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ORIGINAL ARTICLE

The effect of maternal antidepressants on third trimester uteroplacental hemodynamics and the neonatal abstinence syndrome: a retrospective cohort study

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Abstract

The objective of this study is to determine whether maternal antidepressant use during pregnancy influences uteroplacental hemodynamics, thereby affecting fetal growth and gestational age at delivery. The secondary aim was to determine the incidence of neonatal abstinence syndrome (NAS) among infants exposed to antidepressant medications. The charts of women who received obstetrical care and had a history of depression from January 2014 to December 2016 at Mount Sinai Hospital in Toronto, Canada, were reviewed. Exclusion criteria were substance abuse; narcotic or lithium use at the time of delivery.

In total, 205 women met the inclusion criteria (92 took antidepressants; 113 women did not). There were no significant differences in umbilical artery pulsatility index (PI), gestational age at delivery, or birth weight when comparing women based on antidepressant use. A small proportion (18%) of neonates had mild withdrawal symptoms; one baby had a score (≥ 8) consistent with severe NAS. In women with a history of depression, there was no difference in uteroplacental hemodynamics as measured by third trimester Doppler ultrasonography when comparing women who took antidepressant medication versus those who did not. The large majority of babies who were exposed to antidepressants in utero did not show withdrawal symptoms. These results lend support for the relative safety of antidepressants during pregnancy.

Keywords SSRI · Antidepressant · Pregnancy · Depression · Birth outcome · Doppler · Growth

Introduction

Depression and anxiety occur in up to 20% of pregnancies (Bennett et al., 2004; Marcus et al., 2003). Untreated antenatal mood disorders have been linked to preterm birth (PTB), low birth weight, and intrauterine fetal growth restriction (IUGR) (Marcus et al., 2003). Women with antenatal depression and anxiety are more likely to have poor self-care during pregnancy, post-partum depression, and poor maternal-infant bonding (Marcus et al., 2003; Dubber et al., 2015). A recent population-based cohort study showed that maternal suicide accounted for 5.3% of all perinatal maternal deaths (encompassing pregnancy and the first year postpartum) in Ontario, Canada, over a 15-year period (Grigoriadis et al., 2017). This study highlights the importance of adequate treatment of psychiatric symptoms during pregnancy, which may include pharmacotherapy. It has been shown that 3–8% of women will take antidepressants during pregnancy (Charlton et al., 2015). However, much remains unknown about maternal-fetal physiological effects.

Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are the most commonly used antidepressant medications in pregnancy. Although these medications are first-line treatments for depression and anxiety, inconsistent reports have suggested an association with an earlier gestational age at delivery and lowered birth weights (Lund et al., 2009; Oberlander et al., 2006; Viktorin et al., 2016; Wen et al., 2006; Eke et al., 2016). In addition, there remains ongoing concern that babies born to mothers taking SSRIs may have neurobehavioral disturbances, consistent with a neonatal abstinence syndrome (NAS) (Forsberg et al., 2014; Sanz et al., 2005; Levinson-Castiel et al., 2006). Studies have reported the incidence of

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NAS in SSRI-exposed neonates to range from 25 to 30%, with 3–13% rated as severe (≥ 8 on two or more occasions).

Although many have examined the incidence of preterm birth and low birth weight in infants born to mothers taking SSRIs in pregnancy, little is understood about the mechanisms by which this occurs. Serotonin acts as a potent vasoconstrictor but its effect on uteroplacental blood flow is unknown. Abnormal Doppler studies at the time of ultrasound investigation reflect uteroplacental insufficiency, and have been associated with IUGR and pre-eclampsia (Vythilingum et al., 2010). Several studies have shown an association between maternal anxiety in pregnancy and increased uterine artery pulsatility index (PI), which may help explain the link between SSRI use and low birth weight (Vythilingum et al., 2010; Teixeira et al., 1999). However, these findings have not been consistently reproduced and conflicting studies have not shown an association between maternal anxiety and second and third trimester Doppler indices (Harville et al., 2008; Kent et al., 2002).

The first objective of this study was to determine whether maternal antidepressant use during pregnancy influences uteroplacental hemodynamics as measured by umbilical artery Doppler flow. It was hypothesized that SSRI/SNRI use during pregnancy may be negatively associated with altered umbilical artery flow, as measured by Doppler velocimetry. Such alterations may then result in impaired fetal growth and preterm delivery. The second objective of this study was to determine the rate of neonatal abstinence syndrome (NAS) among infants exposed to maternal SSRI and SNRIs.

Materials and methods

Following research ethics board approval (REB: 14-0207-C), a retrospective cohort study was performed of women who received care at Mount Sinai Hospital (MSH) in Toronto, Ontario, Canada, from January 2014–December 2016. Pregnant women were included if they had a self-reported diagnosis of "depression" (current or lifetime). Women were excluded if they gave birth very prematurely (< 28 weeks gestation), or if they used substances of abuse, narcotics, or lithium during pregnancy, as documented in the electronic chart. Substance abuse was self-reported. These criteria were chosen a priori as they may influence symptoms of neonatal abstinence syndrome. Women who experienced an intrauterine fetal demise (IUFD) in the second trimester were excluded as third trimester Doppler ultrasound data was unavailable.

Charts were reviewed to abstract basic demographic information (age, marital status, BMI, smoking status, substance use); maternal medical history; current medication use; Doppler ultrasound indices (umbilical artery PI, systolic/diastolic ratio (S/D), peak systolic velocity (PSV)); obstetrical data (gestational age at birth, birth weight, APGARs, presence of congenital abnormalities) and neonatal outcomes (duration of stay in the NICU, presence or absence of NAS, NAS score and associated symptoms). When a patient self-reported antidepressant use during the pregnancy, this was confirmed by the medical team in the medial record at the time of delivery. NAS scoring was performed by registered nurses for infants whose mothers' self-reported current SSRI or SNRI use at the time of delivery, and not for those who discontinued their medication during pregnancy, as per hospital protocol.

The primary outcome was third trimester umbilical artery Doppler PI. The secondary outcomes were presence of mild (score of ≥ 4 on two or more occasions) or severe (score of ≥ 8 on two or more occasions) NAS, using the Finnegan Scale which is performed routinely on SSRI-exposed infants at MSH (Levinson-Castiel et al., 2006; Finnegan, 1990).

Data were analyzed using SPSS statistical software (Version 25, SPSS Incorporated, Chicago, IL, 2017). Comparisons of the demographic data between the two groups were completed using Student's *t* test for continuous data and Chi-square analysis for categorical data. A univariate analysis of variance (ANOVA) was used to compare the Doppler indices (PI; S/D; PSV of those taking SSRIs, SNRIs or bupropion vs. those who did not), using gestational age as a covariate.

Results

In total, 247 charts were identified and reviewed. Of these, 205 women with a self-reported history of depression were included in the analysis; 42 were excluded. Those excluded from the study did not differ significantly from those who were included when comparing demographic data and birth outcomes. There were co-morbid psychiatric conditions in the included sample; 12 women also reported a history of bipolar disorder; 76 reported a history of anxiety; 5 reported a history of attention deficit disorder; 3 reported a history of post-traumatic stress disorder; 2 reported a history of obsessive-compulsive disorder; and 1 reported a history of schizophrenia.

One patient was excluded as she had an umbilical PI value that was more than 3 standard deviations outside of the mean. Of the women included, 113 had a diagnosis of depression but did not use antidepressant medication during their pregnancy. Ninety-two other women used SSRIs, SNRIs, or bupropion during pregnancy, but 8 women discontinued their medication in the second or third trimester. All women who had taken antidepressant (AD) medication during pregnancy were grouped together for the analyses as it was hypothesized that early exposure would be most predictive of placental hemodynamics, according to the gestational period when the placenta is formed. It should be noted that a sensitivity analysis showed no differences on any of the outcomes of interest when those who discontinued were excluded.

Table 1 shows basic demographic information for the two groups. There were no statistically significant differences between the two groups with respect to age, marital status, educational level, smoking status, or alcohol use in pregnancy. Body mass index (BMI) was found to be significantly higher in the AD group, as compared to those who were not exposed (29.8 vs. 25.1, $p < 0.002$). Of note, there was no significant difference in incidence of hypertensive disorders of pregnancy between groups.

Doppler data was available for 195 (95%) women. Ten women did not have a third trimester ultrasound performed, rendering Doppler data unavailable. However, these women were included to assess secondary outcomes. The third trimester Doppler ultrasound indices are presented in Table 2. There were no significant differences between umbilical artery PI, PSV, and S/D ratio in women exposed to AD in pregnancy, as compared to those who did not. Maternal BMI was not controlled for as BMI data was missing for $n = 34$. Additionally, a Pearson's correlation statistic was performed, and BMI was not found to be significantly associated with any of the Doppler measures.

Birth outcome data was available for 200 (98%) women (Table 3). Of those included in the study, 6 delivered at an outside hospital, rendering birth outcome data unobtainable. There were no significant differences in the gestational age at delivery, birth weight, fetal gender, the proportion of infants delivered preterm, or the delivery type. Median APGAR scores at 1 and 5 min were comparable between the two groups. A total of 8 infants were born with congenital abnormalities and the incidence did not differ between the two groups (Table 4). However, the number of infants admitted to the NICU was significantly higher in the antidepressant group, as compared to those not taking antidepressants (22.4% vs. 8.9%, $p < 0.02$). Further analysis of those admitted to the NICU revealed that 3 infants were admitted to the NICU secondary to congenital abnormalities, 1 for meconium aspiration, 3 for transient tachypnea of the newborn and difficult transition, 1 for observation secondary to maternal myasthenia gravis, 1 following a "code pink" of unknown etiology, and 11 were admitted for complications secondary to prematurity. Reason for admission did not differ greatly between the two groups. The most common reason for admission in both groups was prematurity.

Of the 92 women in the AD group, 8 stopped medication prior to delivery and thus NAS scoring of their infants was not performed. Eighty-three women who delivered at MSH were

Table 1 Demographic information

	Antidepressant medication during pregnancy ($n = 92$)	No antidepressant medication during pregnancy ($n = 113$)
Age	33.6	32.8
BMI	29.8*	25.1*
Marital status	$n = 86$	$n = 109$
Single	7 (8.1)	16 (14.5)
Dating (%)	5 (5.8)	1 (0.9)
Common law (%)	13 (15.1)	21 (19.3)
Married (%)	61 (70.9)	71 (65.1)
Maternal education	$n = 68$	$n = 88$
High school (%)	12	21
College (%)	12	19
University (%)	37	39
Masters or professional degree (%)	7	10
Nulliparous (%)	48 (52.2)	66 (58.4)
Smoker (%)	10 (9.1)	10 (12.2)
Alcohol use (%)	4 (3.6)	2 (2.2)
Hypertensive disease in pregnancy (%)	12 (13.0)	12 (10.6)

*$p < 0.05$

Table 2 Third trimester umbilical artery indices in patients with a history of depression. Stratified by whether or not they took psychotropic medication in pregnancy. Values represent the means (SD)

	Antidepressant medication during pregnancy ($n = 89$)	No antidepressant medication ($n = 106$)
GA at ultrasound (weeks)	34 (4.68)	34.7 (2.96)
Umbilical PI	0.95 (0.19)	1.0 (0.2)
Umbilical PSV	49.2 (11.3)	49.9 (10.5)
Umbilical S/D	2.7 (0.6)	2.8 (0.6)

Table 3 Birth and neonatal outcomes in women with depression. Stratified by whether or not they took psychotropic medication in pregnancy. Values represent the means

	Antidepressant medication during pregnancy ($n = 91$)	No antidepressant medication during pregnancy ($n = 109$)
GA at delivery (SD)	38.1 (2.2)	38.9 (1.7)
Male sex (%)	41 (45)	49 (45)
Preterm (%)	17 (18.7)	15 (13.9)
Birth weight (kg, SD)	3227 (568.2)	3292 (656.6)
Delivery type		
Vaginal delivery (%)	44 (48.3)	57 (52.3)
Operative delivery (%)	10 (11)	12 (11)
Cesarean section (%)	37 (40.7)	40 (36.7)
Median APGAR 1-min	9	9
Median APGAR 5-min	9	9
NICU admission (%)	20 (22.4)*	10 (8.9)*

*$p < 0.05$

Table 4 Congenital anomalies identified in the antidepressant medication and no antidepressant medication groups

Congenital anomaly	Antidepressant medication during pregnancy	No antidepressant medication during pregnancy
Bronchogenic cyst	0	1
Cyanotic heart disease	1	0
Ebstein's anomaly	1	0
Mild ventriculomegaly	0	1
Narrow aortic arch	0	1
Pierre Robin sequence	0	1
Trisomy 21	0	1
Tetrology of Fallot	0	1
Total	2	6

taking AD medication at the time of delivery, and of those, NAS scoring was performed on 77 infants. NAS scoring is not routinely done for bupropion ($n = 1$). Of the remaining infants who did not have NAS scores available, 3 of them were transferred out to the Hospital for Sick Children immediately after birth and 2 had incomplete/missing data.

Of the 77 infants with completed NAS scores, 14 (18.2%) met the criteria for mild NAS (score of ≥ 4 on two or more occasions) and 1 (1.3%) met the criteria for severe NAS (score of ≥ 8 on two or more occasions). In Table 5, the proportion of NAS by drug is presented. The 1 infant who was affected by severe NAS was born to a mother taking fluoxetine. This infant was also exposed to the antipsychotic, quetiapine. Of those classified as mild NAS, 5 (36%) were also exposed to insulin as compared to only 6 (10%) in the no NAS group. Notably, 5 (36%) of the newborns with mild NAS had evidence of hypoglycemia (BS < 2.5 mmol/L), which may represent a mediating or confounding factor. Symptoms of NAS varied widely across those classified as mild NAS. The most common were sleep disturbance in 8 (53%) infants, followed by mild tremors in 5 (33%) infants, and excessive sucking in 5 (33%) infants.

Discussion

In this retrospective cohort study, we did not find a significant difference in uteroplacental blood flow, as measured by umbilical artery PI, when comparing women who took antidepressants during pregnancy to those who did not. There were no significant differences in birth outcomes (gestational age at delivery, birth weight, incidence of congenital anomalies) between the two groups. In babies born to mothers taking antidepressants during pregnancy, the incidence of severe NAS (score of ≥ 8 on two or more occasions) was low ($n = 1$ infant) and the incidence of mild NAS (score of ≥ 4 on two or more occasions) was lower than expected at 18.2%. However, the incidence of NICU admission was higher in the group exposed to antidepressant medication when compared with those who were not exposed (22.4% vs. 8.9%, $p < 0.02$). Overall, these findings provide data to support the relative safety of antidepressant medications taken during pregnancy for a major depressive episode or an anxiety disorder.

Our Doppler study results, showing no significant effect of antidepressant medication, were consistent with those found by Monk et al. in 2012 (Monk et al., 2012). Their study examined uteroplacental blood flow in pregnant women who had a lifetime history of mental illness and found no association between serotonergic antidepressant use and umbilical or uterine artery Doppler indices (Monk et al., 2012). Their cohort was smaller than ours ($N = 101$ pregnant women with a lifetime history of mental illness); of which, 72% were exposed to SSRIs, but was prospective in nature (Monk et al., 2012). Together, these results suggest that maternal antidepressant use does not negatively influence blood flow to the fetus through the maternal-placental unit.

Although few studies have looked specifically at changes in uteroplacental hemodynamics in SSRI-exposed pregnancies, a recent study by Yonkers et al. found an increase in hypertensive disorders among women who took SSRIs during pregnancy (Yonkers et al., 2017). Hypertensive disorders of

Table 5 Incidence of NAS stratified by medication taken during pregnancy. Mild NAS is a score of ≥ 4 on two or more occasions. Severe NAS is a score of ≥ 8 on two or more occasions

Medication	Total	No NAS (%)	Mild NAS (%)	Severe NAS (%)	Stopped medications during pregnancy or NAS scoring not documented (%)
Bupropion	4	3 (75)	0	0	1 (25)
Citalopram	16	12 (75)	2 (12.5)	0	2 (12.5)
Duloxetine	3	1 (33.3)	1 (33.3)	0	1 (33.3)
Escitalopram	26	19 (73.1)	5 (19.2)	0	2 (7.7)
Fluoxetine	7	4 (57.1)	1 (14.2)	1 (14.2)	1 (14.2)
Paroxetine	2	2 (100)	0	0	0
Sertraline	15	9 (60)	1 (6.7)	0	5 (33.3)
Venlafaxine	17	12 (70.6)	4 (23.5)	0	1 (5.9)
Desvenlafaxine	1	0	0	0	1 (100)
Total	92	62 (67.4)	14 (15.2)	1 (1.3)	15 (16.3)

pregnancy are often associated with changes in uteroplacental hemodynamics. However, our study does not support these findings. Women in our cohort who took antidepressant medication did not have a higher incidence of hypertensive disorders of pregnancy, as compared to those who did not. This was further supported by our comparable values of uteroplacental blood flow among exposed and not exposed pregnancies.

The incidences of low birth weight and preterm birth have been reported as increased among infants born to mothers taking SSRIs (Sahingoz et al., 2014; Jarde et al., 2016). In 2014, Sahongiz et al. found that individuals with untreated depression had lowered birth weights and higher incidences of preterm delivery when compared to both healthy controls and those taking antidepressants (Sahingoz et al., 2014). However, this difference was not seen when comparing healthy controls to women with treated depression (Sahingoz et al., 2014). More recently, a systematic review by Jarde et al. in 2016 showed that pregnant women with depression who were not receiving any treatment had a significantly increased risk of preterm birth and infants with small size at birth with a trend toward increased risks for women with more severe depression (Jarde et al., 2016). Another systematic review performed by Eke et al. in 2016 (Eke et al., 2016) looked at the risk of preterm birth among women who took SSRIs while pregnant. Their analysis showed an elevated risk for preterm birth in SSRI-exposed women, when compared to both healthy controls and depressed women who did not take medication (Eke et al., 2016). Our study did not demonstrate a significant effect of maternal antidepressant use on birth weight or the incidence of preterm birth. However, our comparison group consisted of non-medicated women with a lifetime diagnosis of depression, not healthy controls. The mean birth weight in our cohort was 3263 g which is lower than the Canadian mean of 3344 g in 2014 (Statistics Canada, 2015). In our cohort, 16% of all babies born were found to be premature, which is higher than the national average of 8% (2013 statistics) (Statistics Canada, 2016). We may be limited by not having a healthy control group for comparison.

The incidence of NAS, both mild and severe, was lower in our study than previously reported in the literature. Only one infant was found to have "severe NAS" (score of ≥ 8 on two or more occasions), who was born to a mother taking fluoxetine and an antipsychotic (quetiapine) during pregnancy. It is difficult to ascertain the effects of quetiapine as little research is available regarding the potential influence of concomitant antipsychotic use on NAS scores. One recent study looked at the effects of psychotropic medications (including antipsychotics) on infant NAS scores among those exposed to opioid medications during pregnancy (Huybrechts et al., 2017). The use of psychotropic medication increased the risk and severity of NAS among opioid-exposed neonates (Huybrechts et al., 2017). We speculate that the use of quetiapine may have contributed to the elevated NAS scores in this infant, and may not be generalizable to women with monotherapy.

A mild neonatal abstinence syndrome (score of ≥ 4 on two or more occasions) was seen in 14 (18.2%) of infants exposed to SSRIs or SNRIs during pregnancy, which is lower than previously reported. Levinson-Castiel et al. (Levinson-Castiel et al., 2006) were the first group to use the Finnegan score to quantify symptoms of neonatal withdrawal among SSRI-exposed babies. They reported the incidence of severe NAS to be 13% and the incidence of mild NAS to be 17% among a cohort of 60 infants exposed to SSRIs in utero (Levinson-Castiel et al., 2006). More recently, Forsberg et al. (Forsberg et al., 2014) performed a retrospective cohort study of women taking SSRIs during pregnancy. Among 205 infants exposed to SSRIs in utero, they reported severe NAS in 7 infants (3.4%) and mild NAS in 46 infants (22%) (Forsberg et al., 2014). Among our cohort at MSH, the symptoms of withdrawal exhibited by those infants with mild and severe NAS varied widely. The most common symptoms seen were sleep disturbances (i.e., sleeping less than 2 or 3 h between feedings), excessive sucking, and mild tremors. It is important to note that similar symptoms can be seen in non-exposed newborns. To highlight this point, Zimmermann-Baer et al. investigated the variability in NAS scoring in 103 infants born to mothers who did not take medication during pregnancy (Zimmerman-Baer et al., 2010). They found 5/103 infants had high scores between 8 and 11 points, on at least one occasion with the most common symptoms being high-pitched cry, short sleep after feeding, vomiting, and sneezing (Zimmerman-Baer et al., 2010). Although none of the healthy infants in their study met the criteria for severe NAS, the presence of mild NAS was not mentioned. Given that healthy infants can display similar symptoms to infants exhibiting "withdrawal," and that no treatment is required for infants meeting the criteria for mild NAS, patients should be counseled appropriately. Patients can be reassured that 80% of exposed babies who underwent NAS scoring did not meet the criteria for even mild NAS. Further, among babies that exhibit withdrawal, the symptoms are most often mild and self-limited. Based on our results, we hope to reassure patients taking SSRIs and SNRIs that the incidence of clinically significant withdrawal is extremely low (1.3%) and is more likely to occur among those with multiple risk factors.

This study has several limitations. Firstly, it is a retrospective cohort study and some data, including that containing primary and secondary outcomes, were unavailable. It should be noted that the psychiatric diagnoses were reliant on self-report, rather than a formal psychiatric evaluation. Self-report was also used for medication use. Although this was confirmed again at the time of delivery, it is possible that some women did not take their medication as prescribed. In addition, it was difficult to determine the indication for antidepressant use. It is possible that women in the antidepressant group

had more severe symptoms requiring medication, or alternatively, it may be that women in the unmedicated group elected to stop medications prior to pregnancy for personal reasons. We did not have a healthy control group for comparison. As uterine artery measures were unavailable, we used umbilical artery indices as a marker of uteroplacental insufficiency. Some studies have indicated that the uterine artery may be a more reliable marker. Future prospective cohort studies would be beneficial to elucidate a more comprehensive understanding of the possible influence of antidepressant medication on uteroplacental hemodynamics. Lastly, we were unable to determine breastfeeding status of individuals based on chart review alone. This information would be helpful in determining whether or not breastfeeding in exposed infants increases the incidence of severe NAS.

In conclusion, our study demonstrates no difference in uteroplacental blood flow hemodynamics in the third trimester in women taking antidepressant medications. Additionally, infants born to mothers taking antidepressants did not have lower birth weights or more preterm deliveries than their unexposed counterparts. Only a very small proportion of babies exposed to maternal antidepressant medication exhibited severe withdrawal symptoms. These results of this retrospective study lend support for the women who require antidepressant medications during pregnancy.

Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Mount Sinai Hospital Research Ethics Board (MSH REB no. 14-0207-C). As this was a retrospective chart review study, informed consent was not required.

Conflict of interest The authors declare that they have no conflict of interest.

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References

Bennett HA, Einarson A, Taddio A, Koren G, Einarson TR (2004) Prevalence of depression during pregnancy: systematic review. Obstet Gynecol 103:698–709

Charlton RA, Jordan S, Pierini A, Garne E, Neville AJ, Hansen AV, Gini R, Thayer D, Tingay K, Puccini A, Bos HJ, Nybo Andersen AM, Sinclair M, Dolk H, de Jong-van den Berg L (2015) Selective serotonin reuptake inhibitor prescribing before, during and after pregnancy: a population-based study in six European regions. BJOG 122:1010–1020

Dubber S, Reck C, Muller M, Gawlik S (2015) Postpartum bonding: the role of perinatal depression, anxiety and maternal-fetal bonding during pregnancy. Arch Womens Ment Health. 18(2):187–195

Eke AC, Saccone G, Berghella V (2016) Selective serotonin reuptake inhibitor (SSRI) use during pregnancy and risk of preterm birth: a systematic review and meta-analysis. BJOG 123:1900–1907

Finnegan LP (1990) Neonatal abstinence. In: Nelson NM (ed) Current therapy in neonatal–perinatal medicine, 2nd edn. BC Decker Inc, Toronto, Ontario

Forsberg L, Navér L, Gustafsson LL, Wide K. Neonatal adaptation in infants prenatally exposed to antidepressants—clinical monitoring using neonatal abstinence score. PLoS 2014; ONE9(11): e111327, 9

Grigoriadis S, Wilton AS, Kurdyak PA, Rhodes AE, VonderPorten EH, Levitt A, Cheung A, Vigod SN (2017) Perinatal suicide in Ontario, Canada: a 15-year population-based study. CMAJ 189(34):E1085–E1092

Harville EW, Savitz DA, Dole N, Herring AH, Thorp JM, Light KC (2008) Stress and placental resistance measured by Doppler ultrasound in early and mid-pregnancy. Ultrasound Obstet Gynecol 32:23–30

Huybrechts KF, Bateman BT, Desai RJ, Hernandez-Diaz S, Rough K, Mongun H et al (2017) Risk of neonatal drug withdrawal after intrauterine co-exposure to opiods and psychotropic medications: cohort study. BMJ 358:j3326

Jarde A, morais M, Kingston D, Giallo R et al (2016) Does non-pharmacological therapy for antenatal depression reduce risks for the infant? Arch Womens Ment Health. 19(3):549–552

Kent A, Hughes P, Ormerod L, Jones G, Thilaganathan B (2002) Uterine artery resistance and anxiety in the second trimester of pregnancy. Ultrasound Obstet Gynecol 19:177–179

Levinson-Castiel R, Merlob P, Linder N, Dirota L, Klinger G (2006) Neonatal abstinence syndrome after in utero exposure to selective serotonin reuptake inhibitors in term infants. Arch Pediatr Adolesc Med. 160(2):173–176

Lund N, Pedersen LH, Henriksen TB (2009) Selective serotonin reuptake inhibitor exposure in utero and pregnancy outcomes. Arch Pediatr Adolesc Med 163(10):949–954

Marcus SM, Flynn HA, Blow FC, Barry KL (2003) Depressive symptoms among pregnant women screened in obstetrics settings. J Women's Health (Larchmt) 12:373–380

Monk C, Newport DJ, Korotin JH, Long Q, Knight B, Stowe ZN (2012) Uterine blood flow in psychiatric population: impact of maternal depression, anxiety, and psychotropic medication. Biol Psych 72(6):483–490

Oberlander TF, Warburton W, Misri S, Aghajanian J, Hertzman C (2006) Neonatal outcomes after prenatal exposure to selective serotonin reuptake inhibitor antidepressants and maternal depression using population-based linked health data. Arch Gen Psychiatry 63(8):898–906

Sahingoz M, Yuksel G, Karsidag C, Uguz F, Sonmez EO, Annagur BB, Annagur A (2014) Birth weight and preterm birth in babies of pregnant women with major depression in relation to treatment with antidepressants. J Clin Psychopharmacol 34(2):226–229

Sanz EJ, De-las-Cuevas C, Kiuru A, Bate A, Edwards R (2005) Selective serotonin re-uptake inhibitors in pregnant women and neonatal withdrawal syndrome: a database analysis. Lancet 365:482–487

Statistics Canada. Mean and median birth weights by geography. Last updated November 27, 2015. http://www.statcan.gc.ca/pub/84f0210x/2009000/t015-eng.htm (accessed December 15, 2017)

Statistics Canada. Preterm live births in Canada, 2000 to 2013. Last updated October 26, 2016. https://www.statcan.gc.ca/pub/82-625-x/2016001/article/14675-eng.htm (accessed December 15, 2017

Teixeira JM, Fisk NM, Glover V (1999) Association between maternal anxiety in pregnancy and increased uterine artery resistance index: cohort based study. BMJ 318:153–157

Viktorin A, Lichtenstein P, Lundholm C, Almqvist C, D'Onofrio BM, Larsson H, Landén M, Magnusson PKE (2016) Selective serotonin re-uptake inhibitor use during pregnancy: association with offspring birth size and gestational age. Int J Epidemiol 45(1):170–177

Vythilingum B, Geerts L, Fincham D, Roos A, Faure S, Jonkers J, Stein DJ (2010) Association between antenatal distress and uterine artery pulsatility index. Arch Womens Ment Health 13:359–364

Wen SW, Yang Q, Garner P, Fraser W, Olatunbosun O, Nimrod C, Walker M (2006) Selective serotonin reuptake inhibitors and adverse pregnancy outcomes. Am J Obstet Gynecol 194(4):961–966

Yonkers KA, Gilstad-Hayden K, Forray A, Lipkind HS (2017) Association of panic disorder, generalized anxiety disorder and benzodiazepine treatment during pregnancy with risk of adverse birth outcomes. JAMA Psyc 74(11):1145–1152

Zimmerman-Baer U, Notzli U, Rentsch K, Bucher HU (2010) Finnegan neonatal abstinence scoring system: normal values for first 3 days and weeks 5–6 in non-addicted infants. Addiction 105:524–528