A Longitudinal Analysis of the Predictors and Consequences of Prenatal Antidepressant use among Women Requiring these Medications before Pregnancy

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A thesis submitted to the Faculty of Graduate and Postdoctoral Studies in partial fulfillment of the requirements for the degree of Doctor of Philosophy (Ph.D.)

November 21, 2014

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ABSTRACT

Women with chronic conditions who become pregnant have a difficult choice to consider: continue pharmaceutical treatment, though it may have teratogenic risks for the fetus, or stop treatment, though the condition itself may harm both mother and baby. Unfortunately, very little is known about prescription medication use in pregnancy among women requiring treatment for chronic conditions prior to pregnancy to help guide their decisions. This is due, partly, to the scarcity of data from population-based studies assessing the consequences of medication use or discontinuation on pregnancy outcomes. It is also due to problems of confounding that complicate efforts to untangle the roles of medication and disease in pregnancy outcomes.

In this study, we examined a series of questions to address these issues: Are pregnant women more likely to discontinue antidepressant use than are non-pregnant women, i.e. is pregnancy a major determinant of medication discontinuation? What are the maternal characteristics associated with antidepressant discontinuation in pregnancy? Finally, does maternal antidepressant use and discontinuation have consequences on maternal health? The answers may help us broaden our knowledge of an understudied area, as well as shape clinical guidelines.

Our data derive from a large, population-based cohort of women identified through administrative databases maintained by Quebec's health insurance board (RAMQ). We compared medication use in pregnancy among women using antidepressants before pregnancy to medication use in matched non-pregnant women, and determined the predictors of antidepressants discontinuation. We then assessed the risk of pre-eclampsia in women continuing use of antidepressants in pregnancy compared to (a) women who stopped all use in pregnancy; (b) women with a depression diagnosis and no antidepressant use; and (c) women with neither a depression diagnosis nor antidepressant use. Finally, we assessed the risk of miscarriage in women taking antidepressants in the first trimester compared to depressed and non-depressed unexposed women. To account for the risk of induced abortions, which may be

high among antidepressant users, and may bias the miscarriage risk estimates, we employed an appropriate correction factor.

We found that pregnant women are significantly more likely to discontinue antidepressants compared to non-pregnant women, with discontinuation rates differing within classes of antidepressants. The main predictors of continuing use in pregnancy were factors related to disease severity and overall health (e.g. duration of pre-pregnancy antidepressant use, being on welfare and older age). The risk of pre-eclampsia among women who continued antidepressants in the first 20 weeks of pregnancy was significantly higher than those who stopped use before pregnancy; discontinuers and depressed, unexposed women did not have a significantly elevated risk compared to non-depressed unexposed women. Women using antidepressants in the first trimester had an increased risk of miscarriage compared to either depressed or non-depressed unexposed women, and these findings persist even after accounting for induced abortions.

Taken together, the findings of this thesis research suggest that pre-pregnancy antidepressant users are likely to discontinue use in pregnancy, and the likelihood of discontinuation depends on disease severity and medication class. Our results support an association between antidepressant use itself and an increased risk of miscarriage and pre-eclampsia because of the persistent elevated findings in antidepressant users when compared to depressed women, and the higher risks associated with continuers compared to stoppers. While residual confounding by factors related to disease severity cannot be ruled out, our findings are nevertheless relevant to the clinical management of pregnant women requiring the use of antidepressants, and should be considered in physician-patient discussions and decision-making.

RÉSUMÉ

Les femmes souffrant des maladies chroniques font face à une choix difficile quand elles deviennent enceintes: continuer leur traitement pharmaceutique malgré les risques tératogènes, ou arrêter le traitement bien que la maladie non soignée puisse provoquer des problèmes de santé aussi bien chez la mère que chez l'enfant. Malheureusement, très peu est connu sur la consommation de médicaments sur ordonnance pendant la grossesse chez les femmes nécessitant un traitement pharmaceutique avant la grossesse. Une des raisons pouvant expliquer ce manque de connaissances est la rareté des données provenant d'études représentatives de la population qui permettent d'étudier les conséquences de la continuation ou de l'arrêt du traitement pharmaceutique pendant la grossesse. Également, la nature même de la maladie peut devenir un facteur confusionnel qui peut complexifier l'étude de l'association entre la consommation ou non de médicaments et les issues de grossesse.

Dans cette thèse, nous avons étudié une série de questions permettant d'adresser ces problématiques : Les femmes enceintes sont-elles davantage susceptibles de cesser la consommation d'antidépresseurs que les femmes non-enceintes, autrement dit la grossesse est-elle un facteur déterminant vis-à-vis de l'arrêt du traitement pharmaceutique? Quelles sont les caractéristiques maternelles associées à l'arrêt du traitement pendant la grossesse? Enfin, la consommation ou l'arrêt d'antidépresseurs entraine-t'il un risque plus élevé d'issues de grossesse défavorables. Les réponses à ces questions permettront d'approfondir nos connaissances sur un domaine sous-étudié, et de dégager des lignes directrices pour la pratique clinique.

Nos données sont issues d'une large cohorte de femmes à l'échelle de la population, identifiées via les banques de données administratives du Québec et maintenues par la Régie de l'Assurance Maladie du Québec (RAMQ). Nous avons comparé la consommation d'antidépresseurs chez les femmes enceintes prenant ces médicaments avant la grossesse avec la consommation chez les femmes non-enceintes. Nous avons aussi déterminé les facteurs associés à l'arrêt de ces médicaments pendant la grossesse. Par la suite, nous avons évalué la risque de prééclampsie parmi les femmes qui continuent la consommation d'antidépresseurs

pendant la grossesse en comparaison avec (a) les femmes qui arrêtent le traitement pendant la grossesse ; (b) les femmes ayant reçu un diagnostic de dépression mais qui ne consomment pas d'antidépresseurs pendant la grossesse ; et (c) les femmes ayant ni reçu de diagnostic de dépression ni ne consomment d'antidépresseurs. Dans la dernière partie de cette thèse, nous avons évalué le risque d'avortement spontané chez les femmes consommant des antidépresseurs pendant le premier trimestre de grossesse relatif aux femmes soufrant ou non de dépression qui ne consommaient pas d'antidépresseurs pendant la grossesse. Afin de tenir compte du risque plus élevé d'avortement provoqué, qui peut entrainer des biais dans l'estimation du risque d'avortement spontané, nous avons utilisé une méthode correctrice.

Les résultats de notre étude démontrent que les femmes enceintes sont plus susceptibles que les femmes non-enceintes d'arrêter toute consommation d'antidépresseurs pendant la grossesse. Les plus importants prédicteurs de l'arrêt d'antidépresseurs sont liés à la sévérité de la maladie (la durée de l'utilisation avant la grossesse, l'âge maternelle, le statut socio-économique et le type d'antidépresseur). Le risque de prééclampsie parmi les femmes qui continuent la consommation d'antidépresseurs pendant les 20 premières semaines de la grossesse est également plus élevé que chez les femmes qui arrêtent leur traitement avant la grossesse. Ces dernières ainsi que les femmes souffrant de dépression mais ne consommant pas d'antidépresseurs pendant la grossesse ne présentent pas de risque de prééclampsie plus élevé que les femmes ne souffrant de dépression et ne consommant pas d'antidépresseurs. Quant au risque d'avortement spontané, les femmes prenant des antidépresseurs pendant le premier trimestre présentent un risque plus élevé que les femmes soufrant ou non de dépression qui ne consommaient pas d'antidépresseurs pendant la grossesse ; le risque demeure persistant après la prise en compte des avortements provoqués.

Globalement, nos résultats suggèrent que les femmes utilisant des antidépresseurs avant la grossesse sont susceptibles de cesser leur consommation pendant la grossesse, la probabilité d'arrêt dépendant de la sévérité de la maladie et du type d'antidépresseur. Nos résultats démontrent également une association entre la consommation d'antidépresseurs et l'accroissement du risque de prééclampsie et d'avortement spontané soutenus par des

résultats élevés consistants en comparaison aux autres groupes (femmes souffrant de dépression et femmes cessant leur traitement pendant la grossesse). Bien qu'un effet confusionnel résiduel lié à la sévérité de la maladie pourrait persister, nos résultats sont néanmoins pertinents à la pratique clinique et plus particulièrement dans le cadre du suivi par un praticien des femmes enceintes requérant un traitement antidépressif.

ACKNOWLEDGEMENTS

The adage 'It takes a village to raise a child', appears equally applicable to the writing of a doctoral dissertation, and I would like to take this opportunity to acknowledge the many 'villagers'.

I would like to thank my supervisor Dr. Robyn Tamblyn, whose door is always open, for her guidance and support, for her enthusiastic interest in my research, and for continually encouraging me to write compellingly. I am grateful to my committee members: Dr. Olga Basso for her excellent advice, astute comments, and sense of humour; Dr. Michal Abrahamowicz for his outstanding statistical input; and Dr. Robert Gagnon for his advice on clinical practice guidelines.

I owe a heartfelt thank you to Dr. Abby Lippman for her unwavering support, her perceptive writing advice, and above all, her immense generosity of spirit.

I thank the many remarkable people that make up our department: Dr. Gilles Paradis and Dr. Rebecca Fuhrer for guiding our department; the faculty for shaping my understanding of epidemiology; the support staff including Suzanne Larivière, Katherine Hayden, and André Yves Gagnon for facilitating the lives of students; and finally my fellow PhD-mates and friends. Thank you Kate, Sathya, Martine, Britt, Carmen and Aman for the laughter, the kindness and the incredible support over all these years!

Merci à mes trois petits coeurs: Alexandre, for *everything,* but especially for being an incredible father and husband; and our little imps Maya and Ella, for lighting up my life.

I dedicate this thesis to my parents, Drs Noel and Dativa Almeida, who have sacrificed much to ensure the happiness of their children, and to whom I am immensely grateful.

CONTRIBUTION OF AUTHORS

Manuscript 1

Almeida ND, Basso O, Abrahamowicz M, Gagnon R, Tamblyn R. Predictors of antidepressant discontinuation in pregnancy compared to non-pregnant women. *Submitted to Pharmacoepidemiology and Drug Safety.*

Manuscript 2

Almeida ND, Basso O, Abrahamowicz M, Gagnon R, Tamblyn R. Risk of preeclampsia in women using antidepressants: a population-based study to examine the role of depression vs. antidepressants. *Submitted to Obstetrics & Gynecology.*

Manuscript 3

Almeida ND, Basso O, Abrahamowicz M, Gagnon R, Tamblyn R. Risk of miscarriage in women receiving antidepressants in early pregnancy, correcting for induced abortions. *Submitted to Epidemiology.*

I conceived the research protocol, objectives, and study design for the manuscripts in this thesis. I managed and analyzed the data, created the tables and figures, interpreted the results, and wrote up the drafts for all manuscripts.

Dr. Robyn Tamblyn is a James McGill Professor in the department of Epidemiology, Biostatistics, and Occupational Health at McGill University. She is an epidemiologist and nationally recognized CIHR-funded medical scientist with extensive experience in clinical and health services research on prescription drug management. As my thesis supervisor, she oversaw the development of my research protocol, and provided extensive substantive, analytical and editorial feedback for all manuscripts.

Dr. Olga Basso is an Associate Professor in the departments of Epidemiology, Biostatistics, and Occupational Health and of Obstetrics & Gynecology at McGill University. She is an experienced

perinatal epidemiologist, and provided significant input on the substantive and methodological aspects of perinatal epidemiology. She also read drafts of the manuscripts and provided valuable feedback.

Dr. Michal Abrahamowicz is a James McGill Professor in the department of Epidemiology, Biostatistics, and Occupational Health at McGill University. As a distinguished biostatistician, he provided methodological and statistical help, as well as helpful feedback on the manuscripts.

Dr. Robert Gagnon is an obstetrician/gynecologist and Professor in the department of Obstetrics & Gynecology at McGill University. He provided valuable input and advice on clinical aspects of the research, and reviewed drafts of the manuscripts.

STATEMENT OF ORIGINALITY

The work presented in this thesis represents an original contribution to the field of perinatal pharmacoepidemiology. To my knowledge, the maternal and drug-related characteristics of antidepressant continuation/discontinuation in pregnancy have not been previously explored. In addition to being among only a few population-based studies of the association between maternal antidepressant use and adverse pregnancy outcomes, our work builds on previous research by explicitly exploring the role of depression in this association. By studying the risk of adverse outcomes in untreated depressed women, as well as in continuers and discontinuers of antidepressant use in pregnancy, our study attempts to further the understanding of the role of depression vs. antidepressants on these unfavourable pregnancy outcomes. Finally, our study examining the risk of miscarriage among antidepressant users is the first, to my knowledge, to explicitly account for induced abortions, and thus represents a novel contribution to this field.

While I have received guidance from my committee members and co-authors on substantive, clinical, and methodological aspects of this thesis, I declare that the conception, execution and drafting of the work in this thesis were my own.

STATEMENT OF SUPPORT

I received financial support for my doctoral studies in the form of a Frederick Banting and Charles Best Doctoral Scholarship from the Canadian Institutes for Health Research (CIHR). I was also financially supported by the department of Epidemiology, Biostatistics, and Occupational Health, and by Dr. Robyn Tamblyn.

LIST OF ABBREVIATIONS

ACOG: American Congress of Obstetricians and Gynecologists

CI: Confidence Interval

GPRD: General Practice Research Database

MAOI: Monoamine Oxidase Inhibitor

MED-ECHO: Maintenance et exploitation des donées pour l'étude de la clientèle hospitalière (hospitalization database maintained by RAMQ)

RAMQ: Régie de l'Assurance Maladie du Québec

Rx: Prescription

SNRI: Serotonin and Norepinephrine Reuptake Inhibitor

SOGC: The Society of Obstetricians and Gynaecologists of Canada

SSRI: Selective Serotonin Reuptake Inhibitor

TCA: Tricyclic Antidepressant

US FDA: United States Food and Drug Administration

WHO: World Health Organization

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CHAPTER 1: INTRODUCTION

Women of reproductive age are particularly vulnerable to experiencing mental health problems, including anxiety and depression, and are thus more likely to be prescribed antidepressants.[1,2] Studies from both North America and Europe have shown marked increases in the prevalence of antidepressant use in pregnancy, with one US study noting an increase from 2.0% in 1996 to 7.3% in 2004-2005.[3-6]

While some studies have suggested a general decrease in antidepressant prevalence rates in pregnancy compared to pre-pregnancy periods,[7-9] there is a lack of information on the patterns of use among women receiving these medications before pregnancy. Pregnant women may discontinue antidepressant use because of fears of teratogenic effects on the fetus.[10,11] Such fears of teratogenicity, often fanned by widespread media coverage, are not unfounded because associations between maternal antidepressant use and birth defects have been reported in the literature.[12-15] Conversely, the abrupt discontinuation of antidepressant treatment in pregnancy has been associated with a relapse of major depression during pregnancy,[16] and untreated depression in pregnancy may itself contribute to adverse pregnancy outcomes such as spontaneous abortion and preterm birth.[17-20]

Thus, women diagnosed with chronic health problems may be faced with an extraordinarily difficult decision in pregnancy, compelled to weigh the potential risks of medication use on fetal health against the risks to both mother and baby arising from an untreated condition. Exploring the maternal characteristics associated with medication continuation or discontinuation in pregnancy may inform clinicians in their treatment of depressed women, especially with respect to medications that have potentially teratogenic as well as therapeutically beneficial effects. Although there is some evidence suggesting that pregnant women are reluctant to use medication they perceive to be harmful,[10,11] little is known about whether discontinuation rates in pregnancy differ from those in the non-pregnant population because medication non-adherence is common in the general population.[21]

One inherent problem for researchers in this area is that the association of both depression and antidepressants with adverse pregnancy outcomes makes it difficult to tease out the effects of medication on perinatal health in observational studies, and such confounding by indication may explain the conflicting results in the literature. For example, a few studies have reported an association between antidepressant use and risk of congenital heart defects,[22-24] yet recent reviews of this issue have not been able to arrive at a definitive conclusion, partly because depression was not always accounted for in these studies.[12,25-27] Moreover, outcomes such as miscarriages or induced abortions are competing risks for later pregnancy outcomes, and failure to account for these events may result in biased risk estimates. Finally, because most medication use in pregnancy is considered off-label, with pregnant women thereby excluded from drug efficacy trials, earlier studies of antidepressant teratogenicity were based on highly selected populations of women who had participated in teratogenic information services registries.[28]

Only recently have a few population-based studies been undertaken to explore this issue of confounding by the underlying condition.[18,29,30] This requires the inclusion of women with a depression diagnosis but no antidepressant use in studies of continuation/discontinuation to understand the role of antidepressants vs. depression on adverse pregnancy outcomes. Such approaches will enable the creation of incremental exposure risk profiles.

Thus, the **first objective** of this research project was to determine whether antidepressant discontinuation rates differ between pregnant and non-pregnant women requiring their use before pregnancy, and to identify the predictors of antidepressant discontinuation in pregnancy. This objective is explored in my first manuscript (Chapter 5), 'Predictors of antidepressant discontinuation in pregnant women'.

The **second objective** was to examine the risk of adverse pregnancy outcomes associated with maternal antidepressant use taking into account some specific methodological issues. The results of this work are presented in the second and third manuscripts of this thesis (Chapter 6). The first of these, entitled 'Risk of preeclampsia in women using antidepressants: a population-based study to examine the role of depression vs. antidepressants' explores the association of

peri-conceptional antidepressant use and discontinuation on risk of preeclampsia. The second manuscript, 'Risk of miscarriage in women receiving antidepressants in early pregnancy, correcting for induced abortions' examines the risk of miscarriage associated with antidepressant use in the first trimester, after applying a correction factor for risk of induced abortions.

CHAPTER 2: BACKGROUND AND LITERATURE REVIEW

2.1. Trends in the prevalence of antidepressant use in pregnancy

The first antidepressant, a tricyclic called imipramine, was serendipitously discovered in the mid-1950s by Swiss researchers seeking a treatment for schizophrenia.[31] Hailed as a 'miracle cure' for depression, it paved the way for the more popular class of antidepressants known as selective serotonin reuptake inhibitors (SSRIs), which flooded the market in the late 80s. One such SSRI, Prozac, was so popular that in 1994, *Newsweek* magazine declared that it had "attained the popularity of Kleenex".[32] In the ensuing decades, antidepressant prescribing would explode, across countries and demographics.[33-38] In 2008, antidepressants were the third-most commonly prescribed medication in the US. [39]

Women are at a disproportionately greater risk of being diagnosed with depressive disorders than are men, and are consequently more likely to be prescribed antidepressants.[39] A study using data from the National Health and Nutrition Examination Survey (NHANES; 1999-2002) found the prevalence of prescription psychotropic medication use among respondents ≥ 17 years to be 2-fold higher in women than in men;[2] similar results were found in another analysis of survey data of US households with respondents ≥ 6 years conducted in 2005 (13.5% vs. 6.7%).[1]

Some of the sharpest increases in prescription medication use have been seen in women of reproductive age, putting them at a greater risk of exposure to these drugs during pregnancy. Between 1976 and 2008, the use of prescription medication in the first trimester of pregnancy increased by over 60%, with 50% of women reporting use of at least one prescription drug in pregnancy, according to self-reported data from over 30,000 nationally-representative US women.[40] Several North American studies have put the prevalence of prescription medication use any time in pregnancy at 56% to 68%,[41-44] including a recent study using prescriptions claims data in British Columbia that found that 63.5% of women giving birth to a live infant filled at least one prescription at some point during pregnancy.[45]

Studies specifically examining the use of antidepressants in pregnancy, using data from American private or public insurance plans spanning from 1999 to 2010 (the largest of which included 1,106,757 pregnancies in women enrolled in Medicaid between 2000 and 2007), found that the overall prevalence of antidepressant use at some point in pregnancy was approximately 8.0%.[3-6,40] These studies, some of which encompassed the period of health advisories on antidepressant use,[5,6,40] all noted a clear increase in maternal antidepressant use, for example, from 2.0% in 1996 to 7.6% in 2004-2005.[3] A Danish study of 912,322 pregnancies found much lower rates of antidepressant exposure at any point in pregnancy (3.2% in 2010), but still noted a 16-fold increase in prenatal antidepressant exposure from 1997 to 2010.[46] Similarly lower rates were reported using UK primary care data (3.3% in 2006); this study found a 4-fold increase in both pre-pregnancy and pregnancy antidepressant use from 1992 to 2006.[8] The higher antidepressant utilization rates in the United States compared to European countries was also observed in the general population between 2006 and 2012, and the authors suggested varied factors such as better identification of mental health conditions, overprescription and overuse, direct-to-consumer advertising, and cultural differences and beliefs about medication use may all play a role in explaining these differences.[38]

The rise in the use of antidepressants during pregnancy appears to have been driven by an increase in SSRI use;[4,46] the use of other antidepressants, particularly the older tricyclics (TCA) in the prenatal period has remained fairly stable (Figure 2.1).[3,46]

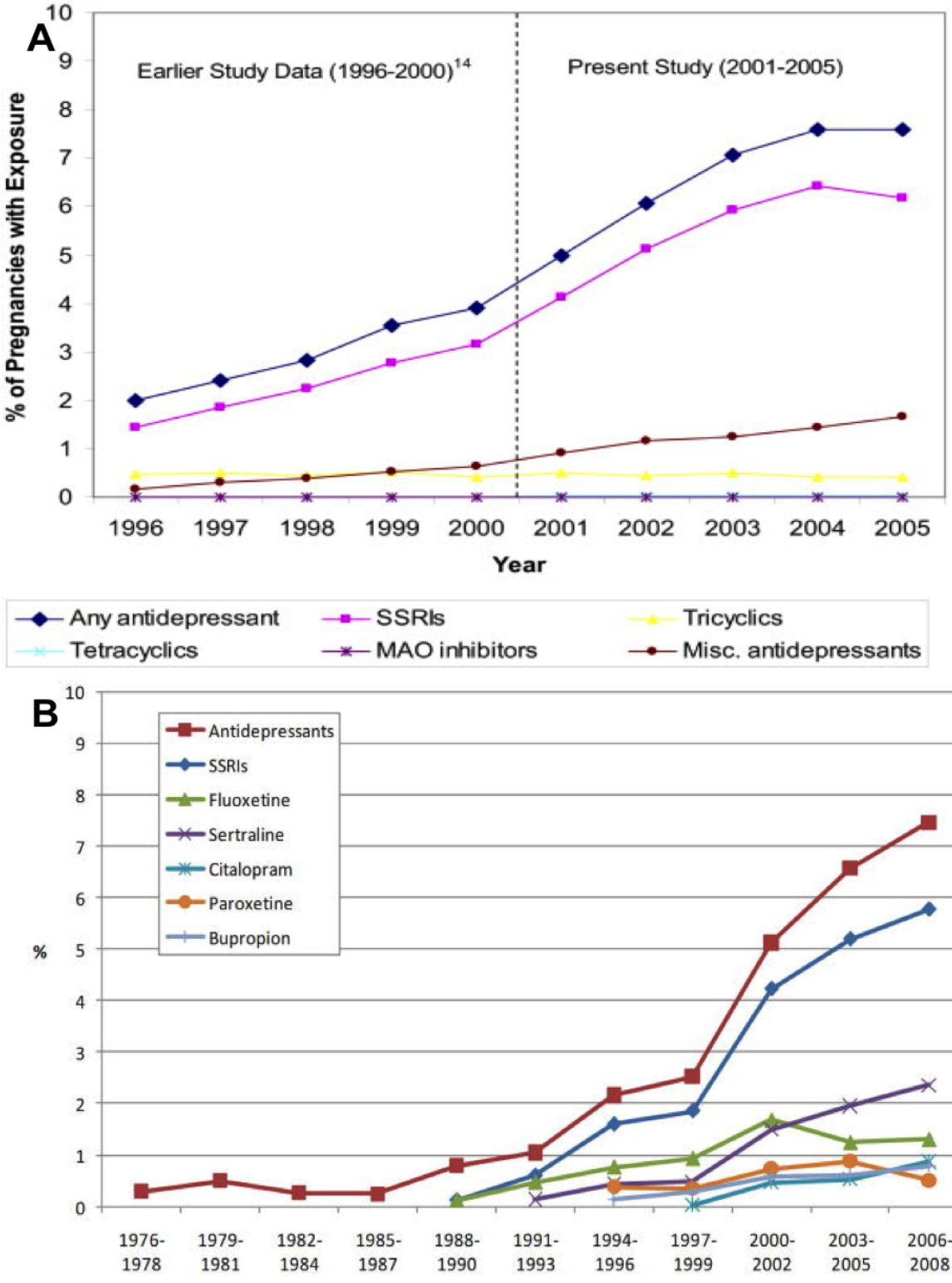

Figure 2.1: Trends in antidepressant use during pregnancy.

A: Use of antidepressants during pregnancy: 1996-2005, various US locations (n=118,935).[3] B: Secular patterns of selected antidepressants during the first trimester BDS, 1976-2008, Boston and Philadelphia centers (n=25,313).[40] Figures reproduced with permission from Elsevier Science.

2.2. Classes of antidepressants and medical guidelines for their use in pregnancy

The prevailing theory on the cause of depression until recently was that depression results from an imbalance in monoamine neurotransmitters, namely, serotonin, norepinephrine and dopamine.[31] Although this hypothesis is currently being challenged,[47] most antidepressants were developed to address this imbalance by inhibiting the reuptake of these neurotransmitters back into the neural receptors and thus increasing their circulation in the synapse. Hence, these monoaminergic antidepressants were classified according to their mechanism of action into: selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and atypical antidepressants.

This section reviews some of the more common antidepressant classes and adverse pregnancy outcomes associated with their use in pregnancy, which are summarized in Table 2.1.

2.2.1. Selective serotonin reuptake inhibitors (SSRIs)

The introduction of a tiny green-and-white pill in 1987, marketed as Prozac (fluoxetine) would revolutionize the treatment of depression, and mark the advent of SSRIs as the main treatment for depression.[48] SSRIs mainly act by blocking the reuptake of the neurotransmitter serotonin (5-hydroxytryptamine or 5-HT) due to their selective affinity for serotonin transporters in the brain, thus significantly enhancing serotonergic neurotransmission.[49] This selective activity contributes to the low side-effect profile of SSRIs, making them the first-line treatment for depression.[49] Although the inhibition of serotonin reuptake occurs almost immediately after treatment, the full therapeutic response to SSRI treatment may take anywhere from three to eight weeks to occur,[50] giving rise to new theories that factors other than serotonin may play a key role in the etiology of depression.[47] SSRIs are also used to treat a variety of other disorders including generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, and premenstrual dysphoric disorder.[48,49]

Adverse pregnancy outcomes associated with use in pregnancy

As SSRIs are the most commonly used treatment for depression,[4,46] more data are available on the safety profiles of SSRIs in pregnancy compared to other classes of antidepressants. Hence, although evidence on their absolute safety in pregnancy is inconclusive, most medical guidelines recommend the use of SSRIs as the first choice of pharmacotherapy in maternal depression.[51,52] The exception is paroxetine, which is contraindicated in the first trimester due to its association with congenital cardiac defects,[12-15] though a recent large population-based study accounting for factors related to depression did not find an association.[53] Other studies have linked sertraline, citalopram and fluoxetine to an increased risk of cardiac defects in the neonate,[13,14,22,24,54] and modest associations have also been reported with other birth defects including anencephaly,[55] craniosynostosis,[55] and hypospadias.[14] Studies accounting for depression severity have found significant increased risks associated with SSRIs and preterm birth,[56-58] and three meta-analyses detected modest associations with spontaneous abortion.[59-61] The occurrence of 'neonatal adaptation syndrome', characterized by irritability, weak cry, tachypnea and hypoglycemia, has been described in a few analyses,[62] and, recently, large studies conducted in various countries have reported an increased association with SSRI use and newborn persistent pulmonary hypertension,[14,63,64] particularly with exposure in late pregnancy (Odds ratio [OR] from a meta-analysis of these studies: 2.50; 95% confidence interval [CI]: 1.32 to 4.73).[65] Finally, SSRI use in the month leading up to delivery was associated with a greater risk of post-partum hemorrhage in a recent study of over 100,000 pregnant Medicaid enrollees.[66]

Despite these risks, SSRIs remain the most commonly prescribed antidepressant in pregnancy, with several studies estimating the proportion of pregnant antidepressant users prescribed SSRIs to be between 79% and 88%.[8,67,6,46]

2.2.2. Tricyclic antidepressants (TCAs)

The introduction of imipramine in the 1950s would revolutionize the field of psychopharmacology, ushering in the first treatments for depression, which would become the

first-line treatment for the next 30 years. [Montreal connection: imipramine was first introduced in North America at the Montreal Douglas Hospital (then the Verdun Protestant Hospital) by Dr. Heinz Lehmann.][31] Tricyclic antidepressants, so named because of their three-ring structure, have a broad mechanism of action, wherein they inhibit the reabsorption of serotonin and norepinephrine, while also blocking the action of other diverse receptors.[68] This generality of action would also result in a host of side effects, including cardiac effects, weight gain, blurred vision, tremors and sexual dysfunction, causing TCAs to slowly fall out of favour as the antidepressant of choice.[69] Treatment with TCAs generally requires up to four weeks to achieve a response, and abrupt discontinuation of treatment is associated with withdrawal symptoms. TCAs are also prescribed for conditions other than depression including bulimia nervosa, post-traumatic stress disorder and smoking cessation.

Adverse pregnancy outcomes associated with use in pregnancy

Some studies have found a greater risk of adverse pregnancy outcomes with non-SSRI medication use in pregnancy relative to SSRI medication. An analysis of over 15,000 pregnancies registered in the Swedish Birth Registry that were exposed to antidepressants found an increased risk of congenital malformations associated with maternal tricyclic antidepressant use, particularly with clomipramine (OR: 1.36; 95% CI: 1.07 to 1.72), but not with SSRIs or SNRIs.[14] Stronger associations with preterm birth and low birthweight were also found for TCA exposure relative to the other classes.[14,70] A recent analysis of over 100,000 pregnant women found an increased risk for preeclampsia among women exposed to TCA and SNRI monotherapy in the second and early third trimester, but not for SSRI exposure.[29] However, in light of new evidence that late pregnancy exposure to SSRIs is associated with a higher risk of persistent pulmonary hypertension in the newborn,[14,63-65] recent reports have suggested that there may be small gain in safety if TCAs (with the exception of clomipramine) rather than SSRIs are used in late pregnancy.[71]

2.2.3. Serotonin and norepinephrine reuptake inhibitors (SNRIs)

The search for a treatment for patients who did not respond to SSRIs, with the aim of developing a medication that acted on more than one site (unlike SSRIs) but without the side effects of TCAs that act on multiple sites, culminated in the development of a new class of antidepressants known as SNRIs.[72] These antidepressants are known as 'dual action' antidepressants due to their mechanism of blocking serotonin and norepinephrine transporter proteins, thus inhibiting the reuptake of the respective neurotransmitters.[73] As most SNRIs have a far greater affinity for the serotonin transporter relative to the norepinephrine transporter, SNRIs at very low doses are sometimes regarded to be essentially SSRIs. The most common side effect is nausea, and other adverse effects include dizziness, constipation, and dry mouth. Response time ranges from two to up to 14 weeks, and abrupt discontinuation may result in discontinuation syndrome (characterized by fatigue, chills, malaise), which is particularly common with venlafaxine. In addition to being prescribed to patients with poor response to first-line treatment with SSRIs,[74] SNRIs are also prescribed for obsessive-compulsive disorder, post-traumatic stress disorder, diabetic peripheral neuropathy, and fibromyalgia.

<u>Adverse pregnancy outcomes associated with use in pregnancy</u>

As the use of SNRIs in pregnancy is less common, there are fewer data available on risk of adverse pregnancy outcomes. Some studies have found an increased risk of miscarriage in women exposed to SNRIs in pregnancy compared to unexposed women (OR for venlafaxine: 2.11, 95% CI: 1.34-3.30),[75,76] while others, using Medicaid data, have reported an increased risk for preeclampsia (OR: 1.57;95% CI: 1.29 to 1.91)[29] and post-partum hemorrhage[66] associated with venlafaxine exposure in late pregnancy. Modest associations between venlafaxine exposure and birth defects such as anencephaly, atrial septal defect secundum have also been reported.[77]

The following classes of antidepressants are not widely used in pregnancy and hence little data are available on their safety profile in pregnancy.

2.2.4. Monoamine oxidase inhibitors (MAOIs)

Along with tricyclic antidepressants, MAOIs belonged to the first-generation of antidepressants. The first MAOI, iproniazid, which was initially being researched as an anti-tubercular agent, was serendipitously discovered to have potent antidepressiveproperties.[31] MAOIs act by inhibiting the action of monoamine oxidase, an enzyme responsible for the metabolism of serotonin, dopamine, and norepinephrine.[78] Because monoamine oxidase is present throughout the body, including in the gastrointestinal tract, there are severe dietary restrictions with the use of MAOIs; ingesting certain types of food can result in a serious hypertensive crisis.[79] As a result of these food contraindications as well as several other side effects, MAOIs are not the first choice of treatment for depression. However, MAOIs may be used for the treatment of atypical or treatment-resistant depression.[78]

2.2.5. Atypical antidepressants

Atypical antidepressants such as bupropion and mirtazapine are most often prescribed to patients diagnosed with major depression who have poor response or intolerable side effects with other antidepressants.[74] Bupropion has been described in the literature as a norepinephrine dopamine reuptake inhibitor (NDRI) due to its blocking of the reuptake of dopamine and norepinephrine.[72,80] A major side effect is the occurrence of seizures, and hence in contraindicated in vulnerable patients.[80] Treatment response may occur from 2 weeks to 14 weeks after starting therapy. Bupropion is also used to treat tobacco dependence, seasonal affective disorder, and attention deficit hyperactivity disorder.

Mirtazapine is not a reuptake inhibitor; instead it acts on both pre- and post-synaptic noradrenergic and serotonergic receptors, thus increasing the release of norepinephrine and serotonin.[81] Mirtazapine is associated with several side effects including dry mouth, weight gain and sedation; abrupt discontinuation can result in withdrawal symptoms.

Small associations between bupropion use in the first trimester and cardiac defects have been reported, though numbers of exposed women were small.[82,83] One study reported an increased

risk of miscarriage with first trimester bupropion use.[84] No association was found between bupropion use in the second and early third trimester and risk for preeclampsia.[29]

2.2.6. Serotonin modulators

Serotonin modulators are a distinct class of antidepressants that act by blocking post-synaptic serotonin receptors and inhibiting the reuptake of post-synaptic serotonin.[72,85] This class includes nefazodone and trazodone; however, nefazodone was withdrawn from Canadian and European markets in 2003 as a result of its association with serious hepatotoxicity.[86] Due to their potential for drug-drug interactions, these medications require extreme caution when used with MAOIs or SSRIs.[85] They may cause several side effects including somnolence and dizziness. In addition to major depression, these drugs may be used to treat premenstrual syndrome, and functional dyspepsia.

2.2.7. General medication guidelines for the treatment of depression in pregnancy

Canadian and American medical guidelines for the treatment of depression in pregnancy recommend that physicians perform an individualized risk-benefit analysis, taking into consideration duration and severity of depression symptoms. [51,52,87] Women receiving treatment for mild to moderate depression may consider a gradual tapering of antidepressants in combination with a switch to other therapies including cognitive behavioural therapy.[88] However, women need to be carefully monitored in the event of abrupt discontinuation.

With respect to the choice of antidepressant in pregnancy, the woman's past response to the medication as well as the drug's side effects and risk profile all need to be considered.[51,52,88] Due to the preponderance of safety data on SSRIs in pregnancy, these antidepressants are considered the first-line pharmacotherapy in pregnancy, with the exception of paroxetine, which in contraindicated in the first trimester.[51,89] Although TCAs have a greater side effect profile and the use of clomipramine is contraindicated in early pregnancy, some have suggested a preference for TCAs over SSRIs in late pregnancy,[88] due to the association of late-term SSRI use with persistent pulmonary hypertension in the newborn.[63-65] SNRIs appear to have a similar

risk profile to SSRIs though data for use in pregnancy are scarce. Similarly sparse data are available for other antidepressants such as duloxetine, bupropion, mirtazapine, trazodone and nefazodone. Third trimester use of all antidepressants may be associated with neonatal adaptation syndrome, although symptoms tend to be mild and self-limiting.[62,70,90,91]

Guidelines recommend that women receive the lowest effective dose of the antidepressant, which may be altered over the course of the pregnancy.[88] Monotherapy is recommended over the use of more than one antidepressant, or the use of antidepressants in combination with benzodiazepines, due to the greater risk profile associated with the latter patterns of use.

Health advisories regarding antidepressant use in pregnancy

In December 2005, The US FDA & Health Canada issued a public health advisory about the increased risk of cardiac birth defects associated with first-trimester use of paroxetine.[92,93] The FDA issued a further warning in July 2006 regarding an increased risk of persistent pulmonary hypertension of the newborn with exposure to SSRIs after 20 weeks. In addition to these advisories specific to pregnancy, antidepressant labels also include a black box warning regarding an increased risk of suicidality in persons younger than 18 years (since 2004) and in adults aged 18-24 years (since 2007). Studies have shown that antidepressant prescribing rates in pregnancy decreased after the first advisory regarding suicidality in 2004,[5,94] but subsequent pregnancy-related advisories did not affect the trend in maternal antidepressant use.[5] There has been a decline in paroxetine use in pregnancy since the advisory;[6] however use of other SSRIs in pregnancy has either increased or remained stable.[3,8,40,46] This thesis uses data from 1998 to 2002, before these advisories were issued; with the exception of paroxetine, antidepressants recommended for use in pregnancy since 2007 are very similar to those used to treat depression from 1998 to 2002.[3,40]

Table 2.1: Classification of antidepressants and their safety profiles in pregnancy[51]

Class	Trade name	Mode of action	Period introduced	FDA drug safety classification*	Evidence of pregnancy complications
Tricyclic antidepressants (TCA)		Block serotonin and norepinephrine transporters and act on diverse receptors	1957-1980		Congenital cardiac defects (particularly with clomipramine);[14] Neonatal adaptation syndrome;[70] Preterm birth and low birth weight;[14,70] preeclampsia
Amitriptyline	Elavil, Endep			C	
Amoxapine	Assendin			C	
Clomipramine	Anafranil			C	
Desipramine	Norpramin			C	
Doxepin	Sinequan, Adepin			C	
Nortriptyline	Pamelor, Aventyl			C	
Protriptyline	Vivactil			C	
Trimipramine or Imipramine	Tofranil			C	
Maprotiline (tetracyclic)	Ludiomil				
Selective serotonin reuptake inhibitors (SSRI)		Selectively block serotonin transporters	1980-1990		Congenital heart defects;[12-15,22,24,54] Preterm birth;[56-58] Neonatal adaptation syndrome;[62] newborn persistent pulmonary hypertension[14,63-65] Congenital heart defects;[12,15,54] contraindicated in early
Citalopram	Celexa			C	
Escitalopram	Lexapro			C	
Fluoxetine	Prozac			C	
Fluvoxamine	Luvox			C	
Sertraline	Zoloft			C	
Paroxetine	Paxil			D	

Class	Trade name	Mode of action	Period introduced	FDA drug safety classification*	Evidence of pregnancy complications
					pregnancy (2008 guidelines)[51]
Serotonin and norepinephrine reuptake inhibitors (SNRIs)		Selectively block serotonin and norepinephrine transporters	1994-2000		Increased risk of miscarriage;[75,76] preeclampsia;[29] and post-partum hemorrhage[66]
Duloxetine	Cymbalta			C	
Venlafaxine	Effexor			C	
MOAIs		Inhibit the action of monoamine oxidase	1980-1995		Unknown
Moclobemide	Manerix				
Phenelzine	Nardil				
Tranylcypromine	Parnate				
Atypical antidepressants					
Bupropion	Wellbutrin	Block the reuptake of norepinephrine and dopamine	1980-1990	B	Increased risk of miscarriage;[84] Cardiac defects [82,83]
Mirtazapine	Remeron		1975-2000	C	
Serotonin modulators		Block post-synaptic serotonin receptors and inhibit the reuptake of post-synaptic serotonin			Unknown
Nefazodone	Serzone		1985-1995	C	
Trazodone	Desyrel			C	

*US FDA pregnancy drug labeling categories:[92] B: Animal studies demonstrate no evidence of harm to the fetus; but no adequate and well-controlled studies exist in pregnant women; C: Animal studies have demonstrated an adverse effect and there are no adequate and well-controlled studies in pregnant women; D: Adequate and well-controlled or observational studies in pregnant women have shown a risk to the fetus. However, the benefits of therapy may outweigh the potential risk.

2.3. Antidepressant discontinuation in pregnancy

2.3.1. Medication non-adherence: definition and predictors

Medication discontinuation falls under the rubric of non-adherence; the World Health Organization (WHO) defines adherence to long-term therapy as 'the extent to which a person's behaviour– taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider'.[95] Thus adherence refers to the intensity of drug therapy (none i.e. complete discontinuation, some, or full adherence to the recommended regimen).

In developed countries, the average adherence to medication among patients suffering from chronic disease is approximately 50%.[96] Non-adherence to antidepressants among patients with depression was estimated to be between 30% and 60%.[21] Poor adherence to a medical regimen not only results in suboptimal management of an illness, resulting in complications and deteriorating health, it also places a significant burden on health care resources and the health system. From a health economics perspective, the effectiveness of a health system cannot be accurately assessed without taking into account adherence rates; hence a vast body of literature has recently been devoted to the creation of effective interventions to improve adherence. [96,97]

The WHO broadly classifies the characteristics associated with non-adherence into five categories: patient-related factors (such as age, gender, health status);characteristics of the condition (disease severity, co-morbidities); characteristics of the therapy (side-effects, duration and complexity of treatment); socioeconomic factors (education, income, health literacy); and attributes of the health care system and service delivery (wait times, continuity of care, health insurance plans).[95] A recent systematic review of 21 studies assessed these categories with respect to antidepressant non-adherence among persons diagnosed with depression, and identified the following predictors of non-adherence: patients perceptions of antidepressants, such as a negative attitude towards taking antidepressants, or concerns about

side-effects; ethnicity; younger age; co-morbidities; no history of antidepressant use; troublesome side-effects; residing in low-income neighbourhoods; fewer physician visits and a weak patient-provider relationship.[97]

2.3.2. Pregnancy as a predictor of antidepressant discontinuation

Pregnancy itself may be a predictor of antidepressant discontinuation or poor adherence, and this question was specifically evaluated in two studies.[8,98] The first study calculated the prevalence of antidepressant use in the pre-pregnancy and pregnancy periods in a Medicaid sample of 3,237 pregnant women matched to non-pregnant women on age, race, state of residence, and the presence of a depression diagnosis or antidepressant claim in pre-pregnancy.[98] Pre-pregnancy was defined as the 120 days before the first prenatal visit for pregnant women or the first routine gynecological check-up for non-pregnant women, which may have resulted in considerable misclassification of the pre-pregnancy period, especially since the authors reported that 25% of pregnant women had their first prenatal visit after the first trimester. The authors reported a decrease in antidepressant prevalence to 27% in pregnancy from 66% in pre-pregnancy, but no parallel decrease in non-pregnant women (62% vs. 66%).

The second study compared time to antidepressant discontinuation in a cohort of 5,229 pregnant women who had received at least one antidepressant prescription in the three months before pregnancy with a matched group of 22,677 non-pregnant women who had also received at least one antidepressant in the three months preceding a randomly selected date.[8] This study used data volunteered to a UK primary care database from 400 general practices between 1992 and 2006 and found a hazard ratio for antidepressant discontinuation in the 1st six weeks of pregnancy of 5.19 (95% CI: 4.85 to 5.56) in pregnant vs. non-pregnant women. Although start of pregnancy was classified more rigorously than the previous study by using recorded gestational age, antidepressant use was ascertained less accurately, as only information on prescriptions written, but not dispensed was available. Furthermore, the authors defined discontinuation as the absence of further prescriptions within 92 days of the

previous prescription, and hence women who may have received another prescription after this period were considered discontinuers. Thus, they may have overestimated discontinuation rates among women who did not visit their family doctor for a prescription renewal within three months (or visited a doctor outside the network), and among women who may have restarted antidepressant use later in pregnancy. This may explain why the authors also noted a steady decline in antidepressant prescribing for non-pregnant women through the pseudo-pregnancy period, though they found much sharper declines in pregnant women, particularly in the first six weeks of pregnancy. Finally, pregnant and non-pregnant women were not matched on date of prescription and hence results may be confounded by secular trends of antidepressant use, because women were more likely to use antidepressants in pregnancy during the latter study years.

2.3.3. Antidepressant discontinuation rates in pregnancy

Most studies assessing the discontinuation of antidepressant use in pregnancy have been limited to reporting the prevalence of antidepressant use before and during pregnancy in a population of pregnant women or pregnancies; the longitudinal prescription patterns within pregnancy of women using antidepressants before pregnancy have received less attention. A Canadian study using health administrative data (RAMQ) reported that the prevalence of antidepressant use in the 12 months before pregnancy among 97,680 pregnant women was 6.6%, which decreased to 3.7%, 1.6% and 1.1% in the first, second, and third trimesters, respectively.[99] Similarly, an analysis of records within the General Practice Research Database or GPRD of 421,645 pregnancies occurring between 1989 and 2010 reported a decrease in the prevalence of antidepressant use from 4.7% in pre-pregnancy to 2.8% and 1.3% in the first and latter trimesters, respectively.[100] Maternal antidepressant use was higher in a US population of over 1 million pregnant Medicaid enrollees (2000-2007): antidepressant prevalence decreased from a pre-pregnancy rate of 6.5% to 6.1% in the first trimester, with further decreases to 3.9% and 3.6% in the subsequent trimesters.[5]

Four studies tracked antidepressant discontinuation rates within pregnancy among women taking antidepressants prior to pregnancy, each with varying emphasis on the different trimesters of pregnancy, and hence complete discontinuation rates in pregnancy were not always evident. The UK study that assessed pregnancy as a predictor of discontinuation reported that of the 5229 women who had received at least one antidepressant before pregnancy, 80%of women had discontinued by 6 weeks of pregnancy.[8] Of the 228,876 pregnancies enrolled in the Tennessee Medicaid Program between 1995 and 2007, 23, 280 (10.2%) women received at least one antidepressant in the 180 days preceding the start of pregnancy, and 75% of these women did not use antidepressants after the first trimester.[7] In the aforementioned UK study using the GPRD, almost 80% of pre-pregnancy users had discontinued all antidepressant use by the third trimester.[100] A Dutch study using health insurance data of 29,000 pregnancies between 2000-2003 reported that 61% of the 1075 women with antidepressant use in the 6 months prior to pregnancy stopped after the first trimester, and 46% of pre-pregnancy users discontinued all use throughout pregnancy.[9]

2.3.4. Predictors of antidepressant use/discontinuation in pregnancy

Discontinuation of antidepressants in pregnancy may be associated with women's beliefs regarding antidepressant treatment in the antenatal period.[10] A small study (n=108) of African American and white women with depressive symptoms recruited from four Midwestern US clinics between 2004 and 2007 found that women reported the greatest confidence in psychotherapy and social support as opposed to antidepressant use for treatment of mental health issues.[11] Women also expressed greater confidence in receiving treatment from mental health professionals than from primary care physicians or obstetrician/gynecologists, though racial differences were noted. Because the decision to use or discontinue antidepressant in pregnancy may also depend on the physician, a small study surveyed family physicians in Australia and Canada, and found that almost 30% of Canadian physicians (40% of Australian GPs) recommend discontinuation in pregnancy.[101]

Factors associated with antidepressant use in pregnancy compared to no use (in univariate analyses) include older age, smoking before or during early pregnancy, higher BMI, higher

parity and having received a diagnosis of depression or other chronic disease prior to pregnancy.[7,30,46,64,76,102] However American and European studies differed in their associations for antidepressant use and socio-economic status, with exposure being associated with higher education in the American study,[7] and with lower education and income levels in the European analyses.[46,76]

Three studies assessed the predictors of antidepressant use in pregnancy in multivariable analyses, comparing exposed women to unexposed pregnant women, but not within a subpopulation of pre-pregnancy users.[4,67,99] Using RAMQ data, Ramos et al. reported that the predictors of antidepressant use on the first day of gestation compared to no use on the first day of gestation were being older, being a welfare recipient, having received a greater number of prescriptions for medications other than antidepressants, having a greater number of physician visits in the 12 months prior to pregnancy, and having received a diagnosis of depression in pre-pregnancy.[99] Cooper et al., using data from women enrolled in the Tennessee Medicaid Plan between 1999-2003 found that women exposed to antidepressants at any point in pregnancy were significantly more likely to be older than 25 years, white and higher educated than unexposed women, in models that included birth year, country of residence, parity and neighbourhood income.[4] The differing results for the association of education and antidepressant exposure between the US and Canadian/European studies may be a reflection of the fact that the US studies were based on Medicaid data which is restricted, by definition, to a low-income population whose education distribution may be very different from that of the general population. Indeed, an analysis of a non-Medicaid population from 10 US states based on retrospectively-collected self-reported data between 1998 and 2005 found no association between higher education or income and antidepressant use anytime in the three months before conception to end of pregnancy, after adjusting for several variables including smoking, alcohol use, folic acid use and parity. In this study, only white race and a diagnosis of pre-pregnancy diabetes were associated with antidepressant exposure.[67]

Only one study evaluated the predictors of discontinuation in a population of woman already taking antidepressants before pregnancy, but the authors only assessed three factors: maternal age, number of antidepressant prescriptions, and a measure of social deprivation which combined neighbourhood-level data on occupation, car ownership, overcrowding and unemployment.[8] In this study using primary care data in the UK from 1992-2006 where discontinuation was defined as no further prescriptions within 92 days of the previous prescription, the authors found that younger women and those with fewer than two prescriptions before pregnancy were more likely to discontinue treatment; they found no association between social deprivation and antidepressant discontinuation.

Thus, the first objective of this thesis was to determine whether medication discontinuation rates differ between pregnant and non-pregnant women who received antidepressants before pregnancy and to identify the predictors of antidepressant discontinuation in pregnancy.

2.4. Antidepressant use and risk of preeclampsia

2.4.1. Preeclampsia definition and prevalence

Preeclampsia is a life-threatening complication of pregnancy characterized by new-onset hypertension (diastolic blood pressure ≥ 90 mm Hg) and proteinuria (≥ 300 mg in 24 hours) occurring on or after the 20th week of gestation. However, the exact definition of preeclampsia has been under considerable debate, and recently the American College of Obstetricians and Gynecologists (ACOG) and the Society of Obstetricians and Gynaecologists of Canada (SOGC) removed the requirement for the presence of proteinuria as a diagnostic criterion, instead defining preeclampsia as elevated blood pressure after 20 weeks of gestation and *either* proteinuria *or* the presence of one or more symptoms of end-organ dysfunction (Table 2.2).[103,104] In Canada for the period of our study (1998-2002), the diagnostic criteria for preeclampsia follow the 2002 recommendations of the American College of Obstetricians and

Gynecologists,[105] which defined preeclampsia as increased blood pressure (≥140/90 mm Hg) after 20 weeks of gestation with proteinuria.

Preeclampsia complicates 2 to 8% of all pregnancies, and remains one of the leading causes of maternal and fetal morbidity and mortality.[106] In Canada, preeclampsia and pregnancy-induced hypertension accounted for 21% of all direct maternal deaths in 1997-2000.[107] The risk of maternal death increases with the progression of preeclampsia to eclampsia or HELLP (Hemolysis, Elevated Liver enzymes, Low Platelets) syndrome. Preeclampsia also increases the risk of preterm birth, intrauterine growth restriction, placental abruption, fetal distress, and stillbirth.

An international comparative study of preeclampsia and pregnancy-induced hypertension trends between 1997 and 2007 reported that rates of preeclampsia declined in Australia and Europe, but increased in the US and Canada.[108] A large US population-based study found that the age-adjusted rates of preeclampsia increased by 25% from 1987 to 2004, with a preeclampsia rate of 29.4 per 1000 deliveries in 2003-2004.

Table 2.2: Classification of hypertensive disorders of pregnancy

ACOG classification (2013)[103]		**SOGC Classification** (2014)[104]	
Disorder (exclusive categories)	**Definition**	**Disorder**	**Definition**
Preeclampsia-eclampsia	New onset BP ≥ 140/90 mm Hg after 20 weeks of gestation on two occasions **AND EITHER** Proteinuria ≥ 300 mg in 24 h **OR** one of the following: Thrombocytopenia; renal insufficiency; impaired liver function; pulmonary edema; cerebral or visual symptoms	Preeclampsia	New onset BP ≥ 140/90 mm Hg after 20 weeks of gestation on two occasions with one or more of the following: New proteinuria **OR** adverse conditions* **OR** severe complications*
Chronic or pre-existing hypertension	BP ≥ 140/90 mm Hg that predates pregnancy	Chronic or pre-existing hypertension • With superimposed preeclampsia	BP ≥ 140/90 mm Hg that develops pre-pregnancy or before 20 weeks gestation Development of one or more of the following at ≥ 20 weeks gestation: Resistant hypertension; new or worsening proteinuria; adverse conditions; severe complications
Gestational hypertension	BP ≥ 140/90 mm Hg after 20 weeks of gestation in absence of proteinuria and other systemic findings	Gestational hypertension • With superimposed preeclampsia	New onset BP ≥ 140/90 mm Hg after 20 weeks of gestation Development of one or more of the following: New proteinuria; adverse conditions; severe complications
Chronic hypertension with superimposed preeclampsia	BP ≥ 140/90 mm Hg that predates pregnancy in association with preeclampsia	Other hypertensive effects	Transient hypertensive effects White-coat hypertensive effects Masked hypertensive effects

* Adverse conditions include headache/visual symptoms; chest pain; elevated white blood cell count/low platelet count; elevated creatinine; elevated bilirubin; abnormal fetal heart rate; intra-uterine growth restriction

Severe complications include eclampsia; stroke; pulmonary edema; very low platelet count; acute kidney disease; hepatic dysfunction; placental abruption; stillbirth

2.4.2. Causes and risk factors of preeclampsia

Preeclampsia has a multifactorial etiology, and its exact causes remain elusive. In fact, so many theories were put forward that Grant and Worley wrote that "the number of theories advanced to explain the etiology and pathophysiology of pre-eclampsia is limited only by the supply of investigators and their access to strong drinks."[109]

The pathophysiology of preeclampsia is currently thought to involve a two-stage process: the first stage is characterized by defective placentation resulting from shallow trophoblastic invasion and impaired remodelling of the maternal spiral arteries; the subsequent poor placental perfusion triggers a series of events starting with the creation of a hypoxic environment, which causes vasoconstriction and increased maternal blood pressure, and eventually leads to generalized vascular endothelial dysfunction (second stage) and the clinical symptoms of preeclampsia.[106,110] Thus, preeclampsia is considered to be a disorder of the maternal-fetal unit, implicating maternal, paternal and fetal genes. As it is primarily a dysfunction of the placenta, removal of the placenta i.e. delivery of the fetus, is the only cure for preeclampsia.

Although the etiology of preeclampsia remains largely unknown, several risk factors have been established and include: nulliparity, multi-fetal pregnancy, a family history of preeclampsia, preeclampsia in a prior pregnancy, high BMI, pre-existing maternal disease (including diabetes, hypertension, chronic kidney disease, thrombotic vascular disease),[111] gestational diabetes, and molar pregnancy.[106,110] Protective factors include a previous completed pregnancy and smoking (which reduces risk by about 30%).[112,113]

2.4.3. Depression and risk of preeclampsia

Depression is a less well-established risk factor for preeclampsia, and several hypotheses have been suggested for the association between maternal mood disorders and preeclampsia risk. One theory implicates heightened activity in the hypothalamic-pituitary-adrenal axis,[114,115] because of documented alterations in plasma cortisol, corticotrophin-releasing hormone, and serotonin levels in pregnant women with depressive disorders.[116,117] Others have theorized that depression and cardiovascular disease share a common immunological response, and hence

depressive symptoms may trigger an inflammatory cascade and endothelial dysfunction that eventually results in elevated blood pressure and preeclampsia.[118,119] Alternatively, depression and related mood disorders may increase preeclampsia risk by their influence on platelet activation, heart rate variability and parasympathetic tone.[120,121]

Five studies have assessed the association between maternal depression or anxiety disorders and risk of preeclampsia with three finding a positive association. These three studies were conducted in different populations (Peru, Helsinki, US) and they found an approximately 2-fold increased risk of preeclampsia in women with depression or anxiety disorders compared to pregnant women without these pathologies.[122-124] However, none of these studies accounted for antidepressant or other psychotropic medication use. The two studies that did not find an association between maternal depression and preeclampsia risk also did not assess use of psychotropic medication and all studies differed in their measures of depression assessment.[17,125]

2.4.4. Antidepressant use and risk of preeclampsia

It has been suggested that antidepressants affect the risk for preeclampsia by increasing extracellular levels of monoamine neurotransmitters, which have been implicated in placental and uterine vessel vasoconstriction.[126] In vitro studies have found that serotonin has vasoactive effects on human placental chorionic veins and umbilical arteries,[127-129] and animal studies have indicated that norepinephrine may cause vasoconstriction in the uterine arteries of pregnant rats.[130] SSRIs have also been shown to decrease uterine artery blood flow and fetal oxygenation in pregnant sheep.[131] Thus antidepressants such as SSRIs, SNRIs, and TCAs, which inhibit the reuptake of serotonin and norepinephrine, may contribute to the pathophysiology of preeclampsia through their role in increasing vasoconstriction and reducing placental blood flow.

Two studies examined the association between antidepressant exposure and risk of pregnancy-induced hypertension, with or without preeclampsia. Toh et al. were the first team to assess the effects of SSRI continuation and discontinuation on risk of gestational hypertension.[132] Pre-pregnancy and pregnancy use of medications, and diagnosis of gestational hypertension were

ascertained using self-reported questionnaires administered after delivery. After adjusting for several factors including maternal age, race, income, education, parity, smoking, and BMI, the authors reported a hazard ratio of 4.86 (95% CI: 2.70 to 8.76) for women who continued SSRIs beyond the first trimester compared to unexposed women, and a hazard ratio of 1.37 (95% CI: 0.50 to 3.76) for women discontinuing in the first trimester. However, the sample size for continuers and discontinuers with gestational hypertension was very small (n=4 for discontinuers with the outcome); furthermore the authors did not account for depression diagnosis or other factors related to depression severity. There is also a possibility of reverse causality because SSRI exposure was not a time-varying variable, and the outcome could have occurred before exposure among women who used SSRIs beyond 20 weeks gestation, especially given the self-reported nature of exposure and outcome ascertainment.

A nested case-control study using Quebec's prescription drug database found that cases of pregnancy-induced hypertension with or without preeclampsia were more likely to have been prescribed antidepressants during pregnancy than controls (OR: 1.53; 95% CI: 1.01 to 2.33), after adjusting for a diagnosis of depression or anxiety.[133] However, in continuation/discontinuation analyses, the authors report that compared to non-users, neither women who discontinued antidepressant treatment in the first trimester (OR: 1.30; 95% CI: 0.83 to 2.03) nor those who continued beyond the first trimester (OR: 1.64; 95% CI: 0.57 to 4.77) had a statistically significant increased risk, though the effect sizes have a clinically significant relevance. They found an increased risk only for SSRI monotherapy, particularly with paroxetine exposure. Although the authors adjusted for depression diagnosis, we are unable to tease out the independent effects of the medication from that of the underlying condition in these analyses.

Recently, a research team has conducted two large population-based studies— one using health services databases in British Columbia, and another with US administrative data — focusing specifically on risk for preeclampsia.[29,30] The authors restricted their population to women who had a recorded diagnosis of depression in the year prior to pregnancy up to 20 weeks of gestation, and reported that women on SNRI and TCA monotherapy between 10 and

20 weeks of gestation had an increased risk of preeclampsia [ORs: 1.95; 95% CI: 1.25 to 3.03 and 3.23; 95% CI: 1.87 to 5.59, respectively] compared to women unexposed in that time period.[30] Unlike the previous studies, this analysis did not find an increased risk for women on SSRI mono- or polytherapy. In continuation/discontinuation analyses restricted to women with antidepressant use in the three months prior to pregnancy, women who continued on SNRI or TCA monotherapy between 10 and 20 weeks' gestation had an increased risk of preeclampsia compared to women who discontinued those antidepressants in the same time period. Interestingly, adjustment for preeclampsia risk factors such as diabetes, primiparity, multifetal gestation, and obesity did not substantially alter the risk estimates; however, adjustment for factors related to depression severity such as number of mental health visits, number of antidepressant classes, antidepressant day's supply and number of depression claims did attenuate the risk estimates. In unadjusted analyses, the authors found no difference in preeclampsia risk between non-depressed, unexposed women and depressed, unexposed women, thus suggesting that depression was not associated with an increased risk of preeclampsia in their study population.

In the second analysis by the same research group in a population of US Medicaid recipients, depressed women who used SNRIs or TCAs in the second and early third trimester of pregnancy had an increased risk of preeclampsia compared to depressed, unexposed women [ORs: 1.52; 95% CI: 1.26 to 1.83, and 1.62; 95% CI: 1.23 to 2.12, respectively].[29] None of the types of SSRIs were associated with an increased risk of preeclampsia relative to unexposed women; however, in continuation/discontinuation analyses, women who continued SSRI use after the first 30 days of gestation had an increased risk compared to those discontinuing within the first 30 days.

Summary of evidence on the association between antidepressant use and preeclampsia

The four preceding studies appear to suggest that antidepressant use in pregnancy is associated with an increased risk of pregnancy-induced hypertension, though the evidence for the risk associated with SSRIs is conflicting. No increased risk for preeclampsia with SSRI exposure was found in the latter two studies, which were the only analyses to attempt to account for factors related to depression by restricting to depressed women. While these results may implicate

different classes of antidepressants, with their different mechanisms of action, in contributing to an increased risk of preeclampsia, it is also possible that women continuing on certain classes of antidepressants may have more severe disease, and this underlying severity may itself contribute to an increased risk.

Thus, confounding by indication is extremely difficult to account for in observational studies. Although efforts can be made to reduce this bias, for example by restricting to depressed women, and by comparing more similar groups of women such as continuers and discontinuers, or those on different classes of antidepressants, it may be impossible to completely eliminate this confounding bias. However, the evidence for the association between depression itself and preeclampsia risk remains inconclusive, particularly as the independent effects of medication were not assessed, and hence further research is necessary to tease out the independent effects of depression and antidepressants on preeclampsia risk.

In this thesis, we aim to further delineate the risks of preeclampsia associated with depression and antidepressant use by creating four mutually-exclusive groups of antidepressant exposure: (i) women with neither a diagnosis for depression nor antidepressant use; (ii) women with a depression diagnosis but no antidepressant use; (iii) pre-pregnancy antidepressant users who discontinued use in pregnancy; and (iv) pre-pregnancy antidepressant users who continued use in the first half of pregnancy. We hypothesized that, if antidepressant use is associated with preeclampsia, over and above depression, we would expect to see an incremental risk of preeclampsia in the exposure groups, with the highest risk among antidepressant continuers.

2.5. Antidepressant use and risk of spontaneous abortion

2.5.1. Definition and prevalence of spontaneous abortion

Spontaneous abortion, or miscarriage, is defined as the clinically recognized loss of pregnancy before the 20th week of gestation.[134] Spontaneous losses after 20 weeks are considered stillbirths or fetal deaths. The incidence of spontaneous abortion in clinically recognized pregnancies up to 20 weeks' gestation is between 8% and 20%. However, the vast majority of

spontaneous abortions occur before 15 weeks, sometimes even before a woman realizes she is pregnant, and hence the incidence when unrecognized pregnancies are considered may be as high as 30% of all pregnancies.[135] The highest risk of spontaneous abortion is between 10 and 12 weeks of gestation, with the risk after 12 weeks of gestation being very low (1-2%).[136,137]

2.5.2. Risk factors

While the exact etiology of miscarriage is unclear, chromosomal abnormalities account for 50% of miscarriages, particularly in those occurring before 15 weeks' gestation.[138] Maternal factors such as uterine structural abnormalities may be associated with later pregnancy losses.[139] While few external causes have been identified, exposure to teratogens may cause congenital anomalies, which in turn increases the risk of a miscarriage.[137] Maternal smoking was found to be a modest predictor,[140,141] and other external causes include drugs,[142] environmental chemicals, and physical and social stressors. Maternal diseases, such as poorly controlled diabetes,[143] thyroid dysfunction,[144] polycystic ovarian syndrome, as well as maternal infections (e.g., Toxoplasma gondii, rubella, herpes simplex)[145] may all increase the risk of miscarriage. The strongest predictors of a spontaneous abortion are history of a previous spontaneous abortion[146] and advanced maternal age.[147]

2.5.3. Depression and spontaneous abortion

Although maternal depressive disorders have been associated with several adverse pregnancy outcomes including preeclampsia,[122-124] and preterm labour,[19] very few studies have explicitly examined the association between maternal depression or anxiety and risk of spontaneous abortion. A UK database study of over 500,000 pregnancies found that women with a diagnosis of depression or anxiety before pregnancy but not during the first trimester had a significantly greater risk of perinatal death, miscarriage and induced abortions compared to women without a diagnosis of depression or anxiety during or before pregnancy.[18] However, women with a depression/anxiety diagnosis in the 1st trimester but no antidepressant prescriptions in that period did not have an increased risk for these outcomes. A study of over a million pregnancies using the Danish Medical Birth Registry found no difference in miscarriage risk among

depressed and non-depressed women unexposed to antidepressants in pregnancy (12.8% vs. 13.5%).[76]

2.5.4. Antidepressants and spontaneous abortion

Earlier studies examining the association between antidepressant use and spontaneous abortion were most often case series or studies based on women calling into Teratogenic Information Services. The latter involved comparing women who self-reported antidepressant use in pregnancy with women calling about non-teratogenic medication use in pregnancy. Such studies create a highly selected population of women, and their results may not be generalizable to all pregnant women.

Three meta-analyses summarizing the literature from 1980 to 2012, using different inclusion/exclusion criteria, found an increased risk of miscarriage among prenatal antidepressant users ranging from 1.45 (95% CI: 1.19 to 1.77) to 1.70 (95% CI: 1.28 to 2.24).[148-150] More recently, four population-based studies have also detected an increased miscarriage risk in exposed women.[18,151-153] While two of these studies also included a comparison group of depressed, unexposed women, none accounted for the increased induced abortion risk in these populations. Table 2.3 summarizes the results from these studies.

Nakhai-Pour et al. conducted a nested case-control study among 5124 pregnant women delivering in Quebec between 1998 and 2003.[75] Women with spontaneous abortions recorded in the administrative databases were matched on gestational age to 51240 women whose pregnancies ended in a live or stillbirth (induced abortions were excluded). They found that women exposed to antidepressants before the index date were at an increased risk of miscarriage (OR: 1.68; 95%CI: 1.28 to 2.04) when compared to women not receiving any prescription medication, after adjusting for several depression and health-related factors.[151] Nakhai-Pour et al. also found an increased risk among for all antidepressant classes when compared to unexposed women, with odds ratios ranging from 1.61 (95% CI: 1.28 to 2.04) for SSRI monotherapy to 2.11 (95% CI: 1.34 to 3.30) for SNRI monotherapy; these risk estimates will likely decrease when compared to depressed women, because of the possible residual confounding due to depression.

A large population-based study using the National Health Services data in the UK of 512,574 pregnancies found similar risks (after excluding abortions) to those of Nakhai-Pour et al.for SSRI and TCA users compared to either depressed or non-depressed unexposed women (Table 2.3).[18] This study did not provide a risk estimate for overall antidepressant use in pregnancy. However, they also estimated the number of induced abortions by exposure group and found a much higher rate among antidepressant users compared to unexposed women, indicating that correcting for induced abortions would lower their estimates.

In contrast, a 2013 population-based study using the Danish National Registry of 1,005,319 pregnancies did not find an increased risk of miscarriage (RR: 1.00; 95%CI: 0.80 to 1.24) when the analyses were restricted to only depressed women.[76] They found an overall risk of miscarriage of 1.14 (95%CI: 0.80 to 1.24) when comparing antidepressant users to unexposed women, with or without depression. The most recent study also used the Danish National Registry (n=1,279,840) and compared women with SSRI use in the first 35 days of pregnancy to those without such use, though it is unclear whether women with no SSRI exposure in this period but exposure before or after the first 35 days of gestation were also considered unexposed.[153] It is also not clear whether women exposed to other antidepressants were considered unexposed. The authors report a hazard ratio (HR) of 1.27 (95% CI: 1.22 to 1.33) for women exposed in the first 35 days of gestation compared to unexposed women, and an HR of 1.24 (95% CI: 1.18 to 1.30) for women discontinuing all SSRI use in the 3-12 months before pregnancy compared to unexposed women. This study did not control for factors related to depression, health comorbidities or other medication use.

Summary of evidence on the association between antidepressant use and miscarriage

The findings from the four preceding studies are not conclusive about the association between prenatal antidepressant use and risk of miscarriage, because the two studies that included depressed unexposed women obtained conflicting results (Table 2.3).[18,76] Furthermore, the definitions of exposure varied widely between all studies, with some defining exposure at any time in the pregnancy,[18] although miscarriages can occur only before 20 weeks, and with others using a very short window of only the first 35 days of pregnancy.[153] Not all studies accounted

for the role of depression, and none adjusted for the increased risk of induced abortions among antidepressant users.

In our study, in addition to including a group of untreated depressed women, we use a correction factor to account for the increased risk of induced abortions. This correction factor was first proposed by Susser et al. for observational studies where the gestational age of miscarriages or induced abortions is unavailable.[154] This method and its accompanying assumptions are further elucidated within the methods section of this thesis (Section 4.5.2), and in the manuscript itself (Section 6.3). Hence, using this correction factor, we aim to calculate the uncorrected and corrected risk of miscarriage among women exposed to antidepressants in pregnancy.

Thus, the second objective of the research for this thesis was to assess the risk of adverse pregnancy outcomes among women using or discontinuing antidepressants in pregnancy, after accounting for methodological concerns such as the effects of depression and induced abortion risk.

Table 2.3: Population-based studies and meta-analyses of the association between antidepressant exposure and miscarriage risk

Name	Study type and N	Overall miscarriage rate	Handling of Induced abortions	Accounted for depression	Antidepressant exposure	Comparison group	Risk estimate
Population-based studies							
Andersen, 2014[153]	Cohort 1997-2010 Danish Medical Birth Registry N= 1, 279,840 pregnancies	11.1%	Included, but censored at time of event (no competing risk analyses performed)	No	**Exposed:** Any SSRI exposure in the first 35 days of pregnancy **Unexposed**: No SSRI exposure in the first 35 days; unclear if unexposed during whole pregnancy	Exposed vs. unexposed in 1) 1st 35 days of pregnancy 2) 3-12 months before pregnancy, but not after 3) 6-12 months before pregnancy 4) 9-12 months before pregnancy	1.27 (1.22, 1.33) 1.24 (1.18, 1.30) Similar to those discontinuing between 3 and 12 months before pregnancy
Kjaersgaard, 2013[76]	Population-based Prospective 1997-2008 Danish National registry N= 1,005,319 pregnancies	11.4%	Excluded	Yes: stratified by depression diagnosis	**Exposed**: Any AD use 30 days before conception up to 1 day before delivery **Unexposed**: No use from 6 months before conception to 1 day before delivery	1. Depressed exposed vs. depressed unexposed 2. Non-depressed exposed vs. non-depressed unexposed 3. Exposed vs. unexposed (marginal)	1.00 (0.08, 1.24) 1.17 (1.13, 1.22) 1.14 (1.10, 1.18)
Ban, 2012[18]	Population-based prospective study UK, 1990-2009 N= 512,574	12.6%	Excluded	Yes: included a comparison group of	**Exposed**: 1st trimester use of SSRI, TCA, or benzodiazepine	1. Exposed vs. non-depressed unexposed	TCA: 1.30 (1.10, 1.50) SSRI: 1.50 (1.30,1.60)

	pregnancies			depressed, unexposed women	**Unexposed:** No history of depression or anxiety No overall risk of any AD use; only class-specific risk	2. Exposed vs. depressed unexposed 3. Depressed unexposed vs. non-depressed unexposed 4. Continuers vs. stoppers	TCA: 1.30 (1.10, 1.50) SSRI: 1.40 (1.20,1.70) 1.00(0.90,1.20) TCA: 1.00 (0.8, 1.30) SSRI: 1.20 (1.00,1.30)
Nakhai-Pour, 2009[75]	Case-control, Canada, 1998-2003 N=56364	7.3%	Excluded	Yes: adjusted for depression-related factors	**Exposed**: Any antidepressant use in pregnancy before miscarriage or matched index date	Exposed vs. unexposed after adjusting for duration of antidepressant exposure, psychiatric visits, comorbidities	Overall OR: 1.68 (1.38, 2.06) TCA: 1.27 (0.85,1.91) SSRI: 1.61 (1.28,2.04) SNRI: 2.11 (1.34,3.30) Other: 1.53 (0.86,2.72)
Meta-analyses							
Ross, 2013[61]	Meta-analysis Only included 3 studies, Random-effects model			None	SSRI exposure		All 11 studies: 1.45 (1.22,1.72) Only 3 included studies: 1.47 (0.99,2.17)
Nikfar, 2012[60]	Meta-analysis 1990-2012 Fixed effects model				SSRI exposure		1.87 (1.50, 2.33)
Hemels, 2005[59]	Meta-analysis Included 6 studies	8.7 %(7.5-9.9%)		One included depressed women	SSRI, TCA, SNRI, trazodone		1.45 (1.19, 1.77)

2.6. Summary

The use of antidepressants before and during pregnancy has steadily increased over the past few decades. Yet, little is known about the longitudinal patterns of prenatal antidepressant use among women receiving these medications before pregnancy. Although studies have suggested that there is a general decrease in antidepressant utilization rates in pregnancy compared to pre-pregnancy periods,[7-9] medication non-adherence is a common problem,[21] and it is unclear whether pregnancy itself is a predictor of antidepressant discontinuation.

Exploring the maternal characteristics associated with medication continuation or discontinuation in pregnancy may provide us with a better understanding of the characteristics of women who may discontinue beneficial therapy, or conversely, of those who may continue on potentially teratogenic medication, enabling the creation of better guidelines to target the most vulnerable populations.

Thus, the **first objective** of this thesis was to determine whether antidepressant discontinuation rates differ between pregnant and non-pregnant women receiving these medications before pregnancy, and to identify the predictors of antidepressant discontinuation in pregnancy.

Several studies have explored the association between maternal antidepressant use and adverse pregnancy outcomes,[18,29,30,75,76,132,133,153] yet not all have accounted for the association between depression itself and these adverse outcomes. Although confounding by indication is extremely difficult to eliminate in observational studies, because unmedicated depressed women may have less severe depression, we attempt to reduce this bias by including unexposed depressed women, as well as continuers and discontinuers in order to explore the incremental effect of depression and antidepressant exposure on preeclampsia risk.

In studies of the association between antidepressant exposure and spontaneous abortion,[18,75,76,153] none have properly accounted for the increased risk of induced abortions in this population. Failure to account for this competing risk may result in spuriously high miscarriage risk estimates. We thus use a correction factor to calculate the induced abortion-adjusted risk of miscarriage in antidepressant-exposed and unexposed depressed women.

Thus, the **second objective** of this thesis was to examine the risk of adverse pregnancy outcomes associated with maternal antidepressant use taking into account the effect of depression and other specific methodological issues.

CHAPTER 3: OBJECTIVES

1) To identify the predictors of antidepressant discontinuation among women receiving these medications before pregnancy.
    a. To determine whether pregnancy itself is a major determinant of antidepressant discontinuation
    b. To determine the predictors of antidepressant discontinuation in pregnancy

2) To assess the consequences of antidepressant use in pregnancy among pre-pregnancy antidepressant users:
    a. To determine if continued use of antidepressants in pregnancy is associated with an increased risk of preeclampsia, over and above the risk associated with depression
    b. To determine if antidepressant use in early pregnancy is associated with an increased risk of miscarriage, after correcting for induced abortion risk

CHAPTER 4: STUDY CONTEXT, POPULATION, AND MEASUREMENT

4.1. Context

The research for this thesis was conducted using data from Quebec's provincial health administrative databases on pregnant women delivering in Quebec between January 1st, 1998 and December 31st, 2002. The Régie de l'assurance maladie du Québec (RAMQ) is the provincial government body that administers the public health and prescription drug insurance plans and remunerates physicians for services. Although all Quebec residents are insured by the provincial health plan, the prescription drug plan only covers individuals 65 years and older, welfare recipients (*prestataire d'assistance emploi*), and employed individuals and their families (*adhérents*) who do not have access to a private drug insurance plan through their employers. Thus, individuals covered by the RAMQ's public drug insurance plan account for approximately 43% of the overall Quebec population and 36% of women between 15 and 45 years of age.[155]

4.2. Study population

Pregnant women were identified from the RAMQ's administrative databases through ICD-9 codes and physician billing codes pertaining to an end of pregnancy recorded between January 1st, 1998 and December 31st, 2002 (Table 4.1). Only the first instance of a record indicating an end of pregnancy was selected in the five year study period. Women were eligible for inclusion in the study cohorts if they

a. Were covered by RAMQ's public drug insurance plan for 24 months before the pregnancy delivery date. Women with interrupted prescription insurance coverage were excluded.

b. Were aged between 15 and 45 years at time of delivery

c. Had received a prescription for an antidepressant in the six months before or during pregnancy

Figure 4.1 shows the flow of women in the creation of the antidepressant cohorts for each of the studies in this thesis.

Table 4.1: ICD-9 codes and physician billing codes pertaining to an end of pregnancy

ICD-9 diagnostic codes	Physician billing codes	Description
634, 635	6900, 6906	Spontaneous abortion
636, 637	6908, 6909, 6938, 6939, 6941, 6947, 6948, 6949, 6951 6952	Induced abortion
650	6903, 6943, 6945, 6950	Vaginal delivery
6697	6912, 6946	Cesarean delivery
	6929, 6933, 15120	Care provided during labour and delivery to mother or newborn

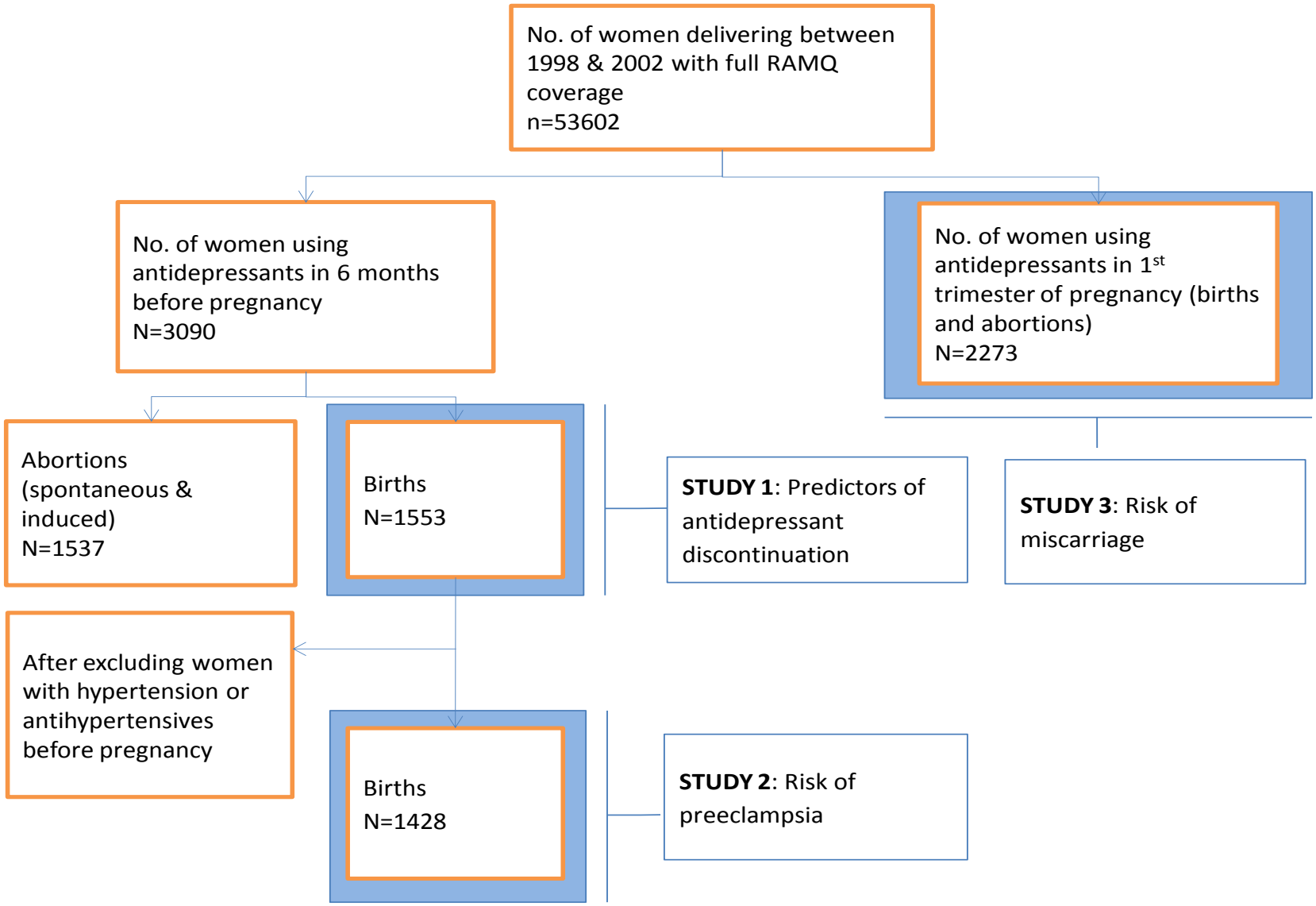

Figure 4.1: Assembly of antidepressant-exposed cohorts of pregnant women for the three studies included in this thesis

4.3. Measurement

4.3.1. Data sources

The study cohorts were created using data from Quebec's health administrative databases. The Régie de l'assurance maladie du Québec (RAMQ), which administers the provincial health and prescription drug insurance plans, maintains a population-based registry on all insured individuals, obtained by linking four databases using unique encrypted health numbers (Table 4.2).

Table 4.2: Databases administered by the Régie de l'assurance maladie du Québec (RAMQ)

Database	Variables
Medicare Beneficiary File (Fichier des bénéficiaires)	Demographic information including age, sex, plan admissibility dates, and date of death
Prescription Drug Database	Contains information on all outpatient prescriptions written by Quebec-licensed physicians, including drug information number (DIN), drug common denominations, drug class, dispensing date, duration, dose, and quantity of medication dispensed
Physician claims database	Contains information on all fee-for-service physician claims for services rendered at clinics and hospitals, including date of service, diagnostic codes, and billing codes.
Maintenance et exploitation des données pour l'étude de la clientèle hospitalière (MED-ECHO)	Contains information pertaining to Quebec hospital admissions and discharges including date of admission, discharge, type of admission, type of establishment, and diagnostic and hospital procedure codes

Validity of prescription claims databases

The advantage of using prescription claims databases over self-report of medication use is that it avoids the inaccuracies associated with poor recall of medication type, dose, and duration. While records of dispensed medications are not as accurate measures of drug exposure as biological markers, they have been shown to be significantly correlated with drug serum levels (r=0.25 to 0.47),[156] and are considered a good proxy to measure medication exposure. In terms

of accuracy, Quebec's prescription claims data (RAMQ) was found to have 83% accuracy for type of drug prescription, 72% accuracy for duration of use, and 69% for quantity of prescription, compared to patient medical records, in a sample of 311 elderly people. In a sample of 65,000 elderly people, data necessary for prescription claims to be filled were missing in less than 0.4% of records.[157]

Disease diagnoses recorded in the medical services claims data of RAMQ for 14,980 elderly patients in Quebec were validated against chart records (gold standard);while most disease diagnoses had specificities over 90%, the highest sensitivities were found for the most prevalent chronic diseases, i.e. hypertension (Se: 51.8%; 95% CI: 49.9,53.6) and diabetes (Se: 60.6%; 95% CI: 59.5,61.7).[158] Depression diagnoses were not evaluated in this study, but a study validating outpatient ICD-9 codes for affective disorders (ICD-9 code: 296), adjustment reaction (309) and depressive disorders (311) recorded in the Saskatchewan Health administrative claims databases against medical chart diagnoses found sensitivity, specificity and positive predictive values of 71%, 85% and 86%.[159] These authors found that the algorithm using the aforementioned three ICD-9 codes and antidepressant use to identify depressed patients had the best sensitivity and specificity compared to more complex algorithms.

Generalizability

The RAMQ insures approximately 36% of women of childbearing age in Quebec, and a study comparing 99 women insured by RAMQ prescription drug plan to 264 women with private drug insurance found that women covered under the RAMQ plan were more likely to be younger, to be immigrants, to have a household income below the poverty-line, to be unemployed, and to have less than post-secondary education.[160] However, both groups were similar in terms of smoking and alcohol intake, BMI, comorbidity profiles, and pregnancy medication use. Our results may not be generalizable to women covered through private insurance; however, internal validity will remain unaffected.

4.3.2. Identification of pregnant women and measurement of the start of pregnancy in administrative data

We identified pregnant women using ICD-9 diagnostic codes and physician billing codes pertaining to an end of pregnancy recorded in the RAMQ databases (Table 4.1). A study of 726 pregnant asthmatic women delivering between 1990 and 2000 found that dates of delivery procedures recorded in the RAMQ and MED-ECHO databases corresponded very well with the delivery date recorded in the woman's medical chart (Pearson correlation: 0.99; 95% CI: 0.99 to 0.99).[161]

Because gestational age was not available to us, we used a previously validated method to estimate start of pregnancy wherein 39 weeks (273 days) is subtracted from the date of delivery for term births recorded in the administrative database, and 35 weeks (245 days) is subtracted from the delivery date of preterm births. In the validation study including 286,432 mother-infant pairs delivering between 1998 and 2007 in British Columbia, the authors compared several algorithms with varying gestational ages for term and preterm births (based on the median gestational age in the population or on medical claims for prenatal testing) with the clinically assessed gestational age recorded in the hospital discharge form.[162] The authors demonstrated that setting gestational age to 39 and 35 weeks for term and preterm births, respectively, was able to accurately classify gestational age to within 2 weeks of clinically recorded gestational age for the vast majority of births; 99% of term births and 75% of preterm births were accurately classified. The inaccurate estimation of gestational age for preterm births will result in differential misclassification of exposure if preterm birth is associated with the outcome. An earlier study that evaluated an algorithm in which gestational age was calculated by subtracting 270 days from the birth date simulated the effect of differential misclassification on relative risk estimates.[163] It found that differential misclassification of exposure resulting in the proportion of false negatives being twice as high in cases than non-cases (lower sensitivity for cases) resulted in far greater attenuation of the true relative risk than in non-differential misclassification. With respect to sensitivity of exposure classification, exposures of longer duration or those associated with chronic use, such as antidepressants had greater sensitivity that those of episodic duration such as anti-infectives. Finally, exposure

ascertained over longer periods of time (first trimester vs. weekly exposure) are more robust to exposure misclassification.

4.3.3. Measurement of antidepressant use

Any antidepressant use in the two years before delivery was identified by the presence of American Hospital Formulary (AHF) codes pertaining to antidepressants (28:16.04) in the RAMQ database. Daily drug availability for each woman was ascertained before and during pregnancy using the prescription dispensing date and days' supply (duration of prescription) to obtain the prescription start and end date. Antidepressants were further classified into four categories as shown in Table 4.3.

Table 4.3: Classification of antidepressant therapeutic classes

AHF class		Categorization of therapeutic classes
28:16.04	28:16.04.20	1. Selective-serotonin reuptake inhibitors (SSRI)
	28:16.04.28	2. Selective norepinephrine reuptake inhibitors (SNRI)
	28:16.04.16	3. Tricyclic antidepressants (TCA)
	28:16.04.12	4. Other (monoamine oxidase inhibitors, serotonin modulators, and atypical antidepressants)

Measurement of continuation/discontinuation in pregnancy

Women with at least one prescription for an antidepressant in the six months before the start of pregnancy were considered pre-pregnancy antidepressant users. These women were labelled discontinuers or stoppers if they had no more antidepressant fillings or days' supply in the period from 30 days after the start of pregnancy to the delivery date. Pre-pregnancy antidepressant users with at least one antidepressant filled from 30 days after the start of pregnancy to the delivery date were considered to be continuers. We included a 30-day lag period because women may not realize they are pregnant at time of conception and may be more likely to discontinue medication once the pregnancy has been recognized.

4.3.4. Measurement of depression

In our studies, a diagnosis of depressive or affective disorders was identified through medical services claims with the ICD-9 diagnostic codes described in Table 4.4.As mentioned earlier, these codes maximized the sensitivity and specificity of identifying depressed patients in the Saskatchewan Health administrative databases compared to more complex algorithms.[159] Relative to medical records, these ICD-9 diagnostic codes recorded in the medical services claims had sensitivity, specificity and positive predictive values of 71%, 85% and 86%.

Table 4.4: Diagnostics codes used to identify depression

ICD-9 code	Description
296.1-3	Affective disorders involving major depression
309.x	Adjustment disorders
311	Depressive disorders

4.3.5. Measurement of adverse pregnancy outcomes

Preterm birth: We identified preterm births in the RAMQ and MED-ECHO databases using ICD-9 codes 644 (Early or threatened labour) and 765 (Disorders relating to short gestation and low birth weight). A study using British Columbia administrative health plans tested the validity of using these codes to identify preterm births against the gestational age recoded in the medical charts, and found a sensitivity and specificity of 0.91 (95%CI: 0.91 to 0.91) and 0.98 (95%CI: 0.98 to 0.98), respectively.[162]

Preeclampsia: Preeclampsia was identified by the presence of ICD-9 codes 642.4 to 642.7 in either the medical services claims (RAMQ) or hospitalization databases (MED-ECHO). A study using the Swedish Medical Birth Registry validated ICD-9 codes to identify preeclampsia against information contained in a random selection of medical charts, and found a positive predictive value of 93% (137 of 148 pregnancies coded as preeclampsia had a corresponding diagnosis in the charts).[164] A review of validation studies evaluating the accuracy of medical diagnoses recorded in databases compared with medical charts found that preeclampsia was generally

more accurately recorded than gestational hypertension, with a kappa statistic indicating good agreement between the gold standard and hospital databases (0.40-0.74).[165]

Spontaneous and induced abortions: Spontaneous abortions were identified by ICD-9 codes of 634 or 761.8; or physician billing codes pertaining to a miscarriage (Table 4.1). Induced abortions were identified by the presence of ICD-9 codes 635, 636, or 637; or corresponding physician billing codes (Table 4.1); and the absence of codes for a spontaneous abortion on the same date. Spontaneous abortions are likely to be underreported in administrative databases, because spontaneous abortions can occur long before a pregnancy is recognized.[135] On the other hand, the RAMQ has several billing (procedure) codes for induced abortion, and hence these are likely to be more completely recorded in the administrative databases. We estimated the number of induced abortions using the aforementioned ICD-9 and billing codes using all RAMQ data available to us in 1998, and obtained a total of 26,331 induced abortions which is close to the Statistics Canada estimate of 31,673 abortions (includes non-residents as well as abortions performed on residents in the US) in Quebec in 1998.[166]

Hospitalizations during pregnancy: All admissions to an acute care inpatient setting in Quebec are recorded in the hospitalization database (MED-ECHO). Hospital discharge data contain standardized coded information including the admission and discharge date, principal diagnosis and 10 diagnostic fields to document relevant co-morbidity, hospital unit, length of stay, and discharge destination.

All-cause hospitalizations were identified through the presence of hospital admission or discharge dates during the estimated pregnancy period (excluding the delivery period). Hospitalizations for mental health problems were any admissions to the psychiatric unit of the hospital, or admissions with ICD-9 codes for mental health disorders during the estimated pregnancy period.

4.4. Study design

Cohorts of pregnant women exposed and unexposed to antidepressants were created using prospectively recorded prescription claims data in the RAMQ databases. Table 4.5 elaborates on the creation of the exposure groups for each of the three studies of this thesis research.

Table 4.5: Definition of exposure groups for each of the three studies

Study	Exposure groups	N	Reference group	N
1. Predictors of antidepressant discontinuation (includes only births)	Pregnant women with at least 1 antidepressant Rx in 6 months before pregnancy	1553	Matched non-pregnant women with at least 1 antidepressant Rx in 6 months before pregnancy period	3497
2. Risk of preeclampsia (includes only births)	1. Pregnant women with at least 1 antidepressant Rx in 6 months before pregnancy who discontinued in pregnancy	764	Women with a neither a depression diagnosis nor antidepressant use in 2 years before delivery	24870
	2. Pregnant women with at least 1 antidepressant Rx in 6 months before pregnancy who continued in pregnancy	664		
	3. Women with a pre-pregnancy depression diagnosis but no antidepressant use in 2 years before delivery	3009		
3. Risk of miscarriage (includes births, spontaneous and induced abortions)	1. Pregnant women with at least 1 antidepressant Rx in 1st trimester	3273	Women with a neither a depression diagnosis nor antidepressant use in 2 years before delivery	32677
	2. Pregnant women with at least 1 Rx for hypothyroid medication in 1st trimester	947		
	3. Women with a pre-pregnancy depression diagnosis but no antidepressant Rx in 2 years before delivery	5106		

4.5. Specific analytical methods

In an effort to untangle the effects of antidepressant use from those of depression with respect to adverse pregnancy outcomes, we incorporated several analytical methods:

- The inclusion of an untreated depressed group of pregnant women
- Comparing pre-pregnancy antidepressant users who continued use to those who discontinued antidepressant use in pregnancy
- A propensity score analysis to balance continuers and discontinuers on factors related to their probability of continuing treatment in pregnancy
- A correction factor to account for an increased risk in induced abortions among antidepressant users when assessing risk of miscarriage

In the following section, the latter two methods will be described in greater detail.

4.5.1. Matched propensity score analysis

Propensity score analysis comes under the umbrella of quasi-experimental designs, which also include marginal structural models (MSM), instrumental variables, difference-in-differences and regression discontinuity analyses. The aim of a quasi-experimental design is to render an observational study as similar as possible to a randomized controlled trial (RCT) in order to estimate the causal effects of treatment. The randomization of treatment in an RCT results in exposure groups becoming similar on measured and unmeasured confounders, thus eliminating the possibility of confounding by these factors. This is not true for observational studies because allocation of treatment is not controlled and hence, some participants may be more or less likely to receive treatment. However, quasi-experimental methods create pseudo-randomized populations that are more balanced on measured confounders, and presumably more balanced on unmeasured and poorly measured confounders, thus enabling less confounded estimation of causal effects of treatment.[167]

A propensity score analysis, first described by Rosenbaum and Rubin, calculates the probability of treatment in each exposure group based on measured variables.[168] The propensity score is calculated using logistic regression where the dependent variable is treatment and the

independent variables include all potential confounding factors known to be associated with the treatment and the outcome of interest. Each treated individual is then matched to an untreated individual on their propensity score, thus replicating an RCT where exposure groups are exchangeable in terms of their probability of treatment (based on measure covariates).[169] Matching methods include 1:1 or k:1 exact or nearest neighbour matching, caliper (a predetermined range) matching and kernel matching. The success of matching is first explored by examining overlap in the histograms of propensity scores of the treated and matched untreated groups. The quality of the matching can be assessed by calculating the standardized difference (d), which is a measure of the absolute difference in the means of covariates in the exposed and unexposed groups, divided by the pooled standard deviations.[170] Differences of greater than 10% are considered evidence of poor matching.[171]

$$d = \frac{|\bar{x}_c - \bar{x}_t|}{\sqrt{\frac{s_c^2 + s_t^2}{2}}} \times 100, \text{ where } \bar{x}_c, \bar{x}_t \text{are means and } s_c^2, s_t^2 \text{ arestandard deviations}$$

The creation of a propensity score is an iterative process; if poor balance is achieved from the first model, further models may add interaction or quadratic terms to improve the matching process. Once appropriate balance between the exposure groups is obtained for all covariates, the matched sample is used to estimate the causal effects of treatment on the outcome, assuming no unmeasured confounding. Conditioning on a single covariate i.e. the propensity score is a particular advantage if the number of outcome events is small, thus improving model fit and efficiency.

In our study, propensity scores were computed for the probability of continuing antidepressant use in pregnancy, based on the following covariates: maternal age, welfare recipient, type and duration of pre-pregnancy antidepressant use, delivery year, number of medications other than antidepressants filled before pregnancy, number of hospitalizations before pregnancy, and number of physician visits before pregnancy. Continuers were matched to discontinuers on their propensity scores using 1:1 nearest neighbour matching without replacement. These matched samples were then used to estimate the effects of antidepressant continuation on outcomes including hospitalizations and preeclampsia.

4.5.2. Correction for induced abortions

Traditionally, miscarriage risk in observational studies is calculated as the total number of miscarriages divided by the total number of births (live births and stillbirths) and miscarriages. However, populations that are at an increased risk of miscarriage are often also at a heightened risk of induced abortions, and failure to take this competing risk into account may result in biased estimates. This potential for bias was demonstrated by Andersen et al. who, using the traditional formula, calculated the risk of fetal loss by maternal age in a large Danish study of 634,272 pregnant women, and found an increased risk at the age extremes.[172] However, teenaged women are much more likely to terminate their pregnancies than have live births,[173] and when the authors recalculated the fetal loss risk only among those pregnancies *intended* to term, by removing the expected number of fetal losses that would have ended in an induced abortion from the numerator and denominator of the risk calculation, the increased risk for very young women vanished (Figure 4.2).

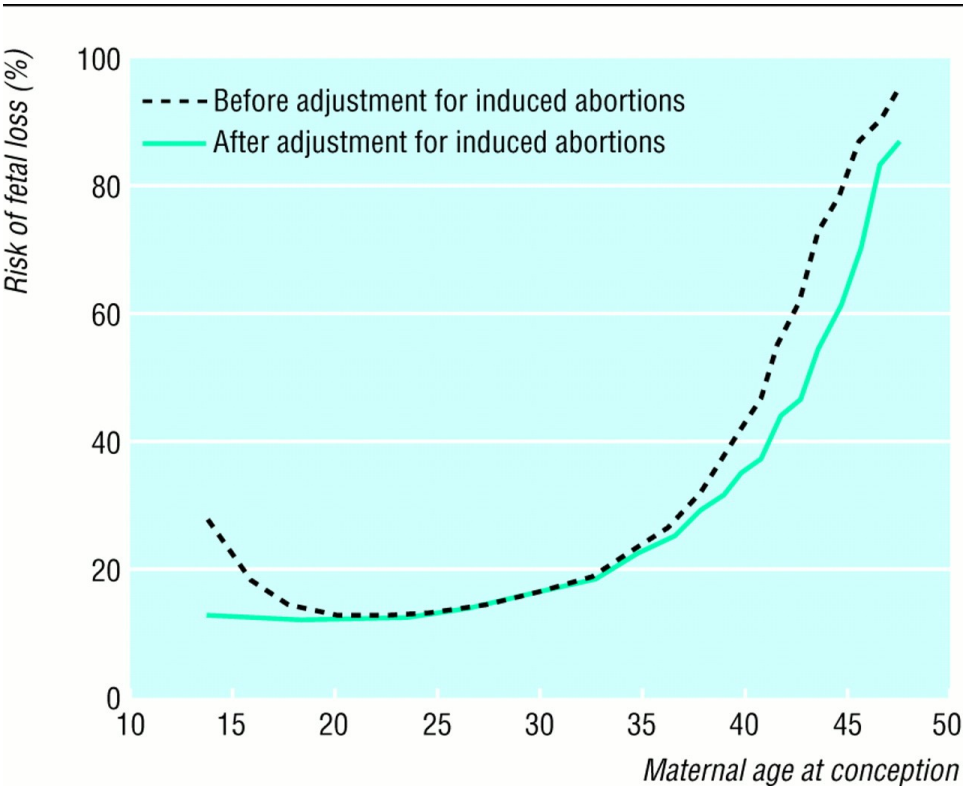

Figure 4.2: Graphical representation of the risk of fetal loss according to maternal age, before and after correction for induced abortions.

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It is plausible that applying a correction factor for induced abortion risk to other high-risk populations may result in a similar diminution in risk. There is evidence that antidepressant use in pregnancy is associated with both an increased risk of miscarriage and induced abortions.[18,28,174] While most studies ignore induced abortions completely in the denominator, thus assuming that pregnancies ending in induced abortions are not at risk of miscarriage, some studies have attempted to address the issue by including all abortions. However, this is akin to assuming that had the pregnancies not been terminated, they would all have progressed to live births, and are thus given the same weight as live births, potentially underestimating the risk.

If the gestational ages of births, miscarriages and induced abortions are available, a competing risks model could be used to account for risk of induced abortions. Studies that use Cox proportional hazards models without competing risks, i.e. where induced abortions are censored at time of event, will obtain higher estimates of the risk of miscarriage, because these induced abortions are eliminated from the risk set.[153,175] Such models assume that competing events are non-informative, i.e. they are independent of the event of interest. However, factors that increase the risk of a miscarriage (depression severity, antidepressant exposure) may also increase the probability of an induced abortion, and these events may not be independent. Hence, a competing risks model, which computes the incidence of the event of interest at a particular time conditional on having survived *both* the competing event and the event of interest until that time, accounts for the competing event by including these observations in the calculation of overall survival.[175]

Our study included in this thesis uses a correction factor first proposed by Susser et al. for observational studies where the gestational age of miscarriages or induced abortions is unavailable.[154] The risk of miscarriage is calculated using the following formula:

$$\frac{No.of\ miscarriages}{No.of\ miscarriages\ + No.of\ births + \frac{1}{2}\ No.of\ induced\ abortions}$$

Half of all induced abortions are included in the denominator because, if pregnancies are at risk of miscarriage in the 1st 20 weeks of gestation (by definition, any fetal loss after 20 weeks is considered a stillbirth),[176,177] and miscarriage and abortions occur, on average, at 10 weeks of gestation,[75,166] then an induced abortion is a pregnancy that is at risk of miscarriage for half the time that a pregnancy ending in a birth is at risk (Figure 4.3). Thus, induced abortions are given half the weight of births in the risk calculation.

The main assumption here is that the gestational age distributions of induced abortions and miscarriages overlap. In their original study, Susser et al. indicate that if the gestational ages do not overlap, then an adjustment to the correction factor is needed, decreasing it if miscarriages occur before induced abortions, and conversely, increasing the value if induced abortions occur later. We feel confident that, given the gestational age data in the published literature,[75,166] the gestational ages in our study do significantly overlap. Furthermore, it is highly unlikely that induced abortions occur later than miscarriages in our population, given the ease of accessibility to abortion services in Quebec, and thus the value of '1/2' would generate the most conservative miscarriage risk estimate, by including the maximum number of induced abortions in the denominator.

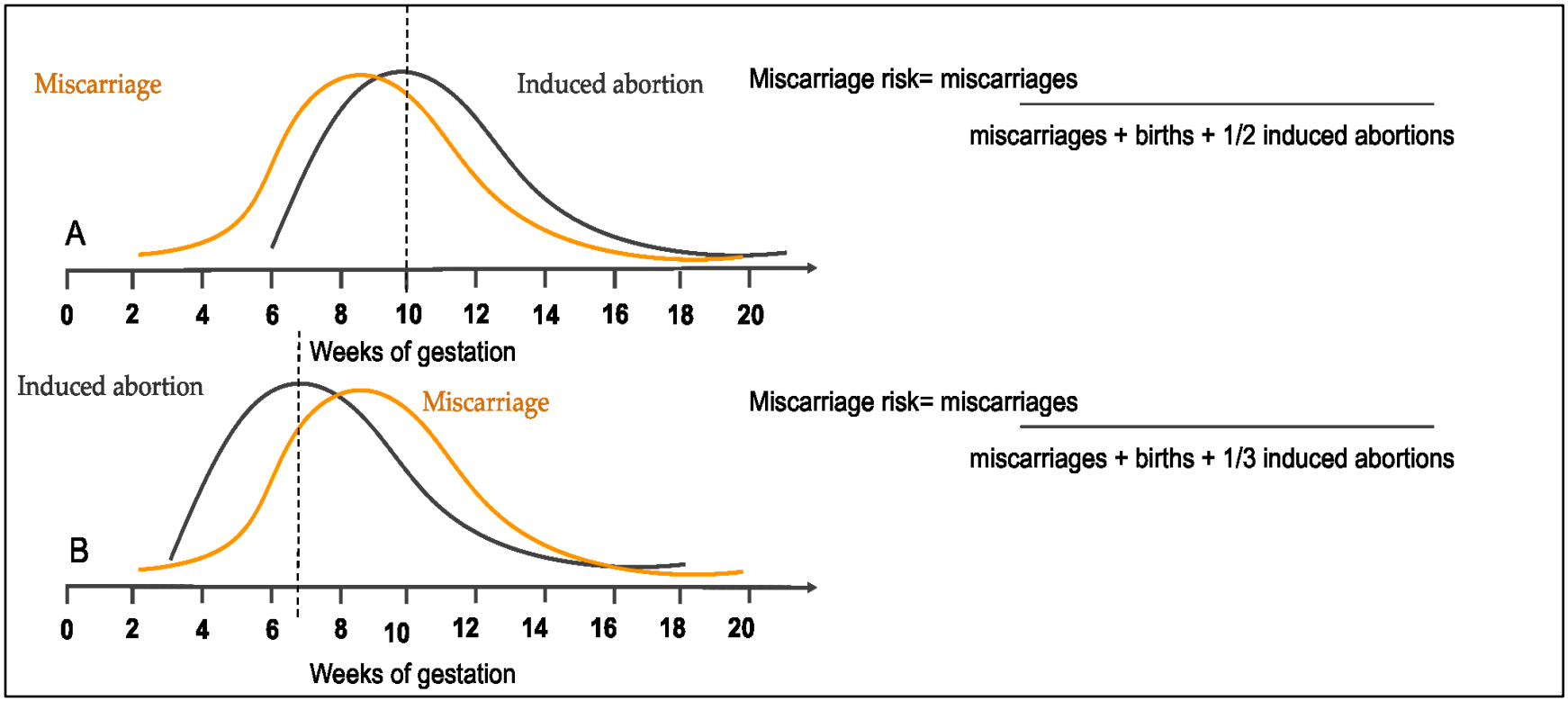

Figure 4.3: Visual representation of the impact of the correction factor for induced abortions.

The orange and black curves represent the hypothetical gestational age distributions of miscarriages and induced abortions, respectively. Pregnancies are at risk of miscarriage in the first 20 weeks of gestation. The dashed line indicates the average gestational age of induced abortions. Panel A: The gestational age distributions of miscarriages and induced abortions overlap, and induced abortions occur on average at 10 weeks gestation. Thus, an induced abortion is a pregnancy that is at risk of miscarriage for half the time a birth is at risk of miscarriage, and half the induced abortions are included in the denominator. Panel B: Induced abortions occur earlier than miscarriages, on average. The average gestational age of induced abortions is 7 weeks, and hence a third of induced abortions are included in the denominator.

CHAPTER 5: PREDICTORS OF ANTIDEPRESSANT DISCONTINUATION IN PREGNANCY

5.1. Preamble

Although a considerable amount of research has been devoted to assessing the prevalence of antidepressant use in pregnancy, little is known about the patterns and predictors of prenatal antidepressant use among women receiving these medications before pregnancy. Moreover, while studies have suggested that the prevalence of antidepressant use decreases in pregnancy, it remains unclear whether pregnancy itself is a predictor of antidepressant discontinuation, because antidepressant non-adherence is common in the general population.

Therefore, this manuscript explores the first objective of the thesis to determine the predictors of antidepressant use in pregnancy. Firstly, we compare the risk of antidepressant discontinuation in pregnant women to that in a group of matched non-pregnant women. Secondly, we determine the predictors of antidepressant discontinuation among pregnant women.

Exploring maternal characteristics associated with medication continuation or discontinuation in pregnancy among women receiving treatment before pregnancy can further our understanding of the factors associated with medication non-adherence in pregnancy, particularly for medications that may be beneficial but have potentially teratogenic effects. An improved understanding of these factors may help physicians make informed decisions regarding the treatment of depressed pregnant women.

5.2. Manuscript 1: Predictors of antidepressant discontinuation in pregnancy

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ABSTRACT

Objective: To explore the characteristics associated with antidepressant discontinuation in pregnancy compared to non-pregnant women taking antidepressants.

Methods: Pregnant women delivering between January 1st, 1998 and December 31st, 2002 were identified using Quebec's health administration databases. Women with at least one prescription for an antidepressant in the six months before pregnancy were matched to up to three non-pregnant women on age and date of first prescription filled in the pre-pregnancy period. Women were considered to have discontinued medication if they had filled at least one prescription in the six month pre-pregnancy period, and then had no prescriptions filled during pregnancy. Multivariable log binomial regression was used to assess the association between demographic, health and medication characteristics, and antidepressant discontinuation in pregnancy. We also assessed the risk of hospitalization in stoppers vs. continuers using propensity score analysis.

Results: Pregnant women were 4.96 (95% CI: 4.30 to 5.72) times more likely than non-pregnant women to discontinue antidepressant use, and 53% of pregnant women discontinued all antidepressant use in pregnancy. Pregnant women were more likely to discontinue antidepressant use if they were younger, not receiving welfare, and had a shorter duration of pre-pregnancy antidepressant use. Women receiving TCAs, MAOIs or atypical antidepressants before pregnancy were more likely to discontinue than those on SSRI monotherapy. Discontinuers were less likely to be hospitalized for mental health problems after 16 weeks of gestation compared to women with continuous antidepressant use in early pregnancy (0.22; 95%CI: (0.08, 0.68).

Conclusion: Our results suggest that pregnant women with less severe disease are more likely to discontinue treatment, but because pregnancy itself is a major predictor of discontinuation, physicians need to pay particular attention to pregnant women requiring pre-pregnancy

pharmacotherapy to ensure that they receive appropriate guidance on antidepressant use in pregnancy. We found that women who discontinued medication did not have an increased risk of mental health hospitalizations in late pregnancy, and future studies need to determine the risks of untreated and treated depression on pregnancy outcomes.

INTRODUCTION

Major depressive disorders are increasingly prevalent among women of child-bearing age, many of whom may require pharmacotherapy during pregnancy.[1,2,39] Approximately 8% of pregnant women in North America are exposed to antidepressants at some point in their pregnancy.[3,4,6,40] The decision to take medication in pregnancy is not easy for women in general,[10] as there are well-founded concerns about fetal teratogenicity.[15,55,59,61,63] However, for women with chronic conditions, the dilemma is compounded by having to weigh this risk against those of leaving a condition untreated, which may harm both mother and baby.[16,20,178]

Complicating matters further is the fact that medical guidelines regarding antidepressant therapy are confusing and constantly changing, since the numerous studies and reviews they are based on often have inconclusive or conflicting findings.[53,55] Thus, it is not surprising that women tend to discontinue medication use in pregnancy, with some studies noting a 46% to 75% decrease in pregnancy antidepressant prevalence compared to pre-pregnancy prevalence.[7-9,98-100]

Very little is known about the predictors of continuation/discontinuation of antidepressants during pregnancy among women requiring treatment before pregnancy.[8] No previous studies have assessed the association of factors such as the type of antidepressant with discontinuation in pregnancy. While it is important to ensure that women avoid teratogenic medication in pregnancy, it is equally important that women who benefit from treatment seek appropriate guidance before abruptly discontinuing therapy, because such discontinuation may have profound effects on both maternal and fetal health.[178] Exploring the predictors of discontinuation in this population may provide us with a better understanding of the characteristics of women who discontinue beneficial therapy, or conversely, of those who continue on potentially teratogenic medication. In addition, little is known about the patterns of antidepressant use in pregnant women compared to non-pregnant women,[8,98] and hence the aim of our study is to identify the maternal characteristics associated with antidepressant discontinuation in pregnant women compared to non-pregnant women taking antidepressants

prior to pregnancy. In an attempt to determine whether antidepressant discontinuation has adverse mental health consequences, we also assess the risk of hospitalization in late pregnancy in discontinuers compared to continuous users.

METHODS

Context

This study was conducted in Quebec, Canada where Quebec's health insurance board (Régie de l'assurance maladie du Québec or RAMQ) maintains a population-based registry of insured individuals. This enables the creation of longitudinal histories of medication use by linking four databases: the prescription claims database contains detailed information on filled prescriptions; the medical services claims database includes information on all physician visits, such as diagnosis, procedure, date and cost of service; the hospitalization database (MED-ECHO) records all hospitalizations in Quebec with detailed discharge diagnoses; and the beneficiary database includes demographic information, such as age, period of coverage, welfare beneficiary, and 3-digit residential postal code. RAMQ's public drug insurance plan covers all individuals over 65, welfare recipients, and employed individuals without private insurance, and its prescription claims database was found to have good agreement with medical charts.[157,158] Individuals covered by RAMQ's public plan account for approximately 43% of the overall Quebec population and for 36% of women between 15-45 years of age.[155]

Study Design and Population

We conducted a cohort study in which prescription medication use was prospectively ascertained among pregnant and non-pregnant women identified from Quebec's public drug insurance plan (RAMQ). Pregnant women aged 15 to 45 years with at least one pregnancy between January 1st, 1998 and December 31st, 2002 were identified using ICD-9 diagnosis codes or physician billing codes corresponding to the date when a pregnancy ended (index date). These included all live births (term and preterm) and stillbirths. If a woman had several pregnancies during the study period, only the first was included (which may, however, not have

been the woman's first pregnancy). Each pregnant woman was matched to up to three non-pregnant women on age and first prescription for an antidepressant received in the six months prior to pregnancy. Non-pregnant women were assigned the same pregnancy start and end date (index date) as the matched pregnant woman, thus creating a pregnancy proxy period for non-pregnant women. The start of follow-up for each woman was 24 months before the end of pregnancy, and women were only included in the study if they were continuously insured by RAMQ for all 24 months, to ensure continuous availability of health services data for the study period. Women were followed for a pre-pregnancy period of 15 months (16 months for women with preterm births) to detect diagnosis and other covariates. As gestational age (GA) was not available to us, we assigned a GA of 39 weeks to term births, and a GA of 35 weeks to preterm births (identified with ICD-9 codes 644.0, 644.2, and 765.x). This method was validated using the British Columbia health administrative databases and was demonstrated to accurately classify gestational age to within 2 weeks of clinically recorded gestational age for the vast majority of births.[162]

Antidepressant exposure

Prescription medication use before and during pregnancy was ascertained by creating a drug-by-day matrix. Availability of a medication on any particular day in the 24-month follow-up period was determined using the date the drug was dispensed as the start date of the prescription, to which the duration of the prescription (days' supply) was added to obtain the prescription end date.

Women were considered exposed to antidepressants if they had filled at least one prescription for an antidepressant, defined by American Hospital Formulary code 28:16.04, in the six months prior to the pregnancy start date. Antidepressant use was restricted to the six months before pregnancy to ensure recent use (women who filled a prescription before this period were also included as long as they continued to use during the six-month pre-pregnancy period). Antidepressants were categorized as: (i) selective serotonin reuptake inhibitors (SSRI) monotherapy; (ii) selective norepinephrine reuptake inhibitors (SNRI) monotherapy; (iii)

tricyclic antidepressants (TCA) monotherapy; (iv) other antidepressant (monoamine oxidase inhibitors, serotonin modulators, and atypical antidepressants) monotherapy; and (v) polytherapy (concurrent or serial use of more than one antidepressant).

Outcome

This study aimed to assess medication discontinuation in pregnancy among women receiving antidepressants in the six months prior to pregnancy. The outcome of interest was whether a woman receiving at least one prescription for a medication in the six months prior to pregnancy discontinued all medication use in pregnancy (or the pregnancy proxy period for non-pregnant women). Use in pregnancy was assessed for the entire duration of the pregnancy after excluding the first 30 days during which a woman may not yet be aware of her pregnancy (Figure 5.1). Discontinuers were those without any dispensings or days' supply extending beyond the first 30 days of pregnancy. If at least one medication was continued beyond the first 30 days of pregnancy, including switches to other classes of antidepressant, the woman was deemed to be continuing use in pregnancy.

Predictors

We assessed the following as potentially influencing medication discontinuation in pregnancy:

Demographic characteristics

We evaluated whether *maternal age* at delivery (modeled as a categorical variable) was associated with discontinuation of medication in pregnancy.[4,99] Increasing age could be a marker of more severe or longer-lasting disease, leading to a lower likelihood of stopping therapy in pregnancy. Alternately, age could be a proxy for education level, with women who are more informed about their disease less likely to discontinue potentially beneficial therapy.[40] We assessed whether being a *welfare recipient* affected medication use in pregnancy because studies have shown that socially disadvantaged populations tend to take more medication,[46,97,99] and may be less likely to discontinue use. Finally, we assessed *year of delivery*

to account for changes in prescribing patterns and guidelines over time that could affect use of medication in pregnancy.

Maternal health characteristics

We hypothesized that women with more severe disease were less likely to stop treatment in pregnancy. Factors related to disease severity and overall health included having received a *diagnosis* of depression before pregnancy; *number of medications* other than antidepressants filled before pregnancy; *number of hospitalizations* before pregnancy; and *number of physician visits* before pregnancy.

Drug characteristics

We evaluated whether antidepressant *therapeutic subclasses* influenced adherence in pregnancy, because certain subclasses are associated with treating resistant or more severe depression,[74,78] and thus may be less likely to be discontinued. Because women could be on more than one therapeutic subclass of drug (e.g. SSRI, SNRI) we further categorized *therapeutic subclass* by monotherapy or polytherapy. Use of two or more drugs could be a marker for more severe disease, with such women being less inclined to stop medication use in pregnancy. We also evaluated whether pre-pregnancy *duration of antidepressant use* was associated with discontinuation in pregnancy, because women with longer-lasting disease may be less likely to stop therapy.

Risk of hospitalization

We assessed whether pregnant women who discontinued all antidepressant use in pregnancy had a greater risk of hospitalization from the 16th week of pregnancy to two weeks before delivery compared to women with continuous antidepressant use before the16th week of pregnancy. Hospitalizations were defined as hospitalizations for any cause, and hospitalizations for mental health problems (admission to the psychiatric unit of the hospital, or admissions with ICD-9 codes for mental health disorders).

Statistical analysis

We performed descriptive analyses to summarize study characteristics of pregnant and non-pregnant women. In multivariable analyses, we used log binomial regression to estimate relative risks (RR) and 95% confidence intervals for the association between maternal characteristics and medication discontinuation in pregnancy. We first analyzed pregnant and non-pregnant women together to determine if discontinuation rates differed by pregnancy status. We then identified predictors of antidepressant discontinuation in pregnancy among pregnant women alone. All models included age, being a welfare recipient, year of delivery, depression diagnosis, previous hospitalizations, number of prescription drugs other than antidepressants, doctor visits before pregnancy, and antidepressant subclass.

In a separate analysis, with an aim to characterize the patterns of antidepressant use in pregnancy, we calculated the proportion of women who discontinued all medication in pregnancy; who continued on the pre-pregnancy class; and who switched to a different subclass.

In analyses assessing risk of hospitalization, we calculated the proportion of women hospitalized from the 16th week of pregnancy to two weeks before delivery for stoppers and continuers. In adjusted analyses, we incorporated the results from our predictor analysis to create a propensity score for medication continuation, matching stoppers and continuers on their propensity for continuing treatment using the nearest neighbour 1:1 matching method.[179] This generates a pseudo-randomized sample balanced on measured predictors of continuation (maternal age, welfare recipient, type and duration of pre-pregnancy antidepressant use, delivery year, number of medications other than antidepressants filled before pregnancy, number of hospitalizations before pregnancy, and number of physician visits before pregnancy).[169]

All analyses were conducted with SAS software, version 9.2 (SAS Institute, Cary, NC).

Sensitivity analysis

We performed a series of sensitivity analyses: First, we restricted our sample to women receiving at least two prescriptions for an antidepressant in the six months prior to pregnancy. We also reran our analyses after excluding preterm births in case there were a large proportion of very preterm births in our sample, which would result in misclassification of the length of pregnancy. Finally, we assessed antidepressant use in pregnancy after including the 1st 30 days of pregnancy.

Our study received ethics approval from the McGill University Institutional Review Board.

RESULTS

A total of 53,602 women with recorded pregnancies between January 1st, 1998 and December 31st, 2002 were continuously insured by RAMQ for 24 months prior to the date of delivery. There were 1553 women whose pregnancies ended in a live or stillbirth and who had at least one prescription for antidepressants in the six months before pregnancy, and these were matched to 3497 non-pregnant women.

Pregnant women were similar to non-pregnant women in age [mean (SD): 29.1 (6.1) vs. 29.7 (6.2) years], proportion of women on welfare (65% vs. 64%), and proportion of women who had received a depression diagnosis in the 15 months before pregnancy (73% vs. 76%) [Table 5.1]. However, pregnant women were more likely than non-pregnant women to be prescribed SSRIs before pregnancy and less likely to be receiving antidepressants classified as 'other' such as monoamine oxidase inhibitors.

Of the 1553 pregnant women receiving antidepressants in the six months before pregnancy, 53% discontinued all antidepressant use in pregnancy; however, only 8% of the 3497 non-pregnant women discontinued all antidepressants in the matched pregnancy proxy period [adjusted RR: 4.96; 95%CI: (4.30, 5.72)] (Table 5.2).

Pregnant women were less likely to discontinue antidepressant use in pregnancy if they were older than 35 years and were receiving welfare (Table 5.3). We found a dose-response relationship between duration of pre-pregnancy antidepressant use and the probability of discontinuation, with longer duration associated with a lower risk of discontinuation. Women receiving monotherapy for TCAs, MAOIs or atypical antidepressants prior to pregnancy were more likely to discontinue all antidepressant use in pregnancy compared to women receiving SSRI monotherapy.

When assessing the patterns of antidepressant use in pregnancy among women on antidepressant monotherapy, we found that at least 70% of women on TCAs or other antidepressant monotherapy before pregnancy discontinued all antidepressant use, while 49% of women receiving SSRI monotherapy did so (Table 5.4). The patterns of antidepressant use among non-pregnant women were very different, with the vast majority of women across all subclasses continuing or switching therapy in the pseudo-pregnancy period.

Pregnant women who discontinued all antidepressant use in pregnancy were less likely to be hospitalized for any cause, or for mental health issues between 16 weeks of pregnancy and two weeks before delivery compared to women with continuous antidepressant use in the first 16 weeks of pregnancy [OR from propensity score analysis: 0.22; 95%CI: (0.08, 0.68)] (Table 5.5).

Results were largely unchanged in sensitivity analyses: When our study population was restricted to women receiving at least two prescriptions for an antidepressant in pre-pregnancy, and when preterm births were excluded, results were similar to the main analysis. When the first 30 days of pregnancy were included for ascertainment of pregnancy antidepressant exposure, being a welfare recipient was no longer a significant predictor.

DISCUSSION

Our study found that pregnant women are more likely to discontinue antidepressant use than non-pregnant women. The proportion of pregnant women stopping all antidepressant use in pregnancy was 53%, and the main predictors of continuing use in pregnancy were older age, longer duration of pre-pregnancy use, and being on welfare. Discontinuation rates also differed by antidepressant sub-class.

Prior literature on the patterns of antidepressant use in pregnancy among women receiving these medications before pregnancy is scarce. A few studies examining the predictors of overall antidepressant prevalence in pregnancy reported that the main predictors of antidepressant use included factors such as older age,[4,67,99] greater number of pre-pregnancy medications,[99] greater number of physician visits,[99] white race,[4,67] and pre-pregnancy diabetes diagnosis.[67] Only one previous study assessed the predictors of discontinuing antidepressants in pregnancy among women already taking these medications prior to pregnancy, but it only examined three factors -age, deprivation index, and number of previous antidepressant prescriptions- and found older age and previous antidepressant use to be strong predictors of antidepressant continuation.[8] The latter study also compared discontinuation rates in pregnant women relative to non-pregnant women, and found a hazard ratio for discontinuation in the first six weeks of pregnancy of 5.19 (95% CI: 4.85, 5.56).However, the authors defined discontinuation as the absence of further prescriptions within 92 days of the previous prescription, and hence may have overestimated discontinuation rates among women who did not visit their family doctor for a prescription renewal within three months (or visited a doctor outside the network), and among women who may have restarted antidepressant use later in pregnancy. The authors also did not match on time of medication use, and hence may be affected by temporal prescribing trends.

Our study found differences in discontinuation rates for different subclasses of antidepressants. Pregnant women receiving tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and atypical antidepressants were more likely to discontinue all antidepressant use in

pregnancy compared to those on SSRI monotherapy. In our study, women prescribed TCAs, MAOIs, and atypical antidepressants before pregnancy had a shorter duration of pre-pregnancy use relative to women on SSRIs, indicating that they may have less severe disease, prompting them to discontinue all use in pregnancy. We did not have indications for antidepressant use, and a recent study using Quebec health-care utilization data indicated that 34% of prescriptions for antidepressants were written for off-label indications (such as neurogenic pain and insomnia).[180] Thus, it is also possible that women taking TCAs, MAOIs, and atypical antidepressants may be using them for indications other than depression and may be more likely to discontinue use in pregnancy. Alternatively, these results may reflect the medical guidelines that SSRIs are the antidepressant of choice in pregnancy,[52,87,181] reassuring women (and their physicians) that these medications may be safely continued.

One of the strongest predictors of discontinuation was duration of use before pregnancy, a proxy for disease severity and dependency i.e. a failure to taper off. Longer use of medication indicates more long-term chronic disease, and these women may be less likely to forego therapy in pregnancy. Women with less experience with antidepressant use may opt for non-pharmacological therapy in pregnancy.[11] Demographic variables such as older age and being a welfare recipient were associated with a lower likelihood of discontinuation in both pregnant and non-pregnant women. Studies of medication adherence have also shown age to be associated with better adherence;[97] this may be due to age being a proxy for disease of a longer duration, and older women may have used antidepressants in previous pregnancies. There is evidence that low socio-economic status is associated with greater prescription medication use,[182,183] but the choice to continue medication in pregnancy could reflect either that these lower income women suffer from more severe disease, or that they are less aware about the teratogenic effects of their medication. We also found some evidence that antidepressant discontinuation rates decreased over time for pregnant women but not for non-pregnant women, indicating that antidepressant use in pregnancy is affected by the prevailing medication guidelines or media coverage of antidepressant safety profiles during that time period.

We assessed mental health hospitalizations as an extreme indicator of depression relapse. Because our predictor analysis suggested that women with more severe disease are more likely to continue antidepressant use in pregnancy, and disease severity is also associated with a greater risk of hospitalization, these associations may result in a high possibility of confounding by indication. Hence, we used a matched propensity score analysis to balance stoppers and continuers on the main predictors of discontinuation, thus achieving a pseudo-randomized population. While we cannot rule out unmeasured confounding due to factors related to depression severity, we found a decreased risk of mental health hospitalizations among discontinuers relative to continuous users. Our results are in contrast to those from a small study that found that women who discontinued antidepressant use at some point before 16 weeks' gestation (n=65) had a greater risk of depression relapse compared to women who maintained their pre-pregnancy antidepressant use (n=81) in that period [Hazard ratio: 5.0 (95% CI: 2.8,9.1)].[16] Although the authors had rich information on depression-related variables such as duration of illness, history of suicidality, and family history of depression, they failed to adjust for these factors even though these differed between women who continued and discontinued treatment. Because untreated depression may have other adverse consequences on perinatal outcomes, future studies need to explore the risks and benefits of non-pharmacological and pharmacological treatments vs. untreated depression in pregnancy.

Strengths and limitations

This study assessed maternal characteristics of medication adherence, but was unable to explore physician characteristics, which may also be important predictors of medication use in pregnancy; this could be an interesting avenue for future research. Furthermore, women's views on antidepressants and their relationships with their physicians may also affect medication adherence in pregnancy.[11,184] Additionally, our results may not be generalizable to women who planned their pregnancies and preemptively stopped all medication use before pregnancy. Thus, our population may be more representative of women with unplanned pregnancies (50% of all pregnancies) or women with more severe disease who preferred to defer the decision until pregnancy. As we used administrative data, we only had information on

prescriptions filled but not actually consumed, though there is evidence that records of dispensed medications compare well with drug serum levels.[156] The strength of this study is that we were able to follow a large cohort of women in a well-defined geographical area over a long period of time, with detailed information on health services use and prescription medication.

Conclusion

Our results imply that pregnant women with more severe disease are less likely to discontinue treatment in pregnancy, but pregnancy itself is a major determinant of medication discontinuation. As our results suggest that women who discontinue treatment have lower risks of hospitalizations than continuers, further studies are needed to assess the risk of adverse perinatal outcomes in treated and untreated depressed women. Equipoise remains about the decision for a pregnant woman to stop antidepressants, and because antidepressants are both actively recommended and increasingly used in pregnancy, conducting randomized trials of antidepressant discontinuation are both ethical and warranted.

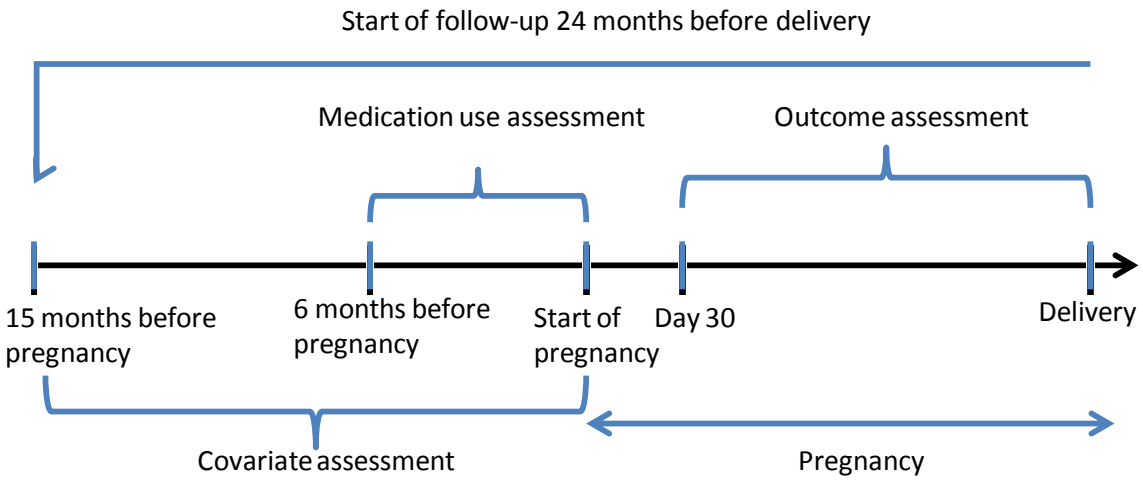

Figure 5.1: Study timeline of medication use, covariate and outcome assessment

Table 5.1: Characteristics of pregnant and non-pregnant women taking antidepressants in the six months before pregnancy

	Pregnant (n=1553)	Non-pregnant (n=3497)
	N (%)	
Welfare recipient	1010 (65)	2234 (63.9)
Depression diagnosis	1125 (72.4)	2657 (76.0)
Hospitalizations	89 (5.7)	391 (11.2)
Year of delivery		
1998	246 (15.8)	534 (15.3)
1999	340 (21.9)	756 (21.6)
2000	357 (23.0)	801 (22.9)
2001	299 (19.3)	669 (19.1)
2002	311 (20.0)	737 (21.1)
Drug subclass		
SSRI monotherapy	733 (47.2)	837 (23.9)
SNRI monotherapy	70 (4.5)	206 (5.9)
TCA monotherapy	230 (14.8)	375 (10.7)
Other monotherapy	83 (5.3)	986 (28.2)
Polytherapy	437 (28.1)	1093 (31.3)
	Mean (SD)	
Age	29.1 (6.1)	29.7 (6.2)
Physician visits before pregnancy	17.8 (15.6)	24.3 (25.8)
Number of antidepressants in the six months before pregnancy	1.4 (0.7)	1.5 (0.8)
Number of other medications	6.7 (5.2)	5.2 (4.8)
Duration of pre-pregnancy antidepressant use (days)	168.8 (149.5)	206.4 (112.5)

Table 5.2: Predictors of antidepressant discontinuation in all women (pregnant women and matched non-pregnant women), n=5050

	Total	Continued in pregnancy N (%)	Stopped in pregnancy N (%)	Adjusted RR (95%CL)
Pregnant				
No	3497	3207 (91.7)	290 (8.3)	1
Yes	1553	738 (47.5)	815 (52.5)	4.96 (4.30, 5.72)
Age				
15-20 years	339	243 (71.7)	96 (28.3)	1.02 (0.88, 1.19)
21-35 years	3795	2908 (76.6)	887 (23.4)	1
>35 years	916	794 (86.7)	122 (13.3)	0.70 (0.60, 0.80)
Welfare recipient				
No	1806	1357 (75.1)	449 (24.9)	1
Yes	3244	2588 (79.8)	656 (20.2)	0.81 (0.73, 0.89)
Depression diagnosis				
No	1262	927 (73.5)	335 (26.5)	1
Yes	3788	3018 (79.7)	770 (20.3)	0.95 (0.86, 1.05)
Psychiatric hospitalizations				
No	4238	3265 (77.0)	973 (23.0)	1
Yes	812	680 (83.7)	132 (16.3)	1.09 (0.94, 1.26)
Antidepressant subclass				
SSRI monotherapy	1570	1135 (72.3)	435 (27.7)	1
SNRI monotherapy	276	227 (82.2)	49 (17.8)	0.83 (0.67, 1.04)
TCA monotherapy	605	405 (66.9)	200 (33.1)	1.13 (1.00, 1.27)
Other monotherapy	1069	919 (86.0)	150 (14.0)	1.10 (0.95, 1.27)
Polytherapy	1530	1259 (82.3)	271 (17.7)	1.06 (0.95, 1.20)
Duration of pre-pregnancy antidepressant use				
0-30 days	452	128 (28.3)	324 (71.7)	1
31-120 days	1037	646 (62.3)	391 (37.7)	0.84 (0.76, 0.92)
121-270 days	2534	2255 (89.0)	279 (11.0)	0.40 (0.35, 0.46)
>270 days	1027	916 (89.2)	111 (10.8)	0.26 (0.22, 0.31)
No. of prescription medications other than antidepressants used in pre-pregnancy				
0-2 drugs	1468	1190 (81.1)	278 (18.9)	1
3-6 drugs	1969	1533 (77.9)	436 (22.1)	0.94 (0.84, 1.06)
>6 drugs	1613	1222 (75.8)	391 (24.2)	0.90 (0.80, 1.03)
No. of physician visits before pregnancy				
0-10	1607	1224 (76.2)	383 (23.8)	1
11-21	1722	1308 (76.0)	414 (24.0)	1.10 (0.99, 1.22)
>21	1721	1413 (82.1)	308 (17.9)	1.08 (0.95, 1.22)

	Total	Continued in pregnancy N (%)	Stopped in pregnancy N (%)	Adjusted RR (95%CL)
Year of delivery				
1998	780	597 (76.5)	183 (23.5)	1
1999	1096	832 (75.9)	264 (24.1)	1.06 (0.93, 1.21)
2000	1158	892 (77.0)	266 (23.0)	1.03 (0.90, 1.18)
2001	968	771 (79.6)	197 (20.4)	0.96 (0.83, 1.11)
2002	1048	853 (81.4)	195 (18.6)	0.93 (0.80, 1.08)

Table 5.3: Predictors of antidepressant discontinuation for pregnant and non-pregnant women separately

	Pregnant (n=1553)				Non-pregnant (n=3497)			
Predictor	Total	Continued in pregnancy N (%)	Stopped in pregnancy N (%)	Adjusted RR (95%CL)	Total	Continued in pregnancy N (%)	Stopped in pregnancy N (%)	Adjusted RR (95%CL)
Pregnant								
No					3497	3207 (91.7)	290 (8.3)	
Yes	1553	738 (47.5)	815 (52.5)					
Age								
15-20	109	35 (32.1)	74 (67.9)	1.07 (0.93, 1.22)	230	208 (90.4)	22 (9.6)	0.88 (0.60, 1.30)
21-35	1197	552 (46.1)	645 (53.9)	1	2598	2356 (90.7)	242 (9.3)	1
>35	247	151 (61.1)	96 (38.9)	0.78 (0.67, 0.90)	669	643 (96.1)	26 (3.9)	0.55 (0.37, 0.82)
Welfare recipient								
No	543	238 (43.8)	305 (56.2)	1	1263	1119 (88.6)	144 (11.4)	1
Yes	1010	500 (49.5)	510 (50.5)	0.87 (0.79, 0.96)	2234	2088 (93.5)	146 (6.5)	0.64 (0.51, 0.80)
Depression diagnosis								
No	422	163 (38.6)	259 (61.4)	1	840	764 (91)	76 (9.0)	1
Yes	1131	575 (50.8)	556 (49.2)	0.93 (0.84, 1.03)	2657	2443 (91.9)	214 (8.1)	0.95 (0.73, 1.23)
Psychiatric hospitalizations before pregnancy								
No	1385	648 (46.8)	737 (53.2)	1	2853	2617 (91.7)	236 (8.3)	1
Yes	168	90 (53.6)	78 (46.4)	0.96 (0.82, 1.12)	644	590 (91.6)	54 (8.4)	1.47 (1.07, 2.03)
Antidepressant subclass used before pregnancy								
SSRI monotherapy	733	372 (50.8)	361 (49.2)	1	837	763 (91.2)	74 (8.8)	1
SNRI monotherapy	70	33 (47.1)	37 (52.9)	0.98 (0.79, 1.22)	206	194 (94.2)	12 (5.8)	0.54 (0.31, 0.95)
TCA monotherapy	230	71 (30.9)	159 (69.1)	1.14 (1.01, 1.28)	375	334 (89.1)	41 (10.9)	1.19 (0.84, 1.70)
Other monotherapy	83	21 (25.3)	62 (74.7)	1.25 (1.09, 1.44)	986	898 (91.1)	88 (8.9)	0.96 (0.72, 1.30)

Predictor	Pregnant (n=1553) Total	Continued in pregnancy N (%)	Stopped in pregnancy N (%)	Adjusted RR (95%CL)	Non-pregnant (n=3497) Total	Continued in pregnancy N (%)	Stopped in pregnancy N (%)	Adjusted RR (95%CL)
Polytherapy	437	241 (55.1)	196 (44.9)	1.01 (0.90, 1.14)	1093	1018 (93.1)	75 (6.9)	1.28 (0.92, 1.79)
Duration of pre-pregnancy antidepressant use								
0-30 days	355	70 (19.7)	285 (80.3)	1	97	58 (59.8)	39 (40.2)	1
31-120 days	417	141 (33.8)	276 (66.2)	0.86 (0.79, 0.94)	620	505 (81.5)	115 (18.5)	0.41 (0.30, 0.56)
121-270 days	383	221 (57.7)	162 (42.3)	0.57 (0.50, 0.65)	2151	2034 (94.6)	117 (5.4)	0.12 (0.09, 0.17)
>270 days	398	306 (76.9)	92 (23.1)	0.32 (0.26, 0.38)	629	610 (97.0)	19 (3.0)	0.06 (0.04, 0.11)
No. of medications other than antidepressants used before pregnancy								
0-2	299	139 (46.5)	160 (53.5)	1	1169	1051 (89.9)	118 (10.1)	1
3-6	599	274 (45.7)	325 (54.3)	1.00 (0.89, 1.13)	1370	1259 (91.9)	111 (8.1)	0.88 (0.68, 1.13)
>6	655	325 (49.6)	330 (50.4)	0.97 (0.85, 1.10)	958	897 (93.6)	61 (6.4)	0.81 (0.59, 1.12)
No. of physician visits before pregnancy								
0-10	548	259 (47.3)	289 (52.7)	1	1059	965 (91.1)	94 (8.9)	1
11-21	583	267 (45.8)	316 (54.2)	1.08 (0.97, 1.20)	1139	1041 (91.4)	98 (8.6)	1.16 (0.89, 1.50)
>21	422	212 (50.2)	210 (49.8)	1.07 (0.94, 1.22)	1299	1201 (92.5)	98 (7.5)	1.06 (0.77, 1.46)
Year of delivery								
1998	246	100 (40.7)	146 (59.3)	1	534	497 (93.1)	37 (6.9)	1
1999	340	147 (43.2)	193 (56.8)	0.98 (0.86, 1.12)	756	685 (90.6)	71 (9.4)	1.50 (1.06, 2.13)
2000	357	165 (46.2)	192 (53.8)	0.96 (0.84, 1.09)	801	727 (90.8)	74 (9.2)	1.41 (0.99, 2.01)
2001	299	161 (53.8)	138 (46.2)	0.86 (0.73, 1.00)	669	610 (91.2)	59 (8.8)	1.56 (1.08, 2.25)
2002	311	165 (53.1)	146 (46.9)	0.90 (0.77, 1.04)	737	688 (93.4)	49 (6.6)	1.20 (0.80, 1.79)

Table 5.4: Patterns of use in pregnancy among women receiving antidepressant monotherapy in the six months before pregnancy

	Use in pre-pregnancy	Pregnancy		
		Discontinued all medication	Continued on same subclass	Switched to another subclass
	N	N (%)	N (%)	N (%)
Antidepressant monotherapy in pregnant women				
SSRI	733	361 (49.2)	353 (48.2)	19 (2.6)
SNRI	70	37 (52.9)	26 (37.1)	7 (10.0)
TCA	230	159 (69.1)	64 (27.8)	7 (3.1)
Other	83	62 (74.7)	17 (20.5)	4 (4.8)
Antidepressant monotherapy in non-pregnant women				
SSRI	837	61 (7.3)	745 (89.0)	31 (3.7)
SNRI	206	4 (1.9)	75 (36.4)	127 (61.7)
TCA	375	16 (4.3)	165 (44.0)	194 (51.7)
Other	986	14 (1.4)	143 (14.5)	829 (84.1)

Table 5.5: Risk of hospitalization in the first four months of pregnancy in women who discontinued all antidepressants in pregnancy compared to continuous users of antidepressants

Hospitalized between 16 weeks of pregnancy and two weeks before delivery	**Stoppers N=815**	**Continuers (used in all first 4 months of pregnancy) N=285**	**OR from propensity score analysis for stoppers vs. continuers***
	N (%)	**N (%)**	
Hospitalized for mental health problems	10 (1.2)	17 (6.0)	0.22 (0.08, 0.68)
Hospitalized for other causes	142 (17.4)	56 (19.7)	0.83 (0.54, 1.23)

* Variables in propensity score calculation: maternal age, being a welfare recipient, antidepressant type, delivery year, number of medications other than antidepressants filled before pregnancy; number of hospitalizations before pregnancy; and number of physician visits before pregnancy

Appendix

Table: Categorization of antidepressant subclasses based on antidepressant used before pregnancy

AHF class		Categorization of therapeutic classes	Trade name
28:16.04	28:16.04.20	Selective-serotonin reuptake inhibitors (SSRI)	Citalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline
	28:16.04.28	Selective norepinephrine reuptake inhibitors (SNRI)	Venlafaxine
	28:16.04.16	Tricyclic antidepressants (TCA)	Amitriptyline, Clomipramine, Desipramine, Doxepin, Imipramine, Maprotiline
	28:16.04.12 28:16.04.92	Other (monoamine oxidase inhibitors (MAOI), serotonin modulators, and atypical antidepressants)	Moclobemide, Phenelzine, Tranylcypromine, Trazodone, Bupropion

CHAPTER 6: CONSEQUENCES OF ANTIDEPRESSANT USE AND DISCONTINUATION IN PREGNANCY (Manuscripts 2 & 3)

6.1. Preambles for Manuscripts 2 and 3

Our previous study found that pregnant women were more likely than non-pregnant women to discontinue antidepressant use, with 53% of pre-pregnancy antidepressant users stopping all use in pregnancy. We take advantage of this result to create a cohort of antidepressant stoppers and continuers in order to assess the risk of continued antidepressant use on adverse pregnancy outcomes. We also incorporate the results of our predictor analysis to compute a propensity score for the probability of antidepressant continuation for continuers and discontinuers. This propensity score was then used to assess the effect of antidepressant continuation on risk of preeclampsia (Manuscript 2).

Some studies have suggested that depression itself is associated with an increased risk of unfavourable pregnancy outcomes, increasing the possibility of confounding by indication in studies of the association between antidepressant use and adverse outcomes. We thus also included a group of depressed women not receiving antidepressants before or during pregnancy to account for factors related to depression, and to determine whether there is indeed an increased risk of adverse outcomes in this population. In the second manuscript of this thesis, we assessed the risk of preeclampsia in unexposed depressed women, continuers and discontinuers relative to unexposed, non-depressed women (Manuscript 2).

Finally, we continue our exploration of the effects of antidepressant use on adverse outcomes by studying the association between antidepressant use and miscarriage risk. Earlier studies of this association have failed to account for induced abortions. We therefore employ a correction factor to adjust for induced abortion risk when comparing the risk of miscarriage in unexposed depressed women, antidepressant users, and women using non-teratogenic medication (hypothyroid medication) to that in unexposed, non-depressed women (Manuscript 3).

6.2. Manuscript 2: Risk of preeclampsia in women using antidepressants: a population-based study to examine the role of depression vs. antidepressants

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ABSTRACT

Objective: To examine the role of depression in influencing preeclampsia risk by assessing risk in untreated depressed women, and in continuers and discontinuers of antidepressant therapy.

Methods: 29,307pregnant women 15 to 45 years delivering between 1998 and 2002 were identified using Quebec's health administration databases. Risk of preeclampsia was assessed in four mutually-exclusive exposure groups: (i) women continuing pre-pregnancy antidepressant therapy; (ii) women discontinuing pre-pregnancy antidepressant use; (iii) depressed women without antidepressant use before or during pregnancy; and (iv) unexposed, non-depressed women. Logistic regression was used to assess the relative risk of preeclampsia after controlling for age, delivery year, being a welfare recipient, number of total medications in pre-pregnancy, pre-pregnancy diabetes diagnosis, and pre-pregnancy hospitalizations and physician visits.

Results: Of the 29,307 women, 3.3% developed preeclampsia. The risk relative to unexposed, non-depressed women was highest for continuers (OR: 2.07; 95% CI: 1.35 to 3.16) and lowest for depressed unexposed women (1.14; 0.93 to 1.41). Women continuing on non-SSRI medications had a higher risk of preeclampsia than those continuing SSRI therapy.

Conclusion: The continued use of antidepressants, particularly non-SSRIs, in early pregnancy may be associated with an increased risk of preeclampsia, independent of that associated with depression. Pregnant women and their physicians need to carefully consider the various treatment options in pregnancy to optimize maternal and fetal health.

INTRODUCTION

Preeclampsia, a potentially serious complication of pregnancy, remains one of the leading causes of maternal and fetal mortality.[106,107,185] It is characterized by the onset of hypertension in the latter half of pregnancy, in conjunction with either proteinuria or end-organ dysfunction.[186] Preeclampsia affects 2% to 8% of all pregnancies, and its prevalence has been increasing in the US and Canada,[187,188] with rates of severe preeclampsia almost 7-fold higher in 2003 compared to 1980. [189]

While the causes of preeclampsia remain elusive, several risk factors have been identified including obesity, primiparity, diabetes[190] and, more recently, antidepressant use.[30] Depressive disorders and the subsequent use of antidepressants are increasingly prevalent among women of child-bearing age,[3,4] and the use of antidepressants in pregnancy has been associated with an increased risk of several adverse outcomes including spontaneous abortion and birth defects.[63,191] However, some studies have indicated that depression itself is associated with preeclampsia risk,[119,123] prompting a need for studies attempting to tease out the effects of the disease from those of the medication used to treat the disease. In an attempt to address this confounding bias, authors of a recent study restricted their analysis to women with a diagnosis of depression, and found an increased risk of preeclampsia among women using antidepressants between 10 and 20 weeks of gestation.[30]

Our study aims to further delineate the risks of preeclampsia associated with depression and antidepressant use by including untreated depressed women, as well as continuers and discontinuers of pre-pregnancy antidepressant use. We hypothesized that, if antidepressant use is associated with preeclampsia, over and above depression, women who continued taking medication during pregnancy would have a higher risk than both untreated depressed women and women who discontinued treatment.

METHODS

Context

This study was conducted in Quebec, Canada where the provincial health plan administrator (RAMQ) maintains four population-based health registries that can be linked to create longitudinal histories of health services and medication use. The prescription claims database contains detailed information on filled prescriptions, such as dispensing date, drug type, quantity and duration of medication; these data were found to have good agreement with medical charts.[157,158] The medical services claims database includes information on all physician visits, such as diagnosis, procedure, date and cost of service. The hospitalization database (MED-ÉCHO), maintained by the Ministry of Health, records all hospitalizations in Quebec. Finally, the beneficiary database includes demographic information, such as age, period of coverage, welfare beneficiary, and 3-digit residential postal code. RAMQ's public drug insurance plan covers all individuals over 65, welfare recipients, and employed individuals without private insurance, accounting for approximately 50% of the total Quebec population and for 36% of women between 15-45 years of age.[155]

Study design and Population

We constructed a historical cohort of pregnant women aged 15 to 45 years with at least one pregnancy between January 1st, 1998 and December 31st, 2002 for whom medical and pharmaceutical services were recorded prospectively. Women were identified using ICD-9 diagnostic codes or physician billing codes referring to the date when a pregnancy ended (index date). These included all live births (term and preterm), stillbirths, recorded miscarriages and induced abortions; only the first recorded pregnancy within the study period for each woman was selected. Each woman was followed from 24 months before the end of pregnancy to one month post-partum, and only those with continuous insurance coverage for this period were included to ensure complete health services data for the study period.

Due to the unavailability of gestational age (GA) at birth in our administrative data, we set length of pregnancy for preterm births (ICD-9 codes 644.0, 644.2, and 765.x) and term births at 35 and 39 weeks, respectively. This method was validated using the British Columbia health administrative databases and was demonstrated to accurately classify GA to within 2 weeks of clinically recorded GA for the vast majority of births.[162]Women with miscarriages or induced abortions were excluded from analyses.

Preeclampsia

The outcome of interest was a diagnosis of preeclampsia after 20 weeks of gestation[106] to one month post-partum in the index pregnancy, identified by the presence of ICD-9 codes of 642.4 to 642.7in either the medical services claims or hospitalization databases. In a large Swedish study, ICD-9 codes used to identify preeclampsia had a positive predictive value of 93% against information contained in medical charts.[164]

Antidepressant use, depression diagnosis, and creation of exposure groups

American Hospital Formulary codes were used to identify women taking antidepressants (28:16.04). Daily drug availability was ascertained using the date the drug was dispensed as the start date of the prescription, and the days' supply of the medication to obtain the prescription end date.

Women were considered exposed to pre-pregnancy antidepressant use if they had received at least one prescription for an antidepressant in the six months prior to pregnancy. Use in pregnancy among pre-pregnancy antidepressant users was assessed for the entire duration of the pregnancy after excluding the first 30 days to allow for medication use before a woman became aware of her pregnancy. Discontinuers were those without any antidepressant dispensings or days' supply extending beyond the first 30 days of pregnancy, and continuers were women with at least one antidepressant continued in the first 20 weeks of pregnancy, excluding the 30-day lag period.

Women were identified as depressed if they had received a diagnosis containing ICD-9 codes 296, 309 and 311. These codes maximized the sensitivity and specificity of identifying depressed patients in the Saskatchewan Health administrative claims databases, with sensitivity, specificity and positive predictive values of 71%, 85% and 86% relative to medical chart records.[159].

We then created four mutually-exclusive exposure groups: (i) continuers; (ii) discontinuers; (iii) unexposed depressed women, i.e. women who had been given a diagnosis of depression (ICD-9 codes: in the 15 months before pregnancy but who had not received a prescription for antidepressants during pregnancy or the 15 months preceding the pregnancy; and (iv) unexposed, non-depressed women, i.e. women who had received neither an antidepressant prescription nor a diagnosis of depression during pregnancy and the 15 months preceding the index pregnancy. Antidepressant use in pregnancy was ascertained for the first 20 weeks of pregnancy to ensure that exposure occurred before preeclampsia diagnosis, which normally occurs after the 24th week of pregnancy. The category including women diagnosed with depression but with no record of antidepressant use was created to determine whether depression or factors related to depression may themselves be associated with preeclampsia risk. None of the four exposure groups included women with a diagnosis of hypertension or prescriptions for antihypertensives before pregnancy, as we wanted to focus on women without pre-existing hypertension.

In separate analyses, we also assessed preeclampsia risk in (i) continuers vs. discontinuers; and in (ii) continuers, and discontinuers vs. unexposed women without depression.

Finally, to assess the risk of preeclampsia by different antidepressant classes, we categorized antidepressant exposure among women continuing use in the first 20 weeks of pregnancy as: selective serotonin reuptake inhibitor (SSRI)monotherapy or polytherapy (concomitant or serial use of an SSRI with another class of antidepressant); and all other antidepressants including selective norepinephrine reuptake inhibitors

(SNRI) and tricyclic antidepressants (TCA). Preeclampsia risk in both these groups was compared, in separate analyses, to risk in (i) unexposed, non-depressed women; (ii) unexposed women with a depression diagnosis; and (iii) antidepressant users who discontinued all use in pregnancy.

This study received ethics approval from the McGill University Institutional Review Board.

Potential confounding variables

Potential confounders of the association between antidepressant use and preeclampsia risk were determined on the basis of factors that potentially caused depression/antidepressant use and preeclampsia. They included: age at delivery (15-20, 21-40, and 41-45 years), because the risk of pre-eclampsia is higher at the age extremes,[192] and medication use is associated with age; being a welfare recipient (y/n) as a measure of socio-economic status;[193,194] and other teratogenic medication (antipsychotics, anticonvulsants, and benzodiazepines)use in 1st trimester (y/n). We also included several pre-pregnancy variables as indicators of a woman's health just prior to the pregnancy: the total number of all prescription medications received in the year preceding the index pregnancy; the total number of physician visits in the year prior to pregnancy; any hospitalizations (y/n) in the year prior to pregnancy; and the presence of a diagnosis for diabetes (y/n) in the preceding year. Finally, year of delivery was included to account for temporal trends in both medication use and preeclampsia risk.

Statistical analysis

Study characteristics of women in the study were tabulated for each of the four exposure groups.

We used logistic regression to obtain adjusted odds ratios of preeclampsia by exposure groups and 95% confidence intervals. We first assessed preeclampsia risk using non-

depressed, unexposed women as the reference group. We then obtained risks relative to women who had received a pre-pregnancy depression diagnosis but had no exposure to antidepressants before and during pregnancy. Finally, we restricted our sample to women who had used antidepressants in the six months prior to pregnancy, and compared preeclampsia risk in continuers vs. discontinuers using a matched propensity score analysis. In such an analysis, stoppers and continuers are matched on their propensity for discontinuing treatment using the nearest neighbour 1:1 matching method.[179] This generates a pseudo-randomized sample balanced on measured predictors of discontinuation (maternal age, welfare recipient, type and duration of pre-pregnancy antidepressant use, delivery year, number of all prescription medications received before pregnancy, number of hospitalizations before pregnancy, and number of physician visits before pregnancy).[169] Finally, to assess whether risk was associated with antidepressant class, women continuing on SSRI and non-SSRI antidepressants were compared to the other three exposure groups.

Sensitivity analyses

To assess the robustness of our results, we reran our analyses after including women who had received antihypertensives or a hypertension diagnosis before pregnancy and adjusted for these variables in the analysis.

All analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina).

RESULTS

Of the 29,307 pregnant women eligible for inclusion in our study, 24,870 women had received neither a depression diagnosis nor a prescription for antidepressants before or during pregnancy; 3009 women had no recorded antidepressant use but a diagnosis for depression before pregnancy; 764 women had used at least one antidepressant in the six months before pregnancy but discontinued all antidepressant use in pregnancy; and 664 women had used at least one antidepressant in the six months before pregnancy

and continued antidepressant use in the first 20 weeks of gestation. Compared to non-depressed, unexposed women, women with either a depression diagnosis or antidepressant use were more likely to be welfare recipients, to have had a preterm birth, and to have used antipsychotics, anticonvulsants or benzodiazepines in early pregnancy. These women were also more likely to be hospitalized and to have a greater number of physician visits in the 12 months before pregnancy (Table 6.1). Women who continued antidepressant use in pregnancy were older, more likely to be welfare recipients, to have received a pre-pregnancy diabetes diagnosis, and to have used antipsychotics, anticonvulsants or benzodiazepines in early pregnancy compared to the other exposure groups.

The overall proportion of preeclampsia in our study sample was 3.3% (958 of 29,307 women). The risk was 3.1% among non-depressed, unexposed women; 3.6% in unexposed women with a depression diagnosis; 3.9% in women who discontinued all antidepressant use throughout pregnancy; and 6.3% in women continuing antidepressant use in the first 20 weeks of pregnancy.

In adjusted multivariable analyses, women continuing antidepressant use in the first 20 weeks of pregnancy had the highest risk of preeclampsia relative to non-depressed, unexposed women (OR: 2.07; 95% confidence interval: 1.35 to 3.16) [Table 6.2]. The corresponding risk for unexposed depressed women and discontinuers was 1.14 (0.93 to 1.41) and 1.27 (0.87 to 1.88), respectively (Table 6.2). When compared to depressed unexposed women, the relative risk of preeclampsia remained significantly elevated among antidepressant continuers, while the risk for women who stopped use in pregnancy was not statistically significant (OR: 1.21; 0.78 to 1.88) (Table 6.3). Antidepressant continuers also had a significantly elevated risk of preeclampsia relative to antidepressant discontinuers (OR: 1.66 ;1.01 to 2.74).

Women who continued on SSRI antidepressants in the first 20 weeks of gestation had a significantly elevated risk of preeclampsia when compared to women either with or without a depression diagnosis, but not relative to discontinuers of all antidepressant use (OR: 1.60; 0.91 to 2.83) [Table 6.4]. Women continuing on non-SSRI antidepressants had a greater risk of preeclampsia than SSRI users relative to all other exposure groups, including discontinuers (OR: 2.23; 1.11 to 4.49).

Sensitivity analyses in which women with pre-existing hypertension were included produced results similar to our main analyses.

Discussion

Our results suggest that antidepressant use in the first 20 weeks of gestation is associated with an increased risk of pre-eclampsia after 20 weeks. Women with a depression diagnosis but no antidepressant use, and those who discontinued antidepressant use in pregnancy did not have an increased risk of pre-eclampsia compared to non-depressed, unexposed women. Women who continued antidepressant use in the first half of pregnancy were at an increased risk of preeclampsia even when compared to discontinuers, particularly among women continuing on non-SSRI antidepressants.

The first study to assess the association between antidepressant continuation in pregnancy and risk of preeclampsia found that women who self-reported SSRI use after the 1st trimester had a significantly elevated risk compared to women reporting no SSRI use in pregnancy (RR: 4.86; 2.70, 8.76), while there was no significant risk for women discontinuing SSRI use before the end of the 1st trimester.[132] The authors of that study did not account for depression; however, in a more recent study that was restricted to depressed women, the authors found no significant risk of preeclampsia among women who used SSRI monotherapy between 10 and 20 weeks of gestation compared to women with depression unexposed to antidepressants before 20 weeks (RR: 1.22; 0.97,

1.54).[30] They did however find an increased risk for TCA and SNRI users compared to unexposed women with depression, which is similar to our results showing a greater risk for non-SSRI antidepressant continuers.

The distinctiveness of our study lies in the systematic creation of and comparison between different exposure profiles to tease out the role of depression vs. antidepressants in preeclampsia risk, with the expectation of seeing an incremental risk of preeclampsia with continued use of antidepressants in pregnancy. It has been theorized that depression and cardiovascular disease share a common immunological response, and hence depressive symptoms may trigger an inflammatory cascade that eventually results in elevated blood pressure and preeclampsia.[118,119] Monoamine neurotransmitters, including serotonin and norepinephrine, have been implicated in the etiology of preeclampsia through their vasoactive effects.[126-129,131] Thus, antidepressants such as SSRIs, SNRIs, and TCAs, which inhibit the reuptake of serotonin and norepinephrine, may affect preeclampsia risk through their role in increasing vasoconstriction and reducing placental blood flow.[195]

However, we found no difference in preeclampsia risk between depressed and non-depressed unexposed women. Furthermore, pre-pregnancy antidepressant users who discontinued all antidepressant use in pregnancy had a higher risk than unexposed depressed women, and the greatest risk occurred among women who stayed on antidepressants in the first half of pregnancy. Such a pattern appears to implicate antidepressant use as a risk factor for preeclampsia, over and above depression. It is possible that women who continue on antidepressants in pregnancy have more severe depression; we attempted to account for these differences related to severity using a propensity score analysis which found an increased risk for continuers compared to discontinuers; nonetheless, we cannot rule out the possibility of residual confounding due to unmeasured factors related to depression severity.

Our results may have been affected by the lack of information on some important risk factors of preeclampsia, including BMI, parity and smoking. Smoking has consistently been associated with a lower risk of preeclampsia;[112] hence, if the proportion of smokers is higher among antidepressant users than unexposed women, as some studies have indicated,[7,46,64,102] not adjusting for smoking would result in an attenuation of the true risk estimate. Primiparity (first pregnancy) is associated with a greater risk of preeclampsia;[196] however, in our study antidepressant users were older, and hence less likely to be primiparous than unexposed women, which has also been shown in previous studies.[7,30,46,64,102] High BMI is also a predictor of preeclampsia,[196] but the association between antidepressant use and BMI remains unclear.[30,46] It is reassuring that a study using British Columbia health-care utilization data that adjusted for BMI, parity, and multifetal gestation found no discernible change in risk estimates, indicating that these variables are not confounders of the association between antidepressant use and preeclampsia risk.[30] Furthermore, discontinuers and continuers of antidepressants were found to be similar for these factors (BMI, parity and smoking) in a previous study,[132] and our propensity score analysis accounting for differences in depression severity found a higher risk of preeclampsia for continuers. Finally, the population covered by Quebec's drug plan (36% of women of childbearing age) over-represents people of lower socio-economic status, which may affect the generalizability of our results to women covered by private insurance, if the association between antidepressant use and risk of preeclampsia differs by socio-economic status. However, the internal validity of our study is unaffected; furthermore, the baseline rate of preeclampsia in our study of 3.3% is similar to that in the Quebec population.[197]

In conclusion, the results of our study suggest that the use of antidepressants, particularly non-SSRI antidepressants, in the 1st half of pregnancy is associated with an increased risk of preeclampsia, over and above the risk associated with women who discontinue all antidepressant use in pregnancy, and the risk in unexposed, depressed

women. Given the deleterious effects of preeclampsia on both maternal and fetal health, physicians must provide particular guidance to women at risk of antidepressant use in the first half of pregnancy, carefully considering the different treatment options available in pregnancy.

Table 6.1: Study characteristics of women in the four exposure groups

		Exposure group N (%)			
	Total n=29307	No medication, no depression n=24870	No antidepressants, depression n=3009	Antidepressant discontinuers n=764	Antidepressant continuers n=664
Age					
15-20	3457	2985 (12.0)	368 (12.2)	71 (9.3)	33 (5.0)
21-40	25457	21598 (86.8)	2573 (85.5)	682 (89.3)	604 (91)
>40	393	287 (1.2)	68 (2.3)	11 (1.4)	27 (4.1)
Welfare recipient	14354	11682 (47)	1749 (58.1)	478 (62.6)	445 (67.0)
Preterm birth	3330	2659 (10.7)	454 (15.1)	135 (17.7)	82 (12.3)
Pre-pregnancy diabetes diagnosis	251	201 (0.8)	32 (1.1)	9 (1.2)	9 (1.4)
Antipsychotic use in 1st trimester	957	320 (1.3)	235 (7.8)	114 (14.9)	288 (43.4)
Hospitalization in previous 12 months	3625	2822 (11.3)	506 (16.8)	161 (21.1)	136 (20.5)
Number of medications in 12 months before pregnancy					
0 -1 drugs	12655	11637 (46.8)	963 (32.0)	27 (3.5)	28 (4.2)
2- 3 drugs	8377	7225 (29.1)	871 (28.9)	153 (20.0)	128 (19.3)
>3 drugs	8275	6008 (24.2)	1175 (39.0)	584 (76.4)	508 (76.5)
Physician visits in 12 months before pregnancy					
0-4 visit	10941	10366 (41.7)	426 (14.2)	68 (8.9)	81 (12.2)
5-11 visits	8949	7699 (31.0)	860 (28.6)	214 (28.0)	176 (26.5)
> 11visits	9417	6805 (27.4)	1723 (57.3)	482 (63.1)	407 (61.3)
Year of delivery					
1998	4698	3880 (15.6)	593 (19.7)	141 (18.5)	84 (12.7)
1999	8528	7371 (29.6)	841 (27.9)	182 (23.8)	134 (20.2)
2000	6543	5557 (22.3)	666 (22.1)	176 (23.0)	144 (21.7)
2001	5297	4512 (18.1)	507 (16.8)	129 (16.9)	149 (22.4)
2002	4241	3550 (14.3)	402 (13.4)	136 (17.8)	153 (23.0)

Table 6.2: Risk of pre-eclampsia in women continuing antidepressant use in pregnancy compared to healthy controls

Predictor	Total n=29,307	Preeclampsia	No pre-eclampsia	Adjusted OR (95%CL)
Comparison groups				
No antidepressant, no depression	24870	778 (3.1)	24092 (96.9)	1
No antidepressant, depression	3009	108 (3.6)	2901 (96.4)	1.14 (0.93, 1.41)
Antidepressant use, stoppers	764	30 (3.9)	734 (96.1)	1.28 (0.87, 1.88)
Antidepressant use, continuers	664	42 (6.3)	622 (93.7)	2.18 (1.52, 3.13)
Age				
15-20	3457	137 (4.0)	3320 (96)	1.45 (1.20, 1.76)
21-39	25457	799 (3.1)	24658 (96.9)	1
>40	393	22 (5.6)	371 (94.4)	1.70 (1.09, 2.63)
Welfare recipient				
No	14953	539 (3.6)	14414 (96.4)	1
Yes	14354	419 (2.9)	13935 (97.1)	0.79 (0.68, 0.92)
Diabetes				
No	29056	938 (3.2)	28118 (96.8)	1
Yes	251	20 (8.0)	231 (92.0)	2.59 (1.62, 4.14)
Antipsychotic, anticonvulsant or benzodiazepine use in 1st trimester				
No	28350	921 (3.2)	27429 (96.8)	1
Yes	957	37 (3.9)	920 (96.1)	0.90 (0.62, 1.31)
Any hospitalization in 12 months before pregnancy				
No	25682	846 (3.3)	24836 (96.7)	1
Yes	3625	112 (3.1)	3513 (96.9)	0.92 (0.73, 1.14)
Number of medications in 12 months before pregnancy				
0-1 drugs	12655	394 (3.1)	12261 (96.9)	1
2-3 drugs	8377	271 (3.2)	8106 (96.8)	1.04 (0.89, 1.23)
>3 drugs	8275	293 (3.5)	7982 (96.5)	1.03 (0.85, 1.24)
Physician visits in the three months before pregnancy				
0-3 visits	10941	351 (3.2)	10590 (96.8)	1
4-8 visits	8949	263 (2.9)	8686 (97.1)	0.90 (0.76, 1.06)
> 8 visits	9417	344 (3.7)	9073 (96.3)	1.13 (0.93, 1.36)
Year of delivery				
1998	4698	113 (2.4)	4585 (97.6)	1
1999	8528	260 (3.0)	8268 (97.0)	1.18 (0.93, 1.50)
2000	6543	254 (3.9)	6289 (96.1)	1.50 (1.17, 1.92)
2001	5297	198 (3.7)	5099 (96.3)	1.41 (1.09, 1.82)

Predictor	Total n=29,307	Preeclampsia	No pre-eclampsia	Adjusted OR (95%CL)
2002	4241	133 (3.1)	4108 (96.9)	1.16 (0.88, 1.53)

Table 6.3: Risk of pre-eclampsia in women continuing antidepressant use in pregnancy compared to depressed women

Predictor	Total n=4437	Preeclampsia	No pre-eclampsia	Adjusted OR (95%CL)
Exposure group				
No medication, depression	3009	108 (3.6)	2901 (96.4)	1
Antidepressant use, stoppers	764	30 (3.9)	734 (96.1)	1.21 (0.78, 1.88)
Antidepressant use, continuers	664	42 (6.3)	622 (93.7)	2.07 (1.35, 3.16)
Age				
15-20	472	15 (3.2)	457 (96.8)	0.90 (0.52, 1.57)
21-39	3859	156 (4.0)	3703 (96.0)	1
>40	106	9 (8.5)	97 (91.5)	2.03 (1.00, 4.13)
Welfare recipient				
No	1765	86 (4.9)	1679 (95.1)	1
Yes	2672	94 (3.5)	2578 (96.5)	0.73 (0.52, 1.03)
Diabetes				
No	4387	176 (4.0)	4211 (96.0)	1
Yes	50	4 (8.0)	46 (92.0)	1.79 (0.62, 5.12)
Antipsychotic, anticonvulsant or benzodiazepine use in 1st trimester				
No	3800	152 (4.0)	3648 (96.0)	1
Yes	637	28 (4.4)	609 (95.6)	0.86 (0.54, 1.37)
Any hospitalization in 12 months before pregnancy				
No	3634	146 (4.0)	3488 (96.0)	1
Yes	803	34 (4.2)	769 (95.8)	1.03 (0.69, 1.56)
Number of medications in 12 months before pregnancy				
0-1 drugs	1018	43 (4.2)	975 (95.8)	1
2-3 drugs	1152	41 (3.6)	1111 (96.4)	0.77 (0.49, 1.20)
>3 drugs	2267	96 (4.2)	2171 (95.8)	0.78 (0.50, 1.22)
Physician visits in the three months before pregnancy				
0-3 visits	575	22 (3.8)	553 (96.2)	1
4-8 visits	1250	39 (3.1)	1211 (96.9)	0.87 (0.50, 1.49)
> 8 visits	2612	119 (4.6)	2493 (95.4)	1.38 (0.83, 2.30)
Year of delivery				
1998	818	23 (2.8)	795 (97.2)	1
1999	1157	47 (4.1)	1110 (95.9)	1.28 (0.76, 2.18)
2000	986	49 (5.0)	937 (95.0)	1.55 (0.90, 2.67)
2001	785	41 (5.2)	744 (94.8)	1.51 (0.86, 2.65)
2002	691	20 (2.9)	671 (97.1)	0.81 (0.42, 1.55)

Table 6.4: Risk of preeclampsia among women continuing SSRI or non-SSRI antidepressants in the first 20 weeks of gestation

	Continuers vs. unexposed, non-depressed women			Continuers vs. unexposed women with depression diagnosis			Continuers vs. discontinuers		
	Total n=25534	Women with preeclampsia n (%)	OR (95% CI)	Total N=3673	Women with preeclampsia n (%)	OR (95% CI)	Total n=1428	Women with preeclampsia n (%)	OR (95% CI)
No antidepressant use in pregnancy	24870	778 (3.1)	1[a]	3009	108 (3.6)	1[b]	764	30 (3.9)	1[c]
SSRI monotherapy or polytherapy	490	28 (5.7)	1.94 (1.26, 3.00)	490	28 (5.7)	1.93 (1.19, 3.13)	490	28 (5.7)	1.60 (0.91, 2.83)
Non-SSRI antidepressants	174	14 (8.1)	2.82 (1.57, 5.08)	174	14 (8.1)	2.72 (1.45, 5.12)	174	14 (8.1)	2.23 (1.11, 4.49)

[a] This group includes only unexposed, non-depressed women

[b] This group includes only unexposed, depressed women

[c] This group includes only pre-pregnancy antidepressant users who discontinued in pregnancy

6.3. Manuscript 3: Risk of miscarriage in women receiving antidepressants in early pregnancy, correcting for induced abortions

ABSTRACT

Objective: Earlier studies on the association between antidepressant use and miscarriage have obtained conflicting results after accounting for the role of depression, and none have taken into account the high risk of induced abortions in women using antidepressants. We thus assess the risk of miscarriage in women exposed to antidepressants in early pregnancy, after correcting for induced abortion risk.

Methods: 41,003pregnant women 15 to 45 years delivering between 1998 and 2002 were identified using Quebec's health administration databases. Women with at least one prescription for an antidepressant in the first trimester were compared to three groups of unexposed controls:(i) women who had received at least one prescription for hypothyroid medication in the first trimester; (ii) women who had received a depression diagnosis before pregnancy, but were not taking antidepressants in the first trimester; and (iii) women who had received neither antidepressants nor a depression diagnosis before or during pregnancy. Log binomial regression was used to assess the relative risk of miscarriage corrected for induced abortion risk, after controlling for age, delivery year, being a welfare recipient, number of total medications, pregnancy antipsychotic use, and pre-pregnancy hospitalizations and physician visits.

Results: The miscarriage risk uncorrected for induced abortions was 15.5%, 12.3% and 8.8% for women exposed to antidepressants; unexposed depressed women; and unexposed, non-depressed women, respectively. These decreased to 10.9%, 9.1% and 7.1% after correction for induced abortions (The induced abortion risk was 46.2%, 40.6% and 31.7%, respectively). In multivariable analysis, the corrected risk of miscarriage relative to unexposed, non-depressed women was 1.24 (1.06 to 1.46) for antidepressant-exposed women and 1.21 (1.09 to 1.35) for unexposed depressed women. The miscarriage risk remained elevated when antidepressant users were compared to unexposed depressed women [1.23 (1.00 to 1.51)]. There was no increased risk of miscarriage for women taking hypothyroid medication in pregnancy.

Conclusion: Antidepressant use in the first trimester is associated with an increased risk of miscarriage when compared to either non-depressed or depressed unexposed women, even after accounting for induced abortions, although the possibility of residual confounding due to factors related to depression severity cannot be ruled out.

INTRODUCTION

There has been a sharp increase in the number of pregnant women requiring prescription medication for treatment of chronic conditions in recent years, due in part to the delayed age at childbearing.[3,4,40] Almost all medication use in pregnancy is considered off-label because drug efficacy trials in pregnant women cannot be conducted safely. As a result, observational studies have been the only means of understanding the association between prenatal prescription medication use and adverse pregnancy outcomes, underscoring the necessity of refining our methods of such studies.

Since the1980s, researchers have sought to study the association between antidepressant use and miscarriage risk. However, the vast majority of these studies were small and compared pregnant women calling Teratogenic Information Services about antidepressant use to those calling about non-teratogenic medication, resulting in a highly selected study population.[174,198,199] In addition, most studies failed to account for the possibility of confounding by the underlying condition, as it has been shown that depression itself is associated with adverse pregnancy outcomes.[18,19,122-124] Only very recently have three, large population-based studies been carried out to tease out these issues.[18,75,76] Two of these studies explicitly included depressed controls, and obtained conflicting results, highlighting the need for further research.[18,76]

A further methodological concern relates to the fact that induced abortions are generally unaccounted for in these studies. If the risk of having an induced abortion depends on the exposure, as may well be the case with depression and antidepressant use, failure to take this competing risk into account may result in biased estimates.[147] The potential for bias is highest in observational studies where miscarriage risk is traditionally calculated as the total number of miscarriages divided by the total number of births and miscarriages.[200] While most studies ignore induced abortions completely in the denominator,[18,75,76] thus assuming that terminated pregnancies are not at risk of miscarriage, including all abortions in the denominator may result in an underestimation of the miscarriage risk.[200]

Therefore, the aim of this study is to build on previous observational studies by estimating the risk of miscarriage associated with prenatal antidepressant use, addressing the issues described above. Specifically, we (i) included a comparison group of depressed pregnant women not using antidepressants (ii) included a group of women with a chronic condition requiring treatment with non-teratogenic medication and, (iii) applied a correction factor to account for the risk of induced abortions.

METHODS

Context

This study was conducted in Quebec, Canada using population-based health registries maintained by Quebec's public health and prescription drug insurance plan administrator (RAMQ). Four such databases were linked, enabling the creation of longitudinal histories of medication use. The prescription claims database contains detailed information on filled prescriptions, such as dispensing date, drug type, quantity and duration of medication, and was found to have good agreement with medical charts.[157,158] The medical services claims database includes information on all physician visits, such as diagnosis, procedure, date and cost of service. The hospitalization database (MED-ÉCHO), maintained by the Ministry of Health, records all hospitalizations in Quebec. Finally, the beneficiary database includes demographic information, such as age, period of coverage, welfare beneficiary, and 3-digit residential postal code. RAMQ's public drug insurance plan covers all individuals over 65, welfare recipients, and employed individuals without private insurance, accounting for approximately 50% of the overall Quebec population and for 36% of women between 15 and 45 years of age.[155]

Study design and Population

We designed a historical cohort of pregnant women aged 15 to 45 years with at least one pregnancy between January 1st, 1998 and December 31st, 2002. Women were identified using ICD-9 diagnostic codes or physician billing codes referring to the date when a pregnancy ended (index date). These included all live births (term and preterm), stillbirths, as well as recorded miscarriages and induced abortions. If a woman had several pregnancies during the study

period, the first recorded pregnancy end date was chosen (this may, however, not correspond to the woman's first-ever pregnancy). The start of follow-up for each woman was 24 months before the end of pregnancy, and women were only included in the study if they were continuously insured by RAMQ for 24 months before the index date, to ensure complete health services data for the study period.

Because gestational age (GA) was not available to us, we set length of pregnancy for preterm births (ICD-9 codes 644.0, 644.2, and 765.x) and term births at 35 and 39 weeks, respectively. This method was validated using the British Columbia health administrative databases and was shown to accurately classify GA to within 2 weeks of clinically recorded GA for the vast majority of births.[162] We set the GA of miscarriages and abortions at 12 weeks based on data issued by the Canadian Institute of Health Information (CIHI), responsible for collecting therapeutic abortion data since 1995. These reported that the vast majority of induced abortions in Canada occurred before 12 weeks, peaking between 9 and 12 weeks of gestation.[173] Similarly, the vast majority of miscarriages occur before 12 weeks, with an average gestational age of 10 weeks.[151] We assessed the robustness of our results with respect to these assumptions by varying the GAs in subsequent sensitivity analyses.

Definition of outcome

The outcome of interest was the occurrence of a miscarriage in the index pregnancy, defined as fetal loss before 20 weeks of gestation. These were identified by the presence of either an ICD-9 code of 634 or 761.8; or physician billing codes pertaining to a miscarriage. Induced abortions were identified by the presence of ICD-9 codes 635, 636, or 637; or corresponding physician billing codes; and the absence of codes for a spontaneous abortion on the same date.

Correction for induced abortions

We used a correction factor for induced abortions first proposed by Susser et al. for observational studies where the gestational age of miscarriages or induced abortions is unavailable, as is the case for many large pharmacological administrative databases.[154] This

correction factor includes the sum of the total number of births, miscarriages, and half of the induced abortions in the denominator of the risk calculation.

$$\frac{No.of\ miscarriages}{No.of\ miscarriages\ + No.of\ births + \frac{1}{2}\ No.of\ induced\ abortions}$$

Half of all induced abortions are included in the denominator because, if pregnancies are at risk of miscarriage in the 1st 20 weeks of gestation (by definition, any fetal loss after 20 weeks is considered a stillbirth),[176,177] and miscarriage and abortions occur, on average, at 10 weeks of gestation,[75,166] then an induced abortion is a pregnancy that is at risk of miscarriage for half the time that a pregnancy ending in a birth is at risk (Figure 6.1). Thus, induced abortions are given half the weight of births in the risk calculation.

The main assumption here is that the gestational age distributions of induced abortions and miscarriages overlap. In their original study, Susser et al. indicate that if the gestational ages do not overlap, then an adjustment to the correction factor is needed, decreasing it if induced abortion occur before miscarriages, and conversely, increasing the value if induced abortions occur later. We feel confident that, given the gestational age data in the published literature,[75,166] the gestational ages in our study do significantly overlap. Furthermore, it is highly unlikely that induced abortions occur later than miscarriages in our population, given the ease of accessibility to abortion services in Quebec, and thus the value of '1/2' would generate the most conservative miscarriage risk estimate, by including the maximum number of induced abortions in the denominator.

Measurement of depression and medication use, and creation of exposure groups

Women were defined as having a diagnosis of depression through the presence of ICD-9 codes 296, 309 and 311 on their medical services claims. These use of these codes were found to maximize the sensitivity and specificity of identifying depressed patients in the Saskatchewan Health administrative claims databases, with sensitivity, specificity and positive predictive values of 71%, 85% and 86% relative to medical chart records.[159]

American Hospital Formulary codes were used to identify women taking antidepressants (28:16.04) or hypothyroid medication (68:36.04). In order to characterize the pattern of prescription medication use, a drug-by-day matrix was created wherein daily drug availability was ascertained using the date the drug was dispensed as the start date of the prescription, to which the duration of the prescription was added to obtain the prescription end date.

Women were considered exposed if they had received at least one prescription for the medication in the 1st trimester (the first 84 days) of pregnancy. We created four mutually-exclusive exposure groups: (1) women who had received at least one prescription for an antidepressant in the first trimester (main exposure group); (2) women who had received at least one prescription for hypothyroid medication in the same exposure period, but not for antidepressants; (3) women who had been given a diagnosis of depression in the 15 months before pregnancy but who had not received a prescription for antidepressants during pregnancy or the 15 months preceding the pregnancy; and (4) women who had received neither prescriptions for antidepressants or hypothyroid medication, nor a diagnosis for the corresponding conditions during pregnancy and the 15 months before pregnancy (reference group). The hypothyroid medication control group was created in order to compare miscarriage risks in women taking medication with different teratogenic profiles; hypothyroid medication is considered safe in pregnancy and is associated with a lowered risk of miscarriage compared to untreated women.[201] The category including women diagnosed with depression but with no record of medication was created to determine whether the underlying disease is associated with miscarriage risk, independent of the medications used to treat it, thus attempting to account for unmeasured confounding due to factors related to depressive disorders. None of the four groups included women taking antihypertensives or who had a diagnosis for hypertension, both of which may be associated with a high risk of miscarriage.[202]

In further analyses, we restricted the antidepressant-exposed group to women who had received a depression diagnosis, and compared them to the unexposed, depressed exposure group, to determine whether these groups differed in miscarriage risk, and thus attempt to assess if antidepressant exposure had an impact independent of the underlying depression.

Finally, to assess the risk of miscarriage by different antidepressant classes, we categorized antidepressant exposure, based on the first prescription during the pregnancy, as: (i) selective serotonin reuptake inhibitors (SSRI); (ii) selective norepinephrine reuptake inhibitors (SNRI); (iii) tricyclic antidepressants (TCA); (iv) other antidepressants; and (v) polytherapy i.e. women who had received more than one class of antidepressants concomitantly or serially in the exposure window. Miscarriage risk in each of these groups was compared to those in unexposed, depressed women.

Potential confounders

We included several variables that might be potential confounders of the association between antidepressant use and miscarriage risk in our analyses. These were: age, (15-20 years, 20-35, and 35-45), because miscarriage risk has been shown to increase at the age extremes,[172] and medication use may increase in older women; being a welfare recipient (y/n) as a proxy for socio-economic status, as low socio-economic position has been associated with greater use of prescription medication, and an increased risk of miscarriage;[193] use of other teratogenic medication (antipsychotics, anticonvulsants, and benzodiazepines) in 1st trimester (y/n) because these drugs may be associated with both antidepressant use and risk of miscarriage, due to potential teratogenicity. We also included several pre-pregnancy variables that might be measures of a woman's health just prior to the pregnancy, and underlying health problems can be associated with both medication use in pregnancy, and adverse pregnancy outcomes. These variables were: the total number of all prescription medications received in the three months prior to pregnancy; the total number of physician visits in the three months prior to pregnancy; and any hospitalizations (y/n) in the three months prior to pregnancy. Finally, year of delivery was included to account for temporal trends in both medication use and abortion risk. We did not adjust for previous miscarriage because doing so may bias the association under study.[203]

Statistical analysis

Descriptive statistics summarizing characteristics of women in the study and the proportion of births, miscarriages and abortions were tabulated for each of the four exposure groups. We estimated the crude uncorrected and corrected risk of miscarriage for the four exposure groups, to assess the change in miscarriage risk after accounting for induced abortions. The crude *uncorrected* miscarriage risk was calculated as the total number of miscarriages divided by the total number of births and miscarriages; the miscarriage risk *corrected* for induced abortions was estimated as the total number of miscarriages divided by the sum of the total number of births, miscarriages and half of the induced abortions.

In multivariable analyses, we used log binomial regression to estimate the adjusted risk of miscarriage and corresponding 95% confidence intervals relative to unexposed, non-depressed women for each of the three other exposure groups. Analysis for the uncorrected miscarriage risk included only women whose pregnancies ended in either a birth or a miscarriage. In order to calculate the adjusted miscarriage risk corrected for induced abortions, we used a weighted log binomial regression analysis where induced abortions were given half the weight of births. In other words, we re-ran our previous analysis including all miscarriages and births, but also including all women with an induced abortion, each with a weight of 0.5, in contrast to a weight of 1 assigned to all other women, resulting in a sample size effectively including only half of all induced abortions.

We also compared the uncorrected and corrected miscarriage risk for women who both received antidepressants in early pregnancy and were diagnosed with depression to risks in women with a depression diagnosis but no exposure to antidepressants. Finally, to assess the miscarriage risk by antidepressant class, women in each of the five antidepressant classes were compared to unexposed, depressed women.

Sensitivity analyses

To assess the robustness of our results, we performed several sensitivity analyses. Firstly, we varied the gestational age of miscarriages and abortions to 8, 10 and 14 weeks, and re-assessed the effect of medication exposure on corrected and uncorrected miscarriage risk. Secondly, we

maintained the gestational age of miscarriages and abortions at 12 weeks, but varied the timing of exposure to (i) any medication use in the 1st trimester (1st 84 days of pregnancy) or the 1st month before pregnancy; (ii) any medication use in both the 1st trimester and the 1st month before pregnancy; (iii) medication use only in the three months before pregnancy, and no medication use in the 1st trimester; and (iv) medication use only in the 1st trimester, and no medication use in the six months before pregnancy.

All analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina).

Our study received ethics approval from the McGill University Institutional Review Board.

RESULTS

Of the 41,003 pregnant women eligible for inclusion in our study, there were 32,677 (80%) women who had received neither a diagnosis nor a prescription for medication for depression, hypertension and hypothyroidism; 5106 (12%) women with no antidepressant use but a diagnosis for depression; 2273 (6%) women who had used at least one antidepressant in the 1st trimester; and 947 (2%) women with at least one prescription for hypothyroid medication in the 1st trimester. Compared to non-depressed, unexposed women, those receiving antidepressants in early pregnancy were older, more likely to be welfare recipients, to have used antipsychotics, anticonvulsants or benzodiazepines in early pregnancy, to be hospitalized before pregnancy and to have a greater number of physician visits in the three months before pregnancy (**Table 6.5**). Depressed, unexposed women were more similar in age to unexposed, healthy women than to antidepressant users, but were more likely to be on welfare and to have used other teratogenic medication than healthy women. Women taking hypothyroid medication in pregnancy were older, but less likely to be on welfare than healthy, unexposed women.

Overall, there were 24,690 (60.2%) births, 13,726 (33.5%) induced abortions, and 2587 (6.3%) miscarriages (**Table 6.6**). Among the four exposure groups, antidepressant users had the lowest proportion of births (45%) and the highest proportion of induced abortions (46%), compared with 62% and 32% of births and induced abortions, respectively, for healthy, unexposed women.

The risk of miscarriage, uncorrected for induced abortions, was 8.8% in women without medication or a diagnosis for depression, hypertension and hypothyroidism; 12.3% in depressed women not receiving antidepressants; 15.5% among antidepressants users in early pregnancy; and 10.2% for hypothyroid medication users. The corresponding risks after correction for induced abortions were 7.1% in healthy, unexposed women; 9.1% among depressed, unexposed women; and 10.9% and 8.6% for antidepressant and hypothyroid medication users, respectively. Because antidepressant users had the highest proportion of induced abortions, the largest drop in miscarriage risk was seen in this group (Figure 6.2).

In adjusted analyses using unexposed, non-depressed women as the reference group, the uncorrected relative risk of miscarriage was 1.31 (95% confidence interval: 1.18 to 1.46) for depressed, unexposed women; 1.38 (1.18 to 1.62) for antidepressant users; and 1.03 (0.82 to 1.29) for hypothyroid medication users (Table 6.7). After correction for induced abortions, the relative risk of miscarriage decreased to 1.21 (1.09 to 1.35) for depressed, unexposed women and to 1.24 (1.06 to 1.46) for antidepressant users (Table 6.8). Both young age [15-20 years; 1.19 (1.06 to 1.34)] and older age [>35 years; 2.11 (1.92 to 2.32)] were independently associated with an increased uncorrected risk of miscarriage, relative to women aged 21 to 35 years. However, upon correction for induced abortions, the youngest women were no longer at an increased risk of miscarriage [1.01 (0.90 to 1.13)].

The uncorrected and corrected risk of miscarriage for antidepressant users with a diagnosis of depression compared to unexposed women with a depression diagnosis were 1.31 (1.06 to 1.61) and 1.23 (1.00 to 1.51), respectively (Table 6.9). After correction for induced abortions, women on SNRI monotherapy [1.73; (1.13 to 2.63)], and polytherapy [1.47; (1.00 to 2.17)] were found to have an increased miscarriage risk, compared to unexposed, depressed women (Table 6.10).

Figure 6.3 shows the results of our sensitivity analyses for antidepressant users compared to healthy, unexposed women; they do not indicate any major changes in risk estimates.

DISCUSSION

The risk of miscarriage among antidepressant users was both statistically and clinically significantly elevated when compared to either healthy or depressed women. Depressed women not taking antidepressants were also more likely to have a miscarriage compared to healthy, unexposed women; in contrast, women receiving hypothyroid medication, considered safe in pregnancy, did not differ from healthy women in miscarriage risk. In our study, SNRI monotherapy and antidepressant polytherapy were associated with an increased risk of miscarriage. These findings persist even after accounting for induced abortions.

Previous reviews and meta-analyses summarizing the literature from 1980 to 2012 have found an increased risk of miscarriage among prenatal antidepressant users ranging from 1.45 (1.19 to 1.77) to 1.70 (1.28 to 2.24).[148-150] While the earlier studies were small, three recent, large population-based studies have also detected an increased miscarriage risk in antidepressant-exposed women. [18,151,152] Two of these studies included a comparison group of depressed, unexposed women, but none accounted for the increased induced abortion risk in these populations.

Nakhai-Pour et al. found that antidepressant users in early pregnancy were at an increased risk of miscarriage (OR: 1.68; 95%CI 1.28 to 2.04) when compared to women not receiving any prescription medication, after adjusting for several depression and health-related factors.[151] They also found an increased risk for all antidepressant classes when compared to unexposed women, with odds ratios ranging from 1.61 (1.28 to 2.04) for SSRI monotherapy to 2.11 (1.34 to 3.30) for SNRI monotherapy; while these estimates are higher than what we found, they will likely decrease when compared to depressed women, because of the possible residual confounding due to depression. A large population-based study using the National Health Services data in the UK of 512,574 pregnancies found elevated risks (after excluding abortions) for all classes of antidepressants compared to either depressed or healthy unexposed women. This study did not provide a risk estimate for overall antidepressant use in pregnancy. In contrast, a 2013 population-based study using the Danish National Registry of 1,005,319 pregnancies did not find an increased risk of miscarriage (RR: 1.00; 95%CI 0.80 to 1.24) when the analyses were restricted to only depressed women. These results could be partly due to the

surprisingly low number of antidepressant-exposed women with a depression diagnosis (11% vs. 75% in our study). They also found a lower risk of miscarriage than earlier studies when comparing antidepressant users to unexposed women, with or without depression (RR: 1.14; 95%CI 1.10 to 1.18).

The etiology of miscarriage remains unclear, though studies have identified uterine malformations and balanced chromosomal rearrangements to be strongly associated with miscarriage risk.[138,139] Thus, antidepressants may increase miscarriage risk by acting directly on chromosomal or placental development.[137] Alternatively, the underlying indication for antidepressant use may increase miscarriage risk, and there is much debate in the literature about whether it is the antidepressants or the underlying depression that is associated with the increased risk. The use of a depressed, unexposed control group may be one way of teasing out these associations.[204] We found that antidepressants users had an increased risk of miscarriage compared to depressed, unexposed women. In addition, women using antidepressants in the three months prior to pregnancy but not in the first trimester had a lower risk of miscarriage than 1st trimester antidepressant users, indicating that stopping antidepressant use before pregnancy appears to decrease the miscarriage risk. Nonetheless, it is possible that untreated depressed women may have less severe disease, and hence there may still be residual confounding by unmeasured factors related to depression severity.

In this study, we employed a correction factor for induced abortions in order to test the hypothesis that the risk of miscarriage is decreased in populations with a high risk of induced abortions. While our study found that our estimate of the miscarriage risk did decrease among antidepressant users after accounting for induced abortions, the sustained elevated risk, even after restricting to depressed women, bolsters the evidence that antidepressant use itself may be associated with an increased risk of miscarriage. With respect to another population at high risk of induced abortions, i.e. very young pregnant women, we found that correction for induced abortions completely eliminated the increased risk of miscarriage, compared to women aged 20 to 35 years. These results demonstrate that the use of a correction factor for induced abortions may prove useful in certain high risk groups.

Limitations

As we used administrative data, we only had information on prescriptions filled but not actually consumed, though there is evidence that records of dispensed medications compare well with drug serum levels.[156] The strength of using administrative databases is the ability to follow a large sample over a long period of time with detailed information on health services and prescription medication use.[157] We did not have information on maternal smoking and alcohol use; however, their associations with miscarriage risk or antidepressant use may not be strong enough to reverse our results.[140,141] It is possible that late-term miscarriages could have been misclassified as induced abortions in our administrative data. This would be an issue if misclassification were differential across exposure groups; however, we had information on induced abortions occurring after 14 weeks of gestation, and found similar rates across all exposure groups. Any non-differential misclassification would bias our results towards the null. Our study uses administrative data that includes women covered by the provincial drug plan (36% of women of childbearing age), who tend to be younger, and have lower household income than women covered by private insurance.[205] While the internal validity of our study will remain unaffected, our results may not be representative of women covered through private insurance if the association between antidepressant use and risk of miscarriage differs by socio-economic status. Nonetheless, the baseline rate of induced abortions in our study of 33% is similar to that of the Quebec population.[166]

In conclusion, our study is the first to account for the risk of induced abortions when assessing the association between prenatal antidepressant use and miscarriage risk. Our results suggest that antidepressant use in the first trimester is associated with an increased risk of miscarriage when compared to both healthy and depressed unexposed women, even after accounting for induced abortions, though we cannot rule out the possibility of residual confounding. We found an increased miscarriage risk for SNRI use and polytherapy, and a clinically relevant elevated risk for TCAs. Our results, combined with those of earlier studies, underscore the need for women and their physicians to discuss these risks when weighing treatment options in pregnancy.

Acknowledgements

We would like to acknowledge Dr. Abby Lippman for helpful comments on earlier versions of this manuscript. Drs Robyn Tamblyn and Michal Abrahamowicz are James McGill Professors. Ms. Nisha Almeida is the recipient of a Canadian Institutes of Health Research doctoral award.

Table 6.5: Characteristics of the 41,003 women belonging to the four exposure groups

		Exposure group N (%)			
	Total	**No medication, no diagnosis**	**No antidepressants, depression**	**Antidepressant use in 1st trimester**	**Hypothyroid medication use in 1st trimester**
	n=41003	**n=32677**	**n=5106**	**n=2273**	**n=947**
Age					
15-20	6373	5402 (16.5)	758 (14.8)	161 (7.1)	52 (5.5)
21-35	30333	24303 (74.4)	3703 (72.5)	1615 (71.1)	712 (75.2)
>35	4297	2972 (9.1)	645 (12.6)	497 (21.9)	183 (19.3)
Welfare recipient	21962	16885 (51.7)	3136 (61.5)	1506 (66.3)	435 (45.9)
Other teratogenic medication use in 1st trimester[1]	2239	609 (1.9)	539 (10.6)	1035 (45.5)	56 (5.9)
Hospitalizations in 3 months before pregnancy	1145	803 (2.5)	179 (3.5)	132 (5.8)	31 (3.3)
Number of medications in three months before pregnancy[2]					
0 drugs	18734	16498 (50.5)	2073 (40.6)	114 (5.0)	49 (5.2)
≥ 1 drug	22269	16179 (49.5)	3033 (59.4)	2159 (95.0)	898 (94.8)
Physician visits in 3 months before pregnancy					
1 visit	24977	21486 (65.8)	2291 (44.9)	723 (31.8)	477 (50.4)
>1 visits	16026	11191 (34.2)	2815 (55.1)	1550 (68.2)	470 (49.6)
Year of delivery					
1998	7538	5953 (18.2)	1119 (21.9)	324 (14.3)	142 (15.0)
1999	11741	9610 (29.4)	1381 (27.0)	496 (21.8)	254 (26.8)
2000	8932	7114 (21.8)	1077 (21.1)	516 (22.7)	225 (23.8)
2001	7069	5544 (17.0)	855 (16.7)	495 (21.8)	175 (18.5)
2002	5723	4456 (13.6)	674 (13.2)	442 (19.4)	151 (15.9)

[1] Antipsychotics, anticonvulsants and benzodiazepines

[2] No. of all prescription medications used in the three months before pregnancy

Table 6.6**:** Number and percent of pregnancy outcomes by exposure group for the 41,003 study participants

	Births		**Miscarriages**		**Induced abortions**		
Exposure group	**N**	**%**	**N**	**%**	**N**	**%**	**Total**
No medication, no diagnosis	20373	62.3	1954	6.0	10350	31.7	32677
No antidepressants, depression	2657	52.0	372	7.3	2077	40.6	5106
Antidepressant use in 1st trimester	1034	45.5	190	8.4	1049	46.2	2273
Hypothyroid medication use in 1st trimester	626	66.1	71	7.5	250	26.4	947
All	24690	60.2	2587	6.3	13726	33.5	41003

Table 6.7**:** Relative risk of miscarriage among women taking medication in the first trimester of pregnancy compared to unexposed women without depression, uncorrected for induced abortions

	Total (births + miscarriages)	Miscarriage N (%)	Crude RR (95%CI)	Adjusted RR (95%CI)
Comparison groups				
No medication, no depression	22327	1954 (8.8)	1	1
No medication, depression	3029	372 (12.3)	1.40 (1.26, 1.56)	1.31 (1.18, 1.46)
Antidepressant use	1224	190 (15.5)	1.77 (1.55, 2.03)	1.38 (1.18, 1.62)
Hypothyroid medication use	697	71 (10.2)	1.16 (0.93, 1.46)	1.03 (0.82, 1.29)
Age				
15-20	3448	334 (9.7)	1.16 (1.04, 1.30)	1.19 (1.06, 1.34)
21-35	21246	1772 (8.3)	1	1
>35	2583	481 (18.6)	2.23 (2.04, 2.45)	2.11 (1.92, 2.32)
Welfare recipient				
No	13035	1237 (9.5)	1	1
Yes	14216	1346 (9.5)	1.00 (0.93, 1.07)	0.92 (0.84, 1.00)
Other teratogenic medication use in 1st trimester[1]				
No	26114	2400 (9.2)	1	1
Yes	1163	187 (16.1)	1.75 (1.53, 2.01)	1.27 (1.09, 1.49)
Number of medications in three months before pregnancy[2]				
0 drugs	12622	1118 (8.9)	1	1
At least 1 drug	14655	1469 (10.0)	1.13 (1.05, 1.22)	1.06 (0.97, 1.14)
Any hospitalization in 3 months before pregnancy				
No	26478	2501 (9.4)	1	1
Yes	799	86 (10.8)	1.14 (0.93, 1.40)	1.05 (0.85, 1.29)
Physician visits in the three months before pregnancy				
1 visit	16569	1493 (9.0)	1	1
>1	10708	1094 (10.2)	1.13 (1.05, 1.22)	1.03 (0.95, 1.12)
Year of delivery				
1998	4711	465 (9.9)	1	1
1999	7971	700 (8.8)	0.89 (0.80, 0.99)	0.87 (0.77, 0.98)

	Total (births + miscarriages)	Miscarriage N (%)	Crude RR (95%CI)	Adjusted RR (95%CI)
2000	6112	583 (9.5)	0.97 (0.86, 1.09)	0.93 (0.82, 1.05)
2001	4737	433 (9.1)	0.93 (0.82, 1.05)	0.88 (0.77, 1.00)
2002	3746	406 (10.8)	1.10 (0.97, 1.25)	1.02 (0.89, 1.16)

[1] Antipsychotics, anticonvulsants and benzodiazepines

[2] No. of all prescription medications used in the three months before pregnancy

Table 6.8: Relative risk of miscarriage among women taking medication in the first trimester of pregnancy compared to unexposed women without depression, corrected for induced abortions

	Total (Births+ miscarriage+ ½ induced abortions)	Miscarriage N (%)	Crude RR (95%CI)	Adjusted RR (95%CI)
Comparison groups				
No medication, no depression	27502	1954 (7.1)	1	1
No medication, depression	4068	372 (9.1)	1.29 (1.16, 1.43)	1.21 (1.09, 1.35)
Antidepressant use	1748	190 (10.9)	1.53 (1.33, 1.76)	1.24 (1.06, 1.46)
Hypothyroid medication use	822	71 (8.6)	1.22 (0.97, 1.52)	1.07 (0.85, 1.34)
Age				
15-20	4910	334 (6.8)	0.99 (0.88, 1.11)	1.01 (0.90, 1.13)
21-35	25790	1772 (6.9)	1	1
>35	3440	481 (14.0)	2.04 (1.85, 2.23)	1.96 (1.78, 2.16)
Welfare recipient				
No	16024	1237 (7.7)	1	1
Yes	18089	1346 (7.4)	0.96 (0.90, 1.04)	0.93 (0.85, 1.01)
Other teratogenic medication use in 1st trimester[1]				
No	32439	2400 (7.4)	1	1
Yes	1701	187 (11.0)	1.49 (1.29, 1.71)	1.14 (0.97, 1.34)
Number of medications in three months before pregnancy[2]				
0 drugs	15678	1118 (7.1)	1	1
At least 1 drug	18462	1469 (8)	1.12 (1.04, 1.20)	1.05 (0.97, 1.14)
Any hospitalization in 3 months before pregnancy				
No	33168	2501 (7.5)	1	1
Yes	972	86 (8.8)	1.17 (0.96, 1.44)	1.1 (0.90, 1.35)
Physician visits in the three months before pregnancy				
1 visit	20773	1493 (7.2)	1	1
>1	13367	1094 (8.2)	1.14 (1.06, 1.23)	1.06 (0.97, 1.15)

	Total (Births+ miscarriage+ ½ induced abortions)	Miscarriage N (%)	Crude RR (95%CI)	Adjusted RR (95%CI)
Year of delivery				
1998	6124.5	465 (7.6)	1	1
1999	9856	700 (7.1)	0.94 (0.84, 1.05)	0.90 (0.80, 1.02)
2000	7522	583 (7.8)	1.02 (0.91, 1.15)	0.97 (0.85, 1.10)
2001	5903	433 (7.3)	0.97 (0.85, 1.10)	0.90 (0.79, 1.03)
2002	4734.5	406 (8.6)	1.13 (0.99, 1.28)	1.04 (0.91, 1.19)

[1] Antipsychotics, anticonvulsants and benzodiazepines

[2]No. of all prescription medications used in the three months before pregnancy

Table 6.9: Relative risk of miscarriage in antidepressant users with depression compared to unexposed, depressed women, uncorrected and corrected for induced abortions

	Uncorrected			Corrected		
Exposure	**Total**	**Miscarriage**	**Adjusted OR* (95%CL)**	**Total**	**Miscarriage**	**Adjusted OR* (95%CL)**
No medication, depression	3029	372 (12.3)	1	4068	372 (9.1)	1
Antidepressant use, depression	889	145 (16.3)	1.31 (1.06, 1.61)	1294	145 (11.2)	1.23 (1.00, 1.51)

* Adjusted for age, being a welfare recipient, use of other teratogenic medication in 1st trimester, number of prescription medication in 3 months before pregnancy, number of mental health visits in 3 months before pregnancy, number of physician visits in 3 months before pregnancy, any hospitalizations in 3 months before pregnancy, and year of delivery

Table 6.10: Relative risk of miscarriage by antidepressant class compared to unexposed, depressed women, uncorrected and corrected for induced abortions

	Uncorrected			Corrected			
Exposure	**Total**	**Miscarriage**	**Adjusted OR (95%CL)**	**Total**	**Induced abortions**	**Miscarriage**	**Adjusted OR (95%CL)**
Unexposed, depressed women	3029	372 (12.3)	1	4068	2077	372 (9.1)	1
SSRI monotherapy	575	80 (13.9)	1.14 (0.89, 1.47)	824	499	80 (9.7)	1.08 (0.84, 1.39)
SNRI monotherapy	84	19 (22.6)	1.89 (1.26, 2.84)	125	82	19 (15.2)	1.73 (1.13, 2.63)
TCA monotherapy	70	16 (22.9)	1.54 (0.97, 2.45)	96	53	16 (16.6)	1.57 (0.98, 2.50)
Other monotherapy	50	6 (12)	0.97 (0.46, 2.03)	74	49	6 (8.0)	0.88 (0.41, 1.88)
Polytherapy	110	24 (21.8)	1.67 (1.15, 2.44)	173	127	24 (13.8)	1.47 (1.00, 2.17)

* Adjusted for age, being a welfare recipient, use of other teratogenic medication in 1st trimester, number of prescription medication in 3 months before pregnancy, number of mental health visits in 3 months before pregnancy, number of physician visits in 3 months before pregnancy, any hospitalizations in 3 months before pregnancy, and year of delivery

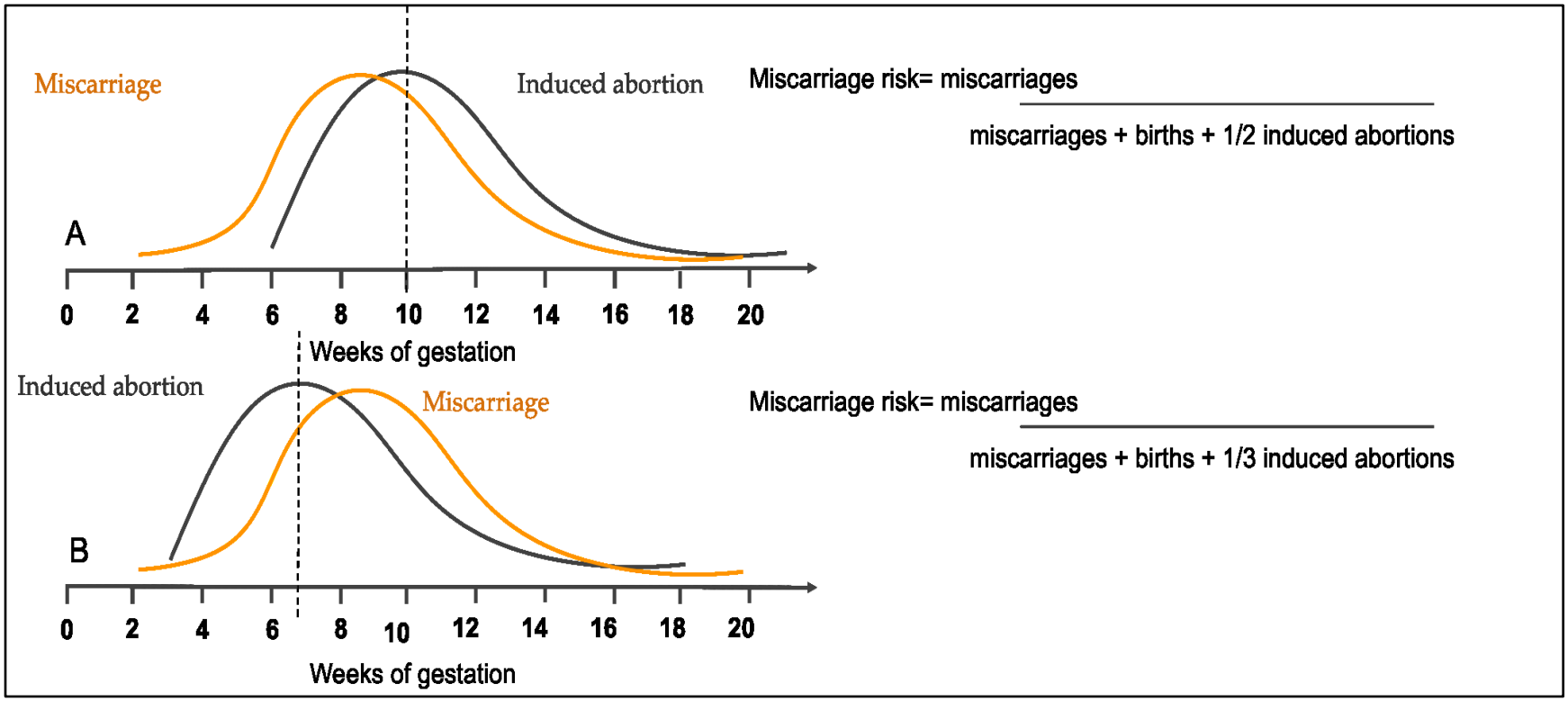

Figure 6.1: Visual representation of the impact of the correction factor for induced abortions

The orange and black curves represent the hypothetical gestational age distributions of miscarriages and induced abortions, respectively. Pregnancies are at risk of miscarriage in the first 20 weeks of gestation. The dashed line indicates the average gestational age of induced abortions. Panel A: The gestational age distributions of miscarriages and induced abortions overlap, and induced abortions occur on average at 10 weeks gestation. Thus, an induced abortion is a pregnancy that is at risk of miscarriage for half the time a birth is at risk of miscarriage, and half the induced abortions are included in the denominator. Panel B: Induced abortions occur earlier than miscarriages, on average. The average gestational age of induced abortions is 7 weeks, and hence a third of induced abortions are included in the denominator.

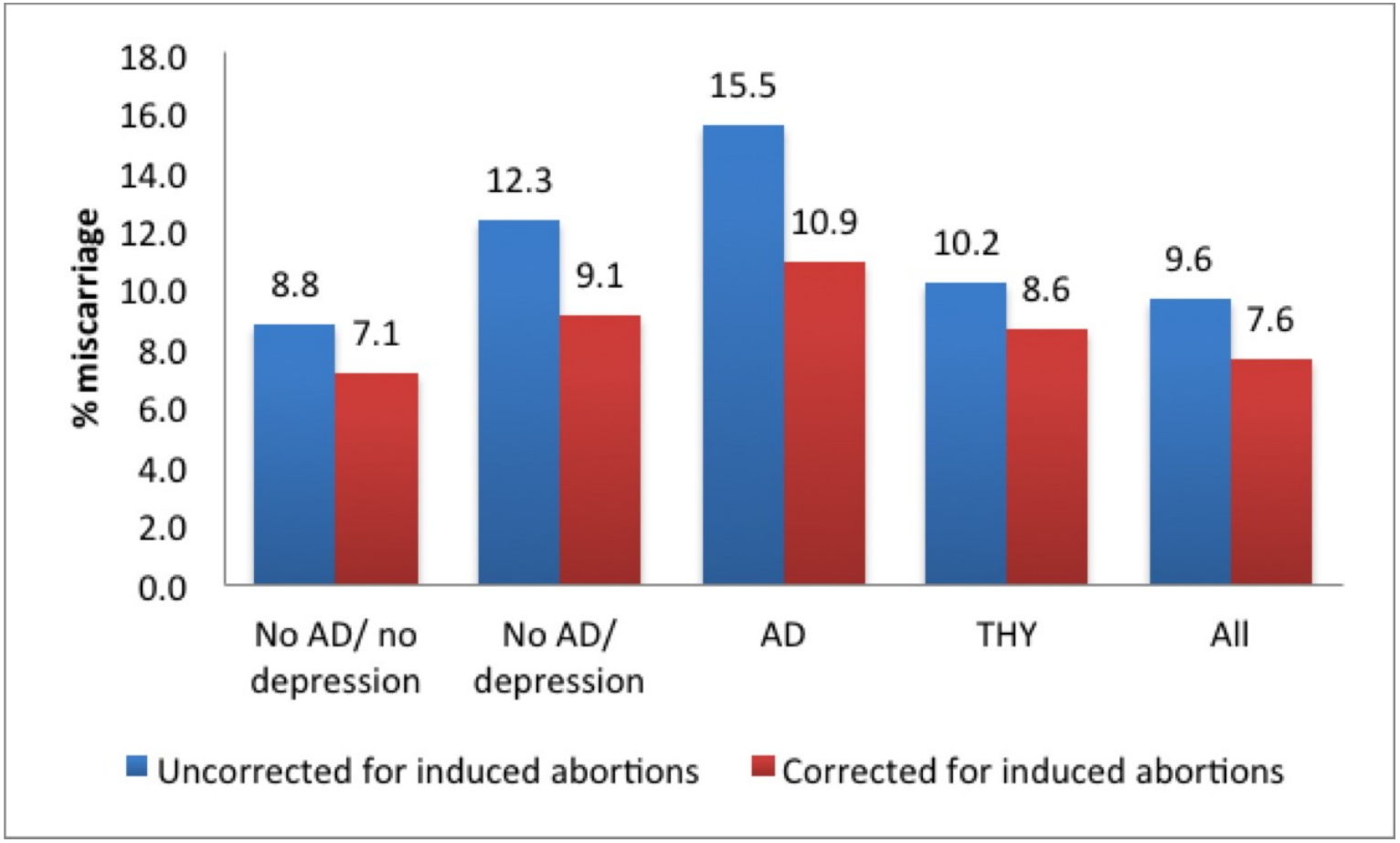

Figure 6.2: Corrected and uncorrected risk of miscarriage by exposure
AD: Antidepressant use; THY: Hypothyroid medication use

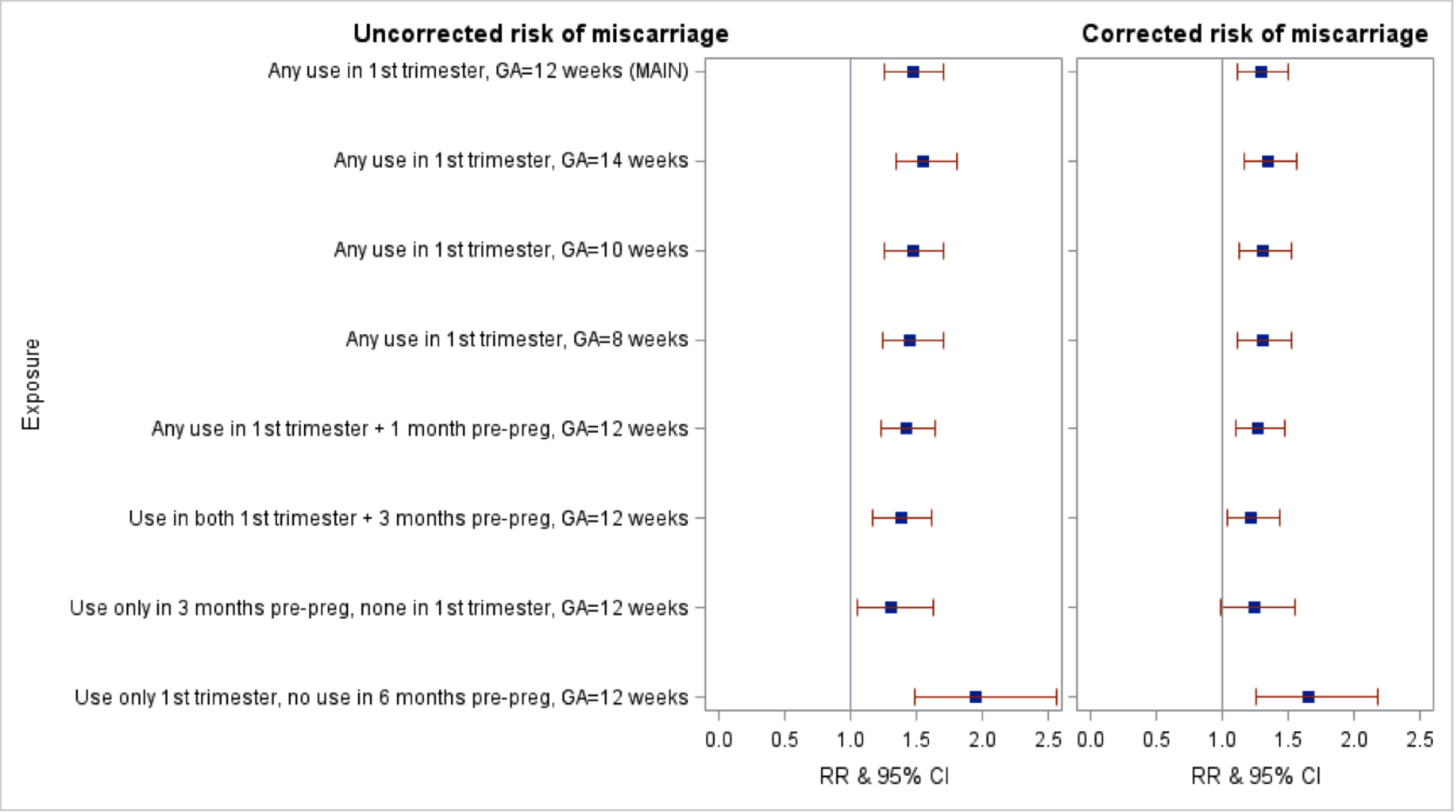

Figure 6.3: Sensitivity analyses for RR of miscarriage among antidepressant users compared to unexposed, non-depressed women

CHAPTER 7: SUMMARY & CONCLUSIONS

This research project focused on an understudied segment of the population: pregnant women, and in particular, pregnant women requiring the use of medications before pregnancy. The findings from this research elucidate the patterns and predictors of prenatal antidepressant utilization in a population of women using these medications before pregnancy, and help in furthering our understanding of the role of depression and antidepressants on adverse pregnancy outcomes.

7.1. Summary of research findings

Our first set of analyses explored the predictors of antidepressant use in pregnancy, including whether pregnancy itself was a predictor of antidepressant discontinuation. Using a population-based cohort of pregnant women who were matched to non-pregnant women on pre-pregnancy antidepressant use, we determined that pregnant women were more likely to discontinue use in pregnancy, after adjusting for several factors associated with medication use including age, income and health services utilization. These findings confirm that pregnancy renders women more wary of the medications they use and they are more inclined to discontinue them. One of the strongest factors associated with antidepressant continuation in pregnancy was the duration of pre-pregnancy antidepressant use, a proxy for disease severity: the longer women used antidepressants before pregnancy, the less likely they were to discontinue use. Other predictors of antidepressant continuation included being older, receiving social assistance (welfare), and the type of pre-pregnancy antidepressant use.

Our results showed that women receiving monotherapy for TCAs or other antidepressants (MAOIs, atypical antidepressants, and serotonin modulators) were more likely to discontinue all antidepressant use in pregnancy compared to those on SSRI monotherapy, even after adjusting for duration of pre-pregnancy use. These findings likely reflect the medical guidelines at the time (1998-2002) that recommended the use of SSRIs as the first-line treatment for major depressive disorder in pregnancy.[52] Indeed, we found that pregnant women were more likely to

use SSRIs than non-pregnant women (47% vs. 24%).Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) belong to the first generation of antidepressants,[31] but are no longer considered the first choice of treatment for depression due to their high side-effect profiles.[69]

For our next set of analyses, we capitalized on our creation of continuer/discontinuer cohorts to address some of the methodological limitations in the existing literature when evaluating the effect of antidepressant use and adverse pregnancy outcomes. Because some studies have suggested that depression itself may be associated with unfavourable pregnancy outcomes,[18,19,122-124] there is a need to untangle the effects of antidepressant use from those of depression.

One such method is the use of a propensity score analysis.[168] Our earlier analyses suggested that women with more severe disease were less likely to discontinue antidepressant use in pregnancy, and disease severity may be associated with a higher risk of adverse outcomes, increasing the possibility of confounding by indication. A propensity score analysis balances continuers and stoppers on their propensity for discontinuation using measured predictors of discontinuation, thus creating a pseudo-randomized population.[179] Using this method, we found that women who discontinued all use in pregnancy had a significantly reduced risk of hospitalizations for mental health problems during pregnancy compared to women with continuous antidepressant use in the first four months of pregnancy.

In a further effort to disentangle the effects of antidepressants and depression, we included a comparison group of depressed women not using antidepressants to explore the effect of untreated depression on adverse pregnancy outcomes. In our study assessing the risk of maternal antidepressant use on preeclampsia, we found that depressed women without antidepressant use before or during pregnancy, as well as pre-pregnancy antidepressant users who discontinued use were not at an increased risk of preeclampsia compared to non-depressed, unexposed women. However, women who continued antidepressant use in the first half of pregnancy did have an increased risk, even when compared to discontinuers, as demonstrated in our propensity score analysis. We also found an incremental risk of

preeclampsia associated with antidepressant exposure: continuers had a greater risk than discontinuers who in turn had a higher risk than untreated depressed women, when compared to unexposed non-depressed women. These results suggest antidepressant use itself may play a role in the increased risk for preeclampsia; however depressed women who choose to forego treatment may have less severe depression, and hence confounding by indication may still exist in these analyses, although we attempted to adjust for factors related to disease severity in our propensity score analysis.

Our final analyses, which explored the risk of miscarriage among antidepressant users, attempted to correct for the high risk of induced abortions in this population, an issue that has been overlooked in the existing literature. We found that despite accounting for the high number of induced abortions, early pregnancy antidepressant use remained a significant risk factor for miscarriage. In this analysis, we also included women treated for hypothyroidism as a control for factors related to having a chronic disease. In our study, women using hypothyroid medication were similar to antidepressant users in age and number of medications used in pre-pregnancy. It is of note that untreated hypothyroidism is associated with an elevated miscarriage risk;[206] we found that women treated for hypothyroidism in pregnancy with a non-teratogenic medication had a risk no different from unexposed healthy women. While the etiologies of hypothyroidism and depression, and their associations with miscarriage may be very different, this result may provide some evidence of the teratogenic potential of antidepressant use on miscarriage risk.

As with most observational studies using administrative databases, our studies were not without limitations. The advantage of administrative databases is the availability of comprehensive data over long periods of time, and that prescription medication use is recorded prospectively and precisely.[157] However, lack of information on lifestyle variables may hamper validity, especially if these are strong confounders of the relationship under study. It is reassuring that other studies showed no attenuation in their risk estimates after adjustment for these variables; the strongest confounders of the antidepressant-adverse birth outcome were factors related to depression severity.[30] The population covered by the RAMQ drug insurance

plan over-represents women of low socio-economic status which may affect the generalizability of our findings to women with private drug insurance. However, women covered by the public and private plans were similar in terms of smoking and alcohol intake, BMI, comorbidity profiles, and pregnancy medication use.[160] Furthermore, the baseline rates of adverse outcomes in our study were similar to that in the Quebec population.[166,197] Finally, this thesis uses older data (1998 to 2002), which may affect generalizability to current practice and use of antidepressants; nonetheless, the distribution of the different classes of antidepressants currently recommended for use in pregnancy is very similar to, if not higher than, that of antidepressants used to treat depression from 1998 to 2002.[3,40]

7.2. Implications and future directions

Antidepressant use in pregnant women is common; however, evidence on the safety of these medications in pregnancy remains inconsistent. For example, the most recent American and Canadian guidelines specify that paroxetine, one of the most commonly prescribed SSRIs, is contraindicated in pregnancy because of its association with cardiac defects.[51,52] Yet, only this year, a large population-based study of over 900,000 women reported in the New England Journal of Medicine that SSRIs including paroxetine were not associated with an increased risk of birth defects.[53] The authors of this latter study restricted their analyses to depressed women, and performed propensity score analysis to account for measured depression-related confounders. Their contradictory findings relative to earlier studies[191] underscore the necessity of refining our methodological tools when studying the association between maternal medication use and adverse birth outcomes. Although confounding by indication may be impossible to completely eliminate, such methods in observational studies may be the best approach. A promising approach may be to combine data from large administrative databases with detailed interview questionnaires on a subset of the population to derive information on important confounders such as maternal smoking, alcohol use, BMI, and pregnancy history.

A further consequence of the conflicting safety findings in the literature is that it remains unclear whether women should discontinue use in pregnancy. Our results showed that pregnant women were far more likely to discontinue use than non-pregnant women, with 53%

stopping all antidepressant use in pregnancy. Some studies have suggested that untreated depression is associated with adverse outcomes,[18,19,122-124] and thus discontinuation of treatment in pregnancy may be unsafe.[16] We did not find an association between untreated depression and preeclampsia, and only a modest association with miscarriage risk. Furthermore, women who discontinued antidepressants actually had a lower risk of hospitalizations for mental health problems compared to continuers. On the other hand, continuers had a consistently increased risk of miscarriage and preeclampsia when compared to either depressed or non-depressed pregnant women. With conflicting results being continually published in the literature, a strong case can be made for including pregnant women in randomized controlled trials. The contradictory findings contribute to the dilemma faced by pregnant women with respect to the decision to use antidepressants in pregnancy. The very fact that these medications are regularly prescribed and used by women in pregnancy, combined with the equipoise regarding their safety in pregnancy supports the inclusion of pregnant women in randomized trials of antidepressant discontinuation.

Our findings, which resulted from the use of methods such as propensity scores, the inclusion of a depressed, untreated group, and continuation/discontinuation analyses, suggest that the use of antidepressants, particularly in early pregnancy, may itself be implicated in an increased risk for miscarriage and preeclampsia. Although current guidelines recommend the use of SSRIs for depression treatment in pregnancy,[52,207] several recent studies have reported an association between late term SSRI use and persistent pulmonary hypertension in the newborn.[14,63,64] Taken together, these findings support a more nuanced approach to the management of pregnant women with depression. If pharmacotherapy is necessary in pregnancy, antidepressants associated with teratogenic effects should be avoided in early pregnancy, while late term use of SSRIs can be substituted for other antidepressants, perhaps TCAs. Particular attention needs to be paid to women who use non-SSRIs in pregnancy; these women may have depression that is non-responsive to traditional SSRIs, and may need to be counseled about avoiding the use of non-SSRIs in early pregnancy. Guidelines have also emphasized the use of non-pharmacological treatments such as cognitive behavioural therapy and interpersonal

psychotherapy,[52] and future studies need to explore the risks and benefits of non-pharmacological and pharmacological treatments vs. untreated depression in pregnancy.

Finally, our research has implications for perinatal studies involving populations at a high risk for induced abortions. Most studies exclude induced abortions from their analyses,[18,75,76] which may lead to an overestimation of the risk. In our study, accounting for induced abortions attenuated, but did not completely eliminate, the increased risk of miscarriage among antidepressant users. With respect to another population at high risk of induced abortions, i.e. very young pregnant women, we found that correction for induced abortions completely eliminated the increased risk of miscarriage, compared to women aged 20 to 35 years. These results demonstrate that the use of a correction factor for induced abortions may prove useful in certain high-risk groups. If the gestational age for births, spontaneous and induced abortions are available, an improvement to our study would be the use of a Cox proportional hazards model with competing risks to account for induced abortions, while assessing the time to miscarriage associated with antidepressant exposure modelled as a time-dependent variable.

7.3. Conclusion

The findings of this thesis indicate that women discontinue antidepressant use in pregnancy, and factors associated with depression severity such as duration and type of pre-pregnancy antidepressant, and maternal age, affect discontinuation rates. Our research advocates for the increased use of improved methodological tools, such as accounting for depression and induced abortions, when studying the association between antidepressants and adverse pregnancy outcomes. The consistent increased risk of unfavourable outcomes associated with antidepressant use in early pregnancy, after accounting for depression and competing risks, suggests that antidepressant use may itself play a role in mediating these outcomes. Depressed women requiring treatment in pregnancy need to be carefully counseled by their physicians in order to make the best decisions that benefit both mother and child.

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