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Impact Of Prenatal Exposure To Antidepressants On Adverse Birth Outcomes

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IMPACT OF PRENATAL EXPOSURE TO ANTIDEPRESSANTS ON ADVERSE BIRTH OUTCOMES

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DEDICATION

To my mother Abha Pahuja, for never letting me compromise, for teaching me how to love life, but most importantly for her resolute refusal to read anything recommended by me including this dissertation. (If no one tells her about this, she will never know)

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ABSTRACT

BACKGROUND: There has been an increase in the diagnosis of depression and the use of antidepressants, especially in women of childbearing age, in the past decade. This has drawn attention to the potential impact of depression and antidepressants on pregnancy and fetal development.

OBJECTIVE: (i) To determine the impact of prenatal exposure to antidepressant on the risk of adverse birth outcomes. (ii) To assess the effect of type of antidepressants on the risk of adverse birth outcomes using selective serotonin reuptake inhibitors as the referent group. (iii) To assess the effect of duration and time of prenatal exposure to antidepressants on the risk of adverse birth outcomes.

METHODS: The study was conducted using a population-based cohort including all singletons deliveries in years 2008 to 2014 in SC Medicaid population. Information on antidepressant medication and diagnosis of depression and birth outcomes were obtained from South Carolina Medicaid database and birth certificates. The exposed group comprised children of mothers who had a diagnosis of depression and used antidepressants at any time during their pregnancy. The reference group comprised children of mothers who had a diagnosis of depression but did not use any antidepressants during pregnancy. We estimated the association using Logistic Regression and Marginal Structural Models.

RESULTS: Approximately 107, 683 women had a diagnosis of depression in the SC Medicaid population. After applying the study inclusion and exclusion criteria, we got the study sample of 4,450 women. And approximately 36% women received antidepressants during pregnancy. (i) In our study we found that using logistic regression the odds of having preterm delivery were 1.58 (95%CI: 1.19 – 2.10) in those who received an antidepressant during pregnancy as compared to those who did not receive any antidepressants at any time during the pregnancy. Using marginal structural models, the odds of preterm delivery were 1.72 times (95% CI: 1.63 – 1.79) in the group that received antidepressants during pregnancy as compared to those who did not. Using logistic regression it was estimated that antidepressant use during pregnancy was associated with higher odds of the infant having low birth weight/being small for gestational age, OR = 1.57 (95% CI: 1.42 – 2.76) and/or NICU admissions, OR: 1.45 (95%CI 1.28 – 2.26). Marginal structural models showed that the prenatal exposure to antidepressants increased the odd of having low birth weight/small for gestational age 1.63 times (95%CI: 1.53 – 1.73) and the odds of having a NICU admission by 1.66 times (95% CI: 1.58 – 1.73). (ii) Upon comparing the different classes of antidepressants to SSRIs we found that the risk of adverse birth outcomes was not significantly different between the different types of antidepressants. Only TCAs had a statistically lower risk of NICU admissions as compared to SSRIs. Using marginal structural models we found that the risk of NICU admissions was 0.85 times (95% CI: 0.65 – 0.97) lower in TCAs as compared to SSRIs. (iii) Exposure to antidepressants in all three trimesters was associated with the risk of adverse birth outcomes. Although the duration of exposure that is the number of days for which the antidepressant was prescribed in each trimester was

not associated with the risk of adverse birth outcomes. Conducting additional analysis we found that the risk of low birth weight/small for gestational age and NICU admissions was higher with exposure in the third and second trimester as compared to the first trimester.

CONCLUSION: In conclusion we found that prenatal exposure to antidepressants is significantly associated with a higher risk of adverse birth outcomes such as preterm delivery, low birth weight/small for gestational age, and NICU admissions, irrespective of the type of antidepressant prescribed and duration and trimester of exposure.

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LIST OF ABBREVIATIONS

Atypicals ..... Atypical Antidepressants

CI..... Confidence Intervals

MSM ..... Marginal Structural Models

NICU.....Neonatal Intensive Care Unit

OR..... Odds Ratio

SNRIs..... Selective Norepinephrine Reuptake Inhibitors

SSRIs.....Selective Serotonin Reuptake Inhibitors

TCAs.....Tricyclic Antidepressants

CHAPTER 1

INTRODUCTION

1.1 DEPRESSION

Depression is a mood disorder that causes a persistent feeling of sadness and loss of interest[1]. Symptoms of depression can be categorized in three groups—mood, cognitive, and physical symptoms. Mood symptoms include depressed, sad, or irritable mood; loss of interest in usual activities; inability to experience pleasure; feelings of guilt or worthlessness; and thoughts of death or suicide[1]. Cognitive symptoms include inability to concentrate and difficulty in making decisions[1]. Physical symptoms include fatigue, lack of energy, feeling either restless or slow, and changes in sleep, appetite, and activity levels[1]. World Health Organization (WHO) recognizes depression as a worldwide epidemic, with 5 percent of the global population suffering from the condition[2]. According to Centers for Disease Control and Prevention (CDC) depression is one of the leading causes of disability in the United States[3]. Depression statistics published by the CDC show that about 9 percent of adult Americans have feelings of hopelessness, despondency, and/or guilt that generate a diagnosis of depression[3]. At any given time, about 3 percent of adults have major depression, also known as major depressive disorder, a long-lasting and severe form of depression[3]. The average age for a person to be diagnosed with depression is 32[3]. The prevalence of depression is comparatively lower

(6.8%) among those age 65 and older[3]. Prevalence of depression is also affected by race, according to the CDC, African-Americans have the highest rate of current depression (12.8 percent), followed by Hispanics (11.4 percent), and whites (7.9 percent) [3]. A report published by National Institute of Mental Health (NIMH) states that women are 70 percent more likely than men to experience depression during the course of their lifetimes[4]. One in four women suffer symptoms of depression at some point during their life[5]. Women of childbearing age are at a higher risk for depression[2-4]. According to the American Congress of Obstetricians and Gynecologists (ACOG) between 14 – 23% of women struggle with symptoms of depression during pregnancy[6].

The personal and societal costs of depression are significant. They include higher rates of death, serious complications for chronic disease patients, significantly higher health care costs for employers, added family caregiver burden and associated substance abuse problems. Studies show that depression is associated with higher mortality rates in all age groups. In the United States, the total economic burden of depression was estimated to be US$ 83.1 billion in 2000, of which US$ 26.1 billion (31%) were direct medical costs, US$ 5.4 billion (7%) were suicide-related mortality costs and US$ 51.5 billion (62%) were workplace costs[6]. Since then the societal cost of depression has increased to $118 billion in 2013[3-4]. According to WHO, major depression carries the heaviest burden of disability among mental and behavioral disorders. It accounts for 3.7 percent of all U.S. disability-adjusted life years (DALYs); and, 8.3 percent of all U.S. years lived with disability (YLDs) [2, 4].

1.2 ANTIDEPRESSANTS

The most common treatments for depression are medication and psychotherapy. Based on their mechanism of action antidepressants are classified into the following therapeutic categories –

- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin-norepinephrine reuptake inhibitors (SNRIs)
- Tricyclic antidepressants (TCAs)
- Monoamine oxidase inhibitors (MAOIs)
- Atypical agents

Antidepressants were one of the 10 most popular type of drug dispensed in US in 2013, with $13.7 billion in sales. According to the National Centre for Health Statistics (NCHS) antidepressants were the third most common prescription drugs taken by Americans of all ages in 2005–2008 and the most frequently used by persons aged 18–44 years[7]. More than 60% of Americans taking antidepressant medication have taken it for 2 years or longer, with 14% having taken the medication for 10 years or more[7]. The CDC and NCHS also report that females are two and half times as likely to take antidepressant medication as males[2, 7].

1.3 DEPRESSION AND ANTIDEPRESSANTS IN PREGNANT WOMEN

In 2005 the prevalence of major depression in pregnant women ranged from 3.1% – 4.9%, and that of major or minor depressive episodes ranged from 8.5% – 11% (minor

depression here refers to sub-threshold depression or depressive disorder not otherwise specified) [8]. Since 2005 the prevalence of depression has increased[9]. According to the American Congress of Obstetrics and Gynecologists the prevalence of depressive disorders (major and minor depression) in pregnant women ranges from 14% to 23%[9-11].

The increase in prevalence of depression has translated to an increase in the use of antidepressants. Over the past decade the proportion of pregnancies with antidepressant use has increased from 5.7% of pregnancies to 13.4% of pregnancies and is projected to increase further [6, 12]. Prevalence of antidepressant prescription is lower during pregnancy as compared to pre-pregnancy and post-partum[13]. The use of antidepressants during pregnancy is mostly during the first trimester[13-14]. Studies show that there is a reduction in the use of antidepressants from the first trimester (3.7%) to the second (1.6%) to the third (1.1%) [12-14].

1.3.1 South Carolina Medicaid Population

According to CDC the current rate of depression in South Carolina is 9.6%[3]. According to a report published by the University of South Carolina in the year 2009 a total of 31,542 female Medicaid recipients had paid claims associated with a primary diagnosis of depression or 3.4 percent of the total Medicaid recipient population[15]. Total medical expenditures for this population were $390,062,477 accounting for 9.03 percent of the state Medicaid expenditures[15]. Another report by the South Carolina Department of Health and Environment Control (DHEC) in the years 2004-2009 approximately 40% of pregnant of women had a diagnosis of depression in South Carolina Medicaid population[16]. Nearly 42% are prescribed antidepressants during pregnancy[16].

1.4 IMPACT OF MATERNAL DEPRESSION AND PRENATAL EXPOSURE TO ANTIDEPRESSANTS ON BIRTH OUTCOMES

Depression during pregnancy has received little attention from healthcare professionals and researchers as compared to postpartum mental health of women[16], mainly due to the belief that pregnancy can have a protective effect against depression[17]. This has resulted in limited knowledge about depression during pregnancy and its impact on fetal growth and development[17]. However, there has been an increase in the diagnosis of depression and the use of antidepressants[18], especially in women of childbearing age[18-20], in the past decade. This has drawn attention to the potential impact of depression and antidepressants on pregnancy and fetal development.

Due to the unusual risk-benefit situation, healthcare providers avoid prescribing drugs during pregnancy[11]. However, studies show that maternal depression can have an impact on the pregnancy and fetus[21]. Untreated depression has been found to be associated with preterm delivery, low birth weight and small for gestational age[22-23]. Although no studies have explored the direct association between maternal depression and structural malformations, some researchers have found that maternal depression is associated with poor fetal and head growth[23], providing evidence that depression may be associated with malformations as well.

A number of studies have explored the association between prenatal exposure to antidepressants and poor birth outcomes. Many of the studies show that exposure to antidepressants during gestation is associated with preterm delivery, low birth weight, small for gestational age, and structural malformations[24-26]. Discontinuing the prescribed

antidepressants can lead to relapse. Approximately 68% of women who stopped taking antidepressants relapsed during pregnancy making the fetus susceptible to the harmful effects of depression[27].

Maternal depression and antidepressants both have been associated with adverse birth outcomes such as pre-term delivery, low birth weight/ small for gestational age and structural malformations[22-26], which makes it difficult to study the independent association between antidepressants and adverse birth outcomes.

1.5 BIOLOGICAL PLAUSIBILITY

1.5.1 Maternal Depression

Depression can have a direct effect on the development of fetus and maintenance of pregnancy[11]. It has been associated mainly with preterm delivery, low birth weight, and spontaneous abortion[11, 14, 28]. Very few studies have looked at the impact of maternal depression on structural malformations. Although the exact pathology of the phenomenon has not been identified there are two widely accepted theories. The first theory proposes that the neurobiological substrates of depression such as glucocorticoids have the ability to cross the placenta and can result in hormonal shifts and interactions, which in turn are detrimental to development of fetus and maintenance of pregnancy[29]. The second theory proposes that the fetus may be affected due to the altered fetal environment caused by maternal depression and stress[28, 29]. Levels of hormones such as gonadal, estrogens and progesterone increase during pregnancy. Production of other hormones such as placental corticotropin-releasing hormone (CRH), cortisol, human chorionic gonadotropin, prolactin, b-endorphin, and thyroid hormone-binding globulin also increases during pregnancy. The production of these hormones is controlled by complex interactions and

feedback systems that exist between the hypothalamicpituitary-ovarian (HPO) axis and the hypothalamicpituitary-adrenal (HPA) axis. The HPA axis plays a vital role, as it's functioning and release of hormones is influenced by pregnancy and by stress[29]. Studies show that women's cortisol levels are higher when they experience negative moods[30]; providing evidence to support a link between the HPA axis and psychological distress during pregnancy[29, 30]. Changes in the HPA axis and subsequent changes in cortisol levels resulting from stress and/or depression can alter the fetal environment.

Depression can also have an indirect impact on the fetus through poor health behaviors, such as poor eating and poor weight gain, and poor sleep and subsequent use of over the-counter medication, alcohol, tobacco, or caffeine[26].

1.5.2 Antidepressants

The potential impact of maternal depression on the development of fetus and maintenance of pregnancy has highlighted the risks of untreated depression; this in turn has contributed to an increased use of antidepressants during pregnancy. Unfortunately prenatal exposure to antidepressants can also result in adverse birth outcomes. Antidepressants can enter the fetal circulation by crossing the placenta[31]. The fetus may also be exposed to the drug through amniotic fluid, which means exposure to even greater amounts than usually considered [31]. Although the biological mechanism is still unclear this exposure has been associated with adverse birth outcomes such as small for gestational age/low birth weight [32,33], preterm delivery[34-36], and structural malformations[37-38].

1.6 ADVERSE BIRTH OUTCOMES

1.6.1 Preterm Delivery

World Health Organization defines preterm delivery as delivery before 37 weeks of gestation are completed[39]. Every year, an estimated 15 million babies are born preterm. In 2013 it preterm birth complications were the leading cause of death among children under 5 years of age, responsible for nearly 1 million deaths[39]. A report published by National Center for Health Statistics stated that the rate of preterm birth in the US is 12.7% [40]. Preterm-related is the leading cause of infant deaths accounting for almost 35%[41]. Preterm birth is also a leading cause of long-term neurological disabilities in children. Preterm birth costs the U.S. health care system more than $26 billion in 2005[41]. The preterm birth rate varies by race and ethnicity[42]. In 2012, 16.53 percent of babies born to non-Hispanic Black women were born preterm, compared to 10.29 percent of babies born to non-Hispanic White women, and 10.15 percent of babies born to Asian/Pacific Islander women. Among babies born to Hispanic women, 11.58 percent were born preterm, while the same was true for 13.25 percent of babies born to American Indian/Alaska Native women [42-43]. Rates of preterm birth vary in different regions of the United States and among states[44]. Preterm birth rates are highest in Mississippi, Alabama, Louisiana, Kentucky, South Carolina, and the District of Columbia and lowest in New Hampshire, Vermont, Oregon, Minnesota, Alaska, Connecticut, and Idaho[45]. According to the March of Dimes the rate of preterm delivery in South Carolina was 13.8%[43].

There are several factors associated with the risk of preterm delivery. Women who have delivered preterm before, or who have experienced preterm labor before, are considered to be at high risk for preterm labor and birth[46]. Multiple gestations or the use of assisted reproductive technology is associated with a higher risk of preterm labor and birth. One study showed that more than 50% of twin births occurred preterm, compared with only 10% of births of single infants[47]. Certain medical conditions such as urinary tract infection, diabetes, sexually transmitted diseases have also been associated with preterm delivery[48]. Preterm labor and birth occur more often among certain racial and ethnic groups. Infants of African American mothers are 50% more likely to be born preterm than are infants of white mothers[49]. Age is also associated with the risk of preterm delivery. Women younger than age 18 are more likely to have a preterm delivery[47]. Women older than age 35 are also at risk of having preterm infants because they are more likely to have other conditions (such as high blood pressure and diabetes) that can cause complications requiring preterm delivery[49]. Other risk factors associated with preterm delivery are certain lifestyle and environmental factors, which include late or no health care during pregnancy, smoking, drinking alcohol, using illegal drugs, domestic violence, including physical, sexual, or emotional abuse, lack of social support, stress, long working hours with long periods of standing and exposure to certain environmental pollutants [48].

Studies show that stress and depression are associated with a higher risk of preterm delivery [48-50]. Some studies also show that the prevalence of preterm delivery is higher in mothers who take antidepressants during pregnancy as compared to those who do not[24-26, 33-34]. Although other studies have concluded that there is no significant

association between exposure to antidepressants during gestation and the odds of having preterm delivery[35-38].

1.6.2 Low Birth Weight/ Small for Gestational Age

Low birth weight (LBW) infant is defined as the one whose weight is less than 2,500 g (5 pounds 8 ounces) regardless of gestational age [40]. Prevalence of low birth weight in the US is about 8% [40]. Small for gestational age (SGA) babies are those who are smaller in size than normal for the gestational age, most commonly defined as a weight below the 10th percentile for the gestational age [51-52]. According to the Centers for Disease Control and Prevention the prevalence of small for gestational age has been on the rise since 2005 and is currently about 11% [53]. The LBW/SGA rate in South Carolina has risen from 9.3% to 10.1%, from 1993 to 2013 [54-55]. The risk of LBW/SGA is significantly greater among African Americans, whose rate is 14.6%, compared with 7.6% of White or Hispanic babies[54-55]. The excess cost to the medical system of supporting a low or very LBW/SGA baby is high. An LBW/SGA baby incurs an average of $16,500 in hospital costs and a very low birth weight baby an average of $95,000 [54]. The total medical cost of LBW/SGA babies in South Carolina is over $160 million per year [55].

There are several risk factors associated with LBW/SGA. Preterm labor is often a cause of LBW/SGA. Certain health conditions such high blood pressure, diabetes and infections may lead to LBW/SGA[46]. Women who don't gain enough weight during pregnancy are more likely to have a LBW/SGA baby than women who gain the right amount of weight. Smoking, drinking alcohol, and illicit drug use has also been

associated with LBW/SGA. Pregnant women who smoke are nearly twice as likely to have a LBW/SGA baby as women who don't smoke[49]. Women younger than 17 years or older than 35 years are more likely to give birth to a LBW/SGA baby[49]. And race/ethnicity is a risk factor as well. In the United States, African-American women are more likely than others to have a LBW/SGA baby. Approximately 13% African-American babies are born with LBW/SGA each year. 8.4 percent of Asian babies, 7.6 percent of Native American babies, and about 7 percent of Hispanic and Non-Hispanic White babies are born with LBW/SGA[53-55].

Studies suggest that depression is an important risk factor for LBW/SGA[56]. Women with depression during pregnancy are at increased risk for LBW/SGA[57]. These studies stress the need for treating antenatal depression to reduce the risk of LBW/SGA. However, literature is conflicted regarding the association between gestational exposure to antidepressants and low birth weight/small for gestational age. Some studies show that prenatal exposure to antidepressants is associated with a higher risk of LBW/SGA[33-34] whereas other studies show that the association is minimal to none[35-38].

1.6.3 NICU Admissions

Preterm and/or low birth weight infants need special care, including additional attention to breastfeeding and breast-milk feeding and to keeping them warm at home and in health facilities. Those with preterm birth complications, including respiratory problems, need appropriate treatment in hospitals. A neonatal intensive-care unit (NICU), also known as an intensive care nursery (ICN), is an intensive-care unit specializing in the care of ill or premature newborn infants[58-59]. Newborns, including those who are full

term and of normal birth weight, are admitted to a NICU for many types of illness. Every newborn admitted to a NICU experiences the benefits of such highly specialized care and is exposed to the associated risks and high costs. Despite the published research into interventions or patterns of care for specific populations, there has been no published study examining NICU admission rates across the entire range of newborn morbidity because the necessary data have, until recently, been unavailable or difficult to access[58-59].

Neonatal intensive care (NICU) admissions increased from 2007 to 2012. In 2012, there were 43.0 NICU admissions per 1000 normal-birth-weight infants (2500-3999 g), while the admission rate for very low-birth-weight infants (<1500 g) was 844.1 per 1000 live births[60]. Overall, admission rates during the 6-year study period increased from 64.0 to 77.9 per 1000 live births (relative rate, 1.22; 95% CI, 1.21-1.22 [P < .001]). Admission rates increased for all birth weight categories. Trends in relative rates adjusted for maternal and newborn characteristics showed a similar 23% increase (95% CI, 1.22-1.23 [P < .001]). During the study period, newborns admitted to a NICU were larger and less premature, although no consistent trend was seen in weight for gestational age or the use of assisted ventilation[60-61].

Maternal depression and antidepressants have been associated with NICU admissions. Studies show that stress and depression are associated with a higher risk of NICU admissions [62-64]. Some studies also show that the prevalence of NICU admissions are higher in infants born to mothers who take antidepressants during pregnancy as compared to those who do not[64-70]. Although other studies have concluded that there is no

significant association between exposure to antidepressants during gestation and the odds of NICU admissions[71-74].

1.7 SUMMARY

A study conducted about perinatal depression in 2005 showed the prevalence of major depression in pregnant women is in the range of 3.1%–4.9%, and that of major or minor depressive episodes is in the range of 8.5%–11% (minor depression here refers to sub-threshold depression or depressive disorder not otherwise specified)[1-2]. Since 2005 the prevalence of depression has increased. According to a recent report published by American Congress of Obstetrics and Gynecologists (2014) the prevalence of depressive disorders (major and minor depression) in pregnant women ranges from 14% to 23%3-4. The prevalence for major depression has reached up to 7.5%[2-4]. This increase in prevalence of depression has directly translated to an increase in the use of antidepressants. Over the past decade the proportion of pregnancies with antidepressant use has increased from 5.7% to 13.4% and is projected to increase further [5-6]. Both untreated depression and antidepressants have been associated with poor birth outcomes such as preterm delivery, low birth weight and small for gestational age[22-26]. There are a variety of other risk factors that have been associated with poor birth outcomes, these include maternal smoking, poor prenatal care, drinking alcohol, using illegal drugs, domestic violence etc[48-50,61]. Maternal depression, in addition to all these risk factors makes assessing the impact of antidepressants alone on the fetus is a challenging [22-23].

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CHAPTER 2

LITERATURE REVIEW

Depression is a growing concern to healthcare professionals. It is a mental illness that can be debilitating to patients and costly and challenging to treat. According to Center of Disease Control and Prevention an estimated 1 in 10 US adults suffer from depression[1]. Women are 70% more likely to suffer depression than men[1]. Depression has become a common problem during and after pregnancy. Prevalence of depressive disorders in pregnant women ranges from 14% to 23%[2-3].

Depression if left untreated during pregnancy can negatively impact the mother and fetus/child. The suffering mothers are most likely to experience inadequate weight gain during pregnancy[4], abuse substances[5] and be at an increased risk of preeclampsia[6-8]. Untreated depression can also be associated with preterm delivery, increased risk for low birth weight infants[9-10], fetal distress, increased risk of neonatal intensive care unit admissions and need for caesarian delivery[10-12]. Hence it is important to treat maternal depression during pregnancy, although only 13% of the women diagnosed with depression get treatment during pregnancy[13]. This might be related to the adverse outcomes associated with the use of antidepressants during pregnancy. Studies show that prenatal exposure to antidepressants is associated with preterm births, low birth weight/small for gestational age, structural malformations and increased risk of

admissions to the neonatal intensive care unit[14-20], autism spectrum disorders and other neurodevelopmental disorders[22-23].

Over the past decade several studies have assessed the association between prenatal exposure to antidepressants and adverse birth outcomes, although the results have been inconsistent.

2.1 PRETERM BIRTH

A number of studies have examined the incidence of preterm birth in women prescribed antidepressants during pregnancy. Most of these studies are observational studies. In most of the studies researchers have looked at the prevalence of preterm birth but in contrast, some studies looked at mean gestational age.

Simon et al (2002)[26], Djulus et al (2006)[27], Oberlander et al (2006)[28], Kallen et al (2004)[29], Suri et al (2007)[30], and Wisner et al (2009)[31] have conducted studies that show that the odds of having preterm delivery are higher when there is exposure to antidepressants during gestation. On the other hand Sivojelezova et al (2004)[32], Malm et al (2005)[33], Andersson et al (2004)[34] and Yonkers et al (2009)[35] have concluded that there is no significant association between exposure to antidepressants during gestation and the odds of having preterm delivery. Studies that have found an association between in utero antidepressant exposure and gestational age typically show a small difference in mean gestation duration of about a week or less [32-33,36]. The study conducted by Einarson et al (2003)[24] showed that the association is dependent on the duration of exposure; that longer exposures are more likely to decrease gestational age[36]. All of these are prospective cohort studies, involving different classes of antidepressants (SSRIs, Mirtazapine, TCA and SNRI). Maschi et al (2008) revealed a correlation between preterm birth and chronic

exposure to antidepressants but not with short term exposure[57]. All of these studies have similar weaknesses, with no measures of actual drug exposure or controls for confounders such as smoking and in particular the effects of underlying depression.

Some studies have tried to control for untreated maternal depression. Oberlander et al (2006)[36] examined 119 547 prescription records matched with hospital separation records and found that SSRI-exposed babies had a higher rate of preterm birth than babies exposed to depression alone ($p < 0.01$). A further study, by the same group, of 3500 cases found that increased length of drug exposure was related to higher risk of low gestational age and low birth weight (Oberlander et al 2008)[28]. These studies are weakened by the fact that hospital records may be unreliable and that the authors did not correct for multiple comparisons. A small prospective study compared women with depression alone and treatment with SSRIs and found a statistically significant higher preterm birth rate in the exposed infants (14% exposed group, 0% depressed group)[28]. In contrast, another small study did not detect any difference between treated and depressed groups [32]. Wisner et al (2009) designed study a looked that looked at five overlapping groups using a prospective design[31]. Patients were classified into those with no SSRI or depression exposure, those with continuous or partial SSRI exposure and those with continuous or partial depression exposure. Unlike most other studies, exposure was confirmed with serum SSRI levels. The group with continuous SSRI exposure had a significantly higher preterm delivery rate with a RR of 5.43 (95%CI 1.98-14.84). The group with continuous depression also had a higher rate but this was no longer statistically significant when controlled for maternal age and race, RR 3.7 (95%CI 0.98-14.13). The partial SSRI and partial depression groups were no different from controls.

Another study conducted by Simon et al (2002)[26] evaluated the effects of prenatal antidepressant exposure on adverse perinatal outcomes using a matched case control study. The authors found that exposure to SSRIs were associated with a 0.9-week decrease in mean gestational age and a 175-g decrease in mean birth weight. The odds of having an adverse birth outcome was 4.3 (95%CI 1.5-12.2) times higher in the SSRI exposed group as compared to the non-exposed group. They also looked at TCA exposure and found that it was not significantly associated with adverse birth outcomes. In this study the authors used a within a group-model health maintenance organization, all infants with apparent prenatal exposure to TCA or SSRI antidepressants were frequency matched to an unexposed comparison group by year of birth, maternal age, and mother's lifetime use of antidepressant drugs and mental health care. A structured blind review of mothers' and infants' medical records examined perinatal outcomes. The authors also concluded that the effects on gestational age and birth weight were not limited to the infants exposed late in pregnancy. A similar finding was reported by Pastuszak et al. (1999) and Ericson et al. (18), while Chambers et al. (1996) found that only third-trimester fluoxetine exposure was associated with a greater risk of premature delivery. On the other hand Suri et al (2004)[30] conducted a cohort study by following 90 women in a prospective, naturalistic design through pregnancy with monthly assessments of symptoms of depression and anxiety using the Structured Clinical Interview for DSM-IV mood module for depression, the Hamilton Depression Rating Scale, the Beck Depression Inventory, and the Perceived Stress Scale. Participants included 49 women with major depressive disorder who were treated with antidepressants during pregnancy (group 1), 22 women with major depressive disorder who were either not treated with

antidepressants or had limited exposure to them during pregnancy (group 2), and 19 healthy comparison subjects (group 3). The primary outcome variables were the infants' gestational age at birth, birth weight, 1- and 5-minute Apgar scores, and admission to the special care nursery. Groups 1, 2, and 3 differed significantly in gestational age at birth (38.5 weeks, 39.4 weeks, 39.7 weeks, respectively), rates of preterm birth (14.3%, 0%, 5.3%, respectively), and rates of admission to the special care nursery (21%, 9%, 0%, respectively). Birth weight and Apgar scores did not differ significantly between groups. Mild to moderate depression during pregnancy did not affect outcome measures. They concluded that prenatal antidepressant use was associated with lower gestational age at birth and an increased risk of preterm birth but not with low birth weight or being small for gestational age. This study is limited by its small sample size. The authors looked at the impact of only one antidepressant that is Fluoxetine and did not account for the dose of the drug.

A retrospective cohort study conducted by Pearson et al (2007)[32] had a similar conclusion that no evidence of major increases in risk of preterm birth or other adverse neonatal outcomes following prenatal exposure to antidepressants, nor between SRIs and TCAs. They compared the medical records of 84 pregnant women with major depressive or anxiety disorders (DSM-IV criteria) who took antidepressants during pregnancy (cases) versus a 2:1 age- and parity-matched control group of 168 unexposed women. Women in the case group had sought psychiatric consultation regarding the use of medication from the Perinatal and Reproductive Psychiatry Program at the Massachusetts General Hospital between 1996 and 2000. There were no significant differences among cases versus controls and their offspring, with respect to various neonatal and obstetrical

outcomes, including gestational age and weight, although 1-minute Apgar scores were slightly lower in exposed infants. Admissions to the special care nursery were more frequent, but briefer and based on relatively minor indications, among case newborns. There were no significant differences in neonatal outcomes between exposures to serotonin reuptake inhibitor (SRI) and tricyclic (TCA) antidepressants. Although the authors of this study controlled for maternal depression they failed to mention the trimester of exposure and doses. Also, the sample size of this study is not large enough to give statistically significant results.

2.1.1 Summary

Preterm birth is a major clinical problem throughout the world. Numerous studies, of varying size and quality, have examined the effects of antidepressant medication use on pregnancy outcomes, including preterm birth. They differ in terms of the timing of the antidepressant exposure during pregnancy and adjustment for potential confounding variables, including lifestyle factors, co-morbidities, and the severity of the underlying depression. Although substantial, the literature is limited by inconsistent results and the lack of an appropriate control group. The majority of studies have used depressed women who are not on antidepressants or women with no depression and no antidepressant prescription as the control group. In both the cases the controls do not help clarify the impact of antidepressants. Also most of the studies have examined prenatal exposure to SSRIs, there is limited information about the other classes of antidepressants[24]. Another concern with the current literature is inadequate controlling of confounding. A number of studies have failed to control for confounders such as maternal smoking[24-25], parity[8,11,24,

duration and time of exposure[13,18,25] to antidepressants and most importantly maternal depression2[4-25].

2.2 LOW BIRTH WEIGHT and SMALL FOR GESTATIONAL AGE

As with pre-term delivery the literature regarding the association between prenatal exposure to antidepressants and risk of low birth weight/small for gestational age (LBW/SGA) has conflicting results (Table 2). Studies conducted by Oberlander et al (2006)[20], Simon et al (2002)[19], and Wen et al (2006)[38] found an association between gestational exposure to antidepressants and low birth weight/small for gestational age. They found that prenatal exposure to antidepressants increased the odds of the infant being low birth weight/ small for gestational age. Although the difference in the odds ratio in the exposed and unexposed group was minimal, this could be a result of the small sample size of these studies. Similar studies conducted by Djulus et al (2006)[19], Sivojelezova et al (2004)[29], Chun-Fai-Chan et al (2005)[39] concluded that there is no association between gestational exposure to antidepressants and low birth weight/small for gestational age.

A prospective cohort study conducted by Casper et al (2003) compared children whose mothers were diagnosed with major depressive disorder in pregnancy and elected not to take medication (n = 13) to children of depressed mothers treated with SSRIs (n = 31) in terms of birth outcomes. The prevalence of preterm birth in the exposed group was found to be 3% as compared to 8% in the non-exposed group (p = 0.53). The mean birth weight of the infants in the exposed group was only 50g lesser as compared to the non-exposed group (p =0.84). Although the authors mention that the healthy lifestyle of the women in the study (eg, use of prenatal vitamins, no smoking, little alcohol use, and

regular exercise) makes this sample different from that of other published pregnancy outcome studies and might have contributed to the finding that antidepressant drugs did not increase the risk of prematurity or low birth weight. Laine et al (2003) and Wisner et al (2009) for confounders such as depression, smoking, maternal age or maternal weight, and these showed no differences in birth weight in babies born to exposed or non-exposed mothers[34,44]. Although the relatively smaller sample size does not give the study sufficient statistical power to detect the differences exposed and unexposed groups in all of these studies.

A similar study conducted by Kallen et al (2004) used data of 997 infants (987 mothers) after maternal use of antidepressants based on prospectively recorded information in antenatal care documents. The study concluded that prenatal exposure to antidepressants increases the risk of LBW/SGA (OR 1.88 95%CI 1.28-2.26). Wen et al (2006) conducted a retrospective cohort study of 972 pregnant women who had been given at least 1 antidepressant prescription in the year before delivery and 3878 pregnant women who did not any antidepressant and who were matched by the year of the infant's birth, the type of institute at birth, and the mother's postal code from 1990 to 2000 in the Canadian province of Saskatchewan. The study showed that the risks of low birth weight (adjusted odds ratio, 1.58; 95% CI, 1.19, 2.11were increased in infants who were born to mothers who had received antidepressants during pregnancy. A prospective case control study conducted by Oberlander et al (2008)[28] showed similar results. The authors used a population-based maternal and neonatal health records that were linked to prenatal maternal prescription records for an antidepressant medication (*n*=3500). After controlling for maternal illness and duration of exposure, using propensity score

matching the study found that longer prenatal exposure increased the risks of lower birth weight ($P<0.05$).

On the other hand Casper et al (2003) conducted a prospective cohort study where children whose mothers were diagnosed with major depressive disorder in pregnancy and elected not to take medication (n = 13) were compared with children of depressed mothers treated with SSRIs (n = 31) on birth outcomes. After the analysis the authors concluded that prenatal exposure antidepressants had no significant impact on the birth weight of the newborn. Suri et al (2004)[30] followed sixty-four outpatient women with an Axis I diagnosis of major depressive disorder or no psychiatric history were followed in each trimester of pregnancy with administration of the CES-D. A subset of the women with depression received treatment with fluoxetine during pregnancy. Subjects with a CES-D score greater than 16 at any time point were further assessed for the presence of an active major or minor depressive episode. The study had analyzable data for 62 women. No significant differences were found in outcome variables between those women with exposure to medication and/or prenatal depressed mood and those women without a history of depression. Another study conducted by Djulus et al (2006)[27] used a prospective cohort study with 2 comparison groups: disease-matched pregnant women diagnosed with depression taking other antidepressants and pregnant women exposed to non-teratogens. The primary outcome was major malformations in neonates; secondary endpoints included spontaneous abortions, therapeutic abortions, gestational age at birth, and mean birth weight. Women were recruited from 5 teratogen information services in Toronto, Canada; Farmington, Conn., U.S.A.; Jerusalem, Israel; Rome, Italy; Sydney, Australia; and from the Drug

Safety Research Unit in Southampton, United Kingdom. Women were recruited into the study from June 2002 to August 2005. The authors found no difference in the mean weight of the infants in the exposed and unexposed groups.

2.2.1 Summary

A large number of studies have looked at the association between prenatal exposure to antidepressants and an increased risk of being low birth weight/small for gestational age. All of these studies are observational with varying study designs and conflicting results. Although the impact of maternal depression and stress on fetal development has been well documented[32-35], many studies fail to control for maternal depression in either design or analysis. In addition a number of studies have failed to control for confounders such as maternal smoking[24-25], parity[8,11,24,] duration and time of exposure[13,18,25] to antidepressants.

2.3 NICU ADMISSIONS

Several studies have analyzed the associate between neonatal outcomes and antidepressant exposure during pregnancy. Most of these studies show some association between gestational exposure to antidepressants and neonatal adaptation difficulties. Neonatal adaptation is measured in various ways, from gross markers such as NICU admission to more subtle evaluations such as behavioral observations, in different studies making it difficult to draw general conclusions. Large database or registry studies have variously suggested an increased 1.5 times increased risk of NICU admission with third trimester exposure compared to first trimester exposure [38], and increased risks of respiratory distress and low

APGAR scores [49].

The 2005 meta-analysis[50] of prospective controlled trials included consideration of 1066 mother – infant pairs and found a three-fold increased risk of SCN/NICU admission. None of the trials in the meta-analysis included a depressed, non-drug-treated group. Two subsequent studies do include such a group. Of these, Ferreira et al (2007) found a significant ($p < 0.001$) increase in abnormal movements, tone and respiratory symptoms in 76 infants exposed to SSRIs or venlafaxine in the third trimester[51]. Sivojelezova et al (2005) found that 132 infants exposed to citalopram in pregnancy had a four-fold increased incidence of NICU admission compared to matched infants exposed to untreated maternal depression or controls[32]. Whereas two other controlled studies did not find an association between antidepressant exposure and neonatal adaptation difficulties. Of these Casper et al (2003) was limited by a small sample size. Maschi et al (2008) on the other hand was a larger trial including 200 women treated with antidepressants and 1200 controls. Although a major limitation of this study was that the information was collected through an interview with the mothers, so data may not be accurate and an underreporting of neonatal complications, especially of the mild ones, is likely. Studies examining the neonatal effects of antenatal exposure to TCAs are limited to case reports and case series. Several case reports describe an association between gestational clomipramine[48-49]and imipramine[50-52] exposures with signs of neonatal adaptation difficulties. In a prospective case series[53] of 18 pregnant women on TCAs (predominantly imipramine), all nine with third trimester exposure had infants with adaptation difficulties. With regard to the newer antidepressants, evidence is scant. Some of the controlled trials include venlafaxine exposure[54-56] and suggest similar neonatal

adaptation difficulties to SSRIs. Mirtazapine features only in case reports[57-58] and in one controlled study[56], with a suggestion of both respiratory and thermoregulatory problems. One case report exists for duloxetine[59] documenting neonatal adaptation symptoms.

2.3.1 Summary

The literature on association between prenatal exposure to antidepressants and an increased risk of NICU admission is limited as compared to the evidence on preterm delivery and low birth weight/small for gestational age. One reason for NICU admissions are not considered an outcome of interest is because they lack specificity. NICU admissions can sometimes be a result of poor birth outcomes like preterm delivery, small for gestational age or structural malformations. Studies that have examined the association between prenatal exposure to antidepressants and an increased risk of NICU admission have also been observational with varying study designs and conflicting results. These studies have failed to control for confounders such as maternal smoking[24-25], parity[8,11,24,] duration and time of exposure[13,18,25] to antidepressants and maternal depression[24-25].

2.4 GAPS IN THE LITERATURE

The current literature related to the risk of adverse birth outcomes following prenatal exposure to antidepressants is dominated by information on SSRIs and to a lesser extent, TCAs and venlafaxine. Many of the published reports have contradictory results with regard to a possible association. These conflicting results are most probably the result of differences in the study cohorts and variation in the power the power of the study due to the sample size which plays a vital role in aiding to detect differences in rare events. Registry studies have been helpful in the sense that they provide information on

large numbers of participants, but they often rely on secondary data about prescriptions being filled and cannot confirm that antidepressants were actually taken.

The main limitation of the existing literature are:

2.4.1 Lack of Controlling for Maternal Depression

Studies show that maternal depression can have an impact on the pregnancy and fetus[60]. Untreated depression has been found to be associated with preterm delivery, low birth weight and small for gestational age[60-61.] Depression can have a direct effect on the development of fetus and maintenance of pregnancy[63]. It has been associated mainly with preterm delivery, low birth weight, and NICU admissions[64-66]. A majority of the studies in the currently literature do not control for maternal depression[68-70].

2.4.2 Inadequate controlling for confounders

Several of the studies examining the impact of prenatal exposure to antidepressants on adverse birth outcomes fail to control for confounders such as smoking status, mother's BMI, gestational diabetes, gestation hypertension, duration and trimester of exposure to antidepressants etc[68-70]. Also majority of studies do not control details about antidepressants such a duration and trimester of exposure.

2.4.3 Large focus on SSRIs

Since SSRIs are the most commonly prescribed antidepressants, a majority of the studies focus on the impact of prenatal exposure to SSRIs alone on adverse birth outcomes[68-70]. Although there is still information available about the impact of prenatal exposure to TCAs, the information related to Atypical and SNRIs is scant[33,45-47].

2.4.4 Observational studies

All the studies conducted to examine the association between prenatal exposure to antidepressants and risk of adverse birth outcomes have been observational. Several standard methods have been used in this setting to estimate the association between prenatal exposure to antidepressants and the risk of adverse birth outcomes[33-35,68-70]. However, none of the methods can be used to establish causality. Ideally a randomized controlled trial would be conducted to establish a causal association. Due to ethical concerns we cannot randomize treatment in this study population.

2.5 SUMMARY

Literature on the association between prenatal exposure antidepressants and risk of adverse birth outcomes though voluminous, is conflicting. Assessing the impact of antidepressants on birth outcomes is a challenging task. It is vital to delineate the effects of maternal depression, severity, other variables such as socioeconomic status, substance use, and comorbidity medical and mental illnesses, from the effect of antidepressants on birth outcomes[3, 14-16]. A systematic review of the relationship between antidepressant use and poor birth outcomes conducted by Udechuku et al (2010) showed that most studies do not have adequate power to detect rare events, and the large database analyses are limited by the lack of appropriate controls[47]. Another systematic review of literature concluded that although statistically significant associations between prenatal antidepressant exposure and adverse birth outcomes are identified, the group differences are small making it difficult to establish clinical significance[48]. Also most studies fail to properly define the exposure, such as specific antidepressant used, indication, dosage, time and duration of use, and number of antidepressants prescribed[48].

All the studies in the current literature are observational studies; ideally, for estimation of the causal effects of prenatal exposure to antidepressants on adverse birth outcome we would need to conduct a randomized controlled trial. A large sample of women should be randomized to different treatment regimens at enrollment, with perfect adherence ensured and no censoring; here, the assumption of no confounding would be reasonable[48]. However, this is not possible in our study since withholding treatment would be unethical. Hence establishing a causal association between prenatal exposure to antidepressants and risk of adverse birth outcomes is not possible.

2.6 AIMS and HYPOTHESIS

Assessing the impact of antidepressants on the fetus is a challenging task as potential confounding factors must be considered. It is vital to distinguish the effects of maternal depression, socioeconomic status, maternal smoking, and comorbidities on birth outcomes from the impact of antidepressants on those same outcomes [22-23]. Although substantial, the literature is limited by inconsistent results and the lack of an appropriate control group. The majority of studies have used depressed women who are not on antidepressants or women with no depression and no antidepressant prescription. In both cases the controls do not help clarify the impact of antidepressants. Also, while most of the studies have examined prenatal exposure to SSRIs, there is limited information about the other classes of antidepressants[24]. Another concern with the current literature is inadequate controlling of confounding. A number of studies have failed to control oconfounders such as maternal smoking [24-25], parity [8,11,24] , duration and time of exposure [13,18,25] to antidepressants and most importantly maternal depression [24-25]–. The study proposes to fill these gaps in the literature by testing the following hypothesis.

Aim 1

To explore the association between prenatal exposure to antidepressants and risk of adverse birth outcomes such as preterm delivery, low birth weight/small for gestational age, and NICU admissions.

Study Hypothesis 1

Depressed women exposed to antidepressants during pregnancy have a higher risk of adverse birth outcomes compared to women not exposed to antidepressants during pregnancy.

Aim 2

To determine the association between types of antidepressant used on the risk of adverse birth outcomes such as preterm delivery, low birth weight/small for gestational age and NICU admissions.

Study Hypothesis 2

The risk of having adverse birth outcomes is higher in women prescribed Selective Serotonin Reuptake Inhibitors compared to those depressed women who have been prescribed other types of antidepressants.

Aim 3

To determine the effect of trimester and duration of antidepressants on the risk of adverse birth outcomes such as preterm delivery, low birth weight/small for gestational age and NICU admissions.

Study Hypothesis 3

Depressed women who have late pregnancy exposure and for a longer duration have greater risk of adverse birth outcomes compared to those with comparatively early pregnancy exposure and shorter duration.

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CHAPTER 3

METHODS

3.1 DATA SOURCE

Data used in this study came from 2 administrative sources: 1) South Carolina Medicaid claims [1], and 2) South Carolina registry of births from South Carolina Department of Health and Environmental Control (DHEC) [2]. The South Carolina Revenue and Fiscal Affairs Office (RFA) created the de-identified dataset by merging South Carolina Medicaid claims with the birth certificates.

3.1.1 South Carolina Medicaid Claims

Medicaid is South Carolina's aid program through which the federal and state governments provide insurance for eligible low-income adults, children, pregnant women, elderly adults and people with disabilities [1-5]. The database contained information regarding an individual's diagnosed medical conditions and the medications prescribed. Medical conditions were coded using the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) codes. The pharmacy claims file of the dataset contained information regarding the prescribed medications coded using National Drug Codes (NDC), generic names and brand names [1-5]. To address medication use as a depression treatment option in low-income pregnant women, we utilized South Carolina

Medicaid claims data to identify a patient population that would most closely represent our target population.

3.1.2 South Carolina Birth Registry

The South Carolina DHEC maintains the South Carolina Registry of Births which is a database of all birth certificates issued in the state of South Carolina[5]. The database contained the following information: birth weight, gestational age, weight for gestational age, maternal height, maternal smoking, maternal alcohol use, maternal race, maternal and paternal occupation, conditions during the pregnancy (ex. gestational hypertension, anemia, eclampsia, gestational diabetes, uterine bleeding), birth abnormalities or anomalies (ex. cleft palate, heart malformations), multiple births, NICU admissions etc. Data from the birth certificates gave us information regarding the birth outcomes such as pre-term delivery, low birth weight/small for gestational age, and NICU admissions which helped us identify the cases accurately.

3.2 SELECTION OF STUDY POPULATION

The study population consisted of pregnant women who were enrolled in SC Medicaid between the years 2008 – 2014 and fulfilled the following inclusion and exclusion criteria.

3.2.1 Inclusion Criteria

- Pregnant women of age between 18 - 50 years
- Pregnancy ending with a delivery (live birth or stillbirth)
- Diagnosis of depression concurrent with pregnancy
- Enrolled for Medicaid continuously for the entire pregnancy (SC Medicaid requires enrollment every month, and the database captures the claims filed

during the months enrolled. Hence to ensure that use antidepressants during the entire term of pregnancy is captured, it is important that the study participant be continuously enrolled in SC Medicaid during that time.)

3.2.2 Exclusion Criteria

- Multiple births
- Illicit drug users (ICD 9 Code – 305.90)

If a woman had more than one pregnancy between 2008 and 2014, then each pregnancy during which all eligibility criteria were fulfilled will be considered separately.

3.3 EXPOSURE

Pharmacy claims were used to identify all antidepressant prescriptions filled or refilled during the pregnancy and before delivery. Study participants with no antidepressant prescriptions during this period were considered unexposed. In this study the following antidepressants were considered (brand name listed in parentheses):

- *Selective serotonin reuptake inhibitors (SSRIs)* – Fluoxetine (Prozac), Fluvoxamine (Luvox), Sertraline (Zoloft), Paroxetine (Paxil), Escitalopram (Lexapro), and Citalopram (Celexa).
- *Tricyclic antidepressants (TCAs)* – Amitriptyline (Elavil), Clomipramine (Anafranil), Desipramine (Norpramin), Doxepin (Sinequan), Imipramine (Tofranil), Nortriptyline (Pamelor, Aventyl), Protriptyline (Vivactil), and Trimipramine (Surmontil).
- *Atypical antidepressant* – Bupropion (Wellbutrin), Duloxetine (Cymbalta), Venlafaxine (Effexor), Mirtazapine (Remeron), and Trazodone (Desyrel).

- *Serotonin-Norepinephrine Reuptake inhibitors (SNRIs)* – Desvenlafaxine (Pristiq), Duloxetine (Cymbalta), Venlafaxine (Effexor), Venlafaxine XR (Effexor XR), Milnacipran (Savella), and Levomilnacipran (Fetzima)..

For study participants who are prescribed more than one class of antidepressant during pregnancy both the classes were considered separately.

3.3.1 Duration of gestational exposure

The duration of gestational exposure was calculated as the number of days the mother had been prescribed the antidepressant in each trimester. To estimate the duration of exposure, we first estimated the date of conception based on the date of delivery and gestational age. It is known that [10-13]

Gestational Age = Date of Delivery – Date of Conception

Gestational age was obtained from the birth certificates, and date of delivery was estimated using the dates corresponding to the delivery procedure codes. Using the date of conception the time period for each trimester was calculated.

1^{st} Trimester = Date of Conception + 90 days

2^{nd} Trimester = Last date of 1^{st} trimester + 90 days

3^{rd} Trimester = Last date of 2^{nd} trimester – Date of Delivery

Based on the dates of the trimester and the dates of exposure, number of days antidepressant was prescribed during each trimester was calculated.

In case there was a change in prescribed antidepressant the antidepressant prescribed for the longer duration was the focus. If duration was similar for both antidepressants, the first antidepressant prescribed was considered.

3.4 OUTCOMES

A study participant was considered to have the outcome if she had one or more of the following adverse birth outcomes:

3.4.1 Preterm delivery

Preterm delivery was defined as a delivery before completion of 37 weeks of gestation[14-18]. We got information on preterm delivery was obtained from birth certificates.

3.4.2 Low birth weight

Low birth weight was defined as birth-weight less than 2,500 g (5 pounds 8 ounces) regardless of gestational age[17, 18-23]. We got information on preterm delivery was obtained from birth certificates.

3.4.3 Small for gestational age

Small gestational age was defined as birth-weight below the 10th percentile of the birth-weights for the gestational age in the given population[19-23]. Indication that the infant was small for gestation age was provided in the birth certificate file. All births covered by SC Medicaid between years 2008-2014 served as the referent group[19].

Although low birth weight and small for gestational age are not the ideal measures for intrauterine growth, these are the two most commonly use measures in the literature. Studies have found misclassification low birth weight as it is associated with

preterm delivery and the magnitude and direction of misclassification differed by preterm and full term birth. Also small for gestational age may not have been calculated accurately as the estimation of gestational age is not always accurate[24-25].

3.4.4 Neonatal Intensive Care Unit Admissions

NICU admission was identified from the birth certificates file. Information on whether the infant had to be admitted to NICU right after birth was recorded in the birth certificates [24-28].

3.5 COVARIATES AND POTENTIAL CONFOUNDERS

3.5.1 Mother's Age

Mother's age was obtained from birth certificates files. For analysis age was categorized as:

- 18 – 28 years
- 29 – 38 years
- ≥ 39 years

3.5.2 Mother's BMI

Pre-pregnancy BMI of the mother was reported in the birth certificate and was categorized as:

- Underweight (BMI < 18.5)
- Normal weight (18.5 ≤ BMI > 25)
- Overweight (25 ≤ BMI > 35)
- Obese (BMI ≥ 35)

3.5.3 Mother's Education

Information regarding the education of the mother at the time of pregnancy was obtained from the birth certificate. It was categorized as:

- Less than high school
- High school or GED
- High school + some college
- Bachelor's degree or more

3.5.4 Kotelchuck Index/Prenatal Care

The Kotelchuck Index, also called the Adequacy of Prenatal Care Utilization (APNCU) Index, is measure used to estimate adequacy of prenatal care a women received during pregnancy[19]. It is calculated using – (i) the date prenatal care began (initiation) and (ii) the number of prenatal visits between prenatal care initiation and delivery (received services). The Kotelchuck index classifies the adequacy of initiation as follows: pregnancy months 1 and 2, months 3 and 4, months 5 and 6, and months 7 to 9, with the underlying assumption that the earlier prenatal care begins the better. To classify the adequacy of received services, the number of prenatal visits is compared to the expected number of visits for the period between initiation and delivery date. The expected number of visits is based on the American College of Obstetricians and Gynecologists prenatal care standards for uncomplicated pregnancies, and is adjusted for gestational age at date of care initiation, and for gestational age at delivery[19].

Kotelchuck Index was categorized as follows:

- Inadequate (< 50%)
- Intermediate (50% to 79%)
- Adequate (80% to 109%)
- Adequate Plus (≥ 110%)

3.5.5 Smoking Status

Mother's smoking status was reported in the birth certificate file. Smoking status was recorded for two time periods, (i) before pregnancy and (ii) during pregnancy.

- During Pregnancy Smoking Status was categorized as:
    - Yes – smoked during pregnancy
    - No – did not smoke during pregnancy
    - Unknown
- Pre-pregnancy Smoking Status was categorized as:
    - Yes – smoked before pregnancy
    - No – did not smoke before pregnancy
    - Unknown

Although the number of cigarettes smoked per day was not reported.

3.5.6 Diabetes

Information regarding the diagnosis of diabetes for the mother was given in the birth certificate and the SC Medicaid medical claims file. The information on diabetes was recorded as:

- Yes – having a diagnosis of diabetes

- No – not having a diagnosis of diabetes

Diagnosis of diabetes was confirmed from the SC Medicaid medical files using ICD-9 codes (648.8).

3.5.7 Gestational Diabetes

Information regarding the diagnosis of gestational diabetes for the mother was given in the birth certificate and the SC Medicaid medical claims file. The information on gestational diabetes was recorders in the birth certificates file as:

- Yes – having a diagnosis of gestational diabetes
- No – not having a diagnosis of gestational diabetes

Diagnosis of gestational diabetes was confirmed from the SC Medicaid medical files using ICD-9 codes (648.8).

3.5.8 Hypertension

Information regarding the diagnosis of hypertension for the mother was given in the birth certificate and the SC Medicaid medical claims file.

The information on gestational diabetes was recorders in the birth certificates file as:

- Yes – having a diagnosis of hypertension
- No – not having a diagnosis of hypertension

Diagnosis of gestational diabetes was confirmed from the SC Medicaid medical files using ICD-9 codes (648.8).

3.5.9 Gestational Hypertension

Information regarding the diagnosis of gestational hypertension for the mother was given in the birth certificate and the SC Medicaid medical claims file.

The information on gestational hypertension was recorders in the birth certificates file as:

- Yes – having a diagnosis of gestational hypertension
- No – not having a diagnosis of gestational hypertension

Diagnosis of gestational hypertension was confirmed from the SC Medicaid medical files using ICD-9 codes (642).

3.5.10 Parity

Parity was defined as the number of pregnancies that end /delivered after 20 weeks gestation. The number of fetuses in a pregnancy does not change the parity. Information regarding parity was obtained from the birth certificates.

3.5.11 Number of Risk Factors

Total number of risk factors for poor birth outcomes present at the birth of an infant were recorded in the birth certificate. The risk factors included poor prenatal care, gestational diabetes, gestational hypertension, race, mother's age, and mother's BMI. As the number of risk factors present increase so does the risk of adverse birth outcome.

3.5.12 Infant Sex

Infant's gender at the time of birth was obtained from the birth certificate file, specified as male and female.

3.5.13 Race

As of 1990, Live Births are reported by race of mother instead of race of child[19]. Race was categorized as follows in the birth certificate files:

- Non-Hispanic White
- Non-Hispanic Blacks
- Hispanics
- Others

3.5.13 Previous Poor Outcomes

The birth certificates contained information regarding experience of adverse birth outcomes associated with a previous pregnancy. Adverse/poor birth outcomes included the following: still born, pre-term delivery, low birth weight/small for gestational age, structural malformations, NICU admissions, and abortions/miscarriages. The information was coded as follows:

- Yes – had at least 1 of the adverse birth outcome in previous pregnancies
- No – did not have any of the adverse birth outcomes in previous pregnancies

3.6 STATISTICAL ANALYSIS

Descriptive statistics (means, median, std. dev., percentages) was used to report and describe the population. Hypothesis testing for categorical variables was conducted using the Chi-square test. Hypothesis testing for continuous variables was conducted using the t-test.

Two statistical methods were used to test the three study hypotheses –

1. Logistic Regression
2. Marginal Structural Models (MSM)

There are several standard methods could be used to estimate the association between prenatal exposure to antidepressants and the risk of adverse birth outcomes. However, none of the methods can establish causality [14-28]. Ideally a randomized controlled trial should be conducted to establish a causal association between gestational exposure to antidepressants and an increased risk of adverse birth outcomes. Due to ethical concerns, we cannot randomize treatment in the study population. Hence we used Marginal Structural Models to estimate the causal effect of gestational exposure to antidepressants on risk of adverse birth outcomes[29-30]. MSMs are a new class of causal models used in epidemiology, the parameters of which are estimated through inverse-probability-of treatment weighting. MSMs provide more robust estimates, with narrower confidence intervals. In addition, a structural classification of bias distinguishes between biases resulting from conditioning on common effects ("selection bias") and those resulting from the existence of common causes of exposure and outcome ("confounding")[30-34].

However the use of MSM in reproductive epidemiology/perinatal epidemiology has been limited. We used two statistical methods because marginal structural models help us delineate antidepressants from depression. Also, marginal structural models give us the tool to statistically mimic a randomized control trial. We used logistic regression like many previously published studies to make our results more comparable.

3.6.1 Method 1 – Logistic Regression

A logistic regression was conducted to calculate the adjusted odds ratios along with 95% confidence intervals using unexposed study population as the referent group.

$\text{Logit}(Y) = \beta_0 + \beta_1 L + \beta_2 A + \beta_3 x_1 + \beta_4 x_2$

Y = adverse birth outcomes (preterm delivery, low birth weight/small for gestational age and NICU admission)

A= use of antidepressants (SSRIs/TCAs/SNRIs/Atypicals)

L= maternal depression

x_1 , x_2 , x_3, ….= covariates such as mother's age, mother's weight, parity and other demographic variables etc

Backward selection was used to identify the variables significant at p-value <0.05. In the analysis mother's age, mother's weight, mother's education, prenatal care (kotelchuck index), smoking status', parity, number of risk factors, infant sex, mother's race, year of birth, use of antidepressants, gestational diabetes, gestational hypertension, and previous poor birth outcomes were found to be significant.

To ensure that the variables in the equation are not correlated with each other we checked for multicollinearity, and found that number of risk factors was correlated to gestational diabetes, gestational hypertension, and previous poor birth outcomes. Number of risk factors included all risk factor associated with the three outcomes such as infections, gestational diabetes, gestation hypertension, previous poor birth outcome etc. Therefore we retained only the number of risk factors and removed other collinear

variables. Multicollinearity can cause issues such as increase in variance of the coefficient estimates and make the estimates very sensitive to minor changes in the model, resulting in unstable and difficult to interpret coefficient estimates. (The correlation matrix of the final set of predictor variables is presented in Appendix A)

3.6.2 Method 2 – Marginal Structural Models

The model was fitted in a two stage process[30]:

1. Each study participant's probability of having their own treatment history was calculated and used to derive inverse-probability-of-treatment weights (IPTW) which were then standardized.
2. The treatment–outcome association was estimated in a regression model that w weighted using the standardized IPTWs.

The Directed Acyclic Graph represents the association between maternal depression (L), antidepressant (A) and adverse birth outcomes (Y)[30-32].

Y represents the adverse birth outcomes (preterm delivery, low birth weight/ small for gestational age, and structural malformations.)

A represents the exposure to antidepressants (dichotomous)

Maternal depression L is a vector that predicts treatment A. 'L' accounts for all variables such as age, race, parity, and other demographics. It also accounts for dose and type of antidepressant.

We first created a pseudo-population using Inverse Probability (IP) weighting where the arrow from the confounders L to the treatment A was removed. Here we assume that the vector L has all the confounders that can open a backdoor path from A to Y. Controlling for L will then eliminate all confounding in the pseudo-population. That is, the association between A and Y in the pseudo-population consistently estimates the causal effect of A on Y. The pseudo-population was created by weighting each individual by the inverse of the conditional probability of receiving the treatment, which are defined as

$$W^A = 1/f(A|L)$$

W^A – Inverse probability weight

A – Exposure to antidepressants

L – Maternal Depression

The denominator f (A|L) is the probability of getting the treatment conditional on the measured confounders given by

$$Pr[A = 1|L]$$

The probability of getting treatment given the individual has depression was $[A = 1|L]$, and the probability that an individual does not get treatment given that she

has depression can be given by $Pr[A = 0|L]$. Although as treatment is dichotomous the following holds true

$$Pr[A = 0|L] = 1 - Pr[A = 1|L]$$

Weights were stabilized using the stabilizing factor f (A). The mean of the stabilized weights was 1, as the size of the pseudo population equals the size of the actual population. The stabilized weight is given by

$$SW^A = f(A)/f(A|L)$$

SW^A – Standardized inverse probability weight

The reason for using stabilized weights was that they are statistically superior to non-stabilized weights and will give comparatively narrower 95% confidence intervals. To estimate $Pr[A = 1|L]$ for each strata of L we fitted a logistic regression model for the probability of having depression with all the covariates. Next estimated the casual difference $E[Y^{a=1}] - E[Y^{a=0}]$ by fitting the mean model $E[Y|A] = \theta_0 + \theta_1 A$ with individuals weighted by their estimated stabilized IP weights given by $\widehat{Pr}[A = 1]/\widehat{Pr}[A = 1|L]$ for the depressed population and $(1 - \widehat{Pr}[A = 1])/(1 - \widehat{Pr}[A = 1|L])$ for those who are not depressed. Using this counterfactual contrast we build the following model

$$E[Y^a] = \beta_0 + \beta_1 a$$

A = 1 – gestational exposure to antidepressants

A = 0 – no gestational exposure to antidepressants

$Y^{a=1}$ – Counterfactual outcome given everyone in the study population received antidepressants

$Y^{a=0}$ – Counterfactual outcome given nobody in the study population received antidepressants

The notations used to describe the model have been borrowed from Robins et al[30, 35-36].

MSMs have been described and used by Hernan and Robins to estimate the causal effect of zidovudine on the survival of human immunodeficiency virus-positive men participating in the Multicenter AIDS Cohort Study[38]. The authors found MSMs to be a better suited model for causal inference as compared to standard statistical models. The assumptions of MSMs are the same as those in point exposure studies - accurate information, and no misspecification of the model [37-38].

Although limited in number there are some perinatal epidemiology studies that have used MSM. For example MSM has been used to establish the causal effect of iron supplement use during pregnancy on odds of anemia at delivery in the presence of time-dependent confounding [34]. Data from pregnant women enrolled in the Iron Supplementation Study (Raleigh, North Carolina, 1997–1999) were used [34]. The authors concluded that if a data set with rich information on confounders is available, MSMs can be used straightforwardly to make robust inferences about causal effects treatments/exposures in epidemiologic research [34].

All statistical analysis will be conducted using Statistical Analysis Software version 9.4. Codes to conduct analysis using marginal structural models were taken from

the Causal Inference Book. (Hernán MA, Robins JM (2016). Causal Inference. Boca Raton: Chapman & Hall/CRC, forthcoming) [30].

3.6.3 Testing Study Hypothesis 1

The risk of adverse birth outcomes such as preterm delivery, low birth weight/small for gestational age, and NICU admissions is higher in woman who received antidepressants during pregnancy as compared to those who did not take antidepressants.

A separate analysis was conducted for each adverse birth outcome – preterm delivery, low birth weight/small for gestational age and NICU admissions, controlling for all the available confounders. The analysis was conducted using logistic regression and marginal structural models. Adjusted odds ratio along with 95% confidence intervals were calculated for the association between antidepressant use during pregnancy and risk of each adverse birth outcomes. Pregnant women with a diagnosis of depression who did not have an antidepressant prescription were considered as the referent group. Mother's age, parity, mother's weight, kotelchuck index, total number of risk factors, and previously poor birth outcomes were found to be significant in the analysis.

3.6.4 Testing Study Hypothesis 2

The risk of adverse birth outcomes such as preterm delivery, low birth weight/small for gestational age, and NICU admissions is higher in woman who received Selective Serotonin Reuptake Inhibitors (SSRIs) antidepressants during pregnancy as compared to other class of antidepressants such as Tricyclic Antidepressants (TCAs), Selective Norepinephrine Reuptake Inhibitors (SNRIs).

The second hypothesis was tested using the same methods. Each antidepressant type was compared to the unexposed group using logistic regression and marginal structural models. In addition we conducted another analysis using SSRIs as the reference group to compare the risk between different classes of antidepressants. Adjusted odds ratios along with 95% confidence intervals were calculated for the association between type of antidepressant use during pregnancy and risk of each adverse birth outcomes. Mother's age, parity, mother's weight, mother's education, kotelchuck index, total number of risk factors, and previously poor birth outcomes were found to be significant in the analysis.

3.6.4 Testing Study Hypothesis 3

Depressed women who have antidepressants during the first trimester of pregnancy (early) and for a longer duration have greater risk of adverse birth outcomes compared to those with exposure in the third trimester of pregnancy (late) and for a shorter duration.

A separate analysis was conducted for each adverse outcome comparing exposure to antidepressant during first, second and third trimester to test the third hypothesis. The analyses were conducting using logistic regression and marginal structural models, controlling for duration of exposure in each trimester. Adjusted odds ratio along with 95% confidence intervals were calculated for the association between antidepressant use during pregnancy and risk of each adverse birth outcomes for 1^{st}, 2^{nd} and 3^{rd} trimesters. Mother's age, parity, mother's weight, mother's education, year of birth, total number of risk factors, and previously poor birth outcomes were found to be significant in the analysis. Also additional analysis was conducted with women who received

antidepressants only in Trimester 1 or 2 or 3, using women who got antidepressants only in the first trimester.

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CHAPTER 4

RESULTS

Study population consisted of pregnant women with a diagnosis of depression, continuously enrolled in Medicaid for the entire term of their pregnancy, during the years 2008 - 2014. During the study period (2008-2014) a total of 411,003 births were financed by SC Medicaid. The prevalence of depression among pregnant women in the SC Medicaid population was 26.2% that is approximately 107,683 women had a diagnosis of depression before or during pregnancy. After applying the study inclusion and exclusion criteria, the study sample comprised of 4,450 women. Out of the 4,450 women included in our analysis, 1,743 had multiple pregnancies during the study period. About half of these women (901) had two pregnancies during the study period, 549 had three pregnancies and 293 had more than three pregnancies during the study period. Each pregnancy had to fulfill the inclusion-exclusion criteria to be included in the study.

Table 1 presents the demographic and clinical characteristics of the study population. A total of 1,641 women in the study population had received at least one antidepressant during their pregnancy and were categorized as exposed. All the others who did not receive any antidepressants during their pregnancy were categorized as unexposed.

The mean age of the study participants was relatively higher in the exposed group compared to the unexposed group (27.6 years vs 24.5 years, respectively). A large number of study participants fell in the age range of 18-28 years [unexposed – 2,250 (80.1%); exposed 1,049 (63.9%)]. Proportion of women aged ≥39 years was smaller [unexposed: 27 (0.96%); exposed: 69 (4.2%)].

Overall, in both exposed and unexposed the proportion of non-Hispanic whites was higher than that of non-Hispanic blacks, Hispanics and others. The proportion of non-Hispanic whites was higher in the exposed (71%) as compared to the unexposed group (60.2%), whereas the proportion of non-Hispanic blacks was relatively lower exposed group (25.8%) as compared to the unexposed group (37.1%). The proportion of Hispanics and other races was significantly lower in the both unexposed and exposed groups.

BMI was obtained from the birth certificates that record the pre-pregnancy BMI of the mother. About half of the study population was either overweight (BMI ≥ 25 to < 30) or obese (BMI of ≥ 30) [unexposed: 1,587 (56.5 %); exposed: 1,008 (61.2 %)]. These results were consistent with observations of other studies that looked at prevalence of obesity in women of the lower socioeconomic strata[1-3]. About one-third of the study participants reported to have less than a high school education [unexposed: 1,170 (41.7 %); exposed: 589 (35.9 %)], and very few had a bachelor's or a higher degree [unexposed: 41 (1.5 %); exposed: 40 (2.4 %)].

According to Kotelchuck Index reported on the birth certificates, the level of prenatal care was 'adequate plus' for more than 45% of the study population, whereas

about 25% were reported to have received ‘inadequate’ or ‘intermediate’ prenatal care. The distribution of population by the levels of prenatal care received was similar in the exposed and unexposed groups.

In the study population the proportion of women smoking before pregnancy was higher than the proportion of women smoking during pregnancy, although the smoking status of a large majority of women was unknown for both before and after pregnancy. Also, the proportions of smokers and non-smokers for both before and during pregnancy were similar in the exposed and unexposed groups.

The prevalence of gestational diabetes was relatively lower in the study population and did not differ significantly between the exposed and unexposed groups[4-5]. However the proportion of women affected by gestational hypertension is within the range projected by the Center of Disease Control (CDC), which is about 5% to 7%[6-7]. The prevalence of pre-pregnancy diabetes and pre-pregnancy hypertension is similar to the prevalence estimated for women below the age of 50 by CDC[8-10].

In about 33% of the women in both the exposed and unexposed group the pregnancy being considered in the study was their second pregnancy. The proportion of first pregnancies considered for study was lower in the exposed group (15.5%) as compared to the unexposed group (27.8%). Higher parity (≥ 3 children) was comparatively more prevalent in the exposed group (4.1%) compared to the unexposed group (2.5 %).

The history of a poor birth outcomes such as pre-term delivery, low birth weight/small for gestational age, NICU admissions or structural malformations, was

relatively higher in the exposed group (16%) as compared to the unexposed group (12.7 %).

The distribution of infant gender was similar across exposed and unexposed groups, the proportion of females (~ 51%) was slightly higher than males (~ 48%). However, the distribution of infants born in exposed and unexposed groups was significantly different each year from 2008-2014. This corresponds with the trend of increase in the number of antidepressant prescribed during pregnancy from 2008-2014[11-12].

Selective Serotonin Reuptake Inhibitors (SSRIs) were the most commonly prescribed antidepressants during pregnancy. A total of 1,152 (69%) of the study participants in the exposed group were prescribed SSRIs. Atypical Antidepressants were prescribed to 254 (15.5%), followed by Selective Norepinephrine Reuptake Inhibitors (SNRIs) prescribed to 171 (10.4%) and Tricyclic Antidepressants (TCAs) prescribed to 83 (2.1%) study participants. (See Table 1)

Table 4.1 Demographic and Clinical Characteristic of Pregnant Women with a Diagnosis of Depression Enrolled in SC Medicaid during their entire term of Pregnancy

Maternal/Infant Characteristics	**No Antidepressant Use During Pregnancy** *N (%)*	**Antidepressants Prescribed During Pregnancy** *N (%)*	**p-value**
Total	2809 (100%)	1641 (100%)	
Mother's Age (Years)			
18 – 28	2250 (80.10%)	1049 (63.92%)	<0.001
29 – 38	532 (18.94%)	523 (31.87%)	<0.001
≥ 39	27 (0.96%)	69 (4.20%)	<0.001
Mother's Weight			

Maternal/Infant Characteristics	No Antidepressant Use During Pregnancy *N (%)*	Antidepressants Prescribed During Pregnancy *N (%)*	p-value
Underweight	232 (7.62%)	105 (6.40%)	<0.001
Normal	990 (35.24%)	528 (32.18%)	<0.001
Overweight	654 (23.28%)	414 (25.23%)	<0.001
Obese	933 (33.21%)	594 (36.20%)	<0.001
Mother's Education			
Less than High School	1170 (41.65%)	589 (35.89%)	<0.001
High School or GED	917 (32.65%)	560 (34.13%)	<0.001
High School + Some College	681 (24.24%)	452 (27.54%)	<0.001
Bachelor's Degree or More	41 (1.46%)	40 (2.44%)	<0.001
Prenatal Care (Kotelchuck Index)			
Inadequate	611 (21.75%)	331 (20.17%)	<0.001
Intermediate	214 (7.62%)	109 (6.64%)	<0.001
Adequate	663 (23.60 %)	388 (23.64%)	<0.001
Adequate Plus	1321 (47.03%)	813 (49.54%)	<0.001
Smoking Status			
Pre-pregnancy	1117 (39.77%)	664 (40.46%)	0.05
During Pregnancy	981 (34.92%)	601 (36.62%)	0.05
Diabetes			
Pre-pregnancy	45 (1.60%)	46 (2.8%)	0.05
Gestational	137 (4.88%)	79 (4.81%)	0.05
Hypertension			
Pre-pregnancy	82 (2.92%)	61 (3.72%)	<0.001
Gestational	163 (5.8 %)	82 (5 %)	<0.001
Parity			
First	782 (27.8%)	254 (15.5 %)	0.05
Second	972 (34.6%)	536 (32.7%)	0.05
Third	606 (21.6%)	446 (27.2%)	<0.001
More than Three	449 (16 %)	405 (24.7%)	<0.001
Number of Risk Factors			
None	1514 (53.9%)	804 (49%)	0.166
One	959 (34.1%)	595 (36.3%)	0.166
Two	267 (9.5%)	175 (10.7%)	0.166

Maternal/Infant Characteristics	No Antidepressant Use During Pregnancy *N (%)*	Antidepressants Prescribed During Pregnancy *N (%)*	p-value
Three or more	69 (2.5%)	67 (4.1%)	0.166
Previous Poor Outcomes	356 (12.7%)	262 (16%)	0.178
Infant Sex			
Male	1448 (51.6%)	852 (52%)	<0.001
Female	1361 (48.5%)	789 (48.1%)	<0.001
Mother's Race			
Non-Hispanic White	1690 (60.2%)	1166 (71%)	<0.001
Non-Hispanic Black	1043 (37.1%)	423 (25.8%)	<0.001
Hispanic	60 (2.1%)	36 (2.2%)	<0.001
Other	16 (0.6%)	16 (1%)	<0.001
Year of Birth			
2008	444 (15.8%)	143 (8.7%)	0.431
2009	437 (15.6%)	176 (10.7%)	0.512
2010	427 (15.2%)	184 (11.2%)	0.223
2011	457 (16.3%)	233 (14.2%)	0.021
2012	426 (15.2%)	253 (15.4%)	0.021
2013	309 (11%)	311 (19%)	0.356
2014	309(11%)	341 (20.8%)	0.511
Antidepressant Use			
Selective Serotonin Reuptake Inhibitors	N/A	1132 (69%)	N/A
Atypical Antidepressants	N/A	254 (15.5%)	N/A
Serotonin–norepinephrine Reuptake Inhibitor	N/A	171 (10.4%)	N/A
Tricyclic Antidepressants	N/A	83 (5.1%)	N/A

Note: *Risk Factors:* poor pre-natal care; previous adverse birth outcomes; gestational diabetes, gestational hypertension, race, mother's age, and mother's BMI, previous poor birth outcomes, etc. *Previous Poor Birth Outcomes:* pre-term delivery; low birth weight/small for gestational age; structural malformations; NICU admissions.; *N/A* – Not applicable; *NICU* – Neonatal Intensive Care Unit

4.1 RESULTS FOR HYPOTHESIS 1

Study Hypothesis 1: Depressed women exposed to antidepressants during pregnancy have a higher risk of adverse birth outcomes compared to women not exposed to antidepressants during pregnancy.

The prevalence of adverse birth outcomes was higher in the exposed group compared to the unexposed group (See Table 2). The prevalence of preterm birth was 17.25% in the exposed group versus 14.31% in the unexposed group (p-value < 0.01). The number of NICU admissions was also higher in the exposed group (8.23%) as compared to the unexposed group (7.62%) (p-value < 0.01). A similar pattern was observed in the low birth weight/small for gestational age infants; the proportion was found to be 17.25% in the exposed group whereas it was 16.59% in the unexposed group (p-value < 0.01) (See Table 2).

These differences in the proportion remained significant after controlling for various confounders such as mother's age, mother's education, parity, mother's weight, mother's race, mother's smoking status during pregnancy and before pregnancy, gestational diabetes and hypertension, adequacy of prenatal care estimated using the Kotelchuck Index etc. A logistic regression was conducted for each outcome controlling for significant confounders. In addition, another analysis was conducted using the marginal structural models to delineate the effect of antidepressants on the birth outcomes from the effect of maternal depression. Both the analysis yielded similar results (See Table 2).

The results for marginal structural models were similar to the results produced using logistic regression. The point estimates were slightly higher, showing stronger association and the confidence intervals were narrower (See Table 2).

4.1.1 Prenatal Exposure to Antidepressants and the Risk of Preterm Delivery

When conducting analysis using logistic regression the odds of having preterm delivery were 1.58 (95%CI: 1.19 – 2.10) times higher in the study participants that received an antidepressant during pregnancy as compared to those who did not receive any antidepressants at any time during the pregnancy.

Whereas, according to the analysis conducted using marginal structural models, the odds of preterm delivery were 1.72 times (95% CI: 1.63 – 1.79) in the group that received antidepressants during pregnancy as compared to the group that did not receive an antidepressant during pregnancy.

4.1.2 Prenatal Exposure to Antidepressants and the Risk of Low Birth Weight/Small for Gestational Age

Using logistic regression it was estimated that antidepressant use during pregnancy was associated with higher odds of the infant having low birth weight/being small for gestational age- OR = 1.57 (95% CI: 1.42 – 2.76.)

Similar result was observed when the analysis was conducted using marginal structural models. the odds of having low birth weight/being small for gestational age were 1.63 times higher in the exposed group (95%CI: 1.53 – 1.73) as compared to the unexposed group.

4.1.3 Prenatal Exposure to Antidepressants and the Risk of NICU Admissions

A similar pattern was observed in the probability of NICU admissions. According to the analysis conducted using logistic regression the odds of an infant being admitted to NICU were almost twice in the exposed group as compared to the unexposed group (OR: 1.45; 95%CI 1.28 – 2.26).

According to marginal structural models, the estimated probability of being admitted in NICU was 1.66 times higher with prenatal exposure to antidepressants than without (95% CI: 1.58 – 1.73).

Table 4.2 Risk of having adverse birth outcomes between depressed pregnant women exposed to antidepressants during pregnancy and those who were not exposed to antidepressants during pregnancy

Adverse Birth Outcomes	**No Antidepressant Use During Pregnancy N (%)**	**Used Antidepres-sants During Pregnancy N (%)**	**Logistic Regression OR (95% CI)**	**Marginal Structural Model OR (95% CI)**
Pre-term Delivery	402 (14.31%)	283 (17.25%)	**1.58** *(1.19 – 2.10)*	**1.72** *(1.63 – 1.79)*
Low Birth Weight/ Small for Gestational Age	466 (16.59%)	283 (17.25%)	**1.57** *(1.42 – 2.76)*	**1.63** *(1.53 – 1.73)*
NICU Admission	214 (7.62%)	135 (8.23%)	**1.45** *(1.28 – 2.26)*	**1.66** *(1.58 – 1.73)*

***Note**: OR – Odds Ratio; NICU – Neonatal Intensive Care Unit; CI – Confidence Interval*

4.1.4 Summary

The prevalence of adverse birth outcomes was higher in the exposed group as compared to the unexposed group. Conducting a logistic regression controlling for all the confounders confirmed the association of the prenatal exposure to antidepressants and an increased risk of adverse birth outcomes. The odds of having an adverse birth outcome ranged from **1.45** (95%CI: 1.28 – 2.26) to **1.72** (95%CI: 1.63 – 1.79). Delineating the effect of antidepressants from depression using marginal structural models showed a stronger association and had narrower confidence intervals as compared to logistic regression.

4.2 RESULTS FOR HYPOTHESIS 2

Study Hypothesis 2: The risk of having adverse birth outcomes is higher in women prescribed Selective Serotonin Reuptake Inhibitors compared to those depressed women who have been prescribed other types of antidepressants.

As previously discussed SSRIs were the most commonly prescribed antidepressants during pregnancy [1152 (68.99%)]. Atypical antidepressants and SNRIs were prescribed to relatively fewer study participants [254 (15.48%) and 171 (10.42%) respectively], TCAs were the least commonly prescribed antidepressants [83 (2.06%)].

4.2.1 Risk of Preterm Delivery Associated with Type of Antidepressants Prescribe during Pregnancy

The risk of having a preterm delivery was higher for all antidepressant classes when compared to the unexposed group. Analysis conducted using logistic regression showed that the odds of having a preterm delivery were 1.95 (95% CI: 1.32 – 2.66) times

higher in study participants that received SSRIs during pregnancy as compared to those who did not receive an antidepressant during pregnancy. Atypical antidepressant were associated with the 1.89 (95%CI: 1.23 – 2.69) times higher odds of having a preterm birth as compared to those who did not receive any antidepressants during pregnancy. SNRIs and TCAs showed a similar association. The odds of preterm birth 1.80 (95%CI: 1.23 – 2.69) times higher in the SNRIs group, and 1.75 (95%CI: 1.32 – 2.89) times higher in the TCA group as compared to those who were not prescribed any antidepressant during pregnancy.

Using marginal structural models a similar pattern was observed. The odds of having preterm delivery were 1.95 (95% CI: 1.71 – 2.15) times higher in the SSRIs group, 1.85 (95% CI: 1.45 – 2.11) times higher in the atypical antidepressants group, 1.75 (95% CI: 1.47 – 2.00) times higher in the SNRIs group, and 1.81 (95% CI: 1.78 – 2.01) times higher in the TCAs group when each group was compared to those who did not receive any antidepressants during pregnancy.

When a logistic regression was conducted using SSRIs as the referent group, we found that the odds of having preterm birth were not significantly associated with the class of antidepressants prescribed during pregnancy. Atypicals and SNRI groups were associated with 1.03 (95% CI: 0.67 – 1.54) times higher odds, and 0.95 (95% CI: 0.74 – 1.82) times higher odds than the SSRIs group. However, these results were not significant as the odds are close to 1 and the confidence interval contains 1. Although not statistically significant, TCAs were associated with relatively lower odds of having a preterm delivery than SSRIs [OR: 0.89 (95% CI: 0.69 – 1.00)].

The group that was prescribed TCAs during pregnancy had lower odds of having preterm delivery as compared to those who were prescribed SSRIs during pregnancy [OR: 0.85 (95% CI: 0.65 – 0.97)]. Atypicals and SNRI groups were associated with 1.08 (95% CI: 0.98 – 1.23) times higher odds, and 1.05 (95% CI: 0.85 – 1.19) times higher odds than the SSRIs group.

Table 4.3 Comparison of Risk of Preterm Delivery between Types of Antidepressants Prescribed during Pregnancy

Risk of Preterm Delivery associated with Class of Antidepressant Prescribed during Pregnancy					
		Referent Group - Unexposed		**Referent Group - SSRIs**	
Class of Antidepre-ssants Prescribed during Pregnancy	**#**	***Logistics Regression OR (95% CI)***	***Marginal Structural Model OR (95% CI)***	***Logistics Regression OR (95% CI)***	***Marginal Structural Model OR (95% CI)***
SSRIs	**933**	**1.95** *(1.32 – 2.66)*	**1.95** *(1.71 – 2.15)*	---	---
Atypicals	**216**	**1.89** *(1.23 – 2.69)*	**1.85** *(1.45 – 2.11)*	**1.03** *(0.67 – 1.54)*	**1.08** *(0.98 – 1.23)*
SNRIs	**140**	**1.80** *(1.21 – 2.03)*	**1.75** *(1.47 – 2.00)*	**0.95** *(0.74 – 1.82)*	**1.05** *(0.85 – 1.19)*
TCAs	**68**	**1.75** *(1.32 – 2.89)*	**1.81** *(1.78 – 2.01)*	**0.89** *(0.69 – 1.00)*	**0.85** *(0.65 – 0.97)*

***Note**: OR – Odds Ratio; NICU – Neonatal Intensive Care Unit; CI – Confidence Interval*

4.2.2 Risk of Low Birth Weight/Small for Gestational Age Associated with Type of Antidepressants Prescribe during Pregnancy

Analysis conducted using logistic regression showed that the odds of having a low birth weight/small for gestational age were 1.78 (95%CI: 1.45 – 2.78) times higher in study participants that received SSRIs during pregnancy as compared to those who did not receive an antidepressant during pregnancy. Atypical antidepressant were associated with the 1.65 (95% CI: 1.21 – 2.69) times higher odds of having a low birth weight/small for gestational age as compared to those who did not receive any antidepressants during pregnancy. SNRIs and TCAs showed a similar association. The odds of low birth weight/small for gestational age 1.69 (95% CI: 1.41 – 2.78) times higher in the SNRIs group, and 1.66 (95% CI: 1.25 – 2.12) times higher in the TCA group as compared to those who were not prescribed any antidepressant during pregnancy.

Using marginal structural models a similar pattern was observed. The odds of having low birth weight/small for gestational age were 1.80 (95%CI: 1.52 – 1.97) times higher in the SSRIs group, 1.70 (95%CI: 1.32 – 1.86) times higher in the atypical antidepressants group, 1.73 (95%CI: 1.50 – 1.89) times higher in the SNRIs group, and 1.71 (95%CI: 1.68 – 1.89) times higher in the TCAs group when each group was compared to those who did not receive any antidepressants during pregnancy.

When a logistic regression was conducted using SSRIs as the referent group, we found that the odds of having low birth weight/small for gestational age were not significantly associated with the class of antidepressants prescribed during pregnancy. Atypicals and SNRI groups were associated with 1.06 (95% CI: 0.59 – 1.66) times higher odds, and 1.02(95% CI: 0.64 – 1.62) times higher odds than the SSRIs group. TCAs were

associated with relatively lower odds of having a low birth weight/small for gestational age than SSRIs [OR: 0.91 (95% CI: 0.68 – 1.10)]. The results were not statistically significant.

According to the marginal structural models it was found that group that was prescribed TCAs during pregnancy had lower odds of having low birth weight/small for gestational age as compared to those who were prescribed SSRIs during pregnancy [OR: 0.95 (95% CI: 0.89 – 1.05)]. Atypicals and SNRI groups were associated with 1.07 (95% CI: 0.75 – 1.14) times higher odds, and 1.05 (95% CI: 0.79 – 1.18) times higher odds than the SSRIs group. However, these results were not statistically significant.

Table 4.4 Comparison of Risk of Low Birth Weight/Small for Gestational Age between Types of Antidepressants Prescribed during Pregnancy

Risk of Risk of Low Birth Weight/Small for Gestational Age associated with Class of Antidepressant Prescribed during Pregnancy					
		Referent Group - Unexposed		**Referent Group - SSRIs**	
Class of Antidepr-essants Prescribed during Pregnancy	**#**	***Logistics Regression OR (95% CI)***	***Marginal Structural Model OR (95% CI)***	***Logistics Regression OR (95% CI)***	***Marginal Structural Model OR (95% CI)***
SSRIs	**935**	**1.78** *(1.45 – 2.78)*	**1.80** *(1.52 – 1.97)*	---	---
Atypicals	**211**	**1.65** *(1.21 – 2.56)*	**1.70** *(1.32 – 1.86)*	**1.06** *(0.59 – 1.66)*	**1.07** *(0.75 – 1.14)*
SNRIs	**141**	**1.69** *(1.41 – 2.78)*	**1.73** *(1.50 –1.89)*	**1.02** *(0.64 – 1.62)*	**1.05** *(0.79 – 1.18)*
TCAs	**70**	**1.66** *(1.75 – 2.12)*	**1.71** *(1.68 – 1.89)*	**0.91** *(0.68 – 1.10)*	**0.95** *(0.89 – 1.05)*

***Note**: OR – Odds Ratio; NICU – Neonatal Intensive Care Unit; CI – Confidence Interval*

4.2.3 Risk of NICU Admissions Associated With Type of Antidepressants Prescribe during Pregnancy

Analysis conducted using logistic regression showed that the odds of having a NICU admissions were 1.92 (95% CI: 1.41 – 2.54) times higher in study participants that received SSRIs during pregnancy as compared to those who did not receive an antidepressant during pregnancy. Atypical antidepressant were associated with the 1.71 (95% CI: 1.32 – 2.76) times higher odds of having a NICU admissions as compared to those who did not receive any antidepressants during pregnancy. SNRIs and TCAs showed a similar association. The odds of NICU admissions 1.83 (95%CI: 1.33 – 2.75) times higher in the SNRIs group, and 1.75 (95% CI: 1.65 – 2.72) times higher in the TCA group as compared to those who were not prescribed any antidepressant during pregnancy.

Using marginal structural models a similar pattern was observed. The odds of having NICU admissions were 1.80 (95%CI: 1.52 – 1.97) times higher in the SSRIs group, 1.80 (95% CI: 1.77 – 2.00) times higher in the atypical antidepressants group, 1.77 (95% CI: 1.32 – 1.97) times higher in the SNRIs group, and 1.84 (95% CI: 1.39 – 1.99) times higher in the TCAs group when each group was compared to those who did not receive any antidepressants during pregnancy.

When a logistic regression was conducted using SSRIs as the referent group, we found that the odds of having NICU admissions were not significantly associated with the class of antidepressants prescribed during pregnancy. Atypicals were associated with 1.04

(95% CI: 0.67 – 1.52) times higher odds than the SSRIs group. Whereas, TCAs and SNRI were associated with relatively lower odds of having a NICU admissions than SSRIs [OR: 0.89 (95% CI: 0.63 – 1.12); OR: 0.95 (95% CI: 0.85 – 1.10) respectively]. However, the results were not statistically significant.

According to the marginal structural models it was found that group that was prescribed TCAs and SNRIs during pregnancy had lower odds of having NICU admissions as compared to those who were prescribed SSRIs during pregnancy [OR: 0.91 (95% CI: 0.87 – 1.09); OR: 0.98 (95% CI: 0.85 – 1.23) respectively]. Atypicals were associated with 1.06 (95% CI: 0.85 – 1.10) times higher odds than the SSRIs group. However, these results were not statistically significant.

Table 4.5 Comparison of Risk of NICU Admissions between Types of Antidepressants Prescribed during Pregnancy

Risk of NICU Admissions associated with Class of Antidepressant Prescribed during Pregnancy					
		Referent Group - Unexposed		**Referent Group - SSRIs**	
Class of Antidepres-sants Prescribed during Pregnancy	#	***Logistics Regression OR (95% CI)***	***Marginal Structural Model OR (95% CI)***	***Logistics Regression OR (95% CI)***	***Marginal Structural Model OR (95% CI)***
SSRIs	**95**	**1.92** *(1.41 – 2.54)*	**1.89** *(1.77 – 2.00)*	---	---
Atypicals	**16**	**1.71** *(1.32 – 2.76)*	**1.80** *(1.32 – 1.97)*	**1.04** *(0.67 – 1.52)*	**1.06** *(0.85 – 1.10)*
SNRIs	**15**	**1.83** *(1.33 – 2.75)*	**1.84** *(1.39 – 1.99)*	**0.95** *(0.85 – 1.10)*	**0.98** *(0.85 – 1.23)*
TCAs	**9**	**1.75** *(1.65 – 2.72)*	**1.79** *(1.67 – 1.96)*	**0.89** *(0.63 – 1.12)*	**0.91** *(0.87 – 1.09)*

***Note**: OR – Odds Ratio; NICU – Neonatal Intensive Care Unit; CI – Confidence Interval*

4.2.4 Summary

When each class of antidepressant was independently compared to the unexposed group, it was found that all the classes of antidepressants were associated with a higher risk of adverse birth outcomes. Both logistic regression and marginal structural models yielded similar results. Upon comparing the different classes of antidepressants to SSRIs we found that the risk of adverse birth outcomes was not significantly different between the different types of antidepressants. Only TCAs had a statistically lower risk of NICU admissions as compared to SSRIs. Using marginal structural models we found that the risk of NICU admissions was 0.85 times (95% CI: 0.65 – 0.97) lower in TCAs as compared to SSRIs. These results are can attributed to a variety of reasons, TCA were prescribed to relatively fewer people as compared to the other antidepressants. Also, TCAs prescription has reduced over the past decade and is mostly prescribed to older women. Mother's of age above 40 are more likely to have poor birth outcomes; this might dilute the association of TCAs and risk of adverse birth outcomes.

4.3 RESULTS FOR HYPOTHESIS 3

Hypothesis 3: Depressed women who have late pregnancy exposure and for a longer duration have greater risk of adverse birth outcomes compared to those with comparatively early pregnancy exposure and shorter duration.

A majority of the study participants received antidepressants during the third trimester of their pregnancy 781, followed by the second trimester 620, and only 158 study participants received antidepressants during the first trimester.

4.3.1 Prenatal Exposure to Antidepressants in the First Trimester of Pregnancy and Risk of Preterm Delivery

According to the analysis conducted using logistic regression it was found that the odds of having preterm delivery were 1.98 times higher (95%CI: 1.2 – 2.1) in the group that was exposed to antidepressants during the first trimester of pregnancy as compared to women who did not receive any antidepressants during the first trimester. Duration of exposure was not significantly associated with the risk of preterm term delivery (OR: 1.07 95%CI: 0.84 – 1.37).

Similar results were observed when the analysis was conducted using marginal structural models. The odds of having a preterm delivery were 1.8 times (95% CI: 1.5 – 2.1) higher in women who received an antidepressant during the first trimester of pregnancy as compared to those who did not receive any antidepressants during the first trimester of pregnancy. Duration of exposure was not significantly associated with the risk of preterm term delivery in the first trimester (OR: 1.13 95%CI: 0.94 – 1.28).

4.3.2 Prenatal Exposure to Antidepressants in the First Trimester of Pregnancy and Risk of Low Birth Weight/Small for Gestational Age

Using logistic regression is was estimated that the probability of having low birth weight/small for gestational age infants was 1.99 (95%CI: 1.9 – 2.4) times higher in the group exposed to antidepressants during the first trimester of pregnancy as compared to those who did not receive an antidepressant during the first trimester of pregnancy. Each unit increase in the duration of exposure in the first trimester was associated with 1.19 times higher odds of having low birth weight/small for gestational age (95%CI 0.95 – 1.48), although the association was not statistically significant.

According to marginal structural models, the odds of having low birth weight/small for gestational age were 1.95 times higher (95%CI 1.6- 2.2) in the group receiving antidepressants during the first trimester of pregnancy as compared to the group which did not receive any antidepressants during first trimester of pregnancy. A unit increase in the duration of exposure to antidepressants was not significantly associated with the risk of low birth weight/small for gestational age (OR: 1.21 95%CI: 0.97 – 1.28).

4.3.3 Prenatal Exposure to Antidepressants in the First Trimester of Pregnancy and Risk of NICU Admission

According to logistic regression the risk of NICU admissions was estimated to be 1.8 (95%CI: 1.5 – 2.2) times higher in the group exposed during the first trimester of pregnancy as compared to those who were not exposed antidepressants during the first trimester of pregnancy. Duration of exposure was not significantly associated with the risk of NICU admissions in the first trimester of pregnancy (OR: 0.98 95%CI: 0.76 – 1.27).

Similarly, the odds of NICU admission estimated using marginal structural models were 1.6 (95%CI: 1.5 – 1.8) times higher in the group exposed to antidepressants in the first trimester as compared to the group that did not receive any antidepressants during the first trimester of the pregnancy. Duration of exposure was not significantly associated with the risk of preterm term delivery in the first trimester (OR: 1.11 95%CI: 0.94 – 1.28).

Table 6 shows the odds of adverse birth outcomes such as preterm delivery, low birth weight/small for gestational age and NICU admission associated with prenatal exposure to antidepressants during the first trimester of pregnancy.

Table 4.6 Risk of having adverse birth outcomes among depressed pregnant women exposed to antidepressants during first trimester of pregnancy and those who were not exposed to any antidepressants during first trimester of their pregnancy

Risk Associated with Prenatal Exposure to Antidepressants in the First Trimester of Pregnancy		
	Logistics Regression OR (95% CI)	***Marginal Structural Model OR (95% CI)***
Pre-term Delivery	**1.98** (1.2 – 2.1)	**1.8** (1.5 – 2.1)
Low Birth Weight/ Small for Gestational Age	**1.99** (1.9 – 2.4)	**1.95** (1.6 – 2.2)
NICU Admission	**1.81** (1.5 – 2.2)	**1.6** (1.3 – 2.1)

***Note**: OR – Odds Ratio; NICU – Neonatal Intensive Care Unit; CI – Confidence Interval*

4.3.4 Prenatal Exposure to Antidepressants in the Second Trimester of Pregnancy and Risk of Preterm Delivery

Analysis conducted using logistic regression showed that the odds of having preterm delivery were 1.8 (95%CI: 1.2 – 2.9) times higher in the group that was exposed to antidepressants during the second trimester of pregnancy as compared to those who did not receive any antidepressants during the second trimester. Duration of exposure was not significantly associated with the risk of preterm term delivery in the second trimester (OR: 1.09 95%CI: 0.77 – 1.57).

Similar results were observed when the analysis was conducted using marginal structural models. The odds of having a preterm delivery were 1.6 (95% CI: 1.6 – 1.9) times higher in women who received an antidepressant during the second trimester of pregnancy as compared to those who did not receive any antidepressants during the second trimester of pregnancy. Duration of exposure was not significantly associated with the risk of preterm term delivery in the second trimester (OR: 1.12 95%CI: 0.92 – 1.25).

4.3.5 Prenatal Exposure to Antidepressants in the Second Trimester of Pregnancy and Risk of Low Birth Weight/Small for Gestational Age

Using logistic regression is was estimated that the probability of having low birth weight/small for gestational age infants was 1.8 (95%CI: 1.6 – 2.1) times higher in the group exposed to antidepressants during the second trimester of pregnancy as compared to those who did not receive an antidepressant during the second trimester of pregnancy. Each unit increase in the duration of exposure in the second trimester was associated with

1.36 times higher odds of having low birth weight/small for gestational age (95%CI 0.98 – 1.58), although the association was not statistically significant.

According to marginal structural models, the odds of having low birth weight/small for gestational age were 1.7 (95%CI: 1.6 – 1.9) times higher in the group receiving antidepressants during the second trimester of pregnancy as compared to the group which did not receive any antidepressant during the second trimester of pregnancy. A unit increase in the duration of exposure to antidepressants was not significantly associated with the risk of low birth weight/small for gestational age (OR: 1.40 95% CI: 0.97 – 1.48).

4.3.6 Prenatal Exposure to Antidepressants in the Second Trimester of Pregnancy and Risk of NICU Admission

According to logistic regression the risk of NICU admissions was estimated to be 1.7 (95%CI: 1.3 – 1.9) times higher in the group exposed during the second trimester of pregnancy as compared to those who were not exposed antidepressants during the second trimester of pregnancy. Duration of exposure was not significantly associated with the risk of NICU admissions in the second trimester of pregnancy (OR: 1.24 95%CI: 0.86 – 1.61).

Similarly, the odds of NICU admission estimated using marginal structural models were 1.7 (95%CI: 1.6 – 1.9) times higher in the group exposed to antidepressants in the second trimester as compared to the group that did not receive any antidepressants during the second trimester of the pregnancy.

Table 7 shows the odds of adverse birth outcomes such as preterm delivery, low birth weight/small for gestational age and NICU admission associated with prenatal exposure to antidepressants during the second trimester of pregnancy. Duration of exposure was not significantly associated with the risk of preterm term delivery in the second trimester (OR: 1.31 95%CI: 0.98 – 1.39).

Table 4.7 Risk of having adverse birth outcomes among depressed pregnant women exposed to antidepressants during second trimester of pregnancy and those who were not exposed to any antidepressants during second trimester of their pregnancy

Risk Associated with Prenatal Exposure to Antidepressants in the Second Trimester of Pregnancy		
	Logistics Regression OR (95% CI)	***Marginal Structural Model OR (95% CI)***
Pre-term Delivery	**1.75** *(1.16 – 2.88)*	**1.64** *(1.61 – 1.86)*
Low Birth Weight/ Small for Gestational Age	**1.76** *(1.55 – 2.10)*	**1.73** *(1.61 – 1.86)*
NICU Admission	**1.66** *(1.32 – 1.92)*	**1.73** *(1.58 – 1.92)*

***Note**: OR – Odds Ratio; NICU – Neonatal Intensive Care Unit; CI – Confidence Interval*

4.3.7 Prenatal Exposure to Antidepressants in the Third Trimester of Pregnancy and Risk of Preterm Delivery

Analysis conducted using logistic regression showed that the odds of having preterm delivery were 1.66 (95%CI: 1.58 – 2.84) times higher in the group that was exposed to antidepressants during the third trimester of pregnancy as compared to those who did not receive any antidepressants during the third trimester. Duration of exposure

was not significantly associated with the risk of preterm term delivery (OR: 1.07 95%CI: 0.76 – 1.49).

Similar results were observed when the analysis was conducted using marginal structural models. The odds of having a preterm delivery were 1.64 (95% CI: 1.58 – 1.80) times higher in women who received an antidepressant during the third trimester of pregnancy as compared to those who did not receive any antidepressants during the third trimester of pregnancy. Duration of exposure was not significantly associated with the risk of preterm term delivery in the third trimester (OR: 1.14 95%CI: 0.95 – 1.35).

4.3.8 Prenatal Exposure to Antidepressants in the Third Trimester of Pregnancy and Risk of Low Birth Weight/Small for Gestational Age

Using logistic regression is was estimated that the probability of having low birth weight/small for gestational age infants was 1.76 (95%CI: 1.32 – 1.99) times higher in the group exposed to antidepressants during the third trimester of pregnancy as compared to those who did not receive an antidepressant during the third trimester of pregnancy. Each unit increase in the duration of exposure in the first trimester was associated with 1.24 times higher odds of having low birth weight/small for gestational age (95% CI: 0.78 – 1.37), although the association was not statistically significant.

According to marginal structural models, the odds of having low birth weight/small for gestational age were 1.66 (95%CI: 1.57 – 1.79) times higher in the group receiving antidepressants during the third trimester of pregnancy as compared to the group which did not receive any antidepressant during the third trimester of pregnancy. A unit increase in the duration of exposure to antidepressants was not

significantly associated with the risk of low birth weight/small for gestational age (OR: 1.32 95% CI: 0.99 – 1.27).

4.3.9 Prenatal Exposure to Antidepressants in the Third Trimester of Pregnancy and Risk of NICU Admission

According to logistic regression the risk of NICU admissions was estimated to be 1.59 (95%CI: 1.14 – 2.00) times higher in the group exposed during the third trimester of pregnancy as compared to those who were not exposed antidepressants during the third trimester of pregnancy. Duration of exposure was not significantly associated with the risk of NICU admissions in the third trimester of pregnancy (OR: 1.35 95%CI: 0.87 – 1.95).

Similarly, the odds of NICU admission estimated using marginal structural models were 1.63 (95% CI: 1.50 – 1.80) times higher in the group exposed to antidepressants in the third trimester as compared to the group that did not receive any antidepressants during the third trimester of the pregnancy. Duration of exposure was not significantly associated with the risk of preterm term delivery in the third trimester (OR: 1.39 95%CI: 0.96 – 1.45).

Table 8 shows the odds of adverse birth outcomes such as preterm delivery, low birth weight/small for gestational age and NICU admission associated with prenatal exposure to antidepressants during the third trimester of pregnancy.

Table 4.8 Risk of having adverse birth outcomes among depressed pregnant women exposed to antidepressants during third trimester of pregnancy and those who were not exposed to any antidepressants during third trimester of their pregnancy

Risk Associated with Prenatal Exposure to Antidepressants in the Third Trimester of Pregnancy		
	Logistics Regression OR (95% CI)	***Marginal Structural Model OR (95% CI)***
Pre-term Delivery	**1.66** *(1.58 – 2.84)*	**1.64** *(1.58 – 1.80)*
Low Birth Weight/ Small for Gestational Age	**1.76** *(1.32 – 1.99)*	**1.66** *(1.57 – 1.79)*
NICU Admission	**1.59** *(1.14 – 2.00)*	**1.63** *(1.50 – 1.80)*

***Note**: OR – Odds Ratio; NICU – Neonatal Intensive Care Unit; CI – Confidence Interval*

Prenatal exposure to antidepressants was found to be associated with adverse birth outcomes such as preterm delivery, low birth weight/small for gestational age, and NICU admissions in all the three trimesters. The duration of exposure, that is the number of days the antidepressant was prescribed during a semester was not significantly associated with the risk of adverse birth outcomes. However, further analysis is required to determine the relatively safe time of exposure to antidepressants in order to minimize the risk of adverse birth outcomes such as preterm delivery, low birth weight/small for gestational age, and NICU admissions.

4.3.10 Additional Analysis

Additional analysis was conducted using only those women who had been prescribed antidepressants in only one trimester of their pregnancy. That is, women who

received antidepressants only in Trimester 1 were compared to women who received antidepressants only in Trimester 2 and women who received antidepressants only in Trimester 3, using women who got antidepressants only in Trimester 1 as the reference group. Using logistic regression we found that the risk of having low birth weight/small for gestational age was 1.3 (95% CI: 1.09 – 1.45) times higher in the third trimester as compared to the first trimester. Also, the risk was 1.2 (95% CI: 1.11 – 1.59) times higher in the second trimester as compared to the first trimester. According to marginal structural models the risk of low birth weight/small gestational age was 1.42 (95% CI: 1.38 – 1.54) times higher in the third trimester and 1.31 (95% CI: 1.26 – 1.39) times higher in the second trimester as compared to the first trimester.

Similar results were observed for NICU admissions. Logistic regression showed that the risk of NICU admissions were 1.21 (95% CI: 1.07 – 1.61) times higher in the third trimester and 1.19 (95% CI: 1.10 – 1.57) times higher in the second trimester as compared to the first trimester. Using marginal structural models the risk of NICU admission was found to 1.29 (95% CI: 1.20 – 1.37) times higher with exposure in the third trimester and 1.25 (95% CI: 1.19 – 1.40) times higher with exposure in the second trimester as compared to the first trimester.

The association of duration was still not statistically significant. The risk of adverse birth outcomes was not affected by the number of days antidepressant was prescribed in the each trimester. This additional analysis was not conducted for preterm delivery due to the nature of the outcome it would be difficult to accurately estimate the exposure.

Table 4.9 Comparison of Risk of Low Birth Weight/ Small for Gestational Age and NICU Admissions between Trimesters of Exposure to Antidepressants

Risk of Low Birth Weight/Small for Gestational Age and NICU Admission by Trimester of Antidepressant Exposure (Using Trimester 1 as the Referent Group)					
	Trim -ester 1	**Trimester 2**		**Trimester 3**	
Adverse Birth Outcome		***Logistics Regression OR (95% CI)***	***Marginal Structural Model OR (95% CI)***	***Logistics Regression OR (95% CI)***	***Marginal Structural Model OR (95% CI)***
Low Birth Weight/ Small for Gestational Age	**RG**	**1.2** (1.11 – 1.59)	**1.31** (1.26 – 1.39)	**1.3** (1.09 – 1.45)	**1.42** (1.38 – 1.54)
NICU Admissions	**RG**	**1.19** (1.10 – 1.57)	**1.25** (1.19 – 1.40)	**1.21** (1.07 – 1.61)	**1.29** (1.20 – 1.37)

***Note**: OR – Odds Ratio; NICU – Neonatal Intensive Care Unit; CI – Confidence Interval; RG – Reference Group*

4.3.11 Summary

Exposure to antidepressants in all three trimesters was associated with the risk of adverse birth outcomes. A separate analysis was conducted for each trimester, where the women getting antidepressants in that semester were compared to those who were not exposed to antidepressants at any time during their pregnancy. Duration in terms of the number of days antidepressants were prescribed during the semester was controlled for as a variable in the analysis. Duration of exposure was not associated with the risk of adverse birth outcomes.

Conducting additional analysis using women who were prescribed antidepressants only in one trimester of their pregnancy and first trimester was sued as the referent group. We found that the risk of low birth weight/small for gestational age and NICU

admissions was higher with exposure in the third and second trimester as compared to the first trimester.

4.4 SUMMARY

Through both the methods of analysis we found that the risk of adverse birth outcomes such as preterm delivery, low birth weight/small for gestational age and NICU admissions were higher in the exposed group as compared to the unexposed group. The odds of having an adverse birth outcome ranged from 1.45 (95%CI: 1.28 – 2.26) to 1.72 (95%CI: 1.63 – 1.79).

All classes of antidepressants that SSRIs, Atypicals, SNRIs, and TCAs when compared to the unexposed group, were found to be associated with a higher risk of adverse birth outcomes. Both logistic regression and marginal structural models yielded similar results. Upon comparing the different classes of antidepressants to SSRIs we found that the risk of adverse birth outcomes was not significantly different between the different types of antidepressants. Only TCAs had a statistically lower risk of NICU admissions as compared to SSRIs. Using marginal structural models we found that the risk of NICU admissions was 0.85 times (95% CI: 0.65 – 0.97) lower in TCAs as compared to SSRIs. These results are can attributed to a variety of reasons, TCA were prescribed to relatively fewer people as compared to the other antidepressants. Also, TCAs prescription has reduced over the past decade and is mostly prescribed to older women.

Exposure to antidepressants in all three trimesters was associated with the risk of adverse birth outcomes. Although the duration of exposure that is the number of days for

which the antidepressant was prescribed in each trimester was not associated with the risk of adverse birth outcomes. Conducting additional analysis we found that the risk of low birth weight/small for gestational age and NICU admissions was higher with exposure in the third and second trimester as compared to the first trimester.

Delineating the effect of antidepressants from depression using marginal structural models showed a stronger association and had narrower confidence intervals as compared to logistic regression.

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CHAPTER 5

DISCUSSION

Depression is a growing concern to healthcare professionals. It is a mental illness that can be debilitating to patients, and is costly and challenging to treat. Women are 70% more likely to suffer depression than men[1]. Depression has become a common problem during and after pregnancy. Prevalence of depressive disorders in pregnant women ranges from 14% to 23%[2-4]. Both depression and antidepressants have been associated with adverse birth outcomes such as preterm delivery[5-12], low birth weight/small for gestational age[5-12] and NICU admissions[5,10-13]. Over the past decade the proportion of pregnancies with antidepressant use has increased from 5.7% of pregnancies to 13.4% of pregnancies and is projected to increase further[1-2,14]. A similar trend was seen in our study; prescription of antidepressants increased from 8.7% in 2008 to 20.8% in 2014.

Over the past decade several studies have assessed the association between prenatal exposure to antidepressants and adverse birth outcomes, although the results have been inconsistent[15-24]. These will be discussed below, and will provide context to the results of the current study.

5.1 IMPACT OF PRENATAL EXPOSURE TO ANTIDEPRESSANTS ON RISK OF PRETERM DELIVERY

Several studies examine the incidence of preterm birth in women exposed to antidepressants during pregnancy[18, 25-32]. These include meta-analysis[25], prospective cohort studies[26,27,30], retrospective cohort studies[28-29,31], and case control studies[32,18]. Some studies examined mean gestational age (rather than preterm delivery)[30]. In the majority of studies, including the current study, prevalence of preterm delivery was considered[28-29,31-32]. In our study we found that prenatal exposure to antidepressants is significantly associated with an increased risk of preterm delivery. Similar results were seen in a meta-analysis of nine studies that showed a significant increase in preterm births with an OR 2.23 (95%CI 1.61 – 2.6)[18]. Several cohort studies which considered different classes of antidepressants (SSRIs, Atypical, TCA and SNRI) demonstrated a statistically significant increase in preterm delivery rates for all classes[21-25, 34-36]. In our study we drew a similar conclusion, all the classes of antidepressants considered were significantly associated with increased odds of preterm delivery. However, no other study estimated the relative odds of different classes of antidepressants compared to one another. Two of the afore mentioned studies showed a relationship between preterm delivery rates and late exposure[24,34]. However in our study we did not find a statistically significant difference in the risk of preterm delivery and trimester of exposure to antidepressants. A prospective cohort study conducted revealed a correlation between preterm birth and chronic exposure to antidepressants but not with short term exposure [37]. In our study we found that duration of exposure was not significant, any exposure to antidepressants during pregnancy was found to be associated with an increased risk of preterm delivery. Some

studies also demonstrated a positive finding between duration of exposure and preterm birth[34-36]. All of these studies have similar weaknesses, with no measures of actual drug exposure or controls for confounders such as smoking and, in particular, the effects of underlying depression. Some of the more rigorous studies have tried to tease out the role of untreated maternal depression. In a study of 119, 547 prescription records matched with hospital separation records, the authors found that SSRI-exposed babies had a higher rate of preterm birth than babies exposed to depression alone ($p > 0.01$)[29]. Similarly, another small prospective study compared women with depression alone and treatment with SSRIs and found a statistically significant higher preterm birth rate in the exposed infants (14% exposed group, 0% depressed group)[38]. In contrast, another small study did not detect any difference between treated and depressed groups[31]. However, in our study we found that the odds of having preterm delivery were significantly higher in depressed women who had a prescription antidepressant during pregnancy as compared to those who did not. Also, our study had the advantage of having a large sample size and detailed drug information.

5.2 IMPACT OF PRENATAL EXPOSURE TO ANTIDEPRESSANTS ON RISK OF BEING LOW BIRTH WEIGHT/SMALL FOR GESTATIONAL AGE

Similar to preterm delivery, a number of studies have examined the impact of prenatal exposure to antidepressants on low birth weight and small for gestational age. A meta-analysis showed a statistically significant risk of low birth weight for gestational age[18]. Similar results were seen in our analysis, where we report that prenatal exposure to

antidepressants was associated with an increased odds of low birth weight/small for gestational age. Several other cohort studies had similar results[26,28,29,33,39-41]; and several others had conflicting results[15,18,24,30,34,43-44]. In one study, authors attempted to increase the sensitivity of the study by using propensity scoring to control for confounders and found an effect on birth weight related to exposure[35]. Only two studies controlled for confounders such as depression, smoking, maternal age or maternal weight, and these showed no differences in birth weight in babies born to exposed or non-exposed mothers[44-45]. These studies were limited by their sample size. An increased possible risk of large birth weights following TCA treatment was reported in one study[34]. Although partially related to higher body mass index in mothers taking antidepressants, the effect did not completely disappear when this was controlled for. However these studies did not control for drug class and duration of antidepressant prescribed.

It needs to be acknowledged here that low birth weight and small for gestational age are not ideal measures for intrauterine growth; however, these are the two most commonly used measures in the literature and are generally considered together[36-39]. Studies show that the low birth weight is strongly associated with pre-term delivery; the magnitude and direction of misclassification of low birth weight differed by preterm and full term birth[40-41]. Small for gestational age has been considered to be relatively more accurate than low birth weight as the weight of infants of the same gestational age is compared[40]. In our study population there were 709 infants having low birth weight and 687 were small for gestational age. A total of 649 infants were diagnosed with both low birth weight and being small for gestational age.

5.3 IMPACT OF PRENATAL EXPOSURE TO ANTIDEPRESSANTS ON RISK OF NICU ADMISSIONS

Relatively fewer studies have examined the association between admission to NICU and prenatal exposure to antidepressants[31,36,39,43-44]. Most of the studies show some association between prenatal exposure to antidepressants and neonatal adaptation difficulties which can be measured in various ways, from gross markers such as NICU admission to more subtle evaluations such as behavioral observations. This variability in outcome measure makes it difficult to draw general conclusions. Large database or registry studies have variously suggested a 1.5 times increased risk of NICU admission with third trimester exposure compared to first trimester exposure [47]. However in our study we found exposure to antidepressants during pregnancy, irrespective of trimester, is associated with increased odds of having NICU admission. Similar to our results, a meta-analysis[48] of prospective controlled trials included consideration of 1066 mother – infant pairs and found a three-fold increased risk of SCN/NICU admission following antidepressant exposure. However, none of the studies in the meta-analysis included a depressed, non-drug-treated group. Two subsequent studies do include such a group. A study conducted in 132 infants found that exposure to citalopram during pregnancy had a four-fold increased incidence of NICU admission compared to matched infants exposed to untreated maternal depression or controls[30]. Two other controlled studies did not find an association between SSRIs exposure and NICU admission, however, these studies were limited by sample size and were prone to recall bias as information was collected through an interview with the mothers. Studies examining the impact of prenatal exposure to TCAs are limited to case reports and case series. Several case reports

describe an association between prenatal exposures to clomipramine[49-50] and imipramine[51-52] with NICU admissions. With regard to the newer antidepressants, evidence is scant. Some of the studies include venlafaxine exposure[53-56] and suggest a similar rate of NICU admissions as that associated with SSRIs. However, none of the studies control for duration and time of exposure and do not estimate the relative impact of the different types of antidepressants.

5.4 ADDRESSING THE GAPS IN THE LITERATURE

In our study, we found that the prenatal exposure to antidepressants is associated with higher odds of having an adverse birth outcome such as preterm delivery, low birth weight/small for gestational age, NICU admissions. This association was not affected by the type of antidepressant prescribed or the trimester of exposure. Our study results are consistent with several studies in the existing literature[26,28,29,33,39-41], but are conflicting with several others[8-11,15,18,24,30,34,43-44]. The current literature on the impact of prenatal exposure to antidepressants on adverse birth outcomes has inconsistent results. There are several possible reasons for these inconsistencies. First, studies have used a variety of different methodologies[18,57-59], which make them difficult to compare. Second, many studies lack an appropriate control, which introduces many threats to internal validity[18,57-59]. Third, most of the studies look only at prenatal exposure to selective serotonin reuptake inhibitors (SSRIs); there is limited information available on other classes of antidepressants[18,57-59]. Fourth a number of studies have failed to control for confounders such as maternal smoking, parity, and duration of exposure to antidepressants and most importantly maternal depression[18,57-59]. Through our study we have tried to address these gaps in the literature in the following ways:

5.4.1 Controlling for Maternal Depression

Studies show that maternal depression can have an impact on the pregnancy and fetus[15]. Untreated depression has been found to be associated with preterm delivery, low birth weight and small for gestational age[15-17].We controlled for maternal depression in our study. The information on maternal depression was obtained from the SC Medicaid claims database using the ICD 9 diagnosis. In addition we have used marginal structural models to delineate the effect of antidepressants from the effect of depression itself on the adverse birth outcomes[62-63].

5.4.2. Larger Focus on SSRIs

Since SSRIs are the most commonly prescribed antidepressants, a majority of the studies focus on the impact of prenatal exposure to SSRIs alone on adverse birth outcomes. Although there is still information available about the impact of prenatal exposure to TCAs, the information related to Atypical and SNRIs is scant. In our study we have examined the association of prenatal exposure to all the classes of antidepressants that SSRIs, Atypical, SNRIs, and TCAs. We also did a comparative analysis using SSRIs as the reference group to estimate relative safety of the antidepressants. We found that there is no statistically significant difference in risk of adverse birth outcomes across the multiple drug classes, compared to SSRIs.

5.4.3. Inadequate Controlling for Confounders

Several of the studies examining the impact of prenatal exposure to antidepressants on adverse birth outcomes fail to control for confounders such as

smoking status, mother's BMI, gestational diabetes, gestation hypertension, duration and trimester of exposure to antidepressants etc. In our study we controlled for all of these confounders. Through the linkage of SC Medicaid claims data with birth certificates we were able to access important information such as mother's smoking status before and during pregnancy, gestational diabetes, gestational hypertensions, mother's BMI, level of prenatal care, and history of poor birth outcomes. In addition to this we also had detailed information regarding the antidepressants prescribed which helped us control for duration and trimester of exposure.

5.4.4. Observational Studies/Establishing a Causal Relationship

All the studies conducted to examine the association between prenatal exposure to antidepressants and risk of adverse birth outcomes have been observational. Several standard methods have been used in this setting to estimate the association between prenatal exposure to antidepressants and the risk of adverse birth outcomes. However, none of the methods can be used to establish causality. Ideally a randomized controlled trial would be conducted to establish a causal association. Due to ethical concerns we cannot randomize treatment in this study population. Hence we used marginal structural models, a relatively new technique that has not been used in the field of reproductive epidemiology[63-64]. In MSM, we used counterfactuals to create a pseudo population that is similar to our actual study population[62]. Using this pseudo population we were able to statistically mimic a randomized control trial[62-66].

The result from the two analysis were in the same direction; both logistic regression and marginal structural models estimated an increase in the risk of adverse birth outcomes. When conducting analysis using logistic regression the odds of having

preterm delivery were 1.58 (95%CI: 1.19 – 2.10) times higher in the study participants that received an antidepressant during pregnancy as compared to those who did not receive any antidepressants at any time during the pregnancy. Whereas, according to the analysis conducted using marginal structural models, the odds of preterm delivery were 1.72 times (95% CI: 1.63 – 1.79) in the group that received antidepressants during pregnancy as compared to the group that did not receive an antidepressant during pregnancy. Similar results were observed for low birth weight/small for gestational age and prevalence of NICU admissions. Using logistic regression it was estimated that antidepressant use during pregnancy was associated with higher odds of the infant having low birth weight/being small for gestational age, OR = 1.57 (95% CI: 1.42 – 2.76) and/or NICU admissions, OR: 1.45 (95%CI 1.28 – 2.26). Marginal structural models showed that the prenatal exposure to antidepressants increased the odd of having low birth weight/small for gestational age 1.63 times (95%CI: 1.53 – 1.73) and the odds of having a NICU admission by 1.66 times (95% CI: 1.58 – 1.73).

Marginal structural models gives a stronger association. This is possibly due to the fact that they control for maternal depression more effectively providing with the effect of antidepressants alone on the risk of adverse birth outcomes. Also, marginal structural models provide us tighter confidence intervals. Marginal structural models and logistic regression both suggest that prenatal exposure to antidepressants is associated with an increased risk of adverse birth outcomes. The weights used in marginal structural models can be interpreted as the number of copies of each observation that are necessary to form a pseudo-population in which use antidepressants is confounded. Hence, the results are more robust with narrower confidence intervals.

5.5 CONCLUSION

In our study we examined the impact of prenatal exposure to antidepressants on adverse birth outcomes such as preterm delivery, low birth weight/small for gestational age and NICU Admissions. We conducted the analysis using two different statistical techniques. First logistic regression, as this is the most commonly used technique and would help us make our results more comparable. Second, we used marginal structural models, a relatively new method which helped us delineate the effect of antidepressants from the effect of depression. Marginal structural models also helped us to mimic a randomized control trial statistically which cannot be conducted practically in this scenario. Using both analyses we found that prenatal exposure to antidepressant is significantly associated with an increase in the odds of having adverse birth outcomes such as preterm delivery, low birth weight/small for gestational age, and NICU admissions. The odds ratio ranged from 1.58-1.99 and were all statistically significant. Further we did a comparative analysis between the different types of antidepressants using SSRIs as the reference group. We found that all antidepressants are associated with the risk of adverse birth outcome, there is no difference in the measure of risk among the various classes of antidepressants compared to the referent category, SSRI. We also found that the duration and trimester of exposure to antidepressant did not significantly impact the risk of adverse birth outcomes.

We addressed some of the key concerns in the existing literature through our study. We not only controlled for maternal depression which is an important confounder but we were also able to control for confounders such as maternal smoking, maternal

BMI, parity, risk of previous adverse birth outcomes etc. We also did an analysis to compare the relative risk of the class of antidepressants on the risk of adverse birth outcome by using SSRIs as the referent group. This analysis gave more insight into the other classes of antidepressants and also attempted to establish their relative safety. We used to separate analytical tools for this study. We used the traditional logistic regression to ensure that our study is comparable to other studies in the current literature. We also used the relatively new marginal structural models to statistically mimic a randomized controlled trial from observational data. In conclusion we found that prenatal exposure to antidepressants is significantly associated with a higher risk of adverse birth outcomes such as preterm delivery, low birth weight/small for gestational age, and NICU admissions, irrespective of the type of antidepressant prescribed and duration and trimester of exposure.

5.5.1 Strengths

The strengths of our study are:

1. This study was conducted using a merged dataset from South Carolina Medicaid and South Carolina Registry of Births which is a database of all birth certificates issued in the state of South Carolina. This provided us a rich data which captured a number of important confounders such as prenatal care, mother's education, mother's weight, uterine bleeding etc. as well as risk factors such as maternal smoking, alcohol use, gestational diabetes, gestational hypertension etc.
2. The merged dataset also allowed us to control for behavioral confounders such as, maternal smoking, maternal alcohol use, maternal race, maternal and paternal occupation, conditions during the pregnancy (ex. gestational hypertension,

anemia, eclampsia, gestational diabetes, uterine bleeding), birth abnormalities or anomalies (ex. cleft palate, heart malformations), multiple births, etc. Data from the birth certificates gave us information regarding the birth outcomes such as pre-term delivery, low birth weight/small for gestational age, and NICU admissions which helped us identify the cases accurately.

3. This study has attempted to explore the causal association between prenatal exposure to antidepressants and risk of adverse birth outcomes using MSM within an observational data set.
4. The South Carolina Medicaid finances about 50% of total births in state. This gave us a large enough sample size to facilitate detailed subgroup analysis and confidently extrapolate our findings to this population results.
5. South Carolina Medicaid has a strong representation of vulnerable populations including racial/ethnic minorities generally representative of the state population. Race and ethnicity are recorded in this database, in contrast to many commercial databases. The South Carolina Medicaid population is relatively homogeneous with respect to the socio-economic status.
6. South Carolina Medicaid Claims database can be merged with the birth certificates which contained information on confounders such as mother's BMI, parity, smoking status etc. Maternal obesity, smoking during pregnancy and parity have been found to significantly associate with the risk of adverse birth outcomes. Having information on these confounders allowed us to control for them in our analysis.

5.5.2 Limitations

Some of the limitations of our study are:

1. The study was conducted using the South Carolina Medicaid database which limits generalizability for the results to other states.
2. Depression is often associated with other psychiatric illnesses, in this study we did not control for other psychiatric disorders or prescription of antipsychotic medicines.
3. Only the month and year of delivery/birth date was given in the Medicaid database hence for the ease analysis we used the 15 of each month as the date. As a result the date of conception and trimester dates might not be accurate.
4. There is a potential of considerable misclassification arising from the use of low birth weight as an outcome. Low birth weight is associated with preterm birth, so the magnitude and direction of misclassification will differ by preterm and full term birth. Also, small for gestational age may not be a perfect measure for intrauterine growth. As the estimated gestational age might not be accurate.
5. Since this is an observational study, we cannot draw a causal inference of association. Although MSM helps statistically mimic a randomized control trial, there might be some unobserved confounders that we could not control for.
6. The causal inference from our MSM depends on two key assumptions
    a. We assumed that the covariates in maternal depression are sufficient to adjust for both confounding and selection bias due to loss to follow-up.

b. We assumed that our MSM for the effect of antidepressants on adverse birth outcomes is correctly specified. In an observational study, these assumptions cannot be tested.

5.5.3. Future Research Recommendations

Current research shows that antidepressant use in pregnancy is well studied and gives sufficient evidence to state that the treatment of pregnant women with antidepressants is a challenging and complex task for the healthcare providers. In our study we have tried to establish a causal association between prenatal exposure to antidepressants and adverse birth outcomes, further research in the field is needed. Studies have not yet adequately controlled for factors that can adversely affect pregnancy and birth outcomes, such as other maternal illness or adverse health behaviors (e.g., alcohol consumption, recreational drugs, etc.). Hence there is a need for more focused studies that take into account these important factors, as they may influence the association between antidepressant exposure and adverse birth outcomes. There is a need to study the duration of exposure with more precision, while taking into account the patient's adherence to the prescribed medications. Also there is a need to examine and clarify a dose response relationship between the prenatal exposure to antidepressants and risk of adverse birth outcomes, if such a relationship exists This would help clinicians know the threshold dose they can use to treat cases that absolutely require pharmacotherapy to control depression. Another recommendation would be to include more recently approved antidepressants. Lastly, there is a need for a more inclusive definition of exposure which measure the dose, duration, trimester of exposure, and the

gaps in therapy. Such a definition would allow a more comprehensive measure of the construct, resulting in more precise results and conclusions.

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APPENDIX A: CORRELATION MATRIX OF THE VARIABLES INCLUDED IN THE ANALYSIS

Table A1 Correlation Matrix of the Variables Included in the Analysis

	Mother's Age (Years)	Mother's Weight	Mother's Education	Prenatal Care (Kotelchuck Index)	Smoking Status	Parity	Number of Risk Factors	Infant Sex	Mother 's Race	Year of Birth	Antidepressant Use
Mother's Age (Years)	1.00										
Mother's Weight	0.27	1.00									
Mother's Education	-0.13	0.05	1.00								
Prenatal Care (Kotelchuck Index)	0.20	0.11	0.16	1.00							
Smoking Status	-0.13	0.04	-0.06	0.12	1.00						
Parity	0.22	0.57	0.25	0.08	0.40	1.00					
Number of Risk Factors	0.52	-0.63	0.31	0.62	0.24	0.24	1.00				
Infant Sex	0.23	0.15	0.03	0.00	-0.64	0.10	-0.36	1.00			
Mother’s Race	-0.45	0.31	-0.07	-0.01	0.59	0.12	0.32	0.34	1.00		
Year of Birth	0.60	-0.44	0.12	0.02	0.55	0.14	0.29	0.33	0.22	1.00	
Antidepressant Use	-0.67	0.52	0.17	0.04	-0.50	0.16	-0.26	0.32	-0.23	-0.28	1.00