3.9)) compared with non-epilepsy births.[23] Exposed PPWE on carbamazepine reported an increased risk of preterm birth (aOR 1.8 (95% CI 1.4-2.4) and neonatal care unit transfers (aOR 2 (95% CI 1.6-2.6)) compared with non-epilepsy births.[23]

Exposed PPWE on valproic acid reported an increased risk of neonatal care unit transfers (aOR 1.8 (95% CI 1.2-2.6)), compared with non-epilepsy births and exposed PPWE on lamotrigine reported an increased risk of neonatal care unit transfers (aOR 1.6 (95% CI 1.2-2.6)) compared with non-epilepsy births.[23]

In 2014, Veiby et al. published a new study using the Medical Birth Registry of Norway between 1999–2011.[93] Veiby et al. reported an increased risk of SGA among all exposed pregnant people (aOR 1.17 (95% CI 1.03-1.33)) and PPWE (aOR 1.19 (95% CI 1.03–1.36)) compared with unexposed pregnant people.[93] Among individual ASMs, SGA risk was highest in topiramate-exposed children followed by carbamazepine, lamotrigine, levetiracetam and valproate.[93]

Razaz et al. conducted a population-based cohort study using the medical birth registry of Sweden from 1997 through 2011.[94] This study included 3586 PPWE and 869,947 PPWOE.[94] Compared to unexposed PPWE, exposed PPWE reported an non-significant increased risk of SGA (aRR 1.25 (95% CI 0.97-1.61)) and neonatal respiratory distress (aRR 1.30 (95% CI 0.90-1.81)).[94]

A cohort study in Thailand by Hsiu-Li Lin et al. studied 2504 PPWE between 2001-2003.[95] Among exposed PPWE and exposed PPWOE respectively the authors reported an increased risk of LBW (aOR 1.13 (95% CI 0.62-2.06 and aOR 1.31 (95% CI 1.02-1.68)), SGA (aOR 1.38 (95% CI 0.94-2.02) and aOR 1.23 (95% CI 1.03-1.46)) and preterm birth (aOR 1.14 (95% CI 0.65-2.00) and 1.35 (95% CI 1.07-1.71)) compared to unexposed healthy pregnant people.[95] Soontornpun et al.

conducted a retrospective cohort study in a tertiary hospital in northern Thailand.[96] The study included 44,708 pregnant people from June 1999 to May 2017; 167 (0.97%) of PPWE were identified as cases.[96] The study showed a higher percentage of SGA and LBW in PPWE compared to PPWOE and the incidence of SGA was significantly higher when epilepsy was active.[96]

Hernandez et al. conducted a prospective study utilizing the North American Antiepileptic Drug Pregnancy Registry between 1997 and 2012. A total of 347 topiramate-, 98 zonisamide-, and 1581 lamotrigine exposed neonates were included in the study.[98] The highest percentage of SGA and LBW prevalence was observed among topiramate users (17.9%, 10.4%) followed by zonisamide (12.2%, 10.2%) and lamotrigine (6.8%, 4.7%).[98] A higher risk of SGA was observed among topiramate (aRR 2.4 (95% CI 2-3.5)) and zonisamide users (aRR 1.6 (95% CI 0.9-2.8)) compared with lamotrigine.[98] The authors found that compared with lamotrigine, exposure to zonisamide and topiramate during pregnancy was associated with a lesser mean of birth weight of 202g and 221g respectively.[98] Lamotrigine exposed pregnant people had similar birth weights compared to the unexposed pregnant people.[98] Preterm birth was reported to be highest among topiramate (10.4%) followed by zonisamide (10.2%) and lamotrigine (7.5%).[98]

A common limitation observed in previously published systematic reviews is using fetal growth restriction (FGR) and intrauterine growth restriction (IUGR) interchangeably with SGA.[99] SGA is a term used to describe newborns who are smaller in size than the usual for their gestational age and is defined as birth weight less than the 10th percentile for the same gestational age.[100] FGR also known as IUGR, implies that fetal growth is being inhibited and that the fetus does not

attain its growth potential.[101] Therefore, it is to say, not all SGA infants have FGR and some larger infants can still be SGA.[101] Therefore, substituting SGA for FGR might potentially affect the results of any systematic review.[86] In a 2017 systematic review by Chen et al., FGR was defined according to the SGA criteria., therefore using FGR as a substitute for SGA might have potentially excluded some of the studies which used SGA exclusively in the manuscripts.[99] Another systematic review by Viale et al. published in 2015 defined FGR as having either SGA or LBW by doing this they failed to differentiate the risk of an infant being born SGA and LBW separately.[43] Being born preterm has been associated with various long- and short-term health outcomes in infants.[87–89] Preterm birth also directly affects the infant's length of hospital stay, NICU admissions, readmissions as well as infant morbidity and mortality.[102–104] Therefore it is necessary to understand the safety of medications among term and preterm infants. Many hospital admissions outcomes such as NICU admissions, readmissions, and length of hospital stay have been associated with an increase in the economic burden among pregnant people.[105,106]

1.9. Knowledge gaps and methodological limitations

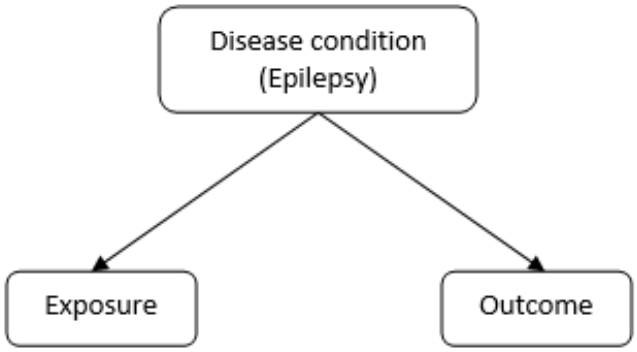
The above studies show that most studies were limited to valproic acid, carbamazepine, phenytoin, lamotrigine, and levetiracetam and did not include nor analyze most of the new-generation drugs.[109–113] The studies also show that lamotrigine is the drug with the least risk of SGA and LBW while valproic acid poses the highest risk.[114,115] Previous studies also show various methodological limitations, including small sample size, failure to adjust for epilepsy severity and unmeasured confounding.[93,95,116] There is a current urgent need for real-world evidence on

the safety of antiepileptic regimens during pregnancy in pregnant people with and without epilepsy to help guide clinicians in their practice and pre-conception counselling of PPWE and PPWOE.

1.9.1. Confounding by Indication

Confounding by indication is a type of confounding where the indication is associated with the outcome as well as the exposure.[117] Confounding by indication is detrimental in observational studies of drug effects during pregnancy, including maternal epilepsy.[118,119] Seizures themselves are associated with various adverse birth outcomes such as malformations and preterm birth,[42] impacting the health of pregnant people and infants[42]. Since seizures due to epilepsy are associated with both ASMs and outcomes, when the study analysis or study design doesn't account for indication bias, the result will possibly be biased by confounding by indication (**Figure 1.3**: Confounding by Indication directed acyclic graph).[86.]

Figure 1.2. Confounding by indication DAG



1.9.2. ASM in non epilepsy and off-label use

Besides their primary use to control seizures, ASMs are used off-label to treat acute and chronic conditions; for example gabapentin use for pain, migraine, restless legs syndrome, some psychiatric disorders, and post-traumatic stress syndrome.[120] In the Medicaid database almost 60% of antiseizure medications claims were for off-label use.[121] Gabapentin (78.9%) is the most prescribed medication for off-label use followed by zonisamide (65.6%), topiramate (52.8%), lamotrigine (51.6%), oxcarbazepine (49.5%), tiagabine (33.5%), levetiracetam (27.9%) and felbamate (14.6%).[121] With the increase in the use of ASMs use for non-epilepsy indications it is essential to study the fetal safety of non-epilepsy use of ASMs.

1.9.3. Increase in the use of gabapentin for non-epileptic conditions.

Gabapentin is a new-generation ASM approved for the treatment of epilepsy in 1993.[122] Subsequently, it was approved for postherpetic neuralgia in 2002 and moderate to severe restless leg syndrome (RLS) in 2011.[123] Currently, gabapentin has no established teratogenic risk. Therefore an increase in the use of gabapentin for both epileptic as well as non-epileptic indications has been observed.[63,122,124] Due to its perceived safety and efficacy in other non-epilepsy conditions such as pain and migraine, there has been an increase in the use of gabapentin for other off-label indications such as diabetic and nondiabetic neuropathy, and fibromyalgia.[125,126] Current literature shows that almost 95% of all gabapentin prescriptions are prescribed for non-epilepsy conditions and are mostly off-label.[127–129] This explains the increase in gabapentin prescriptions despite only being used as an adjuvant for epilepsy treatment.[122,130] There has been an increase in gabapentin misuse in the past few years.[131] Gabapentin abuse

has been reported among 1% of the general population, 40-65% abuse from prescription sources and 15-22% among people who abuse opiates.[131, 132]

Recently few studies reported an increase in malformations, specifically cardiac malformations, and adverse birth outcomes among gabapentin-exposed pregnant people.[124,125] With the lack of established risk and continued increase in the use of gabapentin among pregnant people, further study into its safety in pregnancy is necessary.[70,73] Thus, there is a current need for real-world evidence on gabapentin exposure during pregnancy.

1.10. Rationale and research objectives

1.10.1. Rationale

We conducted a series of studies to answer the current knowledge gaps in our understanding of the safety of ASMs in epilepsy, regarding specific neonatal outcomes with scarce or limited evidence.

1.10.2. Hypothesis and objectives

This thesis aims to synthesize and generate antiseizure medications safety evidence with the following specific objectives addressed in subsequent chapters:

1. To summarize and synthesize the published evidence on the association between ASMs exposure in pregnancy and neonatal birth weight outcomes (Chapter 1: Protocol, Chapter 2: Manuscript).

Hypothesis: Pregnant people exposed to ASMs during pregnancy are associated with an increased risk of adverse growth outcomes

2. To generate evidence using real-world data on the association between ASMs exposure in pregnancy and neonatal birth outcomes (Chapter 3).

   Hypothesis: Pregnant people exposed to ASMs during pregnancy are associated with an increased risk of adverse neonatal outcomes.

3. To generate evidence using real-world data on the association between gabapentin exposure in pregnancy and neonatal birth outcomes (Chapter 4).

   Hypothesis: Pregnant people exposed to gabapentin during pregnancy are associated with an increased risk of adverse neonatal outcomes.

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Chapter 2: Anti-epileptic drug exposure during pregnancy and neonatal birth weight outcomes: protocol for a systematic review and meta-analysis

2.1. Overview

This manuscript is the first part of the evidence synthesis project which examines all the published literature to study the safety of antiseizure medications during pregnancy and neonatal birth weight. This manuscript is the protocol for the systematic review and meta-analysis and consists of all predetermined search strategies, databases, inclusion and exclusion criteria, data extraction and assessment processes. Pre-writing a protocol for a systematic review is necessary to keep the process transparent and accountable.

Citation: Lavu A, Vaccaro C, Shouman W, et al. Anti-epileptic drug exposure during pregnancy and neonatal birth weight outcomes: protocol for a systematic review and meta-analysis. Syst Rev. 2021;10(1):1-3. doi:10.1186/s13643-021-01711-8

2.2. Abstract

Background: The prevalence of epilepsy in pregnant women is estimated at 0.3 - 1%. Anti-epileptic drug (AED) exposure in-utero has been associated with various adverse health outcomes in neonates, including adverse birth weight outcomes.

Objective: This review aims to summarize the published evidence on the association between AED exposure in pregnancy and adverse birth weight outcomes

Methods: Studies assessing AED exposure in pregnancy and neonatal birth weight outcomes, including small for gestational age (SGA), low birth weight (LBW), birth weight (BW), length, head circumference, and cephalization index will be identified in MEDLINE®, EMBASE, Cochrane Library, Scopus, Cumulative Index of Nursing and Allied Health Literature (CINAHL), International Pharmaceutical Abstracts (IPA), and Global Health. Open grey, Theses Canada and ProQuest Dissertations will be used to locate grey literature. Eligible study designs will include both intervention and non-interventional studies. We will not impose any time limit in the review. We will use the Newcastle-Ottawa Scale to assess the methodological quality of observational studies and quasi-experimental studies included in the review. The risk of bias of experimental studies will be appraised using the Cochrane risk-of-bias tool for randomized trials (RoB 2). A meta-analysis will be conducted using a random-effects model.

Discussion: The results from this review could improve clinicians' prescribing decisions by highlighting the safest AEDs for women who are pregnant or planning to conceive based on the evidence currently available. **Systematic review registration:** The study has been registered in Prospero (CRD42020192713). **Keywords:** Small for gestational age, Low birth weight, Epilepsy, Anti-epileptic drugs, Birth weight outcomes.

2.3. Background

Epilepsy is a neurological condition that affects 50 million people worldwide.[1] The prevalence of epilepsy in pregnant women is estimated at 0.3 - 1%.[2,3] Anti-epileptic drug (AED) exposure in-utero has been associated with various adverse health outcomes in neonates including congenital malformations, intrauterine growth restriction, neurological complications, and adverse birth weight outcomes.[4–7] Previous reports suggests that any AED exposure during pregnancy is associated with an increased risk of infants having a low birth weight (LBW) and being small for gestational age (SGA).[5,8,9] Infants with adverse birth weight outcomes like SGA are at a higher risk of stillbirth, impaired thermoregulation, and hypoglycemia at birth.[10] Studies have also linked SGA with various long-term health outcomes, including impaired neurodevelopment throughout childhood, as well as cardiovascular diseases and diabetes in adulthood.[11–16] The safety profile of AEDs varies based on the molecule, generation/class, and dose used.[17,18] AEDs have been broadly classified into old-generation AEDs and new generation-AEDs.[19] Old-generation AEDs were the first introduced drugs to treat epilepsy during the early 1900s, whereas new-generation AEDs were first used in the management of epilepsy in the 1970s.[19] Evidence on the perinatal risk of old-generation AEDs are relatively established when compared to new-generation AEDs.[17] First-generation AEDs have been strongly associated with SGA compared to new-generation AEDs, specifically valproic acid exposure is associated with an increased risk of SGA compared to the new-generation AED lamotrigine, which is believed to be safe.[17,18]

Systematic reviews summarizing the published evidence on AED's safety in pregnancy have mainly focused on malformations and neurological outcomes.[17,20,21] A limited number of

systematic reviews have been published on AEDs exposure during pregnancy and neonatal birth weight outcomes.[22–24] The most common limitation observed in the previously published systematic review was using fetal growth restriction (FGR) and intrauterine growth restriction (IUGR) interchangeably with SGA. SGA is a term used to describe newborns who are smaller in size than the usual for their gestational age and is defined as birth weight less than 10th percentile for the same gestational age. FGR also known as IUGR, implies that fetal growth is being inhibited and that the fetus does not attain its growth potential.[25] Therefore, it is to say, not all SGA infants have FGR, and some larger infants can still be SGA.[25] Therefore, substituting SGA for FGR might potentially affect the results of any systematic review. One recent systematic review by Chen et al. in 2017 defined FGR using SGA definition, therefore using FGR as a substitute for SGA might have potentially excluded some of the studies which used SGA exclusively in the manuscripts.[23] Another systematic review by Viale et al. published in 2015 defined FGR as having either SGA or LBW, by doing this they failed to differentiate the risk of an infant being born SGA and LBW separately.[22] Other published reviews are at least two decades old.[26] Moreover, several original reports were published on new-generation AEDs in the past 20 years, hence the need for an up-to-date review to summarize and evaluate the risks associated with the use of AEDs in pregnancy, specifically adverse birth weight outcomes.

Objective

This systematic review aims to summarize the evidence on the association between AEDs exposure during pregnancy and neonatal birth weight outcomes.

2.4. Methods/Design

A systematic review protocol was developed and registered in the PROSPERO database (CRD42020192713) on 19/08/2020. Preparation of our systematic review protocol was done following the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P) checklist.[27]

2.4.1. Eligibility criteria

Inclusion criteria

This systematic review consists of articles that include women exposed to AEDs during pregnancy. Exposures during the first, second, and third trimesters will be considered. Polytherapy and monotherapy will also be included. No restrictions will be applied in terms of the comparison group, as we will include studies on women with epilepsy (WWE) on AEDs (active comparison), WWE not on AEDs, women without epilepsy (WWOE) on AED, and WWOE not on AED. Study designs that will be included in the review include 1) intervention studies (randomized controlled trials, quasi-randomized trials, and non-randomized trials) and 2) non-interventional studies, including observational studies (cohort studies, case-control studies, and cross-sectional studies), as well as quasi-experimental studies. Only studies published in English and French will be considered. Studies that fulfill our eligibility criteria will be included in the review. (See Table 2.1. for PICO)

Exclusion criteria

To avoid excluding studies that may have misclassified SGA as FGR and IUGR, we will include studies with IUGR or FGR as their outcome in the search strategy. After examining their definitions, studies that identified IUGR or FGR differently from SGA will be excluded during screening. Studies in which AEDs are given exclusively to infants and not to mothers during pregnancy will be excluded. Animal studies, studies containing no original research or data (e.g., reviews), conference abstracts, case reports, case series, and editorial letters will also be excluded.

2.4.2. Outcome measures

Primary outcomes for this systematic review include:

a. Small for gestational age (SGA): A birth weight classified as small for gestational age within the study, or when SGA is not named explicitly but defined as infants ≤10th percentile in birth weight, based on birth weight, gestational age.

b. Low birth weight (LBW): A birth weight classified as low birth weight as defined within the study or birth weight less than 2500 grams (g).

c. Birth weight (BW): weight at birth in grams (g).

Secondary outcomes include head circumference, cephalization index, and birth length (height) defined as:

a. Head circumference: Head circumference at birth in centimeters (cm).

b. Length: Height of the infant in centimeters (cm),

c. Cephalization index: Ratio of the head circumference (HC) to body weight.

Studies that report any of the outcomes defined above with different terminology (e.g. fetal growth restriction or intrauterine growth restriction as a substitute for SGA) will be reclassified according to the terms specified above.

2.4.3. Information sources and literature search

A systematic search strategy was developed with the assistance of a librarian. We will search MEDLINE®, EMBASE, Cochrane Library, Scopus, Cumulative Index of Nursing and Allied Health Literature (CINAHL), International Pharmaceutical Abstracts (IPA), and Global Health for relevant studies. See Additional file 1 for the search strategy that will be used in MEDLINE. The MEDLINE search strategy will be translated to other databases based on their properties. There will not be any time restrictions. Grey literature search will include Open grey, Theses Canada, and EBSCO Open Dissertations. ProQuest Dissertations will be searched using relevant keywords to locate additional studies and reports that are not published in the seven electronic databases previously stated.

The following key terms and subject headings (MeSH) will be used in various combinations and adapted according to each included database: anticonvulsants, convulsion, epilepsy, body weight, infant, low birth weight, small for gestational age, fetal growth restriction, body height, body size, cephalometry, fetal development, pregnancy outcome, pregnant woman, prenatal exposure.

2.4.4. Study selection process

Two authors (AL and CV) will independently screen titles, abstracts, and full-text articles for studies that meet our inclusion criteria using Rayyan (https://www.rayyan.ai/), a free web-tool for the screening process, as determined by our eligibility criteria.[28,29] Any disagreements will be resolved by consensus with a third reviewer. Two authors (SE and WS) will independently screen relevant studies in French identified by AL and CV during the title and abstract screening. We also plan to hand-search the references of the final selected studies to locate additional eligible articles. If there are two publications from the same study with overlapping populations, we will choose the latest publication to be included in the review. We will use the PRISMA guidelines to report the study results.

2.4.5. Data collection process

Two team members (AL and CV) will independently extract information from eligible studies using a data extraction tool. A third member will revise the chart and help resolve any disagreements. Data will include study design, country, data source, drug exposure, sample sizes in exposure and control groups, control groups definitions, birth weight outcomes, exposed and unexposed numbers (raw data) of birth weight outcomes, effect estimates including crude and adjusted odds ratios, prevalence ratios, relative risks, and mean differences, as well as their confidence intervals and p-values.

2.4.6. Methodological quality/risk of bias appraisal

We will use the Newcastle-Ottawa Scale to assess the methodological quality of observational studies and quasi-experimental studies included in the review. The risk of bias of experimental studies will be appraised using the Cochrane risk-of-bias tool for randomized trials (RoB 2).[30] Funnel plots and Egger's test will be used to assess publication bias, and any probable publication bias will be assessed by the fill and trim method.[31] Kappa value will be calculated to assess the agreement between the reviewer's screening and methodological quality scores.[32] The risk of bias analysis will be conducted by two reviewers independent of each other, and any disagreement will be resolved by consensus.

2.4.7. Synthesis of included studies

Characteristics of the included studies for primary and secondary birth weight outcomes will be presented both descriptively and in tables. Pooled estimates of SGA, LBW, BW, head circumference, height, and cephalization index will be presented. Clinical and methodological heterogeneity of included studies will be examined qualitatively. Cochrane's Q test (chi-squared) and Higgins I^2 statistics will be used to assess the statistical heterogeneity of the included studies before conducting the meta-analysis. We will also assess the strength of the evidence and combine the results quantitatively. Whenever homogeneity is considered sufficient for an outcome, a meta-analysis will be conducted. We will conduct a random-effects meta-analysis to calculate pooled odds ratios for dichotomous data and pooled mean differences for continuous data.[33] The study weights, size of the effect, effect consistency, and direction of effect will be represented in each forest plot.[33]

Funnel plots will be depicted for primary and secondary outcomes, including at least ten studies to explore asymmetry that might be explained by clinical, statistical, and methodological heterogeneity.[34] When the individual peculiarities of the studies under investigation are identified, sensitivity analysis will be done accordingly and reported in figures.[33] With a sufficient number of studies, subgroup analysis will be conducted by dose, AED exposure period during pregnancy (first trimester, second trimester, and third trimester), and therapy type (monotherapy and polytherapy) and will be reported in figures.

2.5. Discussion

It is essential to understand how AEDs exposure in pregnancy affects birth weight outcomes in offspring. This is particularly important due to the increased prescribing rates of new-generation AEDs, and the limited evidence of their fetal safety. Cautious prescribing practices of AEDs in women of reproductive age are crucial, as more than 30% of pregnancies are not planned, and some AEDs can potentially reduce contraceptives' efficacy.[35,36] Therefore, placing women of childbearing age on AEDs should be based on recommended care, with sufficient evidence on neonates' safety. Clinicians should make medication choices by balancing the risk of increased seizure frequency in mothers versus the potential of adverse fetal outcomes caused by AED exposure.[37]

There is a need for a well-constructed systematic review focusing on an array of adverse birth weight outcomes potentially caused by AED exposure during pregnancy. We anticipate the presence of fewer published reports on new-generation AEDs and new versus old-generation AEDs. This review will locate reports from numerous sources including grey literature and will

summarize, pool, and evaluate the methodological quality of the studies in a systematic approach.

This will help us expand the knowledge on how the safety of AED during pregnancy varies based on the type of AED and the combination of prescribed AEDs. It will also help physicians make a careful decision regarding the safety of AED use in pregnancy and choose the safest treatment regimen. The knowledge generated through this project will also help in the pre-counseling of women who plan to be pregnant and will help them make rational evidence-based choices along with their physicians.

2.6. List of abbreviations

AEDs: Anti-epileptic drugs; SGA: Small for gestational age; LBW: Low birth weight; BW: Birth weight; WWE: Women with epilepsy; WWOE: Women without epilepsy, IUGR: Intrauterine growth restriction, FGA: Fetal growth restriction IPA: International pharmaceutical abstracts CINAHL: Cumulative index of nursing and allied health literature, Cochrane risk-of-bias tool for randomized trials (RoB 2), PRISMA-P: Preferred reporting items for systematic reviews and meta-analyses protocols, HC: Head circumference.

2.7. Tables

Table 2.1. Eligibility criteria to be included in the review (PICO)

(P)opulation	Pregnant women
(I)ntervention	Anti-epileptic drugs (AED) therapy
(C)omparison	WWOE on AED WWOE not on AED (general population) WWE not on AED WWE on AED (active comparisons)
(O)utcome	Primary outcomes: Birth weight outcomes (SGA, LBW, BW) Secondary outcomes: Head circumference, Cephalization index and birth length (height).
WWOE: Women without epilepsy, WWE: Women with epilepsy, AED: Antiepileptic drug, SGA: Small for gestational age, LBW: Low birth weight and. BW: Birth weight.	

2.8. Additional files

Additional Table 2.1. MEDLINE search

#	Searches
1)	Exp anticonvulsants/
2)	(agent* or drug* adj2 (anticonvuls* or anti convuls* or antiepilep* or anti epilep*)).tw,kw.
3)	(acetazolamide or bromides or carbamazepine or chlormethiazole or clobazam or clorazepate dipotassium or diazepam or dimethadione or estazolam or ethosuximide or felbamate or flunarizine or gabapentin or lacosamide or lamotrigine or levetiracetam or lorazepam or magnesium sulfate or medazepam or mephenytoin mephobarbital or meprobamate or nitrazepam oxcarbazepine or paraldehyde or phenobarbital or phenytoin or pregabalin or primidone or riluzole or thiopental or tiagabine or tiletamine or topiramate or trimethadione or valproic acid or vigabatrin or zonisamide).tw,kw.
4)	Exp seizures/ dt
5)	Exp epilepsy/ dt
6)	(convulsion or seizure or epilepsy).tw,kw.
7)	Brivaracetam/
8)	(brivaracetam or brivlera or briviact).tw,kw.
9)	Eslicarbazepine/
10	(eslicarbazepine* or apitom or zebinix).tw,kw.
11	Fosphenytoin sodium/
12	(fosphenytoin* or cerebyx or pro-epanutin).tw,kw.
13	Ganaxolone/
14	Ganaxolone.tw,kw.
15	Losigamone/
16	Losigamone.tw,kw.
17	Perampanel/
18	(perampanel or fycompa).tw,kw.
19	Piracetam/
20	Piracetam.tw,kw.
21	Pregabalin/
22	(pregabalin or lyrica or lecaent or rewisca).tw,kw.
23	Remacemide/
24	(remacemide*).tw,kw.
25	Retigabine/
26	(retigabine or ezogabine or trobalt).tw,kw.
27	Rufinamide/
28	(rufinamdie or banzel or inovelon).tw,kw.
29	Safinamide/
30	(safinamide or xadago).tw,kw.

31	Stiripentol/
32	(stiripentol or diacomit).tw,kw.
33	Or/1-32**[anticonvulsants concept]**
34	Exp body weight/
35	Body weight*.tw,kw.
36	Birth weight/
37	Birth weight*.tw,kw.
38	Fetal weight/
39	(fetal or foetal) adj weight*.tw,kw.
40	Exp infant, low birth weight/
41	Sga, small for gestational age.tw,kw.
42	(low adj2 (birthweight* or birth weight*) or lbw*).tw,kw.
43	Fetal growth retardation/
44	((fetal or foetal or intrauterine) adj (growth retard* or growth restrict*)).tw,kw.
45	Body height/
46	Body height.tw,kw.
47	Body size/
48	(body adj2 size*).tw,kw.
49	Cephalometry/
50	(cephalometry or craniometry).tw,kw.
51	Head/
52	Head.tw,kw.
53	Fetal development/
54	((fetal or foetal) adj (develop* or growth)).tw,kw.
55	Pregnancy outcome/
56	(pregnancy outcome).tw,kw.
57	Or/34-56 [birth size concept]
58	Exp pregnancy/
59	Pregnant woman/
60	Infant, newborn/
61	(infant* or newborn*).tw,kw.
62	Gestat*.tw,kw.
63	Pregnan*.tw,kw.
64	(prenatal* or pre natal*).tw,kw.
65	Prenatal exposure/
66	Or/58-65 [pregnancy concept]
67	33 and 57 and 66
68	Limit 67 to (english or french)
69	Exp animals/ not (exp animals/ and humans/)
70	68 not 69

Additional Table 2.2. PRISMA-P checklist

PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Reviews 2015 4:1

An Editorial from the Editors-in-Chief of Systematic Reviews details why this checklist was adapted - Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. Systematic Reviews 2016 5:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	2 and 3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	35
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	5 to 14
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	212 to 217
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting	☐	☒	

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		important protocol amendments			
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	208 to 209
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☒	
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	41 to 68
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	70 and 71
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	79 to 92
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	113 to 123
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	Additional file 2
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☐	☒	

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	126 to 129
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	132 to 137
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	120 to 123
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	95 to110
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	140 to 145
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	148 to 156
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	154 to 160
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	160 to 164
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☒	

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	158 to 160
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☒	

Additional Table 2.3. List of AEDs included in the study.

First Generation		Second Generation	Third Generation
1	Carbamazepine	Lamotrigine	Perampanel
2	Diazepam	Gabapentin	Brivaracetam
3	Phenytoin	Pregabalin	Safinamide
4	Valproic acid	Oxcarbazepine	Stiripentol
5	Ethosuximide	Levetiracetam	Eslicarbazepine
6	Clonazepam	Topiramate	Felbamate
7	Phenobarbital	Tiagabine	Fosphenytoin
8	Bromides	Lacosamide	Losigamone
9	Clomethiazole	Rufinamide	Retigabine
10	Clorazepate dipotassium	Vigabatrin	Safinamide
11	Paraldehyde	Clonazepam	Stiripentol
12	Thiopental	Clobazam	Ganaxolone
13		Lorazepam	Remacemide
14		Primidone	
15		Felbamate	
16		Zonisamide	
17		Acetazolamide	
18		Estazolam	
19		Flunarizine	

Additional Table 2.4. Screening steps for located studies.

Level 1 Screening (Titles)

1. Was the study conducted exclusively in humans?
   YES____ NO____ UNCLEAR____

2. Does the study include pregnant women?
   YES____ NO____ UNCLEAR____

3. Is this a relevant study design (experimental studies, quasi-experimental studies, observational studies)?
   YES____ NO____ UNCLEAR____

4. Does the study report perinatal/neonatal outcomes in the newborn?
   YES____ NO____ UNCLEAR____

Level 2 Screening (Abstract)

1. Does the study include pregnant women?
   YES____ NO____ UNCLEAR____

2. Does the study include pregnant women with epilepsy or exposed to AED*?*
   YES____ NO____ UNCLEAR____

3. Does the study report at least one outcome of interest (small for gestational age (SGA), low birth weight (LBW), birth weight (BW), head circumference, length/height, cephalization index)?
   YES____ NO____ UNCLEAR____

4. Is this a relevant study design (experimental studies, quasi-experimental studies, observational studies)?
   YES____ NO____ UNCLEAR____

Level 3 Screening (Full text)

1. Does the study include pregnant women exposed to any of the AEDs predefined (monotherapy or combination)*?*
   a. YES____ NO____

2. Does the study report at least one outcome of interest (small for gestational age (SGA), low birth weight (LBW), birth weight (BW), head circumference, length/height, cephalization index)?
   a. YES____ NO____

3. Is this a relevant study design (experimental studies, quasi-experimental studies, observational studies)?
   a. YES____ NO____

2.9 Author list and contribution of authors

Alekhya Lavu, Christine Vaccaro, Walid Shouman, Silvia Alessi Severini, and Sherif Eltonsy

AL conceived and designed the study. AL, CV, WS, SAS, and SE have contributed to the concept and design of the study. AL, CV, and WS drafted the first protocol. CV registered the protocol in the PROSPERO database. AL and WS drafted the additional files. AL, CV, WS, SAS, and SE contributed to drafting and revising the full manuscript and have approved the manuscript as submitted. AL, CV, WS, SAS, and SE have met the criteria of authorship, and take public responsibility for the manuscript contents. AL is the first author and SE is the corresponding author of the review.

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Chapter 3: Antiseizure Medication Use During Pregnancy and Neonatal Growth Outcomes: A Systematic Review and Meta-Analysis

3.1. Overview

This is the second manuscript from the data synthesis project which summarizes all the published data on antiseizure medications use in pregnancy and neonatal growth outcomes. This chapter systematically analyses all published data from databases inception until October 2022. The outcomes we examined include small for gestational age (SGA), Low birth weight (LBW), birth weight, birth height, head circumference and cephalization index. Two reviewers independently screened the titles, abstracts, and full-text articles. We used Rayyan to screen the selected citations and Revman to pool the studies for meta-analysis (random effects model). Included studies underwent risk of bias (ROB) analysis and publication bias was evaluated. Primary analysis was performed in overall exposure and secondary analysis was conducted among ASMs class exposure, epilepsy subgroup and polytherapy vs monotherapy group. Further sensitivity analysis was also performed based on the ROB analysis scores. The results of dichotomous variables were presented as risk ratios (RR) and 95% Confidence interval (CI), and continuous variables were presented as means in grams (gm) and standard deviation (SD). This study's findings show that there was a significant association between ASMs exposure in pregnancy and SGA, LBW, and birth weight. Birth height and head circumference were not significant.

Citation: Lavu A, Vaccaro C, Zusman E, et al. Antiseizure Medication Use During Pregnancy and Neonatal Growth Outcomes: A Systematic Review and Meta-Analysis. Br J Clin Pharmacol. 2023 ; DOI:https://doi.org/10.1111/bcp.15752

3.2. Abstract

Aim: We aimed to systematically synthesize the current published literature on neonatal growth outcomes associated with antiseizure medications (ASMs) use during pregnancy.

Methods: We searched seven databases, from inception to March 23rd, 2022. We investigated small for gestational age (SGA) and low birth weight (LBW) as primary outcomes and birth weight, birth height, cephalization index and head circumference as secondary outcomes. The primary analysis included pregnant people exposed to any ASM compared with unexposed pregnant people. Subgroup analysis included ASMs class analysis, within epilepsy group analysis and polytherapy compared to monotherapy.

Results: We screened 15,720 citations and included 65 studies in the review. Exposed pregnant people had a significantly increased risk of SGA relative risk (RR) 1.33 (95% CI 1.18 to 1.50, I^2 74%), LBW RR 1.54 (95% CI 1.33 to 1.77, I^2 67%), and decreased birth weight with a mean difference (MD) of -118.87 (95% CI -161.03 to -76.71, I^2 42%) g. A non-significant risk change in birth height and head circumference was observed. In subgroup analysis, ASM polytherapy, within epilepsy and ASMs class analysis were also associated with an increased risk of SGA and LBW.

Conclusion: This meta-analysis demonstrates that pregnant people exposed to ASMs have a significantly increased risk of adverse fetal growth outcomes including SGA and LBW and decreased birth weight compared to unexposed pregnant people. Polytherapy was associated with higher risks compared to monotherapy. Additional studies are warranted on specific ASMs risks. **Registration:** The protocol is registered in Prospero ID#: CRD42020192713

Keywords: Antiseizure medications, Antiepileptic medication, Small for gestational age, Low Birth weight, Birth outcomes, Fetal safety, Seizures, Epilepsy, Convulsions.

3.3. Introduction

Epilepsy is a neurological disease characterized by seizures affecting 50 million people globally.[1,2] Epilepsy affects 0.3-1% of pregnant people every year.[2,3] Seizures in pregnancy could lead to adverse events in pregnant people and infants, such as trauma, stillbirth, and adverse birth outcomes.[3–6] Considering the potential risks faced by both pregnant people and the fetus, it is imperative to minimize seizures frequency and reduce epileptic events during pregnancy.[3–5] In-utero exposure to antiseizure medications (ASMs) was shown to be associated with adverse outcomes among infants, including congenital malformations, neurodevelopmental disorders, preterm birth, and adverse birth weight outcomes.[3,5,7–9] Infants born with adverse birth weight outcomes are at higher risk of developing short- and long-term health conditions, including diabetes and cardiovascular diseases (CVD).[10–12] The long-term impact of ASMs mediated through small for gestational age (SGA) – as compared to SGA in general population – is yet to be defined.[13] Given the negative impacts of both epilepsy and ASM use on fetal development, a better understanding of the risks attributed to each factor is critical to ensure pregnant persons and fetal safety.[6,14]

Most published evidence on in-utero exposure to ASMs focuses on their teratogenic impact and potential neurodevelopmental effects.[7,8] A limited number of reviews examined the association between ASMs use and SGA, low birth weight (LBW), birth weight as well as head

circumference, cephalization index and birth height.[9] Evidence on the impact of ASMs while accounting for confounding by indication (i.e. epilepsy) is limited. We aimed to summarize the published evidence on the in-utero exposure of ASMs and neonatal growth outcomes, including SGA, LBW, birth weight, height, cephalization index and head circumference. We also aimed to provide an analysis that separated ASM exposure from epilepsy.

3.4. Methods

The current systematic review and meta-analysis was registered in Prospero (CRD42020192713) on 19/09/2020 and the protocol has been published in BMC's Systematic Review Journal[15]. In reporting this study we adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[16]

3.4.1. Inclusion criteria

We included all pregnant people using ASMs anytime throughout the pregnancy as well as during the first, second and third trimesters. All ASMs exposures including monotherapy and polytherapy, of both new and old-generation ASMs, were included. All interventional studies (randomized controlled studies, quasi-randomized trials, non-randomized trials) and non-interventional studies, including observational studies (cohort studies, case-control studies, and cross-sectional studies) and quasi-experimental studies were included. Grey literature including theses and dissertations were included. We included studies published in English and French languages.

3.4.2. Exclusion criteria

As stated in the protocol, in order to maintain homogeneity of definitions across studies we excluded studies that misclassified fetal growth restriction (FGR) and intrauterine growth restriction (IUGR) as SGA (see definition in 'outcomes' below).[15] Animal studies, studies containing no original research or data (e.g., reviews), conference abstracts, case reports, case series, and editorial letters were excluded.

3.4.3. Information sources

An information librarian developed the search strategy with the primary author (AL). Databases searched were MEDLINE (Ovid), EMBASE (Ovid), Cochrane Library, Scopus, Cumulative Index of Nursing and Allied Health Literature (CINAHL), International Pharmaceutical Abstracts (IPA)(Ovid), and Global Health (Ovid). Open grey, Theses Canada, EBSCO Open Dissertations, and ProQuest Dissertations were searched using relevant keywords for grey literature. All databases were searched from their inception till October 2020. An updated search was conducted in March 2022.

The following key terms and medical subject headings (MeSH) were used in various combinations and adapted according to each database and grey literature source: anticonvulsants, convulsion, epilepsy, body weight, infant, low birth weight, small for gestational age, fetal growth restriction, body height, body size, cephalometry, fetal development, pregnancy outcome, pregnant woman, and prenatal exposure (entire search strategy is described in Additional Table 3.1a). References cited in the included studies were

searched for relevant articles, and a freehand search was performed in Google Scholar to locate additional relevant articles.

3.4.4. Outcome definitions

The primary outcomes were: 1) SGA, defined as a birth weight classified as small for gestational age within the study or Infants with ≤10th percentile in birth weight, based on birth weight and gestational age and 2) LBW, defined as a birth weight classified as low birth weight within the study or birth weight less than 2500 grams (g). Secondary outcomes included birth weight defined as weight at birth in grams (g), head circumference, defined as head circumference at birth in centimetres (cm), length or height of the infant in cm and cephalization index defined as a ratio of the head circumference to body weight.

3.4.5. Study selection and data extraction

To assess eligibility two authors (AL and CV) independently screened all papers at the title and abstract level. Authors then screened eligible studies at the full-text level. We used Rayyan QCRI (https://www.rayyan.ai/) tool for the screening process. Detailed information on our screening questions can be found in Additional Table 3.1b. All disagreements were resolved by consensus. Publications that had a population or registry overlap were compared and the latest publication was chosen to be included to avoid double counting pregnant people.

3.4.6. Risk of bias assessment (ROB)

Three reviewers (AL, LA, and EZ) appraised the quality of the included studies using the Newcastle-Ottawa Scale.[17] We assessed the selection criteria, comparability between cases and comparison, and the outcome assessment, and each study was given a maximum of 9 stars.

At least two reviewers reviewed each study and resolved the conflicts by consensus.

3.5. Statistical analysis

Characteristics of the included studies for primary and secondary birth weight outcomes are presented descriptively. Pooled estimates of SGA, LBW, birth weight, head circumference, height, and cephalization index were calculated. We used Higgins I^2 statistic to assess the statistical heterogeneity of included studies. When more than two studies are available for an outcome, a meta-analysis was conducted. We used random-effects models to calculate pooled risk ratio (RR) for dichotomous data and pooled mean differences for continuous data.[1819]

We conducted the primary analysis for each primary and secondary outcomes by comparing ASM exposed pregnant people with unexposed pregnant people. Exposed pregnant people were defined as exposed to any ASM including polytherapy, monotherapy and ASM class (studies reporting ASMs exposure as a group). For primary outcomes, we conducted subgroup analysis by 1) ASM class: pregnant people exposed to ASM class (reported as any exposure to ASMs group) compared to unexposed pregnant people, 2) within epilepsy group analysis: exposed pregnant people with epilepsy compared to unexposed pregnant people with epilepsy, and 3) polytherapy vs. monotherapy analysis. Funnel plots were used to assess publication bias.[20] Sensitivity analysis based on risk of bias (ROB) analysis scores was conducted.

3.6. Results

Literature search

We identified a total of 15720 citations in 7 databases according to our search criteria. After deduplication, 4279 studies were excluded leaving a total of 11,381 citations for title, abstract and full-text screening. From other search methods, we identified two additional citations, including one thesis and one study.[21,22] We updated our search in March 2022 and identified 5 new studies to include in our systematic review. The current systematic review includes 65 studies.[5,13,23–79] See Figure 3.1 for the PRISMA diagram. A total of 43 studies had sufficient data to be used in the meta-analyses. The characteristics of the studies were as follows: 15 studies from Asia, 28 from Europe, 15 from North America, one from South America, three from Australia, and three multicenter studies. There were 33 cohort studies and 10 case-control studies used for meta-analysis of various outcomes.

3.6.1. Methodological quality and risk-of-bias analysis

Out of 43 studies, a total of 6 studies had a score ≤6 stars and 37 studies had ≥7 stars (Additional Table 3.1c). We found no significant publication bias in the studies included in our primary analysis of all outcomes (Additional Table 3.1d).

3.6.2. Outcomes

The total number of exposed pregnant people was 25,801 for SGA, 20,558 for LBW, 10,010 for birth weight, 2814 for head circumference and 8242 for birth height.

Primary outcomes

Small for gestational age

A total of 28 studies reported SGA results. Seventeen studies were eligible for primary meta-analysis (see Additional Table 3.1e Summary data of studies included in the meta-analysis of SGA), where pregnant people exposed to any ASMs had a 33% higher risk of SGA compared with unexposed pregnant people (RR 1.33 [95% CI 1.18 to 1.50, I^2 72%]) (Figure 3.2a). In the class exposure analysis (ASM group), exposed pregnant people had a significant increased risk of SGA compared to unexposed pregnant people (6 studies, RR of 1.34 [95% CI 1.25 to 1.43, I^2 14%]) (Table 3.1). Within epilepsy group, meta-analysis showed that pregnant people with epilepsy exposed to ASMs had a RR of 1.17 (95% CI 1.03 to 1.34, I^2 17%) compared to unexposed pregnant people with epilepsy (Figure 3.1.a). Pregnant people exposed to polytherapy had a higher risk of SGA with a RR of 1.48 (95% CI 1.30 to 1.69, I^2 0%) compared to monotherapy (Table 3.1, Additional Table 3.1f).

Low birth weight

A total of 20 studies were eligible for the main meta-analysis, where exposure to any ASM was associated with a 54% higher risk of LBW (RR 1.54 [95% CI 1.33 to 1.77, I^2 67%]) (Figure 3.2b). We pooled three studies for analysis of class exposure of grouped ASMs, showing a significantly increased risk of SGA among exposed pregnant people compared with unexposed pregnant people (RR of 1.58 [95% CI 1.21 to 2.08, I^2 89%]) (Table 3.1). Among pregnant people with epilepsy, ASM use was associated with a non-significant increased risk of LBW [9 studies, RR 1.17 (95% CI 0.93 to 1.48, I^2 50%)] (Figure 3.3b). Pregnant people exposed to polytherapy had a

higher risk of LBW with a RR of 1.68 (95% CI 1.29 to 2.18, I^2 0%) compared to monotherapy exposure. (Table 3.1).

Secondary outcomes

Birth weight

In the meta-analysis of 19 studies, ASM use by exposed pregnant people was associated with a significant decreased birth weight with a mean difference of -118.87(95% CI -161.03 to -76.71, I^2 42%) g compared to unexposed pregnant people. (Figure 3.4a)

Birth height

We identified 10 studies for meta-analysis, where newborns of exposed pregnant people had a non-significant mean difference of -0.18 cm (95% CI -0.39 to 0.03, I^2 22%) in birth height when compared to unexposed pregnant people (Figure 3.4b).

Head circumference

We identified 10 studies for the meta-analysis, where newborns of exposed pregnant people had a non-significant mean difference of 0.33 cm (95% CI -0.55 to 1.25, I^2 98%) of head circumference than compared to unexposed pregnant people) (Figure 3.4c).

Cephalization index

No published studies were identified to assess this outcome in our systematic review.

Sensitivity analysis by ROB scores

We found no significant changes when studies with ROB analysis scores of ≤6 stars were excluded from the analysis (Additional Table 3.1c and Additional Table 3.1g).

3.7. Discussion

In this meta-analysis, newborns of pregnancies exposed to ASMs had a significant increased risk of SGA and LBW and decreased birth weight compared with unexposed pregnancies. We did not find any significant association between ASM exposure during pregnancy and changes in head circumference or birth height. We could not evaluate cephalization index as an outcome due to the lack of published studies.

Our results are in accordance with previous reports. Chen et al. summarized the risk of SGA in ASM exposed pregnant people with epilepsy compared with unexposed healthy pregnant people in a meta-analysis, reporting an OR of 1.26 (95% CI 1.13 to 1.41).[9] A key limitation in Chen et al. review leading to the fewer study inclusions was the use of FGR instead of SGA terms in the search strategy, thereby excluding studies that used SGA alone.[9] Another limitation is comparing exposed PPWE versus unexposed healthy pregnant people, where indication bias becomes a validity threat.[9] Our study reports a higher risk of SGA, which can also be attributed to the fact that we compared exposed PPWE with unexposed PPWE, to account for confounding by indication. The current meta-analysis included 4 additional studies where newer generation ASM might have been more commonly used, which could have been reflected in our results.[50,73,80,81] In our study, newborns of exposed pregnant people were around 119g lighter than unexposed newborns, similar to a published review where ASM exposed pregnant people had approximately 200g lower birth weight.[82] The observed estimates for head circumference and birth height in our review did not reach statistical significance, given the low number of studies included, additional studies are warranted.

In our primary main analysis, we included all exposure types (including monotherapy, polytherapy, ASM grouped as reported, or individual drugs). Given the high variability in the exposure definition in this analysis, we conducted a subgroup analysis using ASM as reported as class exposure (studies reporting ASMs as a class exposure, [yes/no]) for both SGA and LBW. This subgroup analysis confirmed the results observed in the main analysis (Table 3.1).

Confounding by indication is detrimental in observational studies of drug effects during pregnancy, including pregnant persons epilepsy. We conducted a subgroup analysis for SGA and LBW within people with epilepsy to minimize the impact of indication bias and better tease out ASM adverse effects from pregnant persons epilepsy. We found that newborns of pregnant people with epilepsy (PPWE) exposed to ASMs had a 17% higher risk for both SGA (significant) and LBW (non-significant) than unexposed PPWE.

Out of 43 studies included in the meta-analysis, Gaily et al. had the lowest ROB analysis score of 3, where no information on the selection of case and controls was reported and the study lacked adjustments for any additional factors.[30] We included 14 cohort studies and 2 case-control studies that did not include any covariates adjustment.[30,34,64,66,78,42,46,53,54,57,59,60,62] We performed a sensitivity analysis by excluding studies with ROB score of ≤6 without any major changes in the results.

This meta-analysis reported high I^2 values (ranging from 72% to 98%), indicating high heterogeneity among studies for SGA main analysis, LBW main analysis, LBW class analysis, and head circumference. The high heterogeneity was most likely due to the differences in exposure definitions and evolving study designs across the years (small prospective studies to national

database cohorts). Nonetheless, based on the magnitude and consistency of the results, we can conclude that infants born to pregnant people exposed to ASM in-utero are associated with a higher risk of adverse birth weight outcomes, irrespective of the pregnant persons epilepsy status.

ASMs polytherapy was associated with a significant increased risk of SGA (48%) and LBW (68%) compared to monotherapy. Data from Thomson et al. suggest that the ASM type and dose are as important as the number of ASMs in a given polytherapy.[83] Recent studies suggest that valproic acid and topiramate combinations have higher teratogenic risk when compared with other ASMs.[84,85] However, combinations including low-dose valproate are less teratogenic than high-dose valproate monotherapy.[83,86] Importantly, however, careful interpretation of polytherapy analysis is needed, since confounding by severity (epilepsy severity) cannot be ignored. To our knowledge, this meta-analysis is the first to report on within epilepsy and polytherapy analyses for SGA and LBW. Further studies on teratogenic risk of polytherapy must be evaluated based on the type and dose of ASMs accounting for confounding by indication.

Currently, a large body of evidence shows that infants exposed to ASMs in-utero have an increased risk of malformations.[5,13,63] The theorized mechanisms behind ASM teratogenicity include folate deficiency, hypoxia, reoxygenation, apoptosis, genetic susceptibility, or reactive intermediates.[87–89] Fetal growth restriction, which includes adverse growth outcomes, has been related mostly to folate deficiency as it plays a major role in the fetal metabolism during development.[88,89] In one study, increased fetal weight and length in mice pups was observed when ASMs were co-administered with folic acid.[88] More recently, it has been hypothesized

that several ASMs including trimethadione, carbamazepine, and phenytoin can cause embryonic cardiac arrhythmia during the developmental period.[87,89] Cardiac arrhythmia results in embryonic hypoxia followed by reoxygenation and generation of reactive oxygen species, which can lead to tissue damage.[87] Altered expression of placental heterodimeric transporters due to ASMs has also been linked to affected fetal development.[90] Further studies are needed to determine the mechanism by which ASMs can lead to growth restrictions.

It is expected that different ASM will carry different magnitudes of risks in terms of fetal growth restriction.[91] ASMs that are repeatedly associated with an increased risk of fetal growth restrictions include phenobarbital, carbamazepine, and topiramate.[13,23,92] On the other hand, lamotrigine was associated with the least observed risk of adverse birth weight outcomes across different studies.[23,92] Future research on the risk of adverse birth outcomes among individual ASMs – as well as safety evidence on comparable regimens – could better inform current clinical practice.[91] Studying comparable regimens could effectively minimize the impact of confounding by severity. Therefore, it is essential to establish the safety of various comparative treatment regimens to better inform clinicians for optimal management of pregnant persons epilepsy.

3.8. Strengths and limitations

The current review has several strengths. Our review includes the largest sample of pregnant people exposed to ASMs to date. This review is also the first that attempted to account for confounding by indication and polytherapy in subgroup analyses. We assessed the quality of

the included studies and performed a quality-based sensitivity analysis. Limitations of the review should be acknowledged. We combined both cohort and case control studies in our analysis to maximize sample size, which is one of the potential reasons for high statistical heterogeneity reported in some results. Our pooled analysis should be interpreted within the likelihood of presence of potential methodological heterogeneity between the included studies. With the lack of disease severity data available in the published studies, it was not possible to account for confounding by severity in a robust approach. We did not examine the risks associated with individual medication's use nor comparing specific combinations. An analysis of medications driving the higher risks within polytherapy was not feasible.

3.9. Conclusion

This meta-analysis demonstrates that pregnant people taking any ASMs during pregnancy have a significantly increased risk of SGA and LBW compared to unexposed pregnant people, irrespective of the epilepsy status. Polytherapy was associated with greater SGA and LBW risk compared to monotherapy. Given the risks associated with discontinuing epilepsy treatment during pregnancy, careful clinical attention should be given to optimize pregnant persons treatments with lowest risks to newborns. Further studies on the comparative safety of ASMs are recommended to help inform clinical practice.

3.10. Tables

Table 3.1: Relative risk of the primary and secondary outcomes in the main and subgroup analyses.

Outcome	*Main analysis*	*Subgroup analysis*		
	Any ASM exposed vs unexposed	**ASM class exposed vs unexposed**	**Exposed PPWE vs unexposed PPWE**	**Polytherapy vs monotherapy**
Small for Gestational Age *RR [95% CI], I^2*	**1.33[1.18 to 1.50], I^2 72%**	**1.34 [1.25, 1.43], I^2 14%**	**1.17 [1.03, 1.34], I^2 17%**	**1.48 [1.30, 1.69], I^2 0%**
Low Birth Weight *RR [95% CI], I^2*	**1.54 [1.33, 1.77], I^2 67%**	**1.58 [1.21, 2.08], I^2 89%**	1.17 [0.93, 1.48], I^2 50%	**1.68 [1.29, 2.18], I^2 0%**
Birth weight *MD [95% CI], I^2*	**-118.87 [-161.03, -76.71] g, I^2 42%**			
Birth Height *MD [95% CI], I^2*	-0.18 [-0.39,0.03]cm, I^2 22%			
Head circumference *MD [95% CI], I^2*	0.33 [-0.55, 1.21] cm, I^2 98%			

Note: PPWE: pregnant people with epilepsy, ASM: Anti-seizure medications, MD: Mean difference, RR: Risk ratio and cm: centimeters and g: grams, All ASMs is defined as: "all exposure types including monotherapy, polytherapy, ASM

3.11. Figures

Figure 3.1: PRISMA flow chart

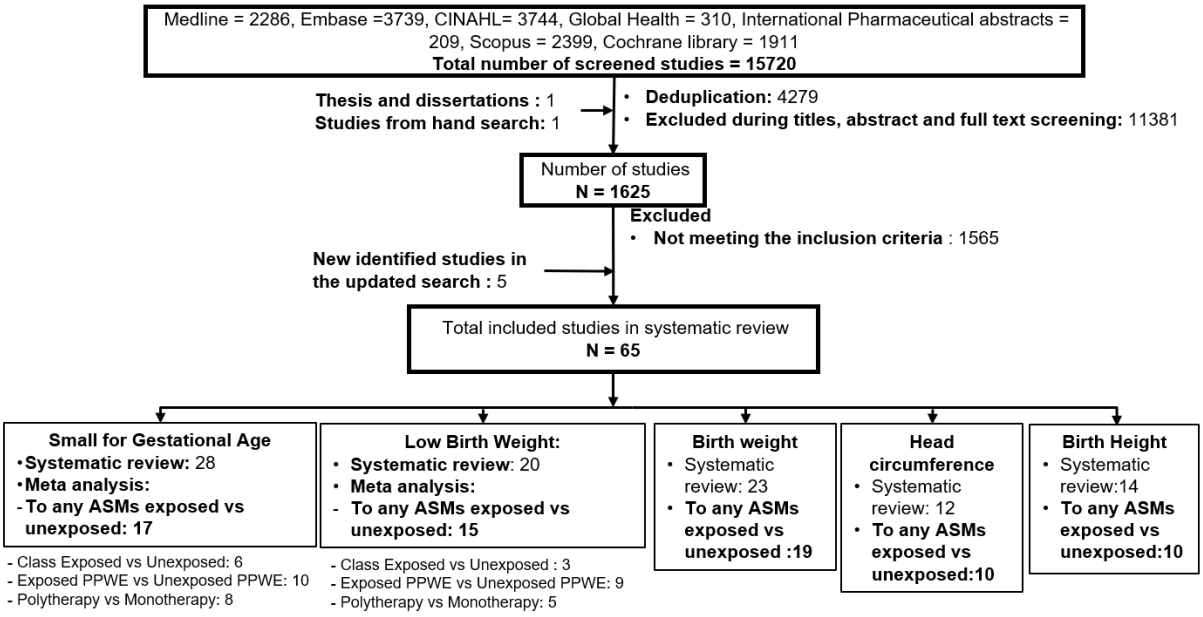
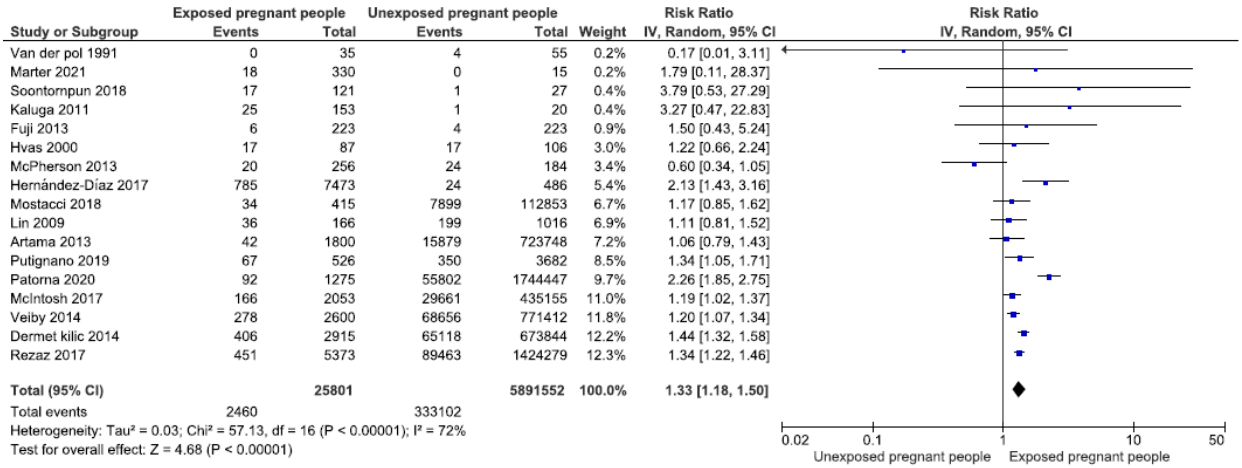


Figure 3.2: Forest plot panel of main analysis of SGA and LBW: pregnant people exposed to any ASM compared with unexposed pregnant people.

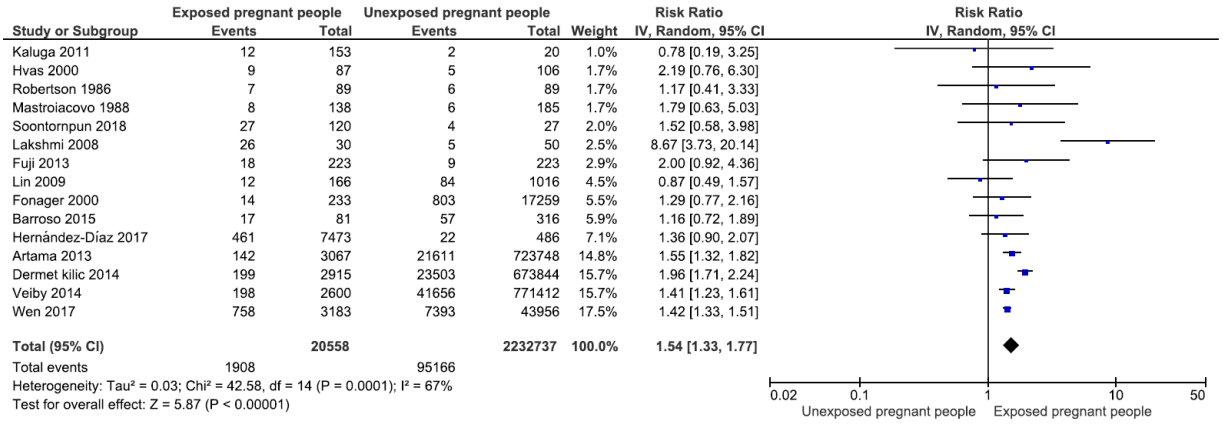
3.2a: Small for gestational age main analysis



Study or Subgroup	Exposed pregnant people Events	Total	Unexposed pregnant people Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Van der pol 1991	0	35	4	55	0.2%	0.17 [0.01, 3.11]
Marter 2021	18	330	0	15	0.2%	1.79 [0.11, 28.37]
Soontornpun 2018	17	121	1	27	0.4%	3.79 [0.53, 27.29]
Kaluga 2011	25	153	1	20	0.4%	3.27 [0.47, 22.83]
Fuji 2013	6	223	4	223	0.9%	1.50 [0.43, 5.24]
Hvas 2000	17	87	17	106	3.0%	1.22 [0.66, 2.24]
McPherson 2013	20	256	24	184	3.4%	0.60 [0.34, 1.05]
Hernández-Díaz 2017	785	7473	24	486	5.4%	2.13 [1.43, 3.16]
Mostacci 2018	34	415	7899	112853	6.7%	1.17 [0.85, 1.62]
Lin 2009	36	166	199	1016	6.9%	1.11 [0.81, 1.52]
Artama 2013	42	1800	15879	723748	7.2%	1.06 [0.79, 1.43]
Putignano 2019	67	526	350	3682	8.5%	1.34 [1.05, 1.71]
Patorna 2020	92	1275	55802	1744447	9.7%	2.26 [1.85, 2.75]
McIntosh 2017	166	2053	29661	435155	11.0%	1.19 [1.02, 1.37]
Veiby 2014	278	2600	68656	771412	11.8%	1.20 [1.07, 1.34]
Dermet kilic 2014	406	2915	65118	673844	12.2%	1.44 [1.32, 1.58]
Rezaz 2017	451	5373	89463	1424279	12.3%	1.34 [1.22, 1.46]
Total (95% CI)		**25801**		**5891552**	**100.0%**	**1.33 [1.18, 1.50]**
Total events	2460		333102			

Heterogeneity: Tau² = 0.03; Chi² = 57.13, df = 16 (P < 0.00001); I² = 72%
Test for overall effect: Z = 4.68 (P < 0.00001)

3.2b: Low birth weight main analysis

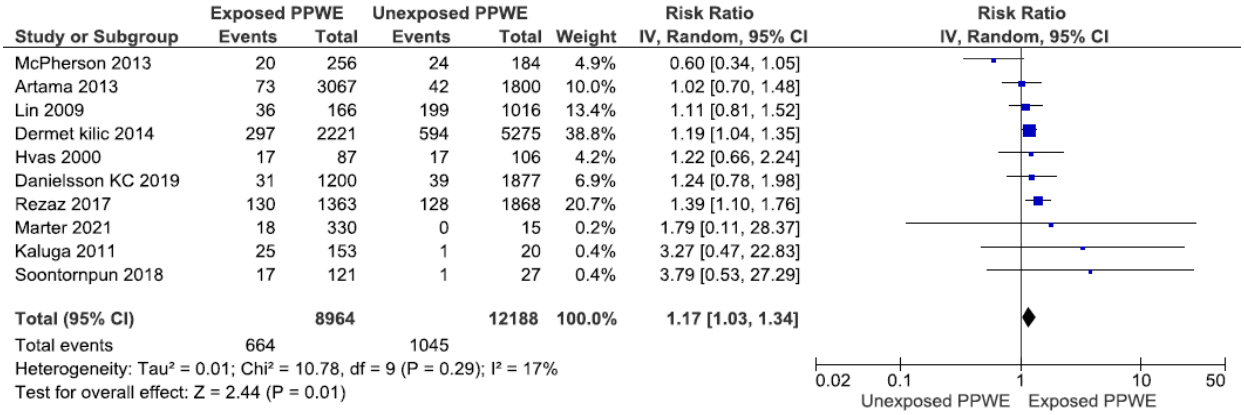


Study or Subgroup	Exposed pregnant people Events	Total	Unexposed pregnant people Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Kaluga 2011	12	153	2	20	1.0%	0.78 [0.19, 3.25]
Hvas 2000	9	87	5	106	1.7%	2.19 [0.76, 6.30]
Robertson 1986	7	89	6	89	1.7%	1.17 [0.41, 3.33]
Mastroiacovo 1988	8	138	6	185	1.7%	1.79 [0.63, 5.03]
Soontornpun 2018	27	120	4	27	2.0%	1.52 [0.58, 3.98]
Lakshmi 2008	26	30	5	50	2.5%	8.67 [3.73, 20.14]
Fuji 2013	18	223	9	223	2.9%	2.00 [0.92, 4.36]
Lin 2009	12	166	84	1016	4.5%	0.87 [0.49, 1.57]
Fonager 2000	14	233	803	17259	5.5%	1.29 [0.77, 2.16]
Barroso 2015	17	81	57	316	5.9%	1.16 [0.72, 1.89]
Hernández-Díaz 2017	461	7473	22	486	7.1%	1.36 [0.90, 2.07]
Artama 2013	142	3067	21611	723748	14.8%	1.55 [1.32, 1.82]
Dermet kilic 2014	199	2915	23503	673844	15.7%	1.96 [1.71, 2.24]
Veiby 2014	198	2600	41656	771412	15.7%	1.41 [1.23, 1.61]
Wen 2017	758	3183	7393	43956	17.5%	1.42 [1.33, 1.51]
Total (95% CI)		**20558**		**2232737**	**100.0%**	**1.54 [1.33, 1.77]**
Total events	1908		95166			

Heterogeneity: Tau² = 0.03; Chi² = 42.58, df = 14 (P = 0.0001); I² = 67%
Test for overall effect: Z = 5.87 (P < 0.00001)

Figure 3.3. Forest plot panel of within epilepsy group analysis for SGA and LBW: pregnant people with epilepsy exposed to any ASM compared with unexposed pregnant people with epilepsy.

3.3a: Small for gestational age within epilepsy group analysis



3.3b: Low birth weight within epilepsy group analysis

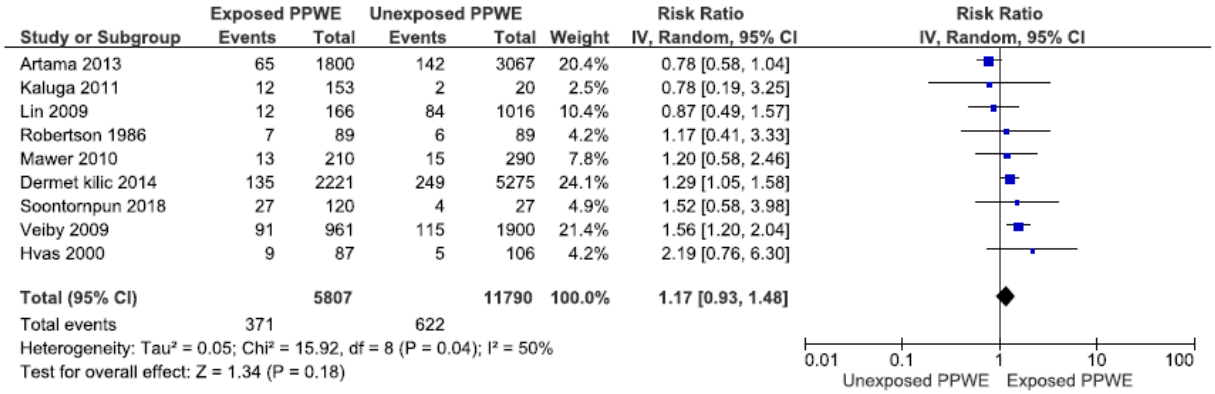
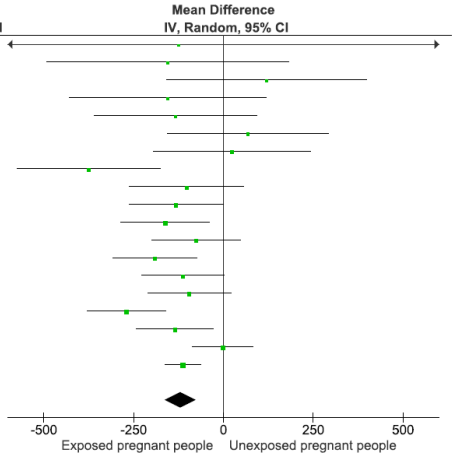


Figure 3.4: Forest plot panel of main analysis of secondary outcomes: Birth weight, birth height, and head circumference

3.4a: Birth weight main analysis: pregnant people exposed to any ASM compared with unexposed pregnant people.

Study or Subgroup	Exposed pregnant people Mean	SD	Total	Unexposed pregnant people Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Unal 2021	3,075	2,096	23	3,200	2,422	92	0.2%	-125.00 [-1114.29, 864.29]
Koc 2018	3,152.32	668.25	30	3,307.41	712.5	35	1.4%	-155.09 [-491.10, 180.92]
Arulmozhi 2006	3,050	550	30	2,930	550	30	2.0%	120.00 [-158.33, 398.33]
Cilliler 2018	2,910.64	754.26	48	3,065.45	507.19	33	2.0%	-154.81 [-429.54, 119.92]
Yerby 1992	3,426	707	62	3,559.1	494.8	46	2.8%	-133.10 [-359.85, 93.65]
Hiilesmaa 1981	3,412	479	126	3,344	436	17	2.9%	68.00 [-155.50, 291.50]
Van der pol 1991	3,422.88	444.78	35	3,399	390	22	3.0%	23.88 [-195.83, 243.59]
Ornoy 2008	2,932	664.44	52	3,307	435	105	3.5%	-375.00 [-573.84, -176.16]
Barroso 2015	2,910	635	82	3,013	723	316	4.8%	-103.00 [-261.89, 55.89]
Vajda 2008	3,383	592	709	3,515	522	68	6.1%	-132.00 [-263.50, -0.50]
Dergisi 2021	3,151.99	526.32	95	3,314	308.03	88	6.6%	-162.01 [-285.88, -38.14]
Fonager 2000	3,406	946	233	3,482	1,256.25	17259	6.6%	-76.00 [-198.91, 46.91]
Gaily 1989	3,449	443.48	117	3,640	436.4	103	7.0%	-191.00 [-307.45, -74.55]
Mastroiacovo 1988	3,194	483	138	3,307	435	105	7.1%	-113.00 [-228.83, 2.83]
Hvas 2000	3,437	605	106	3,532	549	24094	7.1%	-95.00 [-210.38, 20.38]
Diav Citrin 2001	3,046	641	210	3,316	486	210	7.5%	-270.00 [-378.80, -161.20]
Fuji 2013	3,180	605	223	3,315	545	223	7.7%	-135.00 [-241.87, -28.13]
Diav Citrin 2017	3,198	591.85	218	3,200	474.07	865	9.4%	-2.00 [-86.68, 82.68]
Hernández-Díaz 2017	3,340.58	559.97	7473	3,453	537.4	486	12.5%	-112.42 [-161.86, -62.98]
Total (95% CI)			**10010**			**44197**	**100.0%**	**-118.87 [-161.03, -76.71]**

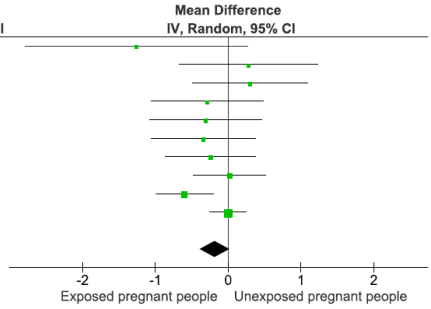
Heterogeneity: Tau² = 3070.55; Chi² = 31.13, df = 18 (P = 0.03); I² = 42%
Test for overall effect: Z = 5.53 (P < 0.00001)



3.4b: Birth height main analysis: pregnant people exposed to any ASM compared with unexposed pregnant people

Study or Subgroup	Exposed pregnant people Mean	SD	Total	Unexposed pregnant people Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Arulmozhi 2006	50.41	2.71	30	51.67	3.29	30	1.8%	-1.26 [-2.79, 0.27]
Yerby 1992	51.08	2.6	62	50.8	2.4	46	4.4%	0.28 [-0.67, 1.23]
Hvas 2000	51.5	3.1	106	51.2	2.5	87	6.1%	0.30 [-0.49, 1.09]
Vajda 2008	50.32	3.05	709	50.61	3.11	68	6.3%	-0.29 [-1.06, 0.48]
Barroso 2015	47.33	3.54	82	47.64	0.76	316	6.3%	-0.31 [-1.08, 0.46]
Dergisi 2021	49.16	3.26	95	49.5	1.35	88	7.2%	-0.34 [-1.05, 0.37]
Mastroiacovo 1988	49.26	2.5	138	49.5	2.4	105	9.1%	-0.24 [-0.86, 0.38]
Hiilesmaa 1981	49.62	1.98	126	49.6	2.2	143	12.7%	0.02 [-0.48, 0.52]
Gaily 1989	49.7	0.2	117	50.3	2.03	103	17.7%	-0.60 [-0.99, -0.21]
Hernández-Díaz 2017	50.6	3.3	6777	50.6	3.2	696	28.4%	0.00 [-0.25, 0.25]
Total (95% CI)			**8242**			**1682**	**100.0%**	**-0.18 [-0.39, 0.03]**

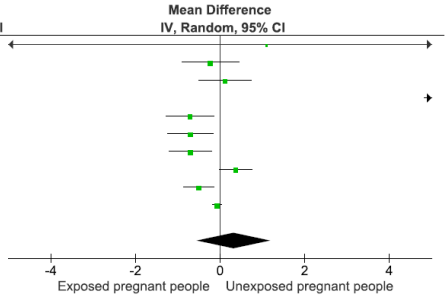
Heterogeneity: Tau² = 0.02; Chi² = 11.55, df = 9 (P = 0.24); I² = 22%
Test for overall effect: Z = 1.70 (P = 0.09)



3.4c: Head circumference main analysis: pregnant people exposed to any ASM compared with unexposed pregnant people

Study or Subgroup	Exposed pregnant people Mean	SD	Total	Unexposed pregnant people Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Hiilesmaa 1981	34.54	1.354	126	33.44	43.6	17	0.2%	1.10 [-19.63, 21.83]
Vajda 2008	34.58	1.79	79	34.81	2.31	68	10.8%	-0.23 [-0.91, 0.45]
Arulmozhi 2006	34.3	0.97	30	34.18	1.44	30	10.9%	0.12 [-0.50, 0.74]
Robertson 1986	39.9	2.2	89	34.5	1.6	89	11.0%	5.40 [4.83, 5.97]
Barroso 2015	33.26	2.57	82	33.97	0.87	316	11.0%	-0.71 [-1.27, -0.15]
Yerby 1992	33.9	1.53	62	34.6	1.3	46	11.0%	-0.70 [-1.23, -0.17]
Hvas 2000	34.5	1.8	87	35.2	1.7	106	11.1%	-0.70 [-1.20, -0.20]
Dergisi 2021	34.87	1.68	95	34.5	0.93	88	11.3%	0.37 [-0.02, 0.76]
Mastroiacovo 1988	33.9	1.43	138	34.4	1.4	105	11.3%	-0.50 [-0.86, -0.14]
Hernández-Díaz S 2014	34.43	2.35	2026	34.5	0.14	457	11.5%	-0.07 [-0.17, 0.03]
Total (95% CI)			**2814**			**1322**	**100.0%**	**0.33 [-0.55, 1.21]**

Heterogeneity: Tau² = 1.74; Chi² = 384.21, df = 9 (P < 0.00001); I² = 98%
Test for overall effect: Z = 0.73 (P = 0.46)



3.12. Appendices

Additional Table 3.1a: EMBASE search strategy

1.	exp anticonvulsive agent/
2.	((Agent* or drug*) adj2 (anticonvule* or anti convuls* or antiepilep* or anti epilep*)).tw,kw.
3.	(Acetazolamide or Bromides or Carbamazepine or Chlormethiazole or Clobazam or Clorazepate Dipotassium or Diazepam or Dimethadione or Estazolam or Ethosuximide or Felbamate or Flunarizine or Gabapentin or Lacosamide or Lamotrigine or Levetiracetam or Lorazepam or Magnesium Sulfate or Medazepam or Mephenytoin or Mephobarbital or Meprobamate or Nitrazepam or Oxcarbazepine or Paraldehyde or Phenobarbital or Phenytoin or Pregabalin or Primidone or Riluzole or Thiopental or Tiagabine or Tiletamine or Topiramate or Trimethadione or Valproic Acid or Vigabatrin or Zonisamide).tw,kw.
4.	exp convulsion/dt
5.	exp seizure/dt
6.	exp epilepsy/dt
7.	brivaracetam/
8.	(brivaracetam or brivlera or briviact).tw,kw.
9.	eslicarbazepine acetate/ or eslicarbazepine/
10.	(eslicarbazepine$ or aptom or zebinix).tw,kw.
11.	fosphenytoin sodium/
12.	(fosphenytoin$ or cerebyx or pro-epanutin).tw,kw.
13.	ganaxolone/
14.	ganaxolone.tw,kw.
15.	losigamone/
16.	losigamone.tw,kw.
17.	perampanel/
18.	(perampanel or fycompa).tw,kw.
19.	piracetam/
20.	piracetam.tw,kw.
21.	pregabalin/
22.	(pregabalin or lyrica or lecaent or rewisca).tw,kw.
23.	remacemide/
24.	remacemide$.tw,kw.
25.	retigabine/
26.	(retigabine or ezogabine or trobalt).tw,kw.
27.	rufinamide/
28.	(rufinamdie or banzel or inovelon).tw,kw.
29.	safinamide/
30.	(safinamide or xadago).tw,kw.
31.	stiripentol/
32.	(stiripentol or diacomit).tw,kw.
33.	or/1-32 [Anticonvulsants Concept]
34.	exp body weight/
35.	body weight.tw,kw.
36.	birth weight/
37.	exp birth weight/
38.	birth weight.tw,kw.
39.	exp fetus weight/
40.	fetus weight.tw,kw.
41.	exp low birth weight/
42.	SGA, small for gestational age.tw,kw.
43.	SGA, small for gestational ,small for date infant.tw,kw.
44.	((Low adj2 (Birthweight* or birth weight*)) or LBW*).tw,kw.
45.	exp intrauterine growth retardation/
46.	((Fetal or foetal or intrauterine) adj (Growth Retard* or growth restrict*)).tw,kw.
47.	body height/
48.	Body Height.tw,kw.
49.	body size/
50.	(body adj2 size*).tw,kw.
51.	cephalometry/
52.	(cephalometry or Craniometry).tw,kw.
53.	fetus development/
54.	((Fetal or foetal) adj (Develop* or growth)).tw,kw.
55.	fetus outcome/
56.	pregnancy outcome/
57.	Pregnancy Outcome.tw,kw.
58.	or/34-57 [outcomes Concept]
59.	exp pregnancy/
60.	pregnant woman/
61.	infant/
62.	(Infant* or newborn*).tw,kw.
63.	gestat$.tw,kw.
64.	pregnan$.tw,kw.
65.	exposure/ or prenatal drug exposure/ or prenatal exposure/
66.	or/59-65 [Pregnancy Concept]
67.	33 and 58 and 66
68.	limit 67 to (english or french)
69.	(animal or animals or canine* or dog or dogs or feline or hamster* or lamb or lambs or mice or monkey or monkeys or mouse or murine or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep* or veterinar*).ti,kw,dq,jx. not (human* or patient*).mp.
70.	(exp animal/ or exp juvenile animal/ or adult animal/ or animal cell/ or animal tissue/ or nonhuman/ or animal experiment/ or animal model/) not human/
71.	68 not (69 or 70)

Additional Table 3.1b: MEDLINE search strategy

1.	exp Anticonvulsants/
2.	((Agent* or drug*) adj2 (anticonvuls* or anti convuls* or antiepilep* or anti epilep*)).tw,kw.
3.	(Acetazolamide or Bromides or Carbamazepine or Chlormethiazole or Clobazam or Clorazepate Dipotassium or Diazepam or Dimethadione or Estazolam or Ethosuximide or Felbamate or Flunarizine or Gabapentin or Lacosamide or Lamotrigine or Levetiracetam or Lorazepam or Magnesium Sulfate or Medazepam or Mephenytoin or Mephobarbital or Meprobamate or Nitrazepam or Oxcarbazepine or Paraldehyde or Phenobarbital or Phenytoin or Pregabalin or Primidone or Riluzole or Thiopental or Tiagabine or Tiletamine or Topiramate or Trimethadione or Valproic Acid or Vigabatrin or Zonisamide).tw,kw.
4.	exp Seizures/dt
5.	exp epilepsy/dt
6.	(Convulsion or seizure or epilepsy).tw,kw.
7.	brivaracetam/
8.	(brivaracetam or brivlera or briviact).tw,kw.
9.	eslicarbazepine/
10.	(eslicarbazepine$ or aptom or zebinix).tw,kw.
11.	fosphenytoin sodium/
12.	(fosphenytoin$ or cerebyx or pro-epanutin).tw,kw.
13.	ganaxolone/
14.	ganaxolone.tw,kw.
15.	losigamone/
16.	losigamone.tw,kw.
17.	perampanel/
18.	(perampanel or fycompa).tw,kw.
19.	piracetam/
20.	piracetam.tw,kw.
21.	pregabalin/
22.	(pregabalin or lyrica or lecaent or rewisca).tw,kw.
23.	remacemide/
24.	remacemide$.tw,kw.
25.	retigabine/
26.	(retigabine or ezogabine or trobalt).tw,kw.
27.	rufinamide/
28.	(rufinamdie or banzel or inovelon).tw,kw.
29.	safinamide/
30.	(safinamide or xadago).tw,kw.
31.	stiripentol/
32.	(stiripentol or diacomit).tw,kw.
33.	or/1-32 [Anticonvulsants Concept]
34.	exp Body Weight/
35.	body weight.tw,kw.
36.	birth weight/
37.	birth weight.tw,kw.
38.	fetal weight/
39.	((fetal or foetal) adj weight*).tw,kw.
40.	exp Infant, Low Birth Weight/
41.	SGA, small for gestational age.tw,kw.
42.	((Low adj2 (Birthweight* or birth weight*)) or LBW*).tw,kw.
43.	Fetal Growth Retardation/
44.	((Fetal or foetal or intrauterine) adj (Growth Retard* or growth restrict*)).tw,kw.
45.	Body Height/
46.	Body Height.tw,kw.
47.	BODY SIZE/
48.	(body adj2 size*).tw,kw.
49.	Cephalometry/
50.	(cephalometry or Craniometry).tw,kw.
51.	Head/
52.	Head.tw,kw.
53.	Fetal Development/
54.	((Fetal or foetal) adj (Develop* or growth)).tw,kw.
55.	Pregnancy Outcome/
56.	Pregnancy Outcome.tw,kw.
57.	or/34-56 [Birth Size Concept]
58.	exp pregnancy/
59.	pregnant woman/
60.	Infant, Newborn/
61.	(Infant* or newborn*).tw,kw.
62.	gestat$.tw,kw.
63.	pregnan$.tw,kw.
64.	(prenatal$ or pre natal$).tw,kw.
65.	prenatal exposure/
66.	or/58-65 [Pregnancy Concept]
67.	33 and 57 and 66
68.	limit 67 to (english or french)
69.	(animal or animals or canine* or dog or dogs or feline or hamster* or lamb or lambs or mice or monkey or monkeys or mouse or murine or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep* or veterinar*).ti,kw,dq,jx. not (human* or patient*).mp.
70.	(animal/ or models, animal/ or disease models, animal/) not human/
71.	68 not (69 or 70)

Additional Table 3.1c: Cochrane Library search strategy

#1 MeSH descriptor: [Anticonvulsants] explode all trees
#2 ((agent* or drug* N2 (anticonvuls* or anti convuls* or antiepilep* or anti epilep*))):ti,ab,kw
#3 ((acetazolamide or bromides or carbamazepine or chlormethiazole or clobazam or clorazepate dipotassium or diazepam or dimethadione or estazolam or ethosuximide or felbamate or flunarizine or gabapentin or lacosamide or lamotrigine or levetiracetam or lorazepam or "magnesium sulfate" or medazepam or mephenytoin or mephobarbital or meprobamate or nitrazepam or oxcarbazepine or paraldehyde or phenobarbital or phenytoin or pregabalin or primidone or riluzole or thiopental or tiagabine or tiletamine or topiramate or trimethadione or "valproic acid" or vigabatrin or zonisamide)):ti,ab,kw
#4 MeSH descriptor: [Seizures] explode all trees
#5 MeSH descriptor: [Epilepsy] explode all trees
#6 ((convulsion or seizure or epilepsy)):ti,ab,kw
#7 ((brivaracetam or brivlera or briviact)):ti,ab,kw
#8 ((eslicarbazepine* or apitom or zebinix)):ti,ab,kw
#9 ((fosphenytoin* or cerebyx or pro-epanutin)):ti,ab,kw
#10 (Ganaxolone):ti,ab,kw
#11 (Losigamone):ti,ab,kw
#12 ((perampanel or fycompa)):ti,ab,kw
#13 (Piracetam):ti,ab,kw
#14 ((pregabalin or lyrica or lecaent or rewisca)):ti,ab,kw
#15 ((remacemide*)):ti,ab,kw
#16 ((retigabine or ezogabine or trobalt)):ti,ab,kw
#17 ((rufinamdie or banzel or inovelon)):ti,ab,kw
#18 ((safinamide or xadago)):ti,ab,kw
#19 ((stiripentol or diacomit)):ti,ab,kw
#20 MeSH descriptor: [Body Weight] explode all trees
#21 ("Body weigh"):ti,ab,kw
#22 MeSH descriptor: [Birth Weight] explode all trees
#23 ("Birth weight"*):ti,ab,kw
#24 MeSH descriptor: [Fetal Weight] this term only
#25 ((fetal or foetal) N weight*):ti,ab,kw
#26 MeSH descriptor: [Infant, Low Birth Weight] explode all trees
#27 (sga or " small for gestational age"):ti,ab,kw
#28 ((low N2 (birthweight* or "birth weight"*) or lbw*)):ti,ab,kw
#29 MeSH descriptor: [Fetal Growth Retardation] this term only
#30 (((fetal or foetal or intrauterine) N3 ("growth retard*" or "growth restrict*"))):ti,ab,kw
#31 MeSH descriptor: [Body Height] this term only
#32 MeSH descriptor: [Body Size] this term only
#33 (("body size" or "body height")):ti,ab,kw
#34 (body N1 size*):ti,ab,kw
#35 MeSH descriptor: [Cephalometry] explode all trees
#36 ((cephalometry or craniometry)):ti,ab,kw
#37 MeSH descriptor: [Fetal Development] explode all trees
#38 ((fetal or foetal) N (develop* or growth)):ti,ab,kw
#39 MeSH descriptor: [Pregnancy Outcome] this term only
#40 ("Pregnancy outcome"):ti,ab,kw
#41 MeSH descriptor: [Pregnancy] explode all trees
#42 MeSH descriptor: [Infant, Newborn] this term only
#43 ((infant* or newborn*)):ti,ab,kw
#44 (Gestat*):ti,ab,kw
#45 (Pregnan*):ti,ab,kw
#46 ((prenatal* or pre natal*)):ti,ab,kw
#47 MeSH descriptor: [Prenatal Exposure Delayed Effects] this term only
#48 ("Prenatal exposure"):ti,ab,kw
#49 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #1 1 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#50 #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 #37 OR #38 OR #39 OR #40
#51 #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48
#52 #49 AND #50 AND #51

Additional Table 3.1d: Scopus search strategy

TITLE-ABS (infant* OR newborn* OR "pregnant women" OR gestat* OR pregnan* OR prenatal* OR "pre natal*") AND (TITLE-ABS ("Body weight*" OR "Birth weight*" OR "body height*" OR ((fetal OR foetal) W/1 weight*) OR sga OR "small for gestational age" OR (low W/2 (birthweight* OR "birth weight*" OR lbw*)) OR (fetal OR foetal OR intrauterine) W/2 ("growth retard*" OR "growth restrict*")) OR (body W/1 size*) OR cephalometry OR craniometry OR ((fetal OR foetal) W/2 (develop* OR growth*)) OR "pregnancy outcome*") AND (TITLE-ABS (anticonvulsant* OR "anti convulsant*" OR ((agent* OR drug*) W/2 (anticonvuls* OR "anticonvuls*" OR antiepilep* OR "anti epilep*")) OR acetazolamide OR bromides OR carbamazepine OR chlormethiazole OR clobazam OR "clorazepate dipotassium" OR diazepam OR dimethadione OR estazolam OR ethosuximide OR felbamate OR flunarizine OR gabapentin OR lacosamide OR lamotrigine OR levetiracetam OR lorazepam OR "magnesium sulfate" OR medazepam OR mephenytoin OR mephobarbital OR meprobamate OR nitrazepam OR oxcarbazepine OR paraldehyde OR phe nobarbital OR phenytoin OR pregabalin OR primidone OR riluzole OR thiopental OR tiagabine OR tiletamine OR topiramate OR trimethadio ne OR "valproic acid" OR vigabatrin OR zonisamide OR brivaracetam OR brivlera OR briviactam OR eslicarbazepine* OR apitom OR zebinix OR ganaxolon e OR losigamone OR perampanel OR fycompa OR piracetam OR pregabalin OR lyrica OR lecaent OR rewisca OR remacemide* OR retig abine OR ezogabine OR trobalt OR rufinamdie OR banzel OR inovelon OR safinamide OR xadago OR stiripentol OR diacomit OR convuls ion* OR seizure* OR epilep*))

Additional Table 3.1e: CINAHL search strategy

S45	S42 AND S43 AND S44
S44	S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41
S43	S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34
S42	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8
S41	(MH "Prenatal Exposure Delayed Effects") OR "Prenatal exposure"
S40	(prenatal* or "pre natal*")
S39	(Pregnan*)
S38	(Gestat*)
S37	(MH "Infant, Newborn")
S36	(MH "Expectant Mothers") OR "Pregnant woman"
S35	(MH "Pregnancy+")
S34	"pregnancy outcome"
S33	(MH "Pregnancy Outcomes")
S32	((fetal or foetal) N (develop* or growth))
S31	(MH "Fetal Development")
S30	"head circumference""
S29	"head circumference""
S28	"head circumference""
S27	(MH "Head Circumference")
S26	(cephalometry or craniometry)
S25	(MH "Cephalometry")
S24	(body N2 size*)
S23	"BODY HEIGHT"
S22	(MH "Body Size")
S21	(MH "Body Height")
S20	(fetal or foetal or intrauterine) N2 (growth retard* or "growth restrict*")
S19	(MH "Fetal Growth Retardation")
S18	(low N2 (birthweight* or "birth weight*") or lbw*
S17	SGA OR "small for gestational age"
S16	(MH "Infant, Small for Gestational Age")
S15	(MH "Infant, Low Birth Weight+") OR (MH "Infant, Very Low Birth Weight")
S14	(fetal or foetal) N weight*
S13	(MH "Fetal Weight")
S12	"Birth weight""
S11	(MH "Birth Weight")
S10	"Body weight""
S9	(MH "Body Weight+")

S8	lecaent or rewisca or remacemide* or retigabine or ezogabine or trobalt or rufinamdie or banzel or inovelon or safinamide or xadago or stiripentol or diacomit
S7	brivaracetam or brivlera or briviactam or eslicarbazepine* or apitom or zebinix or Ganaxolone or Losigamone or perampanel or fycompa or Piracetam or pregabalin or lyrica
S6	(convulsion or seizure or epilepsy)
S5	(MH "Epilepsy+")
S4	(MH "Seizures+")
S3	(acetazolamide or bromides or carbamazepine or chlormethiazole or clobazam or clorazepate dipotassium or diazepam or dimethadione or estazolam or ethosuximide or felbamate or flunarizine or gabapentin or lacosamide or lamotrigine or levetiracetam or lorazepam or "magnesium sulfate" or medazepam or mephenytoin or mephobarbital or meprobamate or nitrazepam or oxcarbazepine or paraldehyde or phenobarbital or phenytoin or pregabalin or primidone or riluzole or thiopental or tiagabine or tiletamine or topiramate or trimethadione or "valproic acid" or vigabatrin or zonisamide)
S2	(agent* or drug* N2 (anticonvuls* or "anti convuls*" or antiepilep* or "anti epilep*"))
S1	(MH "Anticonvulsants+")

Additional Table 3.1f: IPA search strategy

1.	((agent* or drug*) adj2 (anticonvuls* or anti convuls* or antiepilep* or anti epilep*)).mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
2.	(acetazolamide or bromides or carbamazepine or chlormethiazole or clobazam or clorazepate dipotassium or diazepam or dimethadione or estazolam or ethosuximide or felbamate or flunarizine or gabapentin or lacosamide or lamotrigine or levetiracetam or lorazepam or magnesium sulfate or medazepam or mephenytoin mephobarbital or meprobamate or nitrazepam oxcarbazepine or paraldehyde or phenobarbital or phenytoin or pregabalin or primidone or riluzole or thiopental or tiagabine or tiletamine or topiramate or trimethadione or valproic acid or vigabatrin or zonisamide).mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
3.	(convulsion or seizure or epilepsy).mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
4.	(brivaracetam or brivlera or briviact).mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
5.	(eslicarbazepine* or apitom or zebinix).mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
6.	(fosphenytoin* or cerebyx or pro-epanutin).mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
7.	Ganaxolone.mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
8.	Losigamone.mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
9.	(perampanel or fycompa).mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
10.	Piracetam.mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
11.	(pregabalin or lyrica or lecaent or rewisca).mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
12.	remacemide*.mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
13.	(retigabine or ezogabine or trobalt).mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
14.	(rufinamide or banzel or inovelon).mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
15.	(safinamide or xadago).mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
16.	(stiripentol or diacomit).mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
17.	or/1-16 [anticonvulsants concept]
18.	Body weight*.mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
19.	Birth weight*.mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
20.	((fetal or foetal) adj weight*).mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
21.	Sga, small for gestational age.mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
22.	((low adj2 (birthweight* or birth weight*)) or lbw*).mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
23.	((fetal or foetal or intrauterine) adj (growth retard* or growth restrict*)).mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
24.	Body height.mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
25.	(body adj2 size*).mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
26.	(cephalometry or craniometry).mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
27.	Head.mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
28.	fetal.mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
29.	((fetal or foetal) adj (develop* or growth)).mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
30.	pregnancy outcome.mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
31.	or/18-29 [birth size concept]
32.	(infant* or newborn*).mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
33.	Gestat*.mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
34.	Pregnan*.mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
35.	(prenatal* or pre natal*).mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
36.	or/32-35 [pregnancy concept]
37.	17 and 31 and 36
38.	limit 37 to (english or french)

Additional Table 3.1h: Global health search strategy

1.	exp anticonvulsants/
2.	((agent* or drug*) adj2 (anticonvuls* or anti convuls* or antiepilep* or anti epilep*)).tw.
3.	(acetazolamide or bromides or carbamazepine or chlormethiazole or clobazam or clorazepate dipotassium or diazepam or dimethadione or estazolam or ethosuximide or felbamate or flunarizine or gabapentin or lacosamide or lamotrigine or levetiracetam or lorazepam or magnesium sulfate or medazepam or mephenytoin or mephobarbital or meprobamate or nitrazepam or oxcarbazepine or paraldehyde or phenobarbital or phenytoin or pregabalin or primidone or riluzole or thiopental or tiagabine or tiletamine or topiramate or trimethadione or valproic acid or vigabatrin or zonisamide).tw.
4.	exp seizures/
5.	exp epilepsy/
6.	(convulsion or seizure or epilepsy).tw.
7.	(brivaracetam or brivlera or briviact).tw.
8.	(eslicarbazepine* or aptom or zebinix).tw.
9.	(fosphenytoin* or cerebyx or pro-epanutin).tw.
10.	Ganaxolone.tw.
11.	Losigamone.tw.
12.	(perampanel or fycompa).tw.
13.	Piracetam.tw.
14.	(pregabalin or lyrica or lecaent or rewisca).tw.
15.	remacemide*.tw.
16.	(rufinamdie or banzel or inovelon).tw.
17.	(safinamide or xadago).tw.
18.	(stiripentol or diacomit).tw.
19.	or/1-18 [anticonvulsants concept]
20.	exp body weight/
21.	Body weight*.tw.
22.	exp birth weight/
23.	Birth weight*.tw.
24.	((fetal or foetal) adj weight*).tw.
25.	exp low birth weight infants/
26.	Sga, small for gestational age.tw.
27.	((low adj2 (birthweight* or birth weight*)) or lbw*).tw.
28.	growth retardation/
29.	fetal growth/
30.	anthropometric dimensions/
31.	((fetal or foetal or intrauterine) adj (growth retard* or growth restrict*)).tw.
32.	height/
33.	(height or body height).tw.
34.	(body adj2 size*).tw.
35.	body measurements/
36.	(cephalometry or craniometry).tw.
37.	head/ or head dimensions/
38.	(Head or head dimensions).tw.
39.	fetal development/
40.	((fetal or foetal) adj (develop* or growth)).tw.
41.	pregnancy outcome.tw.
42.	or/20-41 [birth size concept]
43.	exp pregnancy/
44.	exp pregnant women/
45.	infants/
46.	neonates/
47.	exp infants/
48.	(infant* or neonates* or newborn*).tw.
49.	Gestat*.tw.
50.	Pregnan*.tw.
51.	(prenatal* or pre natal*).tw.
52.	or/43-51 [pregnancy concept]
53.	19 and 42 and 52

3.13. Author list and contribution of authors

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Chapter 4: Antiseizure Medication Use During Pregnancy and Adverse Neonatal Birth Outcomes: Population-Based Cohort Study

4.1. Overview

This is the first manuscript of the real word data generation project which evaluated the safety of antiseizure medications (ASMs) use in pregnancy and neonatal adverse outcomes. We conducted a cohort study using administrative health databases from Manitoba which included all pregnant people between 1998 to 2021. We conducted crude, adjusted and high dimensional propensity scores (HDPS) logistic regression models using generalized estimating equations with the exchangeable matrix. We adjusted for various socio-demographic and clinical variables in both the full and HDPS model. We analyzed the association in 3 cohorts, any exposure group, within epilepsy group and the non-epilepsy group. We further conducted sensitivity analysis by stratifying the results on preterm/term birth as well as major malformation. The outcomes we evaluated include small for gestational age (SGA), low birth weight (LBW), preterm birth, NICU admissions, pregnant persons length of hospital stay (LOS) (>3days), infant LOS, infant mortality (≤365 days), neonatal mortality (≤27 days), neonatal readmissions, neonatal respiratory distress syndrome, neonatal persistent pulmonary hypertension , and severe neonatal morbidity. The results were present in odds ratios (OR) and 95% confidence interval (CI) and standard error (SE). We found a significant association between ASMs and adverse birth outcomes.

4.2. Abstract

Introduction

Antiseizure medication (ASM) exposure in-utero has been associated with an increased risk of adverse birth outcomes. Since seizures also contributes to the increase in the risk of neonatal adverse outcomes, it is crucial to separate the risk of outcomes caused by the underlying disorder (epilepsy) from ASMs, adjusting for confounding by indication. It is also important to understand the safety of ASMs in off-label use.

Objective

We aimed to study the association between ASM treatment during pregnancy and adverse neonatal birth outcomes among all pregnant people, pregnant people with epilepsy (PPWE), and pregnant people without epilepsy (PPWOE).

Methodology

We conducted a population-based retrospective cohort study of pregnant people in Manitoba from 1998 to 2021. We examined the association between ASMs and the risk of small for gestational age (SGA), low birth weight (LBW), preterm birth, NICU admissions, pregnant persons length of hospital stay (LOS) (>3days), infant LOS, infant mortality (≤365days), neonatal mortality (≤27days), and neonatal readmissions, neonatal respiratory distress syndrome, neonatal persistent pulmonary hypertension, and severe neonatal morbidity. Multivariable regression models were adjusted for clinical characteristics and pregnant persons comorbidities. We conducted crude, adjusted and high dimensional propensity scores (HDPS) models using GEE with exchangeable correlation structure.

Results

We included 297,734 pregnancies, including 4,187 ASM-exposed pregnant people, 881 exposed PPWE, and 3306 exposed PPWOE. Among all exposed pregnant people, we observed a significant increased risk of SGA (adjusted odds ratio [aOR] 1.16, 95% CI 1.04-1.30), LBW (aOR 1.66, 95% CI 1.47-1.88), preterm birth (aOR 1.56, 95% CI 1.41-1.73), NICU admissions (aOR 1.91, 95% CI 1.74-2.10), pregnant peoples LOS (aOR 1.25, 95% CI 1.16-1.35), LOS infant (aOR 1.68, 95% CI 1.56-1.82) and a non-significant increase in the risk of infant mortality (aOR 1.19, 95% CI 0.82-1.72), neonatal mortality (aOR 1.40, 95% CI 0.90-2.16), and neonatal readmissions (aOR 1.10, 95% CI 0.93-1.30), when compared with unexposed pregnant people. In PPWOE, we observed similar increased risks among PPWOE. Among PPWE we observed a non-significant increased risk of SGA (aOR 1.08, 95% CI 0.77-1.50), LBW (aOR 1.14, 95% CI 0.77-1.66), preterm birth (aOR 1.05, 95% CI 0.76-1.44), NICU admissions (aOR 1.26, 95% CI 0.99-1.76), LOS (pregnant people) (aOR 1.16, 95% CI 0.92-1.45), LOS (Infant) (aOR 1.15, 95% CI 0.91-1.46). We observed a significant decrease in severe neonatal morbidity (aOR 0.20, 95% CI 0.07-0.60), and a non-significant decrease in the risk of infant mortality (aOR 0.38, 95% CI 0.13-1.06), neonatal mortality (aOR 0.54, 95% CI 0.84-1.77) and neonatal readmissions (aOR 0.70, 95% CI 0.43-1.16). The results from HDPS models did not show statistical significance and showed attenuated effect estimates, indicating strong unmeasured confounding in adjusted models, which the HDPS models were able to account for.

Conclusion

ASM exposure in pregnant people is associated with a significant increase in adverse birth outcomes, but residual confounding should not be ignored. ASMs for non-epilepsy indications

must be rationalized, especially when safer alternate treatments are available for pregnant people. Larger studies with advance analysis models accounting for unmeasured confounding are recommended to better quantify the true association between ASMs and adverse neonatal outcomes.

4.3. Introduction

Epilepsy is a chronic neurological disorder characterized by uncontrolled seizures.[1] Among pregnant people, epilepsy prevalence is estimated to be between 0.3% to 0.7%.[2] Epilepsy is often associated with significant clinical challenges in pregnant people and adverse neonatal outcomes in infants; therefore, it requires vigilant monitoring and management with antiseizure medications (ASMs).[3] However, ASMs exposure in-utero has also been associated with an increased risk of several adverse birth outcomes, including small for gestational age (SGA), preterm birth and neonatal intensive care unit (NICU) admission.[4–6] Infants with adverse birth outcomes are at a higher risk of stillbirth and impaired thermoregulation at birth and long-term sequelae in adulthood, including impaired neurodevelopment, cardiovascular diseases, and diabetes.[7–9]

Since epilepsy contributes to the increase in the risk of neonatal adverse outcomes, it is crucial to separate the risk of outcomes caused by the underlying disorder (epilepsy) from ASMs, by adjusting for confounding by indication.[10] In recent years, there has been an increase in the non-epileptic use of antiseizure medications (ASMs), but the fetal evidence in this population is not yet established.

Thus, there is a current need for real-world evidence on the safety of ASMs during pregnancy, particularly within the epilepsy group and non epilepsy group. The aim of the current study was to study the association between in-utero exposure of ASMs and adverse neonatal outcomes among all pregnant people, pregnant people with epilepsy (PPWE) and pregnant people without epilepsy (PPWOE).

4.4. Methods

4.4.1. Design and study population

We conducted a cohort study using administrative health data from Manitoba, Canada between April 1st, 2018, to March 31st, 2021. A population-based retrospective cohort study design was used. The pregnancy-children cohort included pregnancies from three groups: all pregnant people, PPWE, and PPWOE.

4.4.2. Data sources

We constructed the cohort using the provincial administrative databases housed at the Manitoba Centre for Health Policy (MCHP) data repository. We used the following data sources to build our cohort 1) drug program information network (DPIN), a claims database (1995/96-2020/21) that connects Manitoba health and all pharmacies in Manitoba.[11] 2) Hospital abstracts database (1992/93-2020/21) contains demographic and clinical information of hospital admissions completed at the point of patient discharge from the hospital.[11] 3) Medical Claims -

Medical Services database (1992/93-2020/21) consists of information on the reimbursements for physician or primary care provider services including the International Classification of Diseases (ICD-9-CM and ICD-10-CM) codes, tariff codes etc.[11] 4) Manitoba Health Insurance Registry (1992/93-2020/21) collects demographic and insurance coverage information.[11] 5. National census database (1992/93-2020/21), is a free use data integrated at the MCHP which contains the residence codes, demographic data used in the calculation of socio-economic status (SES).[11] In addition we also used Hospital Newborn to Mother Link Registry (1992/93-2020/21) to link the infants records with the pregnant parents records.[11] All the patients records in the databases are deidentified and can be linked together by the scrambled Personal Health Identification Numbers (PHIN).[11] Each newborn receives a distinctive PHIN, which is linked to the pregnant parents record, facilitating the creation of our pregnant parent-infant cohort.[11]

4.4.3. Cohort definitions

We created our cohort with pregnant people who had medical insurance coverage for at least 5 years. We excluded stillbirths from our cohort as we had excess missing data in this variable. The gestational age of the newborn is extracted from hospital abstracts, while the trimesters of the pregnant people are defined as follows: The first trimester spans from the 1st day of gestation to the 14th week; the second trimester extends from the 15th to the 25th week, and the third trimester includes the period from the 26th week until the end of pregnancy. Any time during pregnancy refers to the period from the 1st day of gestation to the end of pregnancy.

Exposure to prescribed ASMs is defined as having at least one prescription filled during one of the exposure windows of interest (1st trimester, 2nd trimester, or 3rd trimester) or a prescription filled before the beginning of the exposure window but with a duration overlapping the exposure window.[12] Pregnant people with epilepsy (PPWE) were considered to have epilepsy if they had 1 physician claim or 1 hospitalization (ICD-9 345 or ICD-10 G40/G41) in the 5 years before giving birth.[12,13] ASMs use was identified using the anatomical therapeutic chemical (ATC) code N03A for "anti-epileptics" in the prescription drug data.

4.4.4. Outcomes

We examined 12 outcomes, including **a) Birth weight outcomes:** Small for gestational age[14]**:** Infants ≤10th percentile in birth weight, based on birth weight, gestational age, and sex and low birth weight (LBW)[15]: Birth weight <2,500 grams and recorded in hospital birth records, and **b) Infant health outcomes:** Preterm birth[16]: Live birth where the gestational age is < 37 weeks. Neonatal intensive care unit admissions[16]: Infant admitted to the intensive care unit at age ≤28 days. Infant Mortality[16]: Death among infants within 0 to 365 days of birth. Length of hospital stay (LOS) of pregnant persons[17]: Pregnant persons length of hospital stay >3 days after giving birth. LOS infant[17]: The length of an infant's stay in hospital > 3 days after birth. Neonatal readmissions[18]: Live birth and discharged but re-hospitalized within 28 days (≤28) after discharge. Neonatal Mortality[16]: Death among infants within 0 to 27 days (≤27). Neonatal respiratory distress syndrome[19]: ICD 10: P22.0, ICD-9-CM: 769. Neonatal persistent pulmonary hypertension[16]: ICD-10: P29.3; ICD-9: 747.83. Severe Neonatal Morbidity[16]: Neonatal sepsis, respiratory distress syndrome and other respiratory problems, hypoxic-ischemic

encephalopathy, convulsions of the newborn, brachial plexus injury/palsy and related conditions, persistent fetal circulation/neonatal hypertension and related conditions, grade iii or iv intraventricular hemorrhage (IVH)/ periventricular leukomalacia (PVL), intubation and resuscitation, gastroschisis & omphalocele, diaphragmatic hernia, congenital malformations of the circulatory system (Appendix table 4.2: outcomes definitions).

4.4.5. Covariates

The following were the covariates included in the adjusted models and the expert-specified covariates in the HDPS models. Covariates include pregnant persons age at delivery (0-17, 18-28 (reference (ref)), 29-39 and >40 years), hypertension (ref: yes), diabetes (ref: yes), mood and anxiety disorders (ref: yes), schizophrenia (ref: yes), personality disorder (ref: yes), asthma (ref: yes), coronary heart disease (ref: yes), and pain (ref: yes), SES (ref: low income), multiple births (ref: single birth), area of residence (ref: urban) and teratogenic medication exposure in the first trimester (ref: yes). (Appendix 4.3 and 4.4)

4.5. Statistical analysis

Descriptive statistics included pregnant peoples mean age, pregnant persons comorbidities, socioeconomic status (SES), and residence. We analyzed 3 cohorts including pregnant people exposed to any ASMs compared with unexposed pregnant people, exposed PPWE compared with unexposed PPWE and exposed PPWOE compared with unexposed PPWOE**.** In all cohorts, we conducted two analyses, multivariable logistic regression models and HDPS regression models. We used generalized estimating equations (GEE), with exchangeable matrix given that

pregnancies are the unit of analysis, not pregnant people.[20–22] We performed both the crude and adjusted analysis and presented the results in crude odds ratio (OR) and adjusted odds ratio (aOR), along with the 95% confidence interval (95% CI).[23] In the adjusted model we adjusted for the above specified covariates in section 4.4.5.

High Dimensional Propensity Scores (HDPS) were estimated using 5 data dimensions in all pregnant people in Manitoba. The 5 data dimensions include hospital medical diagnoses and hospital medical procedures (2 dimensions) from hospital abstracts, outpatient medical diagnoses and outpatient tariff codes (2 dimensions) from physician visits were identified during the year prior to infant birth date.[24] Prenatal drug dispensations excluding ASMs (1 dimension) from the Drug Program Information Network were identified during the 12 months prior to infants birth date.

For the HPDS analysis top 300 most repeated variables in the population were chosen.[25] In addition to the 300 variables, additional covariates (specified in section 4.4.5 and Appendix 4.3) were included in the HDPS estimation.[26] We trimmed the overlapping data between the exposed and unexposed groups.[26] Regression models were conducted adjusting for the HDPS values and using GEE, with exchangeable matrix. We presented the results in aOR, along with the 95% CI. We used statistical software SAS® 9.4 (SAS Institute; Cary, NC) for the analysis.

4.6. Results

4.6.1. Characteristics of participants and treatment courses

We studied a total of 297,734 pregnancies from Manitoba (Table 4.1 and Table 4.2) between 1998 to 2021. A total of 4,187 pregnant people were exposed to ASMs including 881 exposed among PPWE and 3306 exposed PPWOE. More than 50% of the exposed pregnant people belonged to the lower socio-economic status group. Among individuals exposed to ASMs in the study population, the proportion of chronic diseases included hypertension (332, 7.93%), diabetes (302, 7.21%), mood and anxiety disorders (2323, 55.48%), schizophrenia (50, 1.19%), personality disorders (119, 2.84%), asthma (681, 16.26%), and chronic pain (1194, 28.52%). Compared to unexposed pregnant people exposed pregnant people had higher proportions of chronic diseases **(Table 4.1)**

4.6.2. Pregnancy outcomes

In our study, during the 23-year study period, 400 (9.55%) infants were born with SGA, 400 (9.55%) with LBW, 429 (10.25%) were born preterm, and 444 (10.60%) of infants required NICU admission. Additionally, 990 (23.65%) pregnant people and 1,132 (27.04%) infants experienced an LOS lasting more than 3 days. Moreover, 32 (0.76%) cases of infant mortality and 22 (0.53%) neonatal mortality were reported, and 166 (3.96%) neonates required readmissions. Counts of neonatal adverse outcomes in all pregnant people, PPWE and PPWOE are included in **Table 4.2.**

All pregnant people

The adjusted analysis revealed that among pregnant people exposed to ASMs, there was a significant increased risk of SGA; aOR 1.16 (95% CI 1.04-1.30), LBW; aOR 1.66 (95% CI 1.47-1.88), preterm birth; aOR 1.56 (95% CI 1.41-1.73), NICU admissions; aOR 1.91 (95% CI 1.74-2.10), LOS of both pregnant people; aOR 1.25 (95% CI 1.16-1.35) and infants; aOR 1.68 (95% CI 1.56-1.82). However, there was a non-significant increased risk of neonatal mortality aOR 1.40 (95% CI 0.90-2.16), infant mortality aOR 1.19 (95% CI 0.82-1.72), neonatal readmissions aOR 1.10 (95% CI 0.93-1.30), and severe neonatal morbidity aOR 1.04 (95% CI 0.90-2.16) and a nonsignificant decrease in neonatal persistent pulmonary hypertension aOR 0.94 (95% CI 0.13-6.92), and neonatal respiratory distress syndrome aOR 0.93 (95% CI 0.32-2.69). In the HDPS adjusted analysis, among all pregnant people exposed to ASMs, there was a significant increased risk of LBW aOR 1.35 (95% CI 1.13-1.60), preterm birth aOR 1.22 (95% CI 1.05-1.42), NICU admissions aOR 1.45 (95% CI 1.25-1.67), LOS of infants aOR 1.25 (95% CI 1.11-1.40). No significant associations were observed for SGA aOR 1.03 (95% CI 0.89-1.20), LOS of pregnant people aOR 1.12 (95% CI 1.00-1.24), neonatal mortality aOR 1.11 (95% CI 0.56-2.20), neonatal readmissions aOR 1.14 (95% CI 0.89-1.46) and severe neonatal morbidity aOR 1.15 (95% CI 0.72-1.82). We observed a significant decrease in the risk of neonatal respiratory distress syndrome aOR 0.02 (95% CI 0.07-0.62) and non-significant decrease in the risk of infant mortality aOR 0.92 (95% CI 0.51-1.66), and neonatal persistent pulmonary hypertension aOR 0.21 (95% CI 0.02-2.11). **(Table 4.3)**

Pregnant people with epilepsy (PPWE)

In the adjusted analysis among PPWE exposed to ASMs, there was a significant decrease in the risk of severe neonatal morbidity aOR 0.20 (95% CI 0.07-0.60). We did not observe a significant risk with SGA; aOR 1.08 (95% CI 0.77-1.50), LBW; aOR 1.14 (95% CI 0.77-1.66), preterm birth; aOR 1.05 (95% CI 0.76-1.44), NICU admissions; aOR 1.26 (95% CI 0.94-1.70), LOS of both pregnant people; aOR 1.16 (95% CI 0.92-1.45) and infants; aOR 1.15 (95% CI 0.91-1.46), neonatal mortality aOR 0.54 (95% CI 0.16-1.77), infant mortality aOR 0.38 (95% CI 0.13-1.06), and neonatal readmissions aOR 0.70 (95% CI 0.433-1.16). In the HDPS adjusted analysis, among exposed PPWE, there was a significant decrease in the risk of infant mortality aOR 0.35 (95% CI 0.13-0.99), neonatal mortality aOR 0.37 (95% CI 0.16-0.88), and severe neonatal morbidity aOR 0.21 (95% CI 0.07-0.69). We observed a non-significant decrease in the risk of SGA aOR 0.82 (95% CI 0.45-1.50), LBW aOR 0.78 (95% CI 0.40-1.53), preterm birth aOR 0.86 (95% CI 0.49-1.54), LOS of infants aOR 0.89 (95% CI 0.57-1.37) and a non-significant increase in the risk of NICU admissions aOR 1.08 (95% CI 0.58-2.02), LOS of pregnant people aOR 1.26 (95% CI 0.82-1.93), and neonatal readmissions aOR 1.79 (95% CI 0.76-4.17). **(Table 4.4)**

Pregnant people without epilepsy (PPWOE)

Exposed PPWOE showed similar risk levels and effect magnitudes in both adjusted and HDPS analyses compared to overall pregnant people group. However, in the adjusted analysis among exposed PPWOE we observed a non-significant increase in risk of neonatal persistent pulmonary hypertension aOR 1.19 (95% CI 0.16-8.78) and neonatal respiratory distress syndrome aOR 1.16 (95% CI 0.39-3.46), compared to unexposed PPWOE. **(Table 4.5)**

4.7. Discussion

In this study, we found a significant association between LBW, preterm birth, Infants LOS and NICU admissions among all pregnant people exposed to ASMs. However, we did not observe a significant increased risk of other outcomes including neonatal readmissions, pregnant peoples LOS, neonatal mortality, and severe neonatal morbidity and neonatal admissions among all exposed pregnant people. The HDPS analysis across all three cohorts, showed a notable reduction in the risk magnitudes of the outcomes, highlighting a strong unmeasured confounding in the adjusted model that was effectively accounted for within the HDPS analysis.

When examining our SGA results among all exposed pregnant people, the risk is lower than those of other published studies.[27,28] In the context of the HDPS model, it is apparent that with the adjustment of unmeasured confounding, the SGA risk diminishes significantly to approximately 3%. Preterm birth has a higher risk among all pregnant people and PPWOE, aligning with the findings in previously published studies.[4,28] This study marks the initial exploration of morbidity, mortality, and readmission outcomes among pregnant people exposed to ASMs. Our results among all exposed pregnant people and PPWOE suggest an increasing risk of morbidity, mortality, and readmission outcomes but they did not reach significance.

In literature having epilepsy itself has been associated with an elevated risk of various adverse neonatal outcomes.[29] In our analysis focused on PPWE, we accounted for the presence of the

underlying disorder (epilepsy) thereby adjusting for confounding by indication. Therefore, risks observed in this analysis are attributable to the exposed ASMs. It is crucial to highlight the significantly lower risk of infant mortality, neonatal mortality, and severe neonatal morbidity among exposed PPWE compared with unexposed PPWE. By adjusting the underlying epilepsy, which serves as the baseline condition in this population, we might have observed such decreased risks. This suggests that PPWE treated with ASMs have a lower risk of infant mortality, neonatal mortality and neonatal morbidity compared to untreated PPW, attributed to better control for epilepsy seizures.

It is also important to note that outcomes such as neonatal persistent pulmonary hypertension and neonatal respiratory distress syndrome are rare outcomes. Considering our current sample size, all pregnant people and PPWOE analysis have yielded results with large wide confidence intervals, signaling potential instability in the analysis. In particular, the analysis did not converge for PPWE, mostly due to the underpowered sample size.

Over the past decade, there has been an increase in the utilization of ASMs for non-epilepsy purposes, particularly for off-label indications and recreational drug use.[12,30] ASMs have been extensively used for off-label indications with examples including the use of gabapentin for pain and anxiety management, and clonazepam for addressing mental health disorders.[12,30] In our study, among PPWOE we observed a significant increased risk of SGA, LBW, preterm birth, LOS of infants and pregnant people, and NICU admissions, and non-significant increased risk of mortality, morbidity and readmission outcomes. With the increase in the use of ASMs for non-

epilepsy indications it is essential to exercise caution when considering ASMs use during pregnancy, especially for non-epilepsy indications with safe alternatives when available.[12,30]

In our study, we included the population during the COVID-19 pandemic (2020-2021). The COVID-19 pandemic has impacted the lives of patients with chronic diseases.[31,32] Lavu et al. reported small but significant changes in the incident and prevalent use of ASM prescriptions in Manitoba with the introduction of public health measures during COVID-19.[33] We believe that with no major changes in the prescription of medication, the data during this period included in our study will not be largely influenced by the COVID 19 pandemic.

ASMs have been linked to various mechanisms of action, with many ASMs linked to multiple mechanisms, still yet to be discovered. Some biological mechanisms have been associated with in-utero exposure to ASMs causing adverse neonatal outcomes in infants. ASMs have been hypothesized to have the capacity to affect hormonal regulation in pregnant people but the mechanism of this association is still unclear.[28] According to a meta-analysis by Zhang et al, PPWE who were exposed to carbamazepine, phenytoin, and valproic acid experienced alterations in thyroid hormones, which are essential for the normal development of the fetus.[28] Studies have shown that ASMs can interfere with placental blood flow, nutrient transport, oxidative stress, and folate deficiency which can lead to various adverse outcomes like growth deficiencies as well as malformations.[34–36] ASMs can also induce epigenetic modifications, influencing fetal development and increasing the susceptibility to certain health conditions later in life.[37] Epilepsy disorder imposes a significant economic burden on both the patients and

health care institutions.[38] A systematic review and meta-analysis by Thompson et al reported that in 2019 direct healthcare costs per person due to epilepsy was reported as $10,659 USD in Canada.[38] The estimated cost of epilepsy globally based on the average costs per person was estimated to be around 113.27 billion USD per year.[38]

The utilization of an administrative database in our study introduces the potential for misclassification bias, although it is more likely to be non-differential.[34] Our prescription database records prescriptions filled but does not capture medication adherence. However, it is worth noting that medications for chronic conditions such as epilepsy are typically continued by pregnant patients.[39] Unfortunately, our database lacks information on the severity of epilepsy, which restricts our ability to adjust for confounding by disease severity. Additionally, our analysis did not account for the indications for ASMs among PPWOE. To address these confounding factors related to indication and disease severity, we conducted an HDPS analysis. This involved the incorporation of the most repeated covariate among all pregnant people in Manitoba that will act as proxies for unmeasured confounders such as disease severity and indication bias in our analysis, allowing us to adjust for both measured and unmeasured confounding variables. Despite employing advanced modelling techniques, it is important to acknowledge the possibility of residual bias in our results.

This Canadian study represents the first comprehensive examination of ASM safety during pregnancy, including analyses of PPWE and those using ASMs for non-epileptic reasons. Within the PPWE analysis, by differentiating the medication's risk from the underlying epilepsy

disorder, we achieved a more comprehensive understanding of the ASMs associated risks. Our study's findings possess applicability beyond the study cohort, extending to similar populations.

4.8. Conclusion

Exposure to ASMs in pregnant people was found to be associated with an elevated risk of adverse birth outcomes, specifically LBW, preterm birth, NICU admission and pregnant persons and infants' LOS. Therefore, careful consideration and rationalization of ASM usage especially in non-epilepsy indications are warranted, particularly when safer alternative treatments are available. Future research must utilize advanced statistical methods and study designs to account for unmeasured confounding.

4.9. Acknowledgements

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4.10. Tables

Table 4.1: Characteristics of pregnant people

	Exposed		***Unexposed***	
	PPWE N (%)	PPWOE N (%)	PPWE N (%)	PPWOE N (%)
Total pregnant people	881 (0.3)	3306 (1.1)	1014 (0.3)	292533 (98.3)
Age of* pregnant people *at birth (mean years)	28.1	29.5	26.7	28.1
Chronic diseases				
• *Hypertension*	36 (4.1)	296 (9)	32 (3.2)	4823 (1.6)
• *Diabetes*	32 (3.6)	270 (8.2)	38 (3.7)	9177 (3.1)
• *Mood and Anxiety disorder*	208 (23.6)	2115 (64)	223 (22)	31208 (10.7)
• *Schizophrenia*	6 (0.8)	44 (1.5)	S	264 (0.1)
• *Personality disorder*	10 (1.3)	109 (3.8)	12 (1.3)	793 (0.3)
• *Chronic pain*	87 (10.9)	594 (20.5)	121 (12.7)	14765 (5.5)
• *Asthma*	147 (16.7)	1047 (31.7)	186 (18.3)	34574 (11.8)
• *Cardiovascular diseases*	S	18 (0.5)	S	288 (0.1)
Singleton birth	858 (97.4)	3214 (97.2)	995 (98.1)	284727 (97.3)
Multiple birth	23 (2.6)	92 (2.8)	19 (1.9)	7806 (2.7)
Exposure to teratogenic drugs	46 (5.2)	310 (9.4)	31 (3.1)	7520 (2.6)
SES				
Q1	267 (30.3)	1981 (41.8)	320 (31.6)	75199 (25.7)
Q2	223 (25.3)	716 (21.7)	209 (20.6)	62927 (21.5)
Q3	177 (20.1)	518 (15.7)	208 (20.5)	54087 (18.5)
Q4	128 (14.5)	367 (11.1)	178 (17.6)	53742 (18.4)
Q5	80 (9.1)	313 (9.5)	96 (9.5)	45762 (15.6)
Urban	487 (55.3)	1995 (60.3)	598 (59)	154567 (52.8)
Rural	394 (44.7)	1311 (39.7)	416 (40.0)	137966 (47.2)

SES: *Socio-economic status**,** PPWE: pregnant people with epilepsy, PPWOE: pregnant people without epilepsy, S= supressed*

Table 4.2: Outcome counts among pregnant people.

Outcomes	***Exposed***		***Unexposed***	
	PPWE N (%)	PPWOE N (%)	PPWE N (%)	PPWOE N (%)
Total Pregnant people	881 (0.3)	3306 (1.1)	1014 (0.3)	292533 (98.3)
SGA	88 (10)	312 (9.4)	94 (9.3)	22505 (7.7)
LBW	85 (9.6)	344 (10.4)	81 (7.3)	15777 (5.4)
Preterm birth	106 (12)	338 (16.3)	119 (11.7)	23434 (8)
NICU admissions	127 (14.4)	669 (20.2)	117 (11.5)	23028 (7.9)
LOS of* pregnant people *(>3 days)	227 (25.8)	763 (23.1)	230 (22.7)	51041(18)
LOS of infants (>3 days)	216 (24.5)	916 (27.7)	216 (21.3)	42858 (14.7)
Infant mortality	6 (0.7)	26 (0.8)	15 (1.5)	1699 (0.6)
Neonatal readmissions	29 (3.3)	137 (4.2)	46 (4.6)	8771 (3)
Neonatal mortality	S	17 (0.5)	10 (1.0)	1109 (0.4)
Neonatal persistent pulmonary hypertension	S	S	S	66.0 (00)
Neonatal respiratory distress syndrome	S	S	S	249 (0.1)
Severe neonatal morbidity	S	38 (1.1)	20 (2)	2334 (0.8)

SGA: small for gestational age, LBW: low birth weight, , SES: Socio economic status, PPWE: pregnant people with epilepsy, PPWOE: pregnant people without epilepsy, S= supressed

Table 4.3: Results of regression models and HDPS analysis evaluating the association Between ASMs and neonatal birth outcomes among all pregnant people

Outcomes	*Crude Models OR (95% CI)*	*Adjusted Models OR (95% CI)*	*HDPS Regression models OR (95% CI)*
SGA	1.24 (1.11-1.38)	**1.16 (1.04-1.30)**	1.03 (0.89-1.20)
LBW	1.92 (1.71-2.15)	**1.66 (1.47-1.88)**	**1.35 (1.13-1.60)**
Preterm birth	1.92 (1.74-2.12)	**1.56 (1.41-1.73)**	**1.22 (1.05-1.42)**
NICU admissions	2.53 (2.32-2.76)	**1.91 (1.74-2.10)**	**1.45 (1.25-1.67)**
LOS of* pregnant people *(>3 days)	1.42 (1.32-1.53)	**1.25 (1.16-1.35)**	1.12 (1.00-1.24)
LOS of infants (>3 days)	2.02 (1.87-2.17)	**1.68 (1.56-1.82)**	**1.25 (1.11-1.40)**
Infant mortality	1.27 (0.88-1.84)	1.19 (0.82-1.72)	0.92 (0.51-1.66)
Neonatal mortality	1.43 (0.93-2.20)	1.40 (0.90-2.16)	1.11 (0.56-2.20)
Severe neonatal morbidity	1.24 (0.90-1.72)	1.04 (0.75-1.44)	1.15 (0.72-1.82)
Neonatal readmissions	1.31 (1.12-1.56)	1.10 (0.93-1.30)	1.14 (0.89-1.46)
Neonatal persistent pulmonary hypertension	1.05 (0.15-7.54)	0.94 (0.13-6.92) *	0.21 (0.02-2.11)
Neonatal respiratory distress syndrome	1.07 (0.38-2.96)	0.93 (0.32-2.69)	**0.02 (0.07-0.62)**

*SGA: small for gestational age, LBW: low birth weight, SES: Socio economic status, PPWE: pregnant people with epilepsy, PPWOE: pregnant people without epilepsy. Adjusted for Pregnant persons age, multiple births, SES, asthma, cardiovascular diseases, multiple birth, pain, psychiatric disorders, schizophrenia, diabetes, hypertension, mood disorders, urban/rural, teratogenic drugs, *Reduced model 1: Exposed to teratogenic drugs 1st trimester, Area of Residence: Rural and urban (reference),,Hypertension, Diabetes, Asthma, Pain, Pregnant persons age(Continuous), SES , and Multiple births, ** Reduced model 2: Hypertension, Diabetes, Asthma, Pain, Pregnant persons age (Continuous) and SES , *** Reduced model 3: Pregnant persons age(Continuous) and SES*

Table 4.4: Results of regression models and HDPS analysis evaluating the association between ASMs and neonatal birth outcomes among PPWE

Outcomes	*Crude Models OR (95% CI)*	*Adjusted Models OR (95% CI)*	*HDPS Regression models OR (95% CI)*
SGA	1.09 (0.80-1.50)	1.08 (0.77-1.50)*	0.82 (0.45-1.50)
LBW	1.24 (0.85-1.79)	1.14 (0.77-1.66)	0.78 (0.40-1.53)
Preterm birth	1.07 (0.79-1.46)	1.05 (0.76-1.44)*	0.86 (0.49-1.54)
NICU admissions	1.32 (0.99-1.76)	1.26 (0.94-1.70)*	1.08 (0.58-2.02)
LOS of* pregnant people *(>3 days)	1.18 (0.95-1.47)	1.16 (0.92-1.45)	1.26 (0.82-1.93)
LOS of infants (>3 days)	1.21 (0.96-1.51)	1.15 (0.91-1.46)*	0.89 (0.57-1.37)
Infant mortality	0.46 (0.17-1.22)	0.38 (0.13-1.06)*	**0.35 (0.13-0.99)**
Neonatal mortality	0.56 (0.18-1.73)	0.54 (0.16-1.77)***	**0.37 (0.16-0.88)**
Severe neonatal morbidity	0.23 (0.08-0.66)	**0.20 (0.07-0.60)***	**0.21 (0.07-0.69)**
Neonatal readmissions	0.72 (0.44-1.17	0.70 (0.43-1.16)**	1.79 (0.76-4.17)
Neonatal persistent pulmonary hypertension	N/A	N/A	N/A
Neonatal respiratory distress syndrome	N/A	N/A	N/A

*SGA: small for gestational age LBW: low birth weight, SES: Socio economic status, PPWE: pregnant people with epilepsy, PPWOE: pregnant people without epilepsy. Adjusted for Pregnant persons age, multiple births, SES, asthma, cardiovascular diseases, multiple birth, pain, psychiatric disorders, schizophrenia, diabetes, hypertension, mood disorders, urban/rural, teratogenic drugs, *Reduced model 1: Exposed to teratogenic drugs 1st trimester, Area of Residence: Rural and urban (reference),,Hypertension, Diabetes, Asthma, Pain, Pregnant persons age(Continuous), SES , and Multiple births, ** Reduced model 2: Hypertension, Diabetes, Asthma, Pain, Pregnant persons age (Continuous) and SES , *** Reduced model 3: Pregnant persons age(Continuous) and SES. N/A: model did not converge*

Table 4.5: Results of regression models and HDPS analysis evaluating the association between ASMs and neonatal birth outcomes among PPWOE

Outcomes	*Crude Models OR (95% CI)*	*Adjusted Models OR (95% CI)*	*HDPS Regression models OR (95% CI)*
SGA	1.95 (1.72-2.21)	**1.14 (1.01-1.29)**	1.04 (0.88-1.22)
LBW	1.23 (1.09-1.39)	**1.64 (1.43-1.88)**	**1.35 (1.13-1.62)**
Preterm birth	2.01 (1.80-2.24)	**1.58 (1.41-1.76)**	**1.21 (1.03-1.42)**
NICU admissions	2.68 (2.43.2.95)	**1.94 (1.75-2.14)**	**1.50 (1.28-1.75)**
LOS of* pregnant people *(>3 days)	1.37 (1.26-1.49)	**1.18 (1.08-1.29)**	1.08 (0.97-1.21)
LOS of infants (>3 days)	2.06 (1.90-2.24)	**1.66 (1.53-1.82)**	**1.25 (1.11-1.41)**
Infant mortality	1.30 (0.86-1.97)	1.21 (0.80-1.84)	0.86 (0.47-1.58)
Neonatal mortality	1.43 (0.88-2.33)	1.38 (0.84-2.27)	1.00 (0.50-2.01)
Severe neonatal morbidity	1.43 (1.01-2.01)	1.17 (0.82-1.66)	1.22 (0.78-1.89)
Neonatal readmissions	1.37 (1.15-1.64)	1.11 (0.93-1.34)	1.18 (0.91-1.53)
Neonatal persistent pulmonary hypertension	1.34 (0.19-9.66)	1.19 (0.16-8.78)**	0.25 (0.02-3.57)
Neonatal respiratory distress syndrome	1.35 (0.48-3.81)	1.16 (0.39-3.46)	**0.27 (0.1-0.75)**

*SGA: small for gestational age, LBW: low birth weight, SES: Socio economic status, PPWE: pregnant people with epilepsy, PPWOE: pregnant people without epilepsy. Adjusted for Pregnant persons age, multiple births, SES, asthma, cardiovascular diseases, multiple birth, pain, psychiatric disorders, schizophrenia, diabetes, hypertension, mood disorders, urban/rural, teratogenic drugs, *Reduced model 1: Exposed to teratogenic drugs 1st trimester, Area of Residence: Rural and urban (reference),,Hypertension, Diabetes, Asthma, Pain, Pregnant persons age(Continuous), SES , and Multiple births, ** Reduced model 2: Hypertension, Diabetes, Asthma, Pain, Pregnant persons age (Continuous) and SES , *** Reduced model 3: Pregnant persons age(Continuous) and SES*

4.11. Appendices

Appendix Table 4.1: Data sources in Manitoba

Database	Years	Data Fields/Variables	Rationale
Drug Program Information Network (DPIN)	1995/96-2020/21	Prescriptions, drugs, characteristics (type, dose, quantity, class), carriers, prescribers, providers, pharmacy	To examine the use of pharmaceutical drugs and define chronic diseases and comorbidities
Hospital abstracts	1992/93-2020/21	Hospitalizations, admission date, birth, diagnoses (ICD-10) and procedures.	To identify the outcomes of interest and disease states/procedures associated with exclusion and inclusion criteria.
Medical Claims - Medical Services	1992/93-2020/21	Date of encounter, specialty, diagnoses (ICD-9) and procedures.	To identify the outcomes of interest, and disease states/procedures associated with exclusion and inclusion criteria.
Manitoba Health Insurance Registry	1992/93-2020/21	Scrambled PHIN, family registration number, date of birth, coverage status, sex, location of residence, migration in/out of province date	Needed to identify individuals with valid MB health insurance for cohort entry. Sex is used as a covariate. Postal codes will be used to calculate socioeconomic variables in combination with census data. Migration status/date helps determine cohort follow-up duration
Hospital Newborn to Mother Link Registry (HNMLR) data	1992/93-2020/21	Contains historical data related to mothers and newborns	To identify mother infant linkage in the administrative database
Public-use Canada Census data	1992/93-2020/21	Contains free to use Canada wide census data available at MCHP	To obtain information on residence and calculate the income quintiles

Appendix Table 4.2: Outcomes definitions

Outcomes definition	
Birth weight outcomes	
• Small for gestational age	Infants ≤10th percentile in birth weight, based on birth weight, gestational age, and sex as recorded in the hospital birth record.[14]
• Low birth weight	Birth weight <2,500 grams and recorded in hospital birth record.[15]
Birth outcomes	
• Preterm birth	Live birth gestational age <37weeks.[16]
• Neonatal intensive care unit admissions	Infant admitted to the intensive care unit at age ≤28 days.[16]
• Neonatal persistent pulmonary hypertension	A syndrome characterized by marked pulmonary hypertension that causes hypoxemia secondary to right-to-left shunting of blood at the foramen ovale and ductus arteriosus.[16]
• Neonatal respiratory distress syndrome	Neonatal respiratory distress syndrome (RDS) occurs from a deficiency of surfactant, due to either inadequate surfactant production, or Surfactant inactivation in the context of immature lungs.[19]
• Pregnant persons length of hospital stay	The length of stay of mother in hospital after giving birth for more than 3 days.[17]
• Infants' length of hospital stay	The length of stay of an infant in hospital after giving birth for more than 3 days.[17]
• neonatal readmissions	Live birth and discharged, but then re-hospitalized within 28 days (≤28) after discharging alive from their birth hospitalization.[18]
• Severe neonatal morbidity	Neonatal sepsis, respiratory distress syndrome and other respiratory problems, hypoxic-ischemic encephalopathy, convulsions of the newborn, brachial plexus injury/palsy and related conditions, persistent fetal circulation/neonatal hypertension and related conditions, grade iii or iv, intraventricular hemorrhage (IVH)/ periventricular leukomalacia (PVL), intubation and resuscitation, gastroschisis & omphalocele, diaphragmatic hernia and congenital malformations of the circulatory system. (Refer to Chapter 4 for ICD codes)[16]
• Neonatal mortality	Death among infants within 0 to 27days.[16]
• Infant mortality	Death among infants within 0 to 365 days of birth.[16]

Appendix Table 4.3: Covariates and comorbidities

Comorbidities	Definitions
Hypertension[40]	Females with one of the following within 1-year before conception • At least one hospital diagnosis for hypertension: (ICD-9-CM, 401: essential hypertension= 401-405 OR ICD-10-CA: I10-I14: essential (primary) hypertension); in the year before conception, OR At least two ambulatory visit diagnoses: (ICD-9-CM codes: 401-405) OR At least two dispensations for hypertension medication
Diabetes[40,41]	Females with one of the following within 3-years before conception: • One or more hospitalizations with a diagnosis of diabetes (ICD-9-CM code 250 diabetes mellitus; ICD-10-CA codes E10-E14 diabetes mellitus), OR Two or more physician visits with a diagnosis of diabetes (ICD-9-CM codes as above), OR One or more prescriptions for medications to treat diabetes (ATC code A10).
Mood and anxiety disorders[42]	Females with one of the following within 1-year before conception • At least one hospitalization (ICD-9-CM codes 296.2-296.8, 300, 309, 311; ICD-10-CA codes F31, F32, F33, F34.1, F38.0, F38.1, F40, F41, F42, F43.1, F43.2, F43.8, F44, F45.0, F45.1, F452, F48, F53.0, F68.0, F93.0, F99 OR One or more physician visits with a diagnosis for depressive disorder, affective psychoses, or adjustment reaction (ICD-9-CM codes 296, 309 or 311) OR Two or more physician visits with a diagnosis for anxiety disorders (ICD-9-CM code 300).
Personality disorders[43]	Females with one of the following within 1-year before birth • At lease one or more hospitalization with a diagnosis for personality disorders in one year before birth ICD-9-CM code: 301; OR ICD-10-CA codes: F21, F34.0, F60, F61, F62, F68.1, F68.8 or F69; OR at least one physician visit with a diagnosis for personality disorders using ICD-9-CM code 301.
Pain	Females with one of the following within 1-year before conception • One or more hospitalization with a diagnosis of pain (ICD-9 code 338; ICD-10 R52 G89 G50) Neuralgia (ICD-9 729.2; ICD-10 M79.2) Migraine and Headaches (ICD-9 346 784; ICD-10 G43 R51) OR One or more codes in the physician data ICD-9 338,346,784.
Schizophrenia[44]	Females with one of the following within 1-year before conception • One or more hospitalization with a diagnosis for schizophrenia: ICD-9-CM code: 295 (schizophrenic disorders); OR ICD-10-CA codes: F20 (schizophrenia), F21 (schizotypal disorder), F23.2 (acute schizophrenia-like psychotic disorder), F25 (schizoaffective disorders); OR One or more physician visits with a diagnosis for schizophrenia using ICD-9-CM code 295.

Asthma[40]	Females with one of the following within 1-year before conception • One or more hospitalizations for asthma (ICD-9-CM Codes 493 and ICD-10-CA Diagnosis Codes J45: asthma and J46: status asthmaticus) OR one or more physician's visit, OR at least one medication prescription for asthma with ATC code: R03A (adrenergics, inhalants), R03B (other drugs for obstructive airway diseases, inhalants), R03C (other drugs for obstructive airway diseases, inhalants), and R03D (other systemic drugs for obstructive airway diseases) and R06AX17 Ketotifen)
Coronary heart disease[40]	Females with one of the following within one-year before conception • One or more hospitalizations with a diagnosis of coronary heart disease using ICD-9-CM Codes 410 – 414: ischemic heart disease and ICD-10-CA Diagnosis Codes I20 – I25: ischaemic heart diseases OR One or more physician visits with a diagnosis of coronary heart disease (ICD codes as above), OR One or more prescriptions for medications to treat coronary heart disease with ATC code:C01 (cardiac therapy), C07 (beta-blocking agents), C08 (calcium channel blockers), and C09 (agents acting on the renin-angiotensin system)
Area of residence[45]	Urban and rural area of residence, Is obtained through census data
Socio economic status (income quantiles)[46]	SES in our study is categorized into Low and high (high used as reference). Where U1, U2, R1, R2 = 1, and U3, U4, U5, R3, R4, R5 = 0 when U is urban, and R is rural, R1/U1 being the lowest income quintiles and U5/R5 being the highest income quintiles). These quantiles are calculated using the Census data
Pregnant persons age[46]	• Pregnant persons age categorization: categorize into 0-17, 18- 28 (reference), 29-39 and >40 years. • Pregnant persons age continuous Is obtained through the Hospital Abstracts data, Hospital Newborn to Mother Link Registry data; and Manitoba Health Insurance Registry data
Exposure to teratogenic agents	Exposure to potential teratogenic medication in the first trimester of pregnancy. The data is obtained from the prescription claims data.
Multiple births and singleton births[16]	**Multiple births:** birth of two or more children during a single delivery with a gestation of 20 weeks or more. **Singleton birth:** the birth of only one child during a single delivery with a gestation of 20 weeks or more. These outcomes are obtained through the hospital abstracts

Appendix Table 4.4: Medications with sufficient evidence of a teratogenic risk in the first trimester

1. acenocoumarin	2. acitretin	3. alitretinoin	4. amethopterin
5. amsacrine	6. axitinib	7. bishydroxycoumarin	8. bleomycin
9. brentuximab	10. busulfan	11. capecitabine	12. thalidomide
13. carbimazole	14. carboplatin	15. carmustine	16. chlorambucil
17. cisplatin	18. cladribine	19. colchicine	20. crizotinib
21. cyclophosphamide	22. cytarabine	23. dacarbazine	24. dactinomycin
25. danazol	26. daunorubicin	27. diethylstilbestrol	28. docetaxel
29. doxorubicin	30. epirubicin	31. estramustine	32. etoposide
33. etretinate	34. exemestane	35. flucytosine	36. fludarabine
37. fluorouracil	38. fluoxymesterone	39. formestane	40. gemcitabine
41. idarubicin	42. ifosfamide	43. imatinib	44. iodine-125 /123
45. iodine-131	46. isotretinoin	47. l-asparaginase	48. leflunomide
49. lenalidomide	50. lithium	51. lomustine	52. mechlorethamine
53. medroxyprogesterone	54. melphalan	55. mephenytoin	56. mephobarbital
57. methandrostenolone	58. methimazole	59. methotrexate	60. methyltestosterone
61. misoprostol	62. mitomycin	63. mitoxantrone	64. MMF
65. nicoumalone	66. oxaliplatin	67. paclitaxel	68. paramethadione
69. pemetrexed	70. penicillamine	71. trimethadione	72. phenytoin
73. primidone	74. procarbazine	75. ribavirin	76. tamoxifene
77. temozolomide	78. teniposide	79. testosterone	
80. thioguanine	81. thiotepa	82. tretinoin	
83. trimethoprim	84. vincristine	85. vinblastine	
86. vindesine	87. vinorelbine	88. warfarin	

4.12. Author list and contribution of authors

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Chapter 5: Gabapentin Use During Pregnancy and Adverse Neonatal Birth Outcomes: A Population-Based Cohort Study

5.1. Overview

This is a cohort study using real word data evaluating the safety of gabapentin use in pregnancy and adverse neonatal outcomes. We conducted the cohort study using administrative health databases from Manitoba including all pregnant people between 1998 to 2021. We conducted crude, adjusted and high dimensional propensity scores (HDPS) logistic regression models using generalized estimation equations. We adjusted for various socio-demographic and clinical variables in both the full and HDPS model. We analyzed the association in 3 cohorts, 1) any exposure group, 2) within epilepsy group and 3) non-epilepsy group. The outcomes we evaluated include small for gestational age (SGA), low birth weight (LBW), preterm birth, NICU admissions, pregnant persons length of hospital stay (LOS) (> 3 days), infants LOS (> 3 days), infant mortality (≤365 days), neonatal mortality (≤27 days), neonatal readmissions, neonatal respiratory distress syndrome, neonatal persistent pulmonary hypertension, and severe neonatal morbidity. The results were presented in odds ratios (OR) and 95% confidence interval (CI) and standard error (SE). We found a significant association between gabapentin and adverse birth outcomes.

5.2 Abstract

Introduction: Gabapentin is a new-generation antiseizure medication (ASM) approved in the treatment of epilepsy. Due to gabapentin's perceived safety in pregnancy and efficacy in reducing pain, there has been an increase in its off-label use. We aim to study the association between gabapentin treatment during pregnancy and adverse neonatal outcomes among all pregnant people, pregnant people with epilepsy (PPWE), and pregnant people without epilepsy (PPWOE).

Methods: We conducted a population-based cohort study among all pregnant people in Manitoba, between 1998 to 2021. We examined the association between gabapentin exposure in-utero and the risk of small for gestational age (SGA), low birth weight (LBW), preterm birth (<37 weeks), NICU admissions, pregnant persons length of hospital stay (LOS)(>3 days), infants LOS, infant mortality (≤365 days), neonatal mortality (≤27 days), neonatal readmissions, neonatal respiratory distress syndrome, neonatal persistent pulmonary hypertension, and severe neonatal morbidity in all pregnant people, PPWE and PPWOE. We performed crude, adjusted and high dimensional propensity scores (HDPS) analysis.

Results: Among 1057 pregnant people exposed to gabapentin, we found a significant increased risk of LBW (aOR 1.95, 95% CI 1.58-2.41), preterm birth (aOR 1.68, 95% CI 1.39-2.03), NICU admissions (aOR 2.04, 95% CI 1.71-2.42), pregnant peoples LOS (aOR 1.33, 95% CI 1.15-1.54), infant LOS (aOR 2.09, 95% CI 1.81-2.41) and neonatal respiratory distress syndrome (aOR 3.36, 95% CI 1.16-9.71) and a non-significant increase in SGA (aOR 1.11, 95% CI 0.90-1.38), infant mortality (aOR 1.29, 95% CI 0.66-2.51), neonatal mortality (aOR 1.60, 95% CI 0.74-3.45), severe

neonatal morbidity (aOR 1.07, 95% CI 0.59-1.96), neonatal persistent pulmonary hypertension (aOR 3.40, 95% CI 0.45-25.7) and neonatal readmissions (aOR 1.09, 95% CI 0.79-1.49) when compared with unexposed pregnant people. In exposed PPWE we found a significant increased risk of infant mortality aOR 5.39 (95% CI 1.11-26.2), and a non-significant increased risk of LBW aOR 1.60 (95% CI 0.57-4.53), preterm birth aOR 1.77 (95% CI 0.77-4.08), NICU admission aOR 1.45 (95% CI 0.61-3.42), LOS of pregnant people aOR 1.73 (95% CI 0.90-3.33), LOS of infants aOR 1.72 (95% CI 0.85-3.50), neonatal mortality aOR 2.68 (95% CI 0.30-23.90), and neonatal readmissions aOR 1.07 (95% CI 0.17-6.65). PPWOE had similar results to that of all pregnant people group. The results from HDPS models showed attenuated estimates and non-significant results, suggesting strong unmeasured confounding.

Conclusion: We observed potential risk for specific neonatal outcomes with gabapentin exposure, however unmeasured confounding can not be dismissed. It is hard to conclude on the safety of gabapentin during pregnancy given the current HDPS results. With the lack of established neonatal safety evidence in current guidelines and the ongoing rise in gabapentin use among pregnant people, It is essential to conduct further research on the prenatal safety of gabapentin with a larger sample size, utilizing advanced statistical models to account for unmeasured confounding.

5.3. Introduction

Gabapentin is a new-generation antiseizure medication (ASM) approved for the treatment of epilepsy in 1993.[1] Subsequently, it was approved for postherpetic neuralgia in 2002 and moderate to severe restless leg syndrome (RLS) in 2011.[2] Currently, gabapentin has no established teratogenic risk.[3] An increase in the use of gabapentin for both epileptic as well as non-epileptic indications has been observed.[4,5] Due to its perceived safety and efficacy in other non-epilepsy conditions such as pain and migraine, there has been an increase in the use of gabapentin for other off-label indications such as diabetic and nondiabetic neuropathy, and fibromyalgia.[6,7] Current literature indicates that almost 95% of all gabapentin prescriptions are prescribed for non-epilepsy conditions and are mostly off-label.[8–10] This explains the increase in gabapentin prescriptions despite only being used as an adjuvant for epilepsy treatment.[1,11] There has been a rapid increase in gabapentin misuse in the past few years.[12] Gabapentin abuse has been reported among 1% of the general population, 40-65% from prescription sources and 15-22% among people who abuse opiates.[12]

Historically ASMs have been associated with various adverse infant outcomes when exposed in in-utero.[13,14] Recently studies reported an increase in cardiac malformations, small for gestational age (SGA), preterm birth and NICU admissions among pregnant people exposed to gabapentin.[15] However gabapentin is considered a medication of probable or unknow fetal risk according to the guidelines. With the lack of established risk and continued increase in the use of gabapentin among pregnant people, further study into its safety in pregnancy is necessary.[4,5] This paper aims to study the association between gabapentin treatment during pregnancy and

adverse neonatal outcomes in pregnant people, pregnant people with epilepsy (PPWE) and pregnant people without epilepsy (PPWOE).

5.4. Methods

5.4.1. Cohort description and data sources

We conducted a population-based cohort study using administrative health data from Manitoba, Canada. Our cohort includes all pregnant people exposed to gabapentin between April 1st 1998, to March 31st 2021 who had medical insurance coverage for at least 5 years. We excluded stillbirths from our cohort as we had excess missing data in this variable. We constructed the cohort using the provincial administrative databases housed at the Manitoba Centre for Health Policy (MCHP) data repository. We used the following data sources to build our cohort 1) drug program information network (DPIN), a claims database (1995/96-2020/21) that connects Manitoba health and all pharmacies in Manitoba.[5] 2) Hospital abstracts database (1992/93-2020/21) contains demographic and clinical information of hospital admissions completed at the point of patient discharge from the hospital.[5] 3) Medical Claims - Medical Services database (1992/93-2020/21) consists of information on the reimbursements for physician or primary care provider services including the International Classification of Diseases (ICD-9-CM and ICD-10-CM) codes, tariff codes etc.[5] 4) Manitoba Health Insurance Registry (1992/93-2020/21) collects demographic and insurance coverage information.[5] 5) National census database (1992/93-2020/21), is a free use data integrated at the MCHP which contains the residence codes, demographic data used in the calculation of socio-economic status (SES).[5] 6. Hospital Newborn to Mother Link Registry database (1992/93-2020/21) is used to link the

infants records with the pregnant parents records.[5] All the patients records in the databases are deidentified and can be linked together by the scrambled Personal Health Identification Numbers (PHIN).[5] Each newborn receives a distinctive PHIN, which is linked to the pregnant parents record, facilitating the creation of our pregnant parent-infant cohort.[5]

The gestational age of the newborn is extracted from hospital abstracts, while the trimesters of the pregnant people are defined as follows: The first trimester spans from the 1st day of gestation to the 14th week; the second trimester extends from the 15th to the 25th week, and the third trimester includes the period from the 26th week until the end of pregnancy.[5,16] Any time during pregnancy refers to the period from the 1st day of gestation to the end of pregnancy. Exposure to a gabapentin prescription is defined as having at least one prescription filled during one of the exposure windows of interest (1st trimester, 2nd trimester, or 3rd trimester) or a prescription filled before the beginning of the exposure window but with a duration overlapping the exposure window.[5] Pregnant people were considered to have epilepsy if they had 1 physician claim or 1 hospitalization (ICD-9 345 or ICD-10 G40/G41) in the 5 years before giving birth.[5,17] Gabapentin use was identified using prescription drug data where gabapentin was coded as N03AX12.

5.4.2. Outcomes

Outcomes assessed in this study include (a) **Birth weight outcomes:** small for gestational age and low birth weight, (b) **Infant health outcomes:** preterm birth, pregnant peoples length of stay (LOS), length of hospital stay of infant, neonatal intensive care unit admissions (NICU),

infant mortality, neonatal readmissions, neonatal mortality, neonatal respiratory distress syndrome, neonatal persistent pulmonary hypertension, severe neonatal morbidity**.** (Appendix 5.2: Outcome definitions)

5.4.3. Covariates

The following are the variables that were used as the expert-specified covariates in HDPS as well as were adjusted for in the adjusted regression model. Covariates include pregnant persons age at delivery (0-17, 18- 28 (reference (ref)), 29-39 and >40 years), hypertension (ref: yes), diabetes (ref: yes), mood and anxiety disorders(ref: yes), schizophrenia (ref: yes), personality disorder (ref: yes), asthma (ref: yes), coronary heart disease (ref: yes), and pain (ref: yes), SES (ref: low income), multiple births (ref: single birth), area of residence (ref: urban) and teratogenic medication exposure in the first trimester (ref: yes). (Appendix 5.3 and 5.4)

5.4.4. Statistical analysis

We calculated descriptive statistics of pregnancies including age at delivery, comorbidities, residence, exposure to teratogenic medications (first trimester) and socioeconomic status (SES). We analyzed 3 cohorts, gabapentin exposed pregnant people compared with unexposed pregnant people**,** gabapentin exposed PPWE compared with unexposed PPWE and gabapentin exposed PPWOE compared with unexposed PPWOE**.** In all cohorts, we conducted logistic regression models and HDPS regression models. For the logistic regression models, we used generalized estimating equations (GEE), with an exchangeable matrix.[18] We performed both the crude and adjusted analysis and presented the results in crude odds ratio (OR) and adjusted

odds ratio (aOR), along with the 95% confidence interval (95% CI).[19] In the adjusted models, we adjusted for the above specified covariates. High Dimensional Propensity Scores (HDPS) were estimated using 5 data dimensions in all pregnant people in our cohort. The 5 data dimensions include hospital medical diagnoses and hospital medical procedures (2 dimensions) from hospital abstracts, outpatient medical diagnoses and outpatient tariff codes (2 dimensions) from physician visits, and prenatal drug dispensations (1 dimension) from the Drug Program Information Network, and all were identified during the year prior to infant birth date.[20] As the first step of HPDS analysis, variables in all data dimensions were ranked based on frequency (once, sporadic, and frequent).[21] The top 300 most repeated variables were chosen to be included in the HDPS estimation.[22] In addition to these variables, covariates (specified in section 5.4.3 and appendix table 5.3) were included in the HDPS estimation.[21] We trimmed the overlapping data between the exposed and unexposed groups.[23] Regression models were then conducted while adjusting for the HDPS values using generalized estimating equations (GEE). We present the results in aOR, along with the 95% CI. We used statistical software SAS® 9.4 (SAS Institute; Cary, NC) for the analysis.

5.5. Results

We studied a cohort of 297,734 pregnancies from Manitoba between 1998 to 2021. The characteristics of the included population are presented in Table 5.1 and Table 5.2. Within this study, 1057 pregnant people were exposed to gabapentin, including 50 PPWE and 1007 PPWOE. Almost 50% of the cohort exposed to gabapentin belonged to the lower strata of socio-economic status.

All pregnant people

In the adjusted analysis among all pregnant people exposed to gabapentin, we observed a significant increased risk of LBW aOR 1.95 (95% CI 1.58-2.41), preterm birth aOR 1.68 (95% CI 1.39-2.03), NICU admissions aOR 2.04 (95% CI 1.71-2.42), LOS of both pregnant people aOR 1.33 (95% CI 1.15-1.54) and infants aOR 2.09 (95% CI 1.81-2.41), and neonatal respiratory distress syndrome aOR 3.36 (95% CI 1.16-9.71). No significant increased risks in any of the following outcomes were observed: SGA aOR 1.11 (95% CI 0.30-1.38), neonatal mortality aOR 1.60 (95% CI 0.74-3.45), infant mortality aOR 1.29 (95% CI 0.66-2.1), neonatal readmissions aOR 1.09 (95% CI 0.79-1.49), neonatal persistent pulmonary hypertension aOR 3.40 (95% CI 0.45-25.7), and severe neonatal morbidity aOR 1.07 (95% CI 0.59-1.96). In the HDPS adjusted analysis, none of the associations were statistically significant. We observed some non-significant trends, including the increase in the risk of LBW aOR 1.31 (95% CI 0.90-1.91), preterm birth aOR 1.07 (95% CI 0.76-1.51), NICU admissions aOR 1.38 (95% CI 0.99-1.94), LOS of infants aOR 1.28 (95% CI 0.99-1.65), neonatal mortality aOR 1.09 (95% CI 0.323.78), and neonatal readmissions aOR 1.18 (95% CI 0.69-2.01) and a non-significant decrease in infant mortality aOR 0.73 (95% CI 0.21-2.58), severe neonatal morbidity aOR 0.54 (95% CI 0.22-1.33), and neonatal respiratory distress syndrome aOR 0.33 (95% CI 0.06-1.76). (**Table 5.3**)

Pregnant people with epilepsy

In the adjusted models among PPWE, we found a significant increased risk of infant mortality aOR 5.39 (95% CI 1.11-26.2), and no risk of LBW aOR 1.60 (95% CI 0.57-4.53), preterm birth aOR 1.77 (95% CI 0.77-4.08), NICU admission aOR 1.45 (95% CI 0.61-3.42), LOS of pregnant people

aOR 1.73 (95% CI 0.90-3.33), LOS of infants aOR 1.72 (95% CI 0.85-3.50), neonatal mortality aOR 2.68 (95% CI 0.30-23.90), and neonatal readmissions aOR 1.07 (95% CI 0.17-6.65). In the HDPS adjusted analysis we found a non-significant increased trend of LBW aOR 3.98 (95% CI 0.83-19.0), preterm birth aOR 1.25 (95% CI 0.07-22.9), NICU admission aOR 6.26 (95% CI 0.90-43.5) and a non-significant decrease in the risk of SGA aOR 0.42 (95% CI 0.05-3.5) and severe neonatal morbidity aOR 0.54 (95% CI 0.22-1.33). (**Table 5.4**)

Pregnant people without epilepsy

In the adjusted model and HDPS model among PPWOE we observed consistent findings resembling those observed across all pregnant people, however in HDPS analysis, we found a significant slight increase in the risk of LOS of infants aOR 1.31 (95% CI 1.01-1.69). (Table 5.5)

5.6. Discussion

In our study, among all pregnant people exposed to gabapentin we found an increased risk of several perinatal outcomes. However, the results did not persist after controlling for a larger set of potential confounders through HDPS. We also observe a significant elevated risk of neonatal respiratory distress syndrome in all pregnant people, and PPWOE. However, it is important to note that in our HDPS analysis compared to the adjusted analysis, the risk shift for neonatal respiratory distress syndrome among all pregnant people, when compared to unexposed pregnant people, changed significantly from a 236% increase to a 67% decrease. Similar trend was also seen among PPWOE. This shift in risk, along with the substantial reduction in the

magnitude of the risk for other outcomes in the HDPS models, suggests the presence of strong unmeasured confounding in the adjusted model. Nonetheless the interpretation of the HDPS model should be considered carefully given the small sample size in some models.

Among exposed PPWE we found a significant increase in the risk of Infant mortality by 439% when compared with unexposed PPWE. However, it's important to highlight that the associated confidence interval is considerably wide, suggesting a low power. Moreover, in the HDPS models among PPWE, several analyses failed to converge, indicating potential stability issues. It is important to note that the sample size for the analysis of PPWE was 50 exposed pregnancies. While in HDPS model we expect to increase the validity of the estimate at the expense of some precision, the trade-off presents a challenge in PPWE group. The trade-off becomes especially problematic as we lost a majority (up to 95%) of the population, particularly considering the initial small sample size (Appendix table 5.5). Therefore, further research within this group is imperative, employing larger sample sizes and advanced statistical methods and study designs that can effectively account for unmeasured confounding.

Currently, gabapentin finds application in various off label uses, including pain management, migraine, and in the treatment of mood and anxiety disorders.[8–10] Notably, in specific scenarios, such as the management of pain during pregnancy, the choice of treatment varies.[24] In cases of chronic pain in pregnancy, low-dose opioids are often used, although there are instances where

gabapentin may be a possible alternative to opioids.[24] This preference for gabapentin over opioids arises from the known risks associated with opioids, including the potential for neonatal opioid withdrawal syndrome (NOWS) and a higher risk of addiction.[24,25] Nonetheless, caution is essential, as the co-use of gabapentin with opioids is on the rise due to the synergistic effects between these substances.[26] Further research is necessary to investigate the safety and efficacy of gabapentin in these off-label applications.

The safety of gabapentin has not yet been established and is uncertain. In Canada, gabapentin is classified as a medication with a probable fetal risk, while in Australia, it is categorized as unknown fetal risk.[3,27] This discrepancy in classification highlights the need for further research and a thorough understanding of gabapentin's effects during pregnancy. The significant recent surge in gabapentin usage, coupled with the absence of established fetal risk but accompanied by reports of adverse neonatal outcomes, highlights the necessity for further studies to ascertain fetal risks.[28]

Gabapentin possesses multiple mechanisms of action, one proposed mechanism revolves around its ability to affect the morphogenesis and development of dopaminergic neurons, potentially, leading to disruptions in brain development and contribute to adverse outcomes in neonates.[29,30] Renal blood flow and glomerular filtration rates experience an increase during pregnancy in the first and second trimesters, subsequently declining in the third trimester.[31,32]

These fluctuations have a notable impact on the serum concentration of gabapentin during pregnancy, especially since the renal route serves as its primary method of elimination, indicating a higher dose to attain the same serum concentration during pre-pregnancy.[33] Therefore, additional research on the dose dependent safety in pregnancy is warranted.

Our study has several limitations to be acknowledged. The absence of disease severity data in our database restricted our ability to incorporate it into our analysis. Furthermore, we did not adjust for non-epilepsy indications and off-label uses of gabapentin. To address these limitations, we employed HDPS analysis, in which we accounted for the 300 most frequently occurring variables in the population. While the HDPS analysis allowed us to address unmeasured confounding to some extent, we recognize that residual confounding may still exist. Our HDPS models were underpowered after trimming. Specifically, the models for PPWE have seen significant reduction (10-95%) in sample during the non-overlap trimming process, significantly affecting the results.

Conclusion

We observed potential risk for specific neonatal outcomes with gabapentin exposure, however unmeasured confounding cannot be ruled out. It is hard to conclude on the safety of gabapentin during pregnancy given the current evidence and our HDPS results. With the lack of established neonatal safety evidence in current guidelines and the ongoing rise in gabapentin use among pregnant people, its necessary to conduct further research on prenatal safety of

gabapentin employing advance statistical methods and study designs capable of addressing unmeasured confounding in large population samples.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

5.7. Tables

Table 5.1: Characteristics of pregnant people

	Exposed		*Unexposed*	
	PPWE N (%)	PPWOE N (%)	PPWE N (%)	PPWOE N (%)
Total pregnant people	50 (0.0)	1007 (0.3)	1845 (0.6)	294832 (99)
Age of pregnant people at birth (mean years)	29.6	30.3	27.3	28.1
Chronic diseases				
• *Hypertension*	10 (20)	125 (12.4)	58 (3.1)	4994 (1.7)
• *Diabetes*	S (10)	156 (15.5)	65 (3.5)	9291 (3.2)
• *Mood and Anxiety disorder*	28 (56)	546 (54.2)	403 (22)	32777 (11.7)
• *Schizophrenia*	S	7 (0.7)	8 (0.4)	336 (0.1)
• *Personality disorder*	S	28 (2.8)	23 (1.2)	1017 (0.3)
• *Chronic pain*	23 (46)	279 (20.5)	217 (11.8)	16619 (5.6)
• *Asthma*	24 (48)	378 (37.5)	309 (16.7)	35243 (12)
• *Cardiovascular diseases*	S	10 (1)	S	296 (0.1)
Singleton birth	50 (0.0)	1007 (0.3)	1845 (0.6)	294832 (99)
Multiple birth	S	28 (208)	42 (2.3)	7870 (2.7)
Exposure to teratogenic drugs	19 (38)	129 (12.8)	510 (27.6)	7898 (2.7)
SES				
Q1	22 (44)	538 (30.6)	304 (32)	76042 (25.8)
Q2	11 (22)	421 (22.8)	198 (20.8)	63431 (21.5)
Q3	10 (20)	375 (20.3)	193 (20.3)	54478 (18.5)
Q4	S	302 (16.4)	160 (16.8)	54027 (18.3)
Q5	S	173 (9.4)	93 (9.8)	46029 (15.6)
Urban	32 (64)	563 (55.9)	1053(57.1)	155999 (52.9)
Rural	18 (36)	444 (44.1)	792 (42.9)	138833 (47.1)
SES: *Socio economic status**,** PPWE: pregnant people with epilepsy, PPWOE: pregnant people without epilepsy, S=Suppressed*				

Table 5.2: Outcome counts among gabapentin exposed pregnant people and gabapentin unexposed pregnant people.

Outcomes	***Exposed***		***Unexposed***	
	PPWE N (%)	PPWOE N (%)	PPWE N (%)	PPWOE N (%)
Total Pregnant people	50 (0)	1007 (0.3)	1845 (0.6)	294832 (99)
SGA	s	94 (9.4)	177 (9.6)	22723 (7.7)
LBW	8 (16)	131 (13)	158 (8.6)	15990 (5.4)
Preterm birth	11 (22)	206 (20.5)	214 (11.6)	23766 (8.1)
NICU admissions	11 (22)	250 (24.8)	233 (12.6)	23447 (8)
LOS of* pregnant people *(>3days)	19 (38)	270 (26.8)	438 (23.7)	51534 (17.5)
LOS of infants (>3 days)	20 (40)	358 (35.6)	412 (22.3)	43416 (14.7)
Infant mortality	S	8 (0.8)	19 (1)	1717 (0.6)
Neonatal readmissions	S	44 (4.4)	72 (3.9)	8864 (3)
Neonatal mortality	S	6 (0.6)	14 (0.8)	1120 (0.4)
Neonatal persistent pulmonary hypertension	S	S	S	66 (0)
Neonatal respiratory distress syndrome	S	S	S	249 (0.1)
Severe neonatal morbidity	S	13 (1.3)	24 (1.3)	2359 (0.8)

SGA: small for gestational age, LBW: low birth weight SES: Socio economic status, PPWE: pregnant people with epilepsy, PPWOE: pregnant people without epilepsy, S: supressed

Table 5.3: Results of logistic regression and HDPS models evaluating the association between gabapentin and neonatal birth outcomes among all pregnant people

Outcomes	*Crude Models OR (95% CI)*	*Adjusted Models aOR (95% CI)*	*HDPS Regression models OR (95% CI)*
SGA	1.19 (0.97-1.47)	1.11 (0.90-1.38)	0.90 (0.64-1.28)
LBW	2.49 (2.04-3.05)	**1.95 (1.58-2.41)**	1.31 (0.90-1.91)
Preterm birth	2.45 (2.04-2.94)	**1.68 (1.39-2.03)**	1.07 (0.76-1.51)
NICU admissions	3.20 (2.72-3.77)	**2.04 (1.71-2.42)**	1.38 (0.99-1.94)
LOS of* pregnant people *(>3 days)	1.72 (1.49-1.98)	**1.33 (1.15-1.54)**	1.05 (0.84-1.33)
LOS of infants (>3 days)	2.87 (2.50-3.30)	**2.09 (1.81-2.41)**	1.28 (0.99-1.65)
Infant mortality	1.53 (0.78-3.01)	1.29 (0.66-2.51)	0.73 (0.21-2.58)
Neonatal mortality	1.84 (0.87-3.88)	1.60 (0.74-3.45)	1.09 (0.32-3.78)
Severe neonatal morbidity	1.48 (0.80-2.72)	1.07 (0.59-1.96)	0.54 (0.22-1.33)
Neonatal readmissions	1.43 (1.05-1.96)	1.09 (0.79-1.49)	1.18 (0.69-2.01)
Neonatal persistent pulmonary hypertension	4.19 (0.58-30.2)	3.40 (0.45-25.7)**	0.85 (0.35-2.04)
Neonatal respiratory distress syndrome	4.08 (1.40-11.9)	**3.36 (1.16-9.71)**	0.33 (0.06-1.76)

*SGA: small for gestational age, LBW: low birth weight, SES: Socio economic status, PPWE: pregnant people with epilepsy, PPWOE: pregnant people without epilepsy. Adjusted for Pregnant persons age, multiple births, SES, asthma, cardiovascular diseases, multiple birth, pain, psychiatric disorders, schizophrenia, diabetes, hypertension, mood disorders, urban/rural, teratogenic drugs, *Reduced model 1: Exposed to teratogenic drugs 1st trimester, Area of Residence: Rural and urban (reference),,Hypertension, Diabetes, Asthma, Pain, Pregnant persons age(Continuous), SES , and Multiple births, ** Reduced model 2: Hypertension, Diabetes, Asthma, Pain, Pregnant persons age (Continuous) and SES , *** Reduced model 3: Pregnant persons age(Continuous) and SES*

Table 5.4: Results of logistic regression and HDPS models evaluating the association between gabapentin and neonatal birth outcomes among PPWE

Outcomes	*Crude Models OR (95% CI)*	*Adjusted Models OR (95% CI)*	*HDPS Regression models OR (95% CI)*
SGA	1.13 (0.47-2.71)	0.94 (0.37-2.42)*	0.42 (0.05-3.5)
LBW	2.23 (1.02-4.88)	1.60 (0.57-4.53)	3.98 (0.83-19)
Preterm birth	2.18 (0.98-4.86)	1.77 (0.77-4.08)*	1.25 (0.07-22.9)
NICU admissions	1.95 (0.92-4.16)	1.45 (0.61-3.42)*	6.26 (0.90-43.5)
LOS* of pregnant people *(>3 days)	2.01 (1.08-3.76)	1.73 (0.90-3.33)	N/A
LOS of infants (>3 days)	2.14 (1.12-4.10)	1.72 (0.85-3.50)*	N/A
Infant mortality	4.46 (1.01-19.7)	**5.39 (1.11-26.2)***	N/A
Neonatal mortality	3.14 (0.42-23.4)	2.68 (0.30-23.9)***	N/A
Severe neonatal morbidity	N/A	N/A	0.54 (0.22-1.33)
Neonatal readmissions	1.30 (0.22-7.55)	1.07 (0.17-6.65)**	N/A
Neonatal persistent pulmonary hypertension	N/A	N/A	N/A
Neonatal respiratory distress syndrome	N/A	N/A	N/A

*SGA: small for gestational age, LBW: low birth weight, SES: Socio economic status, PPWE: pregnant people with epilepsy, PPWOE: pregnant people without epilepsy Adjusted for Pregnant persons age, multiple births, SES, asthma, cardiovascular diseases, multiple birth, pain, psychiatric disorders, schizophrenia, diabetes, hypertension, mood disorders, urban/rural, teratogenic drugs, *Reduced model 1: Exposed to teratogenic drugs 1st trimester, Area of Residence: Rural and urban (reference),,Hypertension, Diabetes, Asthma, Pain, Pregnant persons age(Continuous), SES , and Multiple births, ** Reduced model 2: Hypertension, Diabetes, Asthma, Pain, Pregnant persons age (Continuous) and SES , *** Reduced model 3: Pregnant persons age(Continuous) and SES. N/A: model did not converge*

Table 5.5: Results of logistic regression and HDPS models evaluating the association between gabapentin and neonatal birth outcomes among PPWOE

Outcomes	*Crude Models OR (95% CI)*	*Adjusted Models OR (95% CI)*	*HDPS Regression models OR (95% CI)*
SGA	1.19 (0.95-1.47)	1.11 (0.89-1.39)	0.92 (0.65-1.30)
LBW	2.49 (2.03-3.05)	**1.94 (1.56-2.41)**	1.34 (0.92-1.95)
Preterm birth	2.45 (2.04-2.95)	**1.67 (1.38-2.02)**	1.08 (0.76-1.53)
NICU admissions	3.25 (2.75-3.84)	**2.06 (1.73-2.46)**	1.40 (0.99-1.97)
LOS of pregnant people (>3 days)	1.68 (1.45-1.94)	**1.30 (1.12-1.51)**	1.04 (0.82-1.32)
LOS of Infants (>3days)	2.86 (2.48-3.30)	**2.08 (1.80-2.41)**	**1.31 (1.01-1.69)**
Infant mortality	1.28 (0.59-2.74)	1.08 (0.51-2.29)	0.66 (0.14-3.14)
Neonatal mortality	1.66 (0.74-3.74)	1.44 (0.63-3.31)	1.04 (0.24-4.58)
Severe neonatal morbidity	1.55 (0.84-2.86)	1.13 (0.62-2.08)	0.97 (0.48-1.96)
Neonatal readmissions	1.41 (1.03-1.94)	1.07 (0.78-1.47)	1.19 (0.68-2.09)
Neonatal persistent pulmonary hypertension	4.44 (0.62-32.0)	3.55 (0.47-26.8)**	0.89 (0.40-2.02)
Neonatal respiratory distress syndrome	4.33 (1.47-12.7)	**3.50 (1.20-10.2)**	0.28 (0.04-1.83)

*SGA: small for gestational age, LBW: low birth weight, SES: Socio economic status, PPWE: pregnant people with epilepsy, PPWOE: pregnant people without epilepsy Adjusted for Pregnant persons age, multiple births, SES, asthma, cardiovascular diseases, multiple birth, pain, psychiatric disorders, schizophrenia, diabetes, hypertension, mood disorders, urban/rural, teratogenic drugs, *Reduced model 1: Exposed to teratogenic drugs 1st trimester, Area of Residence: Rural and urban (reference),,Hypertension, Diabetes, Asthma, Pain, Pregnant persons age(Continuous), SES , and Multiple births, ** Reduced model 2: Hypertension, Diabetes, Asthma, Pain, Pregnant persons age (Continuous) and SES , *** Reduced model 3: Pregnant persons age(Continuous) and SES*

5.8. Appendices

Appendix table 5.1 Data sources

Database	Years	Data Fields/Variables	Rationale
Drug Program Information Network (DPIN)	1995/96-2020/21	Prescriptions, drugs, characteristics (type, dose, quantity, class), carriers, prescribers, providers, pharmacy	To examine the use of pharmaceutical drugs and define chronic diseases and comorbidities
Hospital abstracts	1992/93-2020/21	Hospitalizations, admission date, birth, diagnoses (ICD-10) and procedures.	To identify the outcomes of interest and disease states/procedures associated with exclusion and inclusion criteria.
Medical Claims – Medical Services	1992/93-2020/21	Date of encounter, specialty, diagnoses (ICD-9) and procedures.	To identify the outcomes of interest, and disease states/procedures associated with exclusion and inclusion criteria.
Manitoba Health Insurance Registry	1992/93-2020/21	Scrambled PHIN, family registration number, date of birth, coverage status, sex, location of residence, migration in/out of province date	Needed to identify individuals with valid MB health insurance for cohort entry. Sex is used as a covariate. Postal codes will be used to calculate socioeconomic variables in combination with census data. Migration status/date helps determine cohort follow-up duration
Hospital Newborn to Mother Link Registry (HNMLR) data	1992/93-2020/21	Contains historical data related to mothers and newborns	To identify mother infant linkage in the administrative database
Public-use Canada Census data	1992/93-2020/21	Contains free to use Canada wide census data available at MCHP	To obtain information on residence and calculate the income quintiles

Appendix table 5.2 Outcome definitions

Outcomes definition	
Birth weight outcomes	
• Small for gestational age	Infants ≤10th percentile in birth weight, based on birth weight, gestational age, and sex as recorded in the hospital birth record.[34]
• Low birth weight	Birth weight <2,500 grams and recorded in hospital birth record.[35]
Birth outcomes	
• Preterm birth	Live birth gestational age <37weeks.[16]
• Neonatal intensive care unit admissions	Infant admitted to the intensive care unit at age ≤28 days.[16]
• Neonatal persistent pulmonary hypertension	A syndrome characterized by marked pulmonary hypertension that causes hypoxemia secondary to right-to-left shunting of blood at the foramen ovale and ductus arteriosus.[16]
• Neonatal respiratory distress syndrome	Neonatal respiratory distress syndrome (RDS) occurs from a deficiency of surfactant, due to either inadequate surfactant production, or Surfactant inactivation in the context of immature lungs.[36]
• Pregnant persons length of hospital stay	The length of stay of mother in hospital after giving birth for more than 3 days.[37]
• Infants' length of hospital stay	The length of stay of an infant in hospital after giving birth for more than 3 days.[37]
• neonatal readmissions	Live birth and discharged, but then re-hospitalized within 28 days (≤28) after discharging alive from their birth hospitalization.[38]
• Severe neonatal morbidity	Neonatal sepsis, respiratory distress syndrome and other respiratory problems, hypoxic-ischemic encephalopathy, convulsions of the newborn, brachial plexus injury/palsy and related conditions, persistent fetal circulation/neonatal hypertension and related conditions, grade iii or iv, intraventricular hemorrhage (IVH)/ periventricular leukomalacia (PVL), intubation and resuscitation, gastroschisis & omphalocele, diaphragmatic hernia and congenital malformations of the circulatory system. (Refer to Chapter 4 for ICD codes)[16]
• Neonatal mortality	Death among infants within 0 to 27days.[16]
• Infant mortality	Death among infants within 0 to 365 days of birth.[16]

Appendix Table 5.3: Covariates and comorbidities

Comorbidities	Definitions
Hypertension[39]	Females with one of the following within 1-year before conception • At least one hospital diagnosis for hypertension: (ICD-9-CM, 401: essential hypertension= 401-405 OR ICD-10-CA: I10-I14: essential (primary) hypertension); in the year before conception, OR At least two ambulatory visit diagnoses: (ICD-9-CM codes: 401-405) OR At least two dispensations for hypertension medication
Diabetes[39,40]	Females with one of the following within 3-years before conception: • One or more hospitalizations with a diagnosis of diabetes (ICD-9-CM code 250 diabetes mellitus; ICD-10-CA codes E10-E14 diabetes mellitus), OR Two or more physician visits with a diagnosis of diabetes (ICD-9-CM codes as above), OR One or more prescriptions for medications to treat diabetes (ATC code A10).
Mood and anxiety disorders[41]	Females with one of the following within 1-year before conception • At least one hospitalization (ICD-9-CM codes 296.2-296.8, 300, 309, 311; ICD-10-CA codes F31, F32, F33, F34.1, F38.0, F38.1, F40, F41, F42, F43.1, F43.2, F43.8, F44, F45.0, F45.1, F452, F48, F53.0, F68.0, F93.0, F99 OR One or more physician visits with a diagnosis for depressive disorder, affective psychoses, or adjustment reaction (ICD-9-CM codes 296, 309 or 311) OR Two or more physician visits with a diagnosis for anxiety disorders (ICD-9-CM code 300).
Personality disorders[42]	Females with one of the following within 1-year before birth • At lease one or more hospitalization with a diagnosis for personality disorders in one year before birth ICD-9-CM code: 301; OR ICD-10-CA codes: F21, F34.0, F60, F61, F62, F68.1, F68.8 or F69; OR at least one physician visit with a diagnosis for personality disorders using ICD-9-CM code 301.
Pain	Females with one of the following within 1-year before conception • One or more hospitalization with a diagnosis of pain (ICD-9 code 338; ICD-10 R52 G89 G50) Neuralgia (ICD-9 729.2; ICD-10 M79.2) Migraine and Headaches (ICD-9 346 784; ICD-10 G43 R51) OR One or more codes in the physician data ICD-9 338,346,784.
Schizophrenia[43]	Females with one of the following within 1-year before conception • One or more hospitalization with a diagnosis for schizophrenia: ICD-9-CM code: 295 (schizophrenic disorders); OR ICD-10-CA codes: F20 (schizophrenia), F21 (schizotypal disorder), F23.2 (acute schizophrenia-like psychotic disorder), F25 (schizoaffective disorders); OR One or more physician visits with a diagnosis for schizophrenia using ICD-9-CM code 295.

Asthma[39]	Females with one of the following within 1-year before conception • One or more hospitalizations for asthma (ICD-9-CM Codes 493 and ICD-10-CA Diagnosis Codes J45: asthma and J46: status asthmaticus) OR one or more physician's visit, OR at least one medication prescription for asthma with ATC code: R03A (adrenergics, inhalants), R03B (other drugs for obstructive airway diseases, inhalants), R03C (other drugs for obstructive airway diseases, inhalants), and R03D (other systemic drugs for obstructive airway diseases) and R06AX17 Ketotifen)
Coronary heart disease[39]	Females with one of the following within one-year before conception • One or more hospitalizations with a diagnosis of coronary heart disease using ICD-9-CM Codes 410 – 414: ischemic heart disease and ICD-10-CA Diagnosis Codes I20 – I25: ischaemic heart diseases OR One or more physician visits with a diagnosis of coronary heart disease (ICD codes as above), OR One or more prescriptions for medications to treat coronary heart disease with ATC code:C01 (cardiac therapy), C07 (beta-blocking agents), C08 (calcium channel blockers), and C09 (agents acting on the renin-angiotensin system)
Area of residence[44]	Urban and rural area of residence, Is obtained through census data
Socio economic status (income quantiles)[45]	SES in our study is categorized into Low and high (high used as reference). Where U1, U2, R1, R2 = 1, and U3, U4, U5, R3, R4, R5 = 0 when U is urban, and R is rural, R1/U1 being the lowest income quintiles and U5/R5 being the highest income quintiles). These quantiles are calculated using the Census data
Pregnant persons age[45]	• Pregnant persons age categorization: categorize into 0-17, 18- 28 (reference), 29-39 and >40 years. • Pregnant persons age continuous Is obtained through the Hospital Abstracts data, Hospital Newborn to Mother Link Registry data; and Manitoba Health Insurance Registry data
Exposure to teratogenic agents	Exposure to potential teratogenic medication in the first trimester of pregnancy. The data is obtained from the prescription claims data.
Multiple births and singleton births[16]	**Multiple births:** birth of two or more children during a single delivery with a gestation of 20 weeks or more. **Singleton birth:** the birth of only one child during a single delivery with a gestation of 20 weeks or more. These outcomes are obtained through the hospital abstracts

Appendix table 5.4 Medications with sufficient evidence of a teratogenic risk in the first trimester

1) acenocoumarol	2) acitretin	3) alitretinoin	4) amethopterin
5) amsacrine	6) axitinib	7) bishydroxycoumarin	8) bleomycin
9) brentuximab	10) busulfan	11) capecitabine	12) carbamazepine
13) carbimazole	14) carboplatin	15) carmustine	16) chlorambucil
17) cisplatin	18) cladribine	19) colchicine	20) crizotinib
21) cyclophosphamide	22) cytarabine	23) dacarbazine	24) dactinomycin
25) danazol	26) daunorubicin	27) diethylstilbestrol	28) docetaxel
29) doxorubicin	30) epirubicin	31) estramustine	32) etoposide
33) etretinate	34) exemestane	35) flucytosine	36) fludarabine
37) fluorouracil	38) fluoxymesterone	39) formestane	40) gemcitabine
41) idarubicin	42) ifosfamide	43) imatinib	44) iodine-125 /123
45) iodine-131	46) isotretinoine	47) l-asparaginase	48) leflunomide
49) lenalidomide	50) lithium	51) lomustine	52) mechlorethamine
53) medroxyprogesterone	54) melphalan	55) mephenytoin	56) mephobarbital
57) methandrostenolone	58) methimazole	59) methotrexate	60) methyltestosterone
61) misoprostol	62) mitomycin	63) mitoxantrone	64) MMF
65) nicoumalone	66) oxaliplatin	67) paclitaxel	68) paramethadione
69) pemetrexed	70) penicillamine	71) phenobarbital	72) phenytoin
73) primidone	74) procarbazine	75) ribavirin	76) tamoxifene
77) temozolomide	78) teniposide	79) testosterone	80) thalidomide
81) thioguanine	82) thiotepa	83) tretinoin	84) trimethadione
85) trimethoprim	86) valproic a'	87) vinblastine	88) vincristine
89) vindesine	90) vinorelbine	91) warfarin	a.

Appendix Table 5.5: Exposed sample size percentage lost in HDPS in gabapentin exposed cohort.

Outcomes	***All pregnant people***	***PPWE***	***PPWOE***
	Regression adjustment with overlap trimming	**Regression adjustment with overlap trimming**	**Regression adjustment with overlap trimming**
	%	%	%
SGA	15.17	24	14.38
LBW	7.63	30.95	7.26
Preterm birth	9.64	96.00	19.76
NICU admissions	11.81	92.31	10.70
LOS of pregnant people	14.87	N/A	14.13
LOS of infants	9.13	N/A	11.22
Infant mortality	8.60	75	9.91
Neonatal mortality	11.05	N/A	13.39
Severe neonatal morbidity	9.10	9.10	0.29
Neonatal readmissions	8.67	69.57	10.08
Neonatal persistent pulmonary hypertension	3.13	N/A	1.69
Neonatal respiratory distress syndrome	1.23	N/A	1.79
SGA: small for gestational age, LBW: low birth weight, LOS: length of hospital, SES: Socio economic status, PPWE: pregnant people with epilepsy, PPWOE: pregnant people without epilepsy, S: Suppressed. N/A: model did not converge			

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Chapter 6: Additional results

6.1. Overview

We conducted various sensitivity analysis for the cohort study and have listed all additional results in this chapter. Every table from the following list is proceeded with an explanation and justification. **6.2) Stratified analysis** by preterm birth and malformations: Table 6.1a: ASMs stratification by preterm birth and Table 6.1b: ASMs stratification by malformations**, 6.3) Exposure by trimester**: Table 6.2a: Pregnant peoples characteristics exposed to ASMs in 1st trimester, Table 6.2b: Outcome numbers in pregnant people exposed to ASMs in 1st trimester, Table 6.2c: Pregnant people characteristics exposed to ASMs in 2nd & 3rd trimester, Table 6.2d: Outcome numbers in pregnant people exposed to ASMs in 2nd and 3rd trimester. **6.4) HDPS matching**: Table 6.3a: Exposed sample size percentage lost due to HDPS methods in ASMs exposed cohort, Table 6.3b: Exposed sample size percentage lost due to HDPS methods in gabapentin exposed, Table 6.4a: Outcome counts among pregnant people exposed to ASMs, Table 6.4b: ASM exposure during pregnancy in all pregnant people and neonatal adverse outcomes with matching, Table 6.4c: ASM exposure during pregnancy in PPWE and neonatal adverse outcomes with matching, Table 6.4d: ASM exposure during pregnancy in PPWOE and neonatal adverse outcomes with matching, Table 6.5a: Outcome counts among all pregnant people exposed to gabapentin, Table 6.5b: Gabapentin exposure during pregnancy in all pregnant people and neonatal adverse outcomes with matching, Table 6.5c: Gabapentin exposure during pregnancy in PPWE and neonatal adverse outcomes with matching and Table 6.5d: Gabapentin exposure during pregnancy in PPWOE and neonatal adverse outcomes with

matching. These additional results give us a better understanding of the population and our analyses.

6.2. Stratified analysis by preterm birth and malformations:

In our cohort study, we observed that preterm birth and malformations may play a role in the causal pathway (as depicted in Figures 6.1a and Figure 6.1b). As a result, we undertook a sensitivity analysis by stratifying our investigation based on preterm birth and the presence of malformations. This allowed us to examine the relationship between antiseizure medications (ASMs) and various adverse outcomes in both term and preterm pregnancies, as well as pregnancies with and without malformations. Our findings revealed an association with varying magnitudes across both term and preterm pregnancies, as well as between pregnancies with and without major malformations. (Table 6.1a & Table 6.1b). Among term pregnancies, the outcomes closely resembled the ASM exposure among all pregnancies results (Table 4.3), as this group primarily consists of term pregnancies. In the preterm pregnancies, by study design we are adjusting for the preterm status, as preterm births are present in both the exposed and unexposed groups. The magnitude of risk for adverse outcomes in the preterm pregnancies group was lower than the ASMs exposure among all pregnancies results (Table 4.3), suggesting

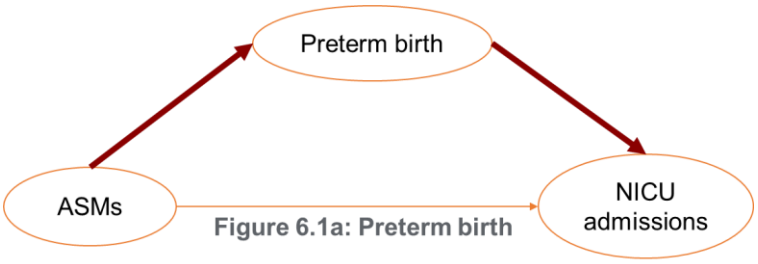

Figure 6.1a: Preterm birth

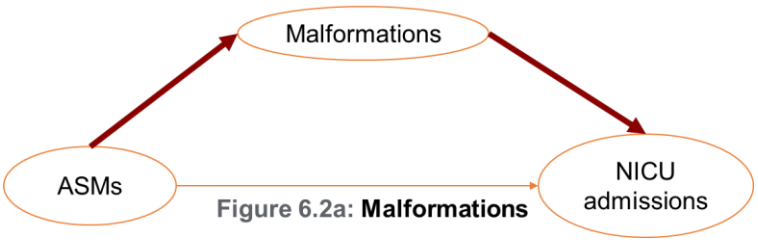

Figure 6.2a: **Malformations**

that some of the reduced magnitude is attributable to adjusting for preterm birth itself. Among infants without malformations the results resembled the ASM's overall population results (Table 4.3), as this group primarily includes infants without malformations. In the group of infants with malformations, we observe higher risk magnitudes for neonatal adverse outcomes than compared to those without malformations. Similar to the analysis of preterm pregnancies, in infants with malformations, we adjust for the risk attributed to malformations in the analysis by study design, as malformations are present in both the exposed and unexposed groups. Future research to investigate the mediation effects of preterm births and malformations, employing mediation analysis to quantify the associations (both direct and indirect) is warranted.

Table 6.1a: Results of logistic regression models evaluating the association between ASMs and neonatal birth outcomes among all pregnant people stratified by preterm birth.

Outcomes	*Term*		*Preterm*	
	Crude Models OR (95% CI)	**Adjusted Models OR (95% CI)**	**Crude Models OR (95% CI)**	**Adjusted Models OR (95% CI)**
SGA	1.28 (1.14-1.44)	1.18 (1.05-1.33)	0.97 (0.74-1.28)	1.01 (0.76-1.34)
LBW	1.89 (1.53-2.32)	1.53 (1.24-1.90)	1.12 (0.95-1.31)	1.22 (1.03-1.45)
NICU admissions	2.98 (2.6-3.33)	2.12 (1.89-2.39)	1.41 (1.19-1.66)	1.23 (1.03-1.46)
LOS of pregnant people	1.34 (1.23-1.46)	1.21 (1.11-1.33)	1.06 (0.90-1.24)	0.97 (0.82-1.16)
LOS of infants	1.96 (1.79-2.14)	1.65 (1.50-1.81)	1.35 (1.12-1.63)	1.21 (0.99-1.46)
Infant mortality	0.66 (0.29-1.52)	N/A	0.87 (0.58-1.33)	1.06 (0.68-1.63)
Neonatal mortality	0.32 (0.04-2.47)	N/A	0.90 (0.58-1.39)	1.14 (0.72-1.80)
Severe neonatal morbidity	1.21 (0.82-1.78)	1.05 (0.71-1.56)	0.85 (0.49-1.50)	0.78 (0.44-1.38)
Neonatal readmissions	1.33 (1.12-1.59)	1.12 (0.94-1.35)	1.16 (0.76-1.75)	0.98 (0.63-1.50)
Neonatal persistent pulmonary hypertension	1.46 (0.20-10.6)	0.93 (0.11-8.21)*	N/A	N/A
Neonatal respiratory distress syndrome	N/A	N/A	0.96 (0.39-2.37)	1.01 (0.39-2.62)

*SGA: small for gestational age, LBW: low birth weight, SES: Socio economic status, LOS: length of hospital stay, PPWE: pregnant people with epilepsy, PPWOE: pregnant people without epilepsy. Adjusted for Pregnant persons age, multiple births, SES, asthma, cardiovascular diseases, multiple birth, pain, psychiatric disorders, schizophrenia, diabetes, hypertension, mood disorders, urban/rural, teratogenic drugs, *Reduced model 1: Exposed to teratogenic drugs 1st trimester, Area of Residence: Rural and urban (reference),,Hypertension, Diabetes, Asthma, Pain, Pregnant persons age(Continuous), SES , and Multiple births, ** Reduced model 2: Hypertension, Diabetes, Asthma, Pain, Pregnant persons age (Continuous) and SES , *** Reduced model 3: Pregnant persons age(Continuous) and SES, OR: Odds ratio, Cl: Confidence interval. N/A: model did not converge*

Table 6.1b: Results of logistic regression models evaluating the association between ASMs and neonatal birth outcomes among all pregnant people stratified by malformations.

Outcomes	*No major malformation*		*Major malformations*	
	Crude Models OR (95% CI)	**Adjusted Models OR (95% CI)**	**Crude Models OR (95% CI)**	**Adjusted Models OR (95% CI)**
SGA	1.28 (1.13-1.44)	1.18 (1.05-1.33)	1.42 (0.98-2.05)	N/A
LBW	1.83 (1.47-2.27)	1.46 (1.17-1.83)	2.09 (1.53-2.86)	1.95 (1.41-2.71)
Preterm birth	1.97 (1.79-2.16)	1.65 (1.50-1.82)	2.21 (1.58-3.09)	1.72 (1.21-2.43)
NICU admissions	3.21 (2.85-3.62)	2.23 (1.96 -2.53)	2.22 (1.67-2.94)	1.74 (1.29-2.34)
LOS of pregnant people	1.33 (1.22-1.46)	1.21 (1.11-1.32)	1.39 (1.03-1.87)	1.16 (0.85-1.59)
LOS of infants	1.97 (1.79-2.16)	1.65 (1.50-1.82)	2.29 (1.70-3.08)	1.83 (1.34-2.49)
Infant mortality	0.74 (0.27-2.08)	N/A	0.80 (0.39-1.62)	0.95 (0.45-2.01)
Neonatal mortality	N/A	N/A	1.12 (0.58-2.19)	1.41 (0.70-2.86)
Severe neonatal morbidity	1.44 (0.92-2.24)	N/A	0.74 (0.41-1.33)	0.74 (0.40-1.35)
Neonatal readmissions	1.34 (1.11-1.61)	1.11 (0.92-1.34)	1.15 (0.73-1.81)	N/A
Neonatal persistent pulmonary hypertension	3.48 (0.47-25.8)	N/A	N/A	N/A
Neonatal respiratory distress syndrome	N/A	N/A	N/A	N/A

*SGA: small for gestational age, LBW: low birth weight, SES: Socio economic status, LOS: length of hospital, PPWE: pregnant people with epilepsy, PPWOE: pregnant people without epilepsy. Adjusted for pregnant persons age, multiple births, SES, asthma, cardiovascular diseases, multiple birth, pain, psychiatric disorders, schizophrenia, diabetes, hypertension, mood disorders, urban/rural, teratogenic drugs, *Reduced model 1: Exposed to teratogenic drugs 1st trimester, Area of Residence: Rural and urban (reference),,Hypertension, Diabetes, Asthma, Pain, Pregnant persons age(Continuous), SES , and Multiple births, ** Reduced model 2: Hypertension, Diabetes, Asthma, Pain, Pregnant persons age (Continuous) and SES , *** Reduced model 3: Pregnant persons age(Continuous) and SES, OR: Odds ratio, Cl: Confidence interval. N/A: model did not converge*

6.3. Exposure by trimester

In this sensitivity analysis, we provide patient characteristics along with adverse outcome data for pregnant people exposed to ASMs and gabapentin during the first trimester (Table 6.2a and Table 6.2b) and the second and third trimesters (Table 6.2c and Table 6.2d). Our findings revealed that the level of exposed pregnant people with epilepsy (PPWE) remained consistent between the first trimester and the second and third trimesters. In contrast, number of exposed pregnant people without epilepsy (PPWOE) decreased significantly by 40%. Additionally, we observed a similar percentage of adverse outcomes and population characteristics.

Table 6.2a: Pregnant peoples characteristics exposed to ASMs in 1st trimester.

	Exposed		*Unexposed*	
	PPWE N (%)	PPWOE N (%)	PPWE N (%)	PPWOE N (%)
Total pregnant people	809 (0.3)	2976 (1)	1086 (0.4)	292863 (98.4)
*Age of **pregnant people** at birth (mean years)*	28.2	29.6	26.7	28.1
Chronic diseases				
• *Hypertension*	35 (4.3)	279 (9.4)	33 (3)	4840 (1.7)
• *Diabetes*	29 (3.6)	252 (8.5)	41 (3.8)	9195 (3.1)
• *Mood and Anxiety disorder*	197 (24.4)	1965 (66)	234 (21.5)	31358 (10.7)
• *Schizophrenia*	6 (0.7)	44 (1.5)	21.5 (4)	299 (0.1)
• *Personality disorder*	13 (1.6)	121 (4.1)	12(1.1)	924 (0.3)
• *Chronic pain*	98 (12.1)	649 (21.8)	142 (13.1)	16249 (5.5)
• *Asthma*	140 (17.3)	958 (32.2)	193 (17.8)	34663 (11.8)
• *Cardiovascular diseases*	S	16 (0.5)	S	290 (0.1)
Singleton birth	788 (97.4)	2886 (97)	1065 (98.1)	285055 (97.3)
Multiple birth	21 (2.6)	90 (3)	21 (1.9)	7808 (2.7)
Exposure to teratogenic drugs	43 (5.3)	284 (9.5)	34 (3.1)	7546 (2.6)
SES				
Q1	242 (29.9)	1244 (41.8)	345 (31.8)	75336 (25.7)
Q2	206 (25.5)	642 (21.6)	226 (20.8)	63001 (21.5)
Q3	165 (20.4)	483 (16.2)	220 (20.3)	54122 (18.5)
Q4	119 (14.7)	322 (10.8)	187 (17.2)	53787 (18.4)
Q5	71 (8.8)	276 (9.3)	105 (9.7)	45799 (15.6)
Urban	450 (55.6)	1784 (59.9)	635 (58.5)	154778 (52.8)
Rural	359 (44.4)	1192 (40.1)	451 (41.5)	138085 (47.2)

ASM: antiseizure medications, SGA: small for gestational age, LGA: large for gestational age, LBW: low birth weight SES: Socio economic status, PPWE: pregnant people with epilepsy, PPWOE: pregnant people without epilepsy, S: Suppressed

Table 6.2b: Outcome numbers in pregnant people exposed to ASMs in 1st trimester.

Outcomes	*Exposed*		*Unexposed*	
	PPWE N (%)	PPWOE N (%)	PPWE N (%)	PPWOE N (%)
Total pregnant people	809 (0.3)	2976 (1)	1086 (0.4)	292863 (98.4)
SGA	80 (9.9)	282 (9.5)	102 (9.4)	22535 (7.7)
LBW	83 (10.3)	317 (10.7)	83 (7.6)	15804 (5.4)
Preterm birth	102 (12.6)	500 (16.8)	123 (11.3)	23472 (8)
NICU admissions	118 (14.6)	607 (20.4)	126 (11.6)	23090 (7.9)
LOS of pregnant people	198 (24.8)	684 (23.3)	246 (22.9)	49365 (17.1)
LOS of infants	200 (24.7)	837 (28.1)	232 (21.4)	42937 (14.7)
Infant mortality	6 (0.7)	24 (0.8)	15 (1.4)	1707 (0.6)
Neonatal mortality	S (0.6)	15 (0.5)	10 (0.9)	111 (0.4)
Severe neonatal morbidity	S	30 (1)	20 (1.8)	2342 (0.8)
Neonatal readmissions	26 (3.2)	122 (4.1)	49 (4.6)	8786 (3)
Neonatal persistent pulmonary hypertension	S	S	S	66 (0.02)
Neonatal respiratory distress syndrome	S	S	S	249 (0.1)

ASM: antiseizure medications, SGA: small for gestational age, LOS: length of hospital, LGA: large for gestational age, LBW: low birth weight SES: Socio economic status, PPWE: pregnant people with epilepsy, PPWOE: pregnant people without epilepsy, S: Suppressed

Table 6.2c: Pregnant people characteristics exposed to ASMs in 2nd & 3rd trimester.

	Exposed		***Unexposed***	
	PPWE N (%)	PPWOE N (%)	PPWE N (%)	PPWOE N (%)
Total pregnant people	778 (0.3)	1781 (0.6)	117 (0.4)	294058 (98.8)
Age of pregnant people at birth (mean years)	28.2	30	26.7	28.1
Chronic diseases				
• *Hypertension*	31 (4)	154 (8.6)	37 (3.3)	4965 (1.7)
• *Diabetes*	28 (3.6)	154 (8.6)	42 (3.8)	9293 (3.2)
• *Mood and Anxiety disorder*	170 (21.9)	1146 (64.3)	261 (23.4)	32177 (10.9)
• *Schizophrenia*	6 (0.8)	23 (1.3)	S	320 (0.1)
• *Personality disorder*	12 (1.5)	70 (3.9)	13 (1.2)	975 (0.3)
• *Chronic pain*	83 (10.7)	380 (21.3)	157 (14.1)	16518 (5.6)
• *Asthma*	124 (15.9)	616 (34.6)	209 (18.7)	35005 (11.9)
• *Cardiovascular diseases*	S	7 (0.4)	S	299 (0.1)
Singleton birth	755 (97)	1719 (96.5)	1098 (98.3)	286222 (97.3)
Multiple birth	23 (3)	62 (3.5)	19 (1.7)	7836 (2.7)
Exposure to teratogenic drugs	37 (4.8)	188 (10.6)	40 (3.6)	7642 (2.6)
SES				
Q1	234 (30.1)	805 (45.2)	353 (31.6)	75775 (25.8)
Q2	198 (25.4)	384 (21.6)	234 (20.9)	63259 (21.5)
Q3	155 (19.9)	254 (14.3)	230 (20.6)	54351 (18.5)
Q4	112 (14.4)	189 (10.6)	194 (17.4)	53920 (18.3)
Q5	76 (9.8)	142 (8)	100 (9)	45933 (15.6)
Urban	429 (55.1)	1096 (61.5)	656 (58.7)	155466 (52.9)
Rural	349 (44.9)	685 (38.5)	461 (41.3)	138592 (47.1)

ASM: antiseizure medications, SGA: small for gestational age, SES: Socio economic status, PPWE: pregnant people with epilepsy, PPWOE: pregnant people without epilepsy, S: Suppressed

Table 6.2d: Outcome numbers in pregnant people exposed to ASMs in 2nd and 3rd trimester.

Outcomes	*Exposed*		*Unexposed*	
	PPWE N (%)	PPWOE N (%)	PPWE N (%)	PPWOE N (%)
Total pregnant people	798 (0.3)	2893 (1.1)	950 (0.3)	267712 (98.3)
SGA	78 (10)	174 (9.8)	104 (9.3)	22643 (7.7)
LBW	76 (9.8)	221 (12.4)	90 (8.1)	15900 (5.4)
Preterm birth	92 (11.8)	334 (18.8)	133 (11.9)	23638 (8)
NICU admissions	110 (14.1)	426 (23.9)	134 (12)	23271 (7.9)
LOS of pregnant people	199 (26)	405 (23.1)	245 (22.1)	49644 (17.1)
LOS of infants	198 (25.1)	575 (32.3)	237 (21.2)	43199 (14.7)
Infant mortality	S	15 (0.8)	16 (1.4)	1710 (0.6)
Neonatal mortality	S	10 (0.6)	11 (1)	116 (0.4)
Severe neonatal morbidity	S	27 (1.5)	21 (1.9)	2345 (0.8)
Neonatal readmissions	25 (3.2)	78 (4.4)	50 (4.5)	8830 (3)
Neonatal persistent pulmonary hypertension	S	S	S	67 (0)
Neonatal respiratory distress syndrome	S	S	S	249 (0.1)

ASM: antiseizure medications, SGA: small for gestational age, LBW: low birth weight, LOS: length of hospital, SES: Socio economic status, PPWE: pregnant people with epilepsy, PPWOE: pregnant people without epilepsy, S: Suppressed

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6.4. HDPS matching

There are 4 different approaches in High dimensional propensity score (HDPS) analysis including regression adjustment, matching, stratification, and weighting methods.[1]

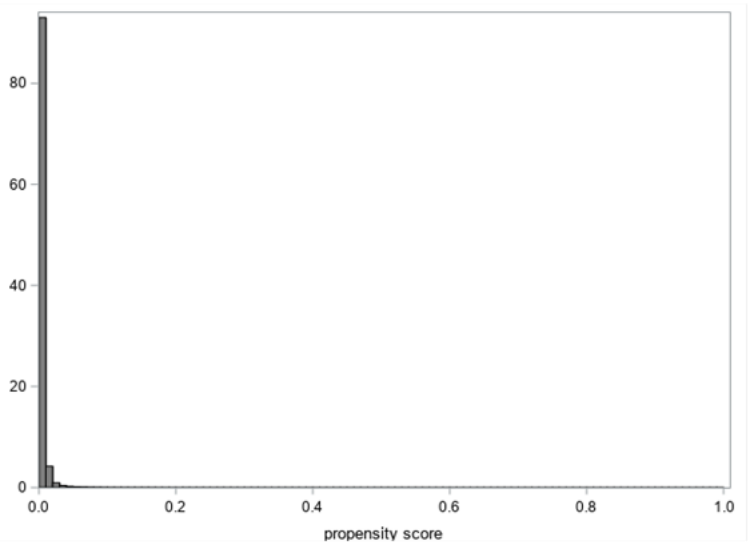

Figure 6.2a: Unexposed population propensity score distribution

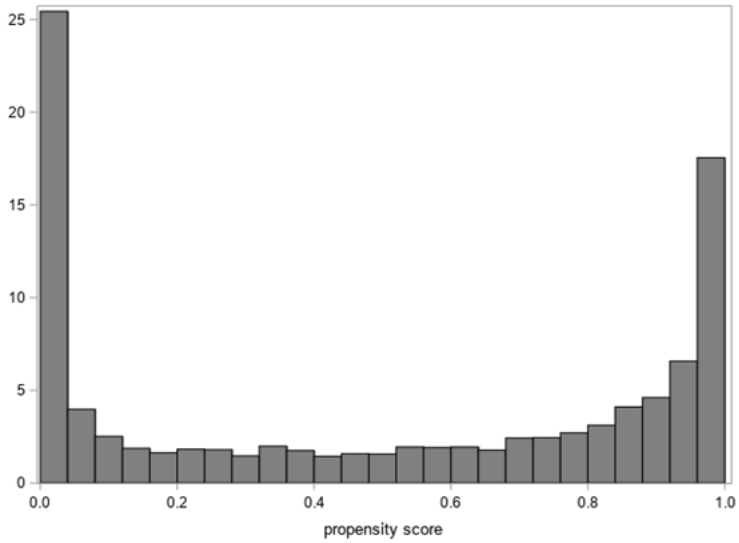

Figure 6.2b: Exposed population propensity score distribution

The application of HDPS weighting methods introduces the risk of individuals with significantly high weights unduly affecting the estimates, resulting in increased variance.[1] In our research, it's notable that the HDPS scores for unexposed pregnant people predominantly cluster at the extreme end, which indicates that weighting method doesn't work well with this data (as illustrated in **figure 6.2a & 6.2b).**[1] The lower sample size, especially among pregnant people with epilepsy (PPWE) as well as gabapentin exposure, stratification method would lead to less sample within strata and by using low number of strata to overcome the low sample, we might causes variability of propensity scores within each stratum, thus, leading to possible residual confounding.[1,2]

Therefore, we decided to evaluate the other two methods, matching and regression adjustment. In the subsequent analysis, we examined matching and regression methods. We observed that matching led to a sample size reduction of 30-60%, whereas regression resulted in a 1-5% reduction. These percentages further diminished in PPWE analysis, with matching leading to a 50-80% reduction, and regression models causing a 3-5% reduction. After careful consideration, we opted for the regression models, which preserved the sample, even though we acknowledge that matching is a better method considering the administrative database, but not in case of this project.[1] Considering bias adjustment and validity we observed that matching in most analysis, did not lead to better bias adjustment that warrants their use over regression. While the results might vary slightly, the bias precision balance favors the use of regression HDPS with overlap trimming.

Table 6.3a: Exposed sample size percentage lost due to HDPS methods in ASMs exposed cohort.

Outcomes	*All pregnant people*		*PPWE*		*PPWOE*	
	Regression adjustment with overlap trimming	**Matching**	**Regression adjustment with overlap trimming**	**Matching**	**Regression adjustment with overlap trimming**	**Matching**
	%	**%**	**%**	**%**	**%**	**%**
SGA	1.77	37.03	39.97	78.18	1.1	32.01
LBW	1.41	37.12	37.69	78.52	0.95	31.79
Preterm birth	6.42	40.71	40.65	73.29	0.98	30.64
NICU admissions	4.88	39.97	38.20	75.07	0.76	30.41
*LOS (*pregnant *people)*	0.91	37.07	35.38	76.00	1.19	30.41
LOS (infants)	0.69	36.01	34.14	75.34	0.63	29.12
Infant mortality	0.58	39.25	14.29	69.94	1.40	32.87
Neonatal mortality	0.46	38.10	17.24	65.87	1.34	32.62
Severe neonatal morbidity	0.48	37.83	5.02	54.50	0.92	30.94
Neonatal readmissions	1.63	38.93	32.00	79.22	1.05	32.48
Neonatal persistent pulmonary hypertension	0.86	12.80	N/A	N/A	0.88	14.95
Neonatal respiratory distress syndrome	0.74	25.96	2.38	16.91	1.27	32.89

SGA: small for gestational age, LBW: low birth weight, LOS: length of hospital, SES: Socio economic status, PPWE: pregnant people with epilepsy, PPWOE: pregnant people without epilepsy, S: Suppressed. N/A: model did not converge

Table 6.3b: Exposed sample size percentage lost due to HDPS methods in gabapentin exposed cohort.

Outcomes	*All pregnant people*		*PPWE*		*PPWOE*	
	Regression adjustment with overlap trimming	**Matching**	**Regression adjustment with overlap trimming**	**Matching**	**Regression adjustment with overlap trimming**	**Matching**
	%	%	%	%	%	%
SGA	15.17	50.24	24	98	14.38	47.75
LBW	7.63	48.42	30.95	78.57	7.26	49.30
Preterm birth	9.64	47.86	96.00	94	19.76	52.94
NICU admissions	11.81	47.24	92.31	N/A	10.70	47.42
LOS of pregnant people	14.87	47.76	N/A	N/A	14.13	46.78
LOS of infants	9.13	45.66	N/A	N/A	11.22	44.53
Infant mortality	8.60	49.57	75	95.83	9.91	49.15
Neonatal mortality	11.05	50.38	N/A	N/A	13.39	50.05
Severe neonatal morbidity	9.10	50.38	9.10	50.38	0.29	1.44
Neonatal readmissions	8.67	50	69.57	89.13	10.08	49.58
Neonatal persistent pulmonary hypertension	3.13	48.77	N/A	N/A	1.69	48.31
Neonatal respiratory distress syndrome	1.23	49.95	N/A	N/A	1.79	49.25

SGA: small for gestational age, LBW: low birth weight, LOS: length of hospital, SES: Socio economic status, PPWE: pregnant people with epilepsy, PPWOE: pregnant people without epilepsy, S: Suppressed. N/A: model did not converge

Table 6.4a: Outcome counts among all pregnant people exposed to ASMs.

Outcomes	*Regression adjustment with overlap trimming*				*Matching*			
	Exposed		Unexposed		Exposed		Unexposed	
	N	Event	N	Event	N	Event	N	Event
SGA	3716	384	269428	22480	2382	228	2377	233
LBW	3703	422	272814	15538	2362	242	2426	178
Preterm birth	3515	637	266046	23186	2227	338	2258	307
NICU admissions	3370	785	266252	22796	2127	420	2221	326
*LOS of **pregnant people***	3143	956	236175	48157	1996	530	2027	499
LOS of infants	3034	1117	246789	42220	1955	591	2005	541
Infant mortality	4131	32	289256	1689	2524	17	2514	27
Neonatal mortality	4146	22	289843	1102	2578	13	2576	15
Severe neonatal morbidity	4125	42	285955	2307	2577	50	2577	50
Neonatal readmissions	3935	165	279732	8661	2443	104	2461	86
Neonatal persistent pulmonary hypertension	4150	S	290565	65	3650	S	3647	S
Neonatal respiratory distress syndrome	4152	S	290412	251	3097	S	3092	S

SGA: small for gestational age, LBW: low birth weight, LOS: length of hospital, SES: Socio economic status, PPWE: pregnant people with epilepsy, PPWOE: pregnant people without epilepsy, S: Suppressed

Table 6.4b: Results of logistic regression and HDPS regression and matching models evaluating the association between ASMs and neonatal birth outcomes among all pregnant people

Outcomes	*Regression models*		*HDPS models*	
	Crude OR (95% CI)	**Adjusted OR (95% CI)**	**Regression adjustment with overlap trimming OR (95% CI)**	**Matching OR (95% CI)**
SGA	1.24(1.11-1.38)	1.16(1.04-1.30)	1.03 (0.89-1.20)	0.98 (0.81-1.18)
LBW	1.92(1.71-2.15)	1.66(1.47-1.88)	1.35 (1.13-1.60)	1.41 (1.14-1.74)
Preterm birth	1.92(1.74-2.12)	1.56(1.41-1.73)	1.22 (1.05-1.42)	1.12 (0.94-1.33)
NICU admissions	2.53(2.32-2.76)	1.91(1.74-2.10)	1.45 (1.25-1.67)	1.36 (1.15-1.60)
LOS of pregnant people	1.42 (1.32-1.53)	1.25 (1.16-1.35)	1.12 (1.00-1.24)	1.08 (0.94-1.25)
LOS of infants	2.02(1.87-2.17)	1.68(1.56-1.82)	1.25 (1.11-1.40)	1.12 (0.98-1.28)
Infant mortality	1.27(0.88-1.84)	1.19(0.82-1.72)	0.92 (0.51-1.66)	0.62 (0.31-1.19)
Neonatal mortality	1.43(0.93-2.20)	1.40(0.90-2.16)	1.11 (0.56-2.20)	0.87 (0.38-1.95)
Severe neonatal morbidity	1.24(0.90-1.72)	1.04(0.75-1.44)	1.15 (0.72-1.82)	1.00 (0.56-1.79)
Neonatal readmissions	1.31(1.12-1.56)	1.10(0.93-1.30)	1.14 (0.89-1.46)	1.22(0.90-1.66)
Neonatal persistent pulmonary hypertension	1.05(0.15-7.54)	0.94(0.13-6.92)*	0.21(0.02-2.11)	0.26(<0.001-1.714)
Neonatal respiratory distress syndrome	1.07(0.38-2.96)	0.93(0.32-2.69)	0.02 (0.07-0.62)	0.17 (0.004-1.37)

*SGA: small for gestational age, LBW: low birth weight, LOS: length of hospital, SES: Socio economic status, PPWE: pregnant people with epilepsy, PPWOE: pregnant people without epilepsy. Adjusted for Pregnant persons age, multiple births, SES, asthma, cardiovascular diseases, multiple birth, pain, psychiatric disorders, schizophrenia, diabetes, hypertension, mood disorders, urban/rural, teratogenic drugs, *Reduced model 1: Exposed to teratogenic drugs 1st trimester, Area of Residence: Rural and urban (reference),,Hypertension, Diabetes, Asthma, Pain, Pregnant persons age(Continuous), SES , and Multiple births, ** Reduced model 2: Hypertension, Diabetes, Asthma, Pain, Pregnant persons age (Continuous) and SES , *** Reduced model 3: Pregnant persons age(Continuous) and SES, OR: Odds ratio, Cl: Confidence interval.*

Table 6.4c: Results of logistic regression and HDPS regression and matching models evaluating the association between ASMs and neonatal birth outcomes among PPWE

Outcomes	*Regression models*		*HDPS models*	
	Crude OR (95% CI)	**Adjusted OR (95% CI)**	**Regression adjustment with overlap trimming OR (95% CI)**	**Matching OR (95% CI)**
SGA	1.09 (0.80-1.50)	1.08 (0.77-1.50)*	0.82 (0.45-1.50)	0.63 (0.28-1.37)
LBW	1.24 (0.85-1.79)	1.14 (0.77-1.66)	0.78 (0.40-1.53)	0.85 (0.34-2.05)
Preterm birth	1.07 (0.79-1.46)	1.05 (0.76-1.44)*	0.86 (0.49-1.54)	1.39 (0.64-3.09)
NICU admissions	1.32 (0.99-1.76)	1.26 (0.94-1.70)*	1.08 (0.58-2.02)	0.92 (0.49-1.71)
LOS of pregnant people	1.18 (0.95-1.47)	1.16 (0.92-1.45)	1.26 (0.82-1.93)	1.41 (0.86-2.36)
LOS of infants	1.21 (0.96-1.51)	1.15(0.91-1.46)*	0.89 (0.57-1.37)	0.97 (0.59-1.59)
Infant mortality	0.46 (0.17-1.22)	0.38 (0.13-1.06)*	0.35 (0.13-0.99)	1.00 (<0.001-19)
Neonatal mortality	0.56 (0.18-1.73)	0.54 (0.16-0.77)***	0.37 (0.16-0.88)	N/A
Severe neonatal morbidity	0.23 (0.08-0.66)	0.20 (0.07-0.60)*	0.21 (0.07-0.69)	0.33 (0.03-1.86)
Neonatal readmissions	0.72 (0.44-1.17	0.70 (0.43-1.16)**	1.79 (0.76-4.17)	2.5 (0.41-26.25)
Neonatal persistent pulmonary hypertension	N/A	N/A	N/A	N/A
Neonatal respiratory distress syndrome	N/A	N/A	N/A	1 (<0.001-19)

*SGA: small for gestational age, LBW: low birth weight, LOS: length of hospital, SES: Socio economic status, PPWE: pregnant people with epilepsy, PPWOE: pregnant people without epilepsy. Adjusted for Pregnant persons age, multiple births, SES, asthma, cardiovascular diseases, multiple birth, pain, psychiatric disorders, schizophrenia, diabetes, hypertension, mood disorders, urban/rural, teratogenic drugs, *Reduced model 1: Exposed to teratogenic drugs 1st trimester, Area of Residence: Rural and urban (reference),,Hypertension, Diabetes, Asthma, Pain, Pregnant persons age(Continuous), SES , and Multiple births, ** Reduced model 2: Hypertension, Diabetes, Asthma, Pain, Pregnant persons age (Continuous) and SES , *** Reduced model 3: Pregnant persons age(Continuous) and SES, OR: Odds ratio, CI: Confidence interval. N/A: model did not converge*

Table 6.4d: Results of logistic regression and HDPS regression and matching models evaluating the association between ASMs and neonatal birth outcomes among PPWOE.

Outcomes	*Regression models*		*HDPS models*	
	Crude OR (95% CI)	**Adjusted OR (95% CI)**	**Regression adjustment with overlap trimming OR (95% CI)**	**Matching OR (95% CI)**
SGA	1.95 (1.72-2.21)	1.14 (1.01-1.29)	1.04 (0.88-1.22)	0.94 (0.76-1.17)
LBW	1.23 (1.09-1.39)	1.64 (1.43-1.88)	1.35 (1.13-1.62)	1.31 (1.05-1.62)
Preterm birth	2.01 (1.80-2.24)	1.58 (1.41-1.76)	1.21 (1.03-1.42)	1.15 (0.96-1.38)
NICU admissions	2.68 (2.43.2.95)	1.94 (1.75-2.14)	1.5 (1.28-1.75)	1.31 (1.11-1.55)
LOS of pregnant people	1.37 (1.26-1.49)	1.18 (1.08-1.29)	1.08 (0.97-1.21)	1.11 (0.96-1.30)
LOS of infants	2.06 (1.90-2.24)	1.66 (1.53-1.82)	1.25 (1.11-1.41)	1.23 (1.06-1.14)
Infant mortality	1.30 (0.86-1.97)	1.21 (0.80-1.84)	0.86 (0.47-1.58)	0.63 (0.28-1.37)
Neonatal mortality	1.43 (0.88-2.33)	1.38 (0.84-2.27)	1.00 (0.5-2.01)	0.83 (0.32-2.11)
Severe neonatal morbidity	1.43 (1.01-2.01)	1.17 (0.82-1.66)	1.22 (0.78-1.89)	1.56 (0.80-3.13)
Neonatal readmissions	1.37 (1.15-1.64)	1.11 (0.93-1.34)	1.18 (0.91-1.53)	1.25 (0.92-1.71)
Neonatal persistent pulmonary hypertension	1.34 (0.19-9.66)	1.19 (0.16-8.78)**	0.25 (0.02-3.57)	0.50 (0.01-9.61)
Neonatal respiratory distress syndrome	1.35 (0.48-3.81)	1.16 (0.39-3.46)	0.27 (0.1-0.75)	0.12 (<0.001-0.65)

*SGA: small for gestational age, LBW: low birth weight, LOS: length of hospital, SES: Socio economic status, PPWE: pregnant people with epilepsy, PPWOE: pregnant people without epilepsy. Adjusted for Pregnant persons age, multiple births, SES, asthma, cardiovascular diseases, multiple birth, pain, psychiatric disorders, schizophrenia, diabetes, hypertension, mood disorders, urban/rural, teratogenic drugs, *Reduced model 1: Exposed to teratogenic drugs 1st trimester, Area of Residence: Rural and urban (reference),,Hypertension, Diabetes, Asthma, Pain, Pregnant persons age(Continuous), SES , and Multiple births, ** Reduced model 2: Hypertension, Diabetes, Asthma, Pain, Pregnant persons age (Continuous) and SES , *** Reduced model 3: Pregnant persons age(Continuous) and SES, OR: Odds ratio, Cl: Confidence interval.*

Table 6.5a: Outcome counts among all pregnant people exposed to gabapentin.

Outcomes	*Regression adjustment with overlap trimming*				*Matching*			
	Exposed		**Unexposed**		**Exposed**		**Unexposed**	
	N	%	N	%	N	%	N	%
SGA	817	78	249261	20912	485	40	485	40
LBW	847	125	243290	13858	473	55	482	46
Preterm birth	759	183	250604	21765	438	86	441	83
NICU admissions	708	201	239066	20994	420	108	432	96
LOS of pregnant people	647	234	230220	47136	397	117	411	103
LOS of infants	617	307	234922	40016	369	154	389	134
Infant mortality	957	10	277206	1594	528	S	521	7
Neonatal mortality	934	7	243903	889	521	S	522	3961
Severe neonatal morbidity	949	12	262465	2119	518	S	518	S
Neonatal readmissions	917	41	251437	7880	502	23	506	19
Neonatal persistent pulmonary hypertension	1024	S	224854	53	541	S	541	S
Neonatal respiratory distress syndrome	1044	S	236436	201	527	S	527	11023

SGA: small for gestational age, LBW: low birth weight, LOS: length of hospital, SES: Socio economic status, PPWE: pregnant people with epilepsy, PPWOE: pregnant people without epilepsy, S: Suppressed

Table 6.5b: Results of logistic regression and HDPS regression and matching models evaluating the association between gabapentin and neonatal birth outcomes among all pregnant people

Outcomes	*Regression models*		*HDPS models*	
	Crude OR (95% CI)	**Adjusted OR (95% CI)**	**Regression adjustment with overlap trimming OR (95% CI)**	**Matching OR (95% CI)**
SGA	1.19 (0.97-1.47)	1.11 (0.90-1.38)	0.90 (0.64-1.28)	1.00 (0.62-1.62)
LBW	2.49 (2.04-3.05)	1.95 (1.58-2.41)	1.31 (0.90-1.91)	1.22 (0.79-1.89)
Preterm birth	2.45 (2.04-2.94)	1.68 (1.39-2.03)	1.07 (0.76-1.51)	1.04 (0.74-1.46)
NICU admissions	3.20 (2.72-3.77)	2.04 (1.71-2.42)	1.38 (0.99-1.94)	1.16 (0.84-1.60)
LOS of pregnant people	1.72 (1.49-1.98)	1.33 (1.15-1.54)	1.05 (0.84-1.33)	1.17 (0.86-1.60)
LOS of infants	2.87 (2.50-3.30)	2.09 (1.81-2.41)	1.28 (0.99-1.65)	1.22 (0.92-1.63)
Infant mortality	1.53 (0.78-3.01)	1.29 (0.66-2.51)	0.73 (0.21-2.58)	0.29 (0.03-1.50)
Neonatal mortality	1.84 (0.87-3.88)	1.60 (0.74-3.45)	1.09 (0.32-3.78)	1.33 (0.23-9.10)
Severe neonatal morbidity	1.48 (0.80-2.72)	1.07 (0.59-1.96)	0.54 (0.22-1.33)	1.00 (0.23-4.35)
Neonatal readmissions	1.43 (1.05-1.96)	1.09 (0.79-1.49)	1.18 (0.69-2.01)	1.24 (0.62-2.49)
Neonatal persistent pulmonary hypertension	4.19 (0.58-30.2)	3.40 (0.45-25.7)**	0.85 (0.35-2.04)	N/A
Neonatal respiratory distress syndrome	4.08 (1.40-11.9)	3.36 (1.16-9.71)	0.33 (0.06-1.76)	0.29 (0.03-1.50)

*SGA: small for gestational age, LBW: low birth weight, LOS: length of hospital, SES: Socio economic status, Adjusted for Pregnant persons age, multiple births, SES, asthma, cardiovascular diseases, multiple birth, pain, psychiatric disorders, schizophrenia, diabetes, hypertension, mood disorders, urban/rural, teratogenic drugs, *Reduced model 1: Exposed to teratogenic drugs 1st trimester, Area of Residence: Rural and urban (reference),,Hypertension, Diabetes, Asthma, Pain, Pregnant persons age(Continuous), SES , and Multiple births, ** Reduced model 2: Hypertension, Diabetes, Asthma, Pain, Pregnant persons age (Continuous) and SES , *** Reduced model 3: Pregnant persons age(Continuous) and SES, OR: Odds ratio, Cl: Confidence interval. N/A: model did not converge.*

Table 6.5c: Results of logistic regression and HDPS regression and matching models evaluating the association between gabapentin and neonatal birth outcomes among PPWE

Outcomes	*Regression models*		*HDPS models*	
	Crude OR (95% CI)	**Adjusted OR (95% CI)**	**Regression adjustment with overlap trimming OR (95% CI)**	**Matching OR (95% CI)**
SGA	1.13 (0.47-2.71)	0.94 (0.37-2.42)*	0.42 (0.05-3.5)	N/A
LBW	2.23 (1.02-4.88)	1.60 (0.57-4.53)	3.98 (0.83-19.0)	0.05 (0.01-9.61)
Preterm birth	2.18 (0.98-4.86)	1.77 (0.77-4.08)*	1.25 (0.07-22.9)	1.00 (<0.01-19.0)
NICU admissions	1.95 (0.92-4.16)	1.45 (0.61-3.42)*	6.26 (0.9-43.5)	N/A
LOS of pregnant people	2.01 (1.08-3.76)	1.73 (0.90-3.33)	N/A	N/A
LOS of infants	2.14 (1.12-4.10)	1.72 (0.85-3.50)*	N/A	N/A
Infant mortality	4.46 (1.01-19.7)	5.39 (1.11-26.2)*	N/A	N/A
Neonatal mortality	3.14 (0.42-23.4)	2.68 (0.30-23.9)***	N/A	N/A
Severe neonatal morbidity	N/A	N/A	0.54 (0.22-1.33)	1.00 (0.23-4.35)
Neonatal readmissions	1.30 (0.22-7.55)	1.07 (0.17-6.65)**	N/A	1.00 (<0.01-19)
Neonatal persistent pulmonary hypertension	N/A	N/A	N/A	N/A
Neonatal respiratory distress syndrome	N/A	N/A	N/A	N/A

*SGA: small for gestational age, LBW: low birth weight, LOS: length of hospital, PPWE: pregnant people with epilepsy, Adjusted for Pregnant persons age, multiple births, SES, asthma, cardiovascular diseases, multiple birth, pain, psychiatric disorders, schizophrenia, diabetes, hypertension, mood disorders, urban/rural, teratogenic drugs, *Reduced model 1: Exposed to teratogenic drugs 1st trimester, Area of Residence: Rural and urban (reference),,Hypertension, Diabetes, Asthma, Pain, Pregnant persons age(Continuous), SES , and Multiple births, ** Reduced model 2: Hypertension, Diabetes, Asthma, Pain, Pregnant persons age (Continuous) and SES , *** Reduced model 3: Pregnant persons age(Continuous) and SES, OR: Odds ratio, Cl: Confidence interval. N/A: model did not converge.*

Table 6.5d: Results of logistic regression and HDPS regression and matching models evaluating the association between gabapentin and neonatal birth outcomes among PPWOE

Outcomes	*Regression models*		*HDPS models*	
	Crude OR (95% CI)	**Adjusted OR (95% CI)**	**Regression adjustment with overlap trimming OR (95% CI)**	**Matching OR (95% CI)**
SGA	1.19 (0.95-1.47)	1.11 (0.89-1.39)	0.92 (0.65-1.30)	1.06 (0.64-1.78)
LBW	2.49 (2.03-3.05)	1.94 (1.56-2.41)	1.34 (0.92-1.95)	1.07 (0.70-1.63)
Preterm birth	2.45 (2.04-2.95)	1.67 (1.38-2.02)	1.08 (0.76-1.53)	0.85 (0.61-1.19)
NICU admissions	3.25 (2.75-3.84)	2.06 (1.73-2.46)	1.40 (0.99-1.97)	1.57 (1.12-2.20)
LOS of pregnant people	1.68 (1.45-1.94)	1.30 (1.12-1.51)	1.04 (0.82-1.32)	1.11 (0.81-1.53)
LOS of infants	2.86 (2.48-3.30)	2.08 (1.80-2.41)	1.31 (1.01-1.69)	1.10 (0.83-1.46)
Infant mortality	1.28 (0.59-2.74)	1.08 (0.51-2.29)	0.66 (0.14-3.14)	1.00 (0.23-4.35)
Neonatal mortality	1.66 (0.74-3.74)	1.44 (0.63-3.31)	1.04 (0.24-4.58	3.0 (0.24-157.49)
Severe neonatal morbidity	1.55 (0.84-2.86)	1.13 (0.62-2.08)	0.97 (0.48-1.96)	1.30 (0.53-3.31)
Neonatal readmissions	1.41 (1.03-1.94)	1.07 (0.78-1.47)	1.19 (0.68-2.09)	1.22 (0.63-2.42)
Neonatal persistent pulmonary hypertension	4.44 (0.62-32.0)	3.55 (0.47-26.8)**	0.89 (0.40-2.02)	N/A
Neonatal respiratory distress syndrome	4.33 (1.47-12.7)	3.50 (1.20-10.2)	0.28 (0.04-1.83)	1.00 (0.13-78.50)

*SGA: small for gestational age, LBW: low birth weight, LOS: length of hospital, SES: Socio economic status, PPWE: pregnant people with epilepsy, PPWOE: pregnant people without epilepsy. Adjusted for Pregnant persons age, multiple births, SES, asthma, cardiovascular diseases, multiple birth, pain, psychiatric disorders, schizophrenia, diabetes, hypertension, mood disorders, urban/rural, teratogenic drugs, *Reduced model 1: Exposed to teratogenic drugs 1st trimester, Area of Residence: Rural and urban (reference),,Hypertension, Diabetes, Asthma, Pain, Pregnant persons age(Continuous), SES , and Multiple births, ** Reduced model 2: Hypertension, Diabetes, Asthma, Pain, Pregnant persons age (Continuous) and SES , *** Reduced model 3: Maternal age(Continuous) and SES, OR: Odds ratio, Cl: Confidence interval. N/A: model did not converge*

6.5. References

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Chapter 7: Conclusion and future recommendations

7.1. General conclusion

In conclusion, this thesis has undertaken a comprehensive evaluation of the safety of antiseizure medications (ASMs) during pregnancy using real-world data, through a combination of evidence synthesis and evidence generation studies. This research has shed light on the risks associated with ASMs and provided valuable insights into their impact on adverse birth outcomes.

The systematic review and meta-analysis presented in chapter 3 revealed a significant increase in the risk of small for gestational age (SGA) and low birth weight (LBW) among pregnant people exposed to ASMs, irrespective of their epilepsy status.[1,2] The findings emphasized the importance of carefully managing epilepsy treatment during pregnancy to minimize risks to newborns.[1] Polytherapy was associated with higher risks, highlighting the need for optimizing treatment strategies.[1]

The evidence generation project presented in chapter 4 and 5, focused on in-utero exposure to ASMs and gabapentin, further reinforcing the notion that ASMs exposure in pregnancy are associated with elevated risks of certain adverse birth outcomes such as LBW, preterm birth, and neonatal intensive care unit (NICU) admission among all pregnant people and pregnant people without epilepsy (PPWOE). Gabapentin exposure during pregnancy was associated with an increased risk of LBW, preterm birth, NICU admissions and length of hospital stay (LOS) of pregnant people and infants among pregnant people in the adjusted regression analysis, but these results did not reach statistical significance in the high-dimensional propensity score

(HDPS) analysis. Our results in both chapter 4 and 5 also indicate a strong unmeasured confounding in the adjusted regression analysis which was accounted for in the HDPS analysis.

Additionally, the study on gabapentin, which is increasingly used among pregnant people, revealed concerning findings, particularly for those without epilepsy. The increased magnitudes of adverse birth outcome risk among PPWOE exposed to gabapentin even though they did not reach statistical significant highlights the need for further research to understand gabapentin safety during pregnancy in both populations with and without epilepsy.

The cohort studies highlight the necessity for a thoughtful and rationalized approach to ASM/gabapentin usage in pregnant people, especially when safer alternative treatments are available. Larger studies with advance analysis models and study designs accounting for unmeasured confounding are recommended to further study the association between ASMs/gabapentin and adverse neonatal outcomes especially among pregnant people with epilepsy (PPWE) and PPWOE.

In conclusion, the findings of this thesis stress the importance of cautious consideration and individualized treatment planning for pregnant people taking ASMs. While ASMs remain crucial for managing epilepsy, their use in pregnancy should be carefully weighed against potential risks. Moreover, the need for ongoing research into the safety of ASMs, including gabapentin, in pregnancy is clear. This work provides a solid foundation for future investigations and contributes valuable knowledge to inform clinical practice and improve the well-being of pregnant people and their newborns.

7.2. Clinical implications and Impact

The prescription patterns of various ASMs among pregnant people have evolved over time, reflecting advancements in safer drug options and a decrease in medications associated with established or suspected risks during pregnancy.[3,4] In recent years, we've observed a decline in the use of certain ASMs, such as valproic acid and topiramate, among pregnant people.[3,4] In contrast, newer ASMs like gabapentin have gained prominence, alongside the emergence of promising medications with high efficacy but necessitating further evaluation for pregnancy safety, such as cenobamate and levetiracetam.[3,4]

Our findings indicate that exposure to ASMs and gabapentin during pregnancy significantly elevates the risk of infant's LOS, preterm birth, and NICU admissions. Additionally, there is a slight increase in the risk of adverse birth weight outcomes. The mortality and morbidity risk are yet not established therefore we recommend that clinicians exercise caution and thoroughly assess the risks and benefits before prescribing ASMs/gabapentin during pregnancy, especially for off-label indications.

Our research provides clinicians with a deeper insight into the safety profiles of ASMs and specifically gabapentin. Our study also generates information which aims to empower pregnant people, enabling them to make informed decisions when prescribed ASMs, including gabapentin, and understand potential complications associated with their treatment choices.

7.3. Future recommendations

While we learned a lot from the results, there are several venues for the investigation that should be explored to address the new knowledge gaps created. Firstly, we recommend conduction multisite Canadian studies. In both our evidence synthesis and evidence generation projects, we have identified that a few of our analyses were underpowered, particularly in the PPWE group and with regards to the exposure to gabapentin. Given the limited data available in each Canadian province, we strongly recommend the initiation of a comprehensive Pan-Canadian study. This would enable a more robust evaluation among of risk within the Canadian population.

Secondly, we recommend active comparator studies. Our project reported a consistent increase in the risk of specific adverse outcomes, such as LBW, preterm birth, NICU admissions, and LOS for infants exposed to ASMs. It is imperative to conduct further analyses with a primary focus on active comparator study designs. Specifically, we recommend comparing the safety of ASMs among currently used ASMs medication and combinations, to gain deeper insights into safety. Given the absence of a standardized treatment regimen for epilepsy, comparing clinically used ASMs and their combinations through an active comparators approach will ultimately lead to enhanced clinical practices and a better understanding of the safety profile of ASMs, including gabapentin during pregnancy.[7–10]

Our third recommendation is to investigate the safety of gabapentin for both prescribed and off-label use. The exponential increase in the utilization of gabapentin over the past few years, coupled with its expanding off-label usage and the potential for abuse, is a cause for concern.[3,6,11] Additional research on the safety of gabapentin is clearly warranted.[14–18]

Finally, we recommend employing advanced statistical methods and study designs to address unmeasured confounding in the analysis. Our studies revealed a significant reduction in the risk magnitudes in the HDPS analysis compared to the adjusted regression analysis, indicating unmeasured confounding in the latter. Therefore, we recommend future studies to adapt advance statistical analysis methods and study designs that can account for unmeasured confounding.

7.4. Conclusion

With the reported adverse neonatal outcomes risk associated with in-utero exposure to ASMs, clinicians should carefully assess the risk-benefit ratio before prescribing these medications. Moreover, the use of gabapentin requires thorough scrutiny, among pregnant people without epilepsy. Subsequent research, including multi-site investigations, active comparator studies, advance statistical methods and study designs accounting for unmeasured confounding and examinations specifically focusing on the off-label safety of gabapentin is needed.

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Thesis Appendix

Appendix A Research ethics (HERB)

University of Manitoba | Research Ethics and Compliance

Research Ethics Bannatyne
P126-770 Bannatyne Avenue
Winnipeg, MB R3E 0W3
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HEALTH RESEARCH ETHICS BOARD (HREB)

CERTIFICATE OF ANNUAL APPROVAL

PRINCIPAL INVESTIGATOR:	INSTITUTION/DEPARTMENT:	ETHICS #:
Alekhya Lavu	U of M/Pharmacy	HS23674 (H2020:089)
HREB MEETING DATE (If applicable):	**APPROVAL DATE:**	**EXPIRY DATE:**
NA	February 5, 2024	February 18, 2025
STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (If applicable):		
Dr. Sherif Eltonsy		

PROTOCOL NUMBER:	PROJECT OR PROTOCOL TITLE:
NA	Antiepileptic treatments during pregnancy and birth weight outcomes (Linked to H2020:090)
SPONSORING AGENCIES AND/OR COORDINATING GROUPS:	
Manitoba Medical Service Foundation (MMSF)	

Submission Date of Investigator Documents:	HREB Receipt Date of Documents:
January 22, 2024	January 22, 2024

REVIEW CATEGORY OF ANNUAL REVIEW: **Full Board Review** ☐ **Delegated Review** ☒

THE FOLLOWING AMENDMENT(S) and DOCUMENTS ARE APPROVED FOR USE:

Document Name (if applicable)	Version (if applicable)	Date

Annual approval

*Annual approval implies that the most recent **HREB approved** versions of the protocol, Investigator Brochures, advertisements, letters of initial contact or questionnaires, and recruitment methods, etc. are approved.*

Consent and Assent Form(s):

CERTIFICATION

The University of Manitoba (UM) Health Research Board (HREB) has reviewed the annual study status report for the research study/project named on this *Certificate of Annual Approval* as per the category of review listed above and was found to be acceptable on ethical grounds for research involving human participants. Annual approval was granted by the Chair or Acting Chair, UM HREB, per the response to the conditions of approval outlined during the initial review (full board or delegated) of the annual study status report.

HREB ATTESTATION

The University of Manitoba (UM) Health Research Board (HREB) is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulations of Manitoba. In respect to clinical trials, the HREB complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations of Canada and carries out its functions in a manner consistent with Good Clinical Practices.

QUALITY ASSURANCE
The University of Manitoba Research Quality Management Office may request to review research documentation from this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

CONFLICT OF INTEREST
Any Principal or Co-Investigators of this study who are members of the UMHREB did not participate in the review or voting of this study.

CONDITIONS OF APPROVAL:

1. The study is acceptable on scientific and ethical grounds for the ethics of human use only. ***For logistics of performing the study, approval must be sought from the relevant institution(s).***
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. This approval is valid until the expiry date noted on this certificate of annual approval. **A Bannatyne Campus Annual Study Status Report** must be submitted to the REB within 15-30 days of this expiry date.
5. Any changes of the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to the HREB for consideration in advance of implementation of such changes on the **Bannatyne Campus Research Amendment Form.**
6. Adverse events and unanticipated problems must be reported to the REB as per Bannatyne Campus Research Boards Standard Operating procedures.
7. The UM HREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report.**

Please quote the above Human Ethics Number on all correspondence.
Inquiries should be directed to the REB Secretary **Telephone**: (204) 789-3255/ **Fax:** (204) 789-3414

Appendix B Research ethics (HIPC/PHRPC)

Research Manitoba

RITHIM

Provincial Health Research Privacy Committee (PHRPC)
Amendment Approval

February 5, 2024

HIPC No. 2019/2020-61
file number to be quoted on all correspondence

Application date: October 8, 2023
Submission received: November 23, 2023
Approval date: February 5, 2024
Researcher name: Alekhya Lavu (student)
Project title: Antiepileptic Therapies during Pregnancy and Birth Weight Outcomes

Thank you for submitting the protocol ***amendment*** form for the proposed protocol changes for this project named above. The Provincial Health Research Privacy Committee (PHRPC) has ***approved*** your revisions and you may consider this message as official notification of amendment approval.

If you have any questions or concerns, please do not hesitate to contact the RITHIM Program Officer (PHRPC Lead) at PHRPC@researchmb.ca.

Yours truly,

Chair, Provincial Health Research Privacy Committee (PHRPC)

PLEASE ALWAYS USE THE MOST RECENT VERSION OF PHRPC FORMS FROM THE PHRPC WEBSITE

- see 'Forms & Guides' at https://www.rithim.ca/phrpc-submission-information