Published in final edited form as:
Biol Psychiatry. 2012 September 15; 72(6): 483–490. doi:10.1016/j.biopsych.2012.05.006.

Uterine Blood Flow in a Psychiatric Population: Impact of Maternal Depression, Anxiety, and Psychotropic Medication

Catherine Monk[1], **D. Jeffrey Newport**[2], **Jeffrey H. Korotkin**[3], **Qi Long**[4], **Bettina Knight**[2], and **Zachary N. Stowe**[2]

[1]Department of Psychiatry, Behavioral Medicine, Columbia University

[2]Department of Psychiatry and Behavioral Sciences, Women's Mental Health Program, Emory University

[3]Department of Obstetrics & Gynecology, Emory University

[4]Rollins School of Public Health, Department of Biostatistics and Bioinformatics, Emory University

Abstract

Background—Accumulating evidence suggests that fetal exposure to maternal psychiatric symptoms is associated with future risk for psychopathology. One potential pathway is distress–linked constriction in uterine or umbilical blood flow (UBF). With approximately 6.6% of pregnant women taking an antidepressant, an ecologically valid investigation of this hypothesis must consider the potential concomitant influence of pharmacotherapy on UBF.

Methods—Pregnant women (n=101) with lifetime histories of mental illness were evaluated every 4–6 weeks during gestation for mood symptoms and medication use; women underwent an ultrasound examination for UBF at approximately 25 weeks gestation.

Results—No associations were observed between UBF and three assessments of maternal prenatal depression and anxiety (acute: coincident with the UBF scan; proximal: within two weeks of the scan; chronic: serial symptom ratings). Chronic and acute use of bupropion was associated with reduced UBF even after controlling for pregnancy complications. Chronic use of atypical antipsychotics also was associated with decreased UBF. There were no associations between serotonergic antidepressant use and UBF.

Conclusions—Contrary to a popular hypothesis, depression and anxiety–associated reductions in UBF may not be a pathway by which risk is conferred during prenatal development. However,

Corresponding Author: Catherine Monk, Ph.D., Behavioral Medicine/CUMC, 1150 St. Nicholas Ave., Suite 1-121, New York, NY 10032, 212.851.5576 phone, 212.851.5580 fax, cem31@columbia.edu.

Financial Disclosures
Dr. Monk has received research support from NARSAD, NIH, the March of Dimes, the Wharton Fund, and the Sackler Foundation. Dr. Newport has received research support from Eli Lilly, GSK, Janssen, NIH, NARSAD and Wyeth, has served on speaker or advisory boards for Astra-Zeneca, Eli Lilly, GSK, Pfizer and Wyeth and has received honoraria from Astra-Zeneca, Eli Lilly, GSK, Pfizer, and Wyeth. Dr. Korotkin has received honoraria for talks from Genzyme genetics and Tocos Medical, which now is Alere. Dr. Long has received support from NIH and Veteran Affairs. Ms. Knight has received research support from NIH, NARSAD, Wyeth, BMS, Cyberonics, Eli Lilly, Forest, Janssen and Novartis. A family member is a GSK employee and holds GSK stock options. Dr. Stowe has received research support from NIH, GSK, Pfizer and Wyeth, has served on speaker or advisory boards for Pfizer, Eli Lilly, Wyeth, BMS, and GSK, and has received honoraria from Eli Lilly, GSK, Pfizer, and Wyeth.

while requiring replication, our findings suggest that prenatal bupropion exposure may be associated with reductions in UBF.

Keywords

pregnancy; depression; uterine blood flow; bupropion; SSRIs; neurobehavioral development; psychopathology

Introduction

Psychiatric disorders increasingly are conceptualized as reflecting deviation in basic dimensions of functioning resulting from genetic and environmental influences occurring over the course of development (1,2). The prenatal period is the initial window for the identification of factors impacting neurobehavioral trajectories (3). Accumulating evidence suggests that maternal distress during pregnancy leads to decrements in children's cognitive and psychosocial development, independent of maternal postnatal symptoms (see (4) (5) for reviews)[1]. Animal models are consistent, showing associations with increased distractibility and anxiety in offspring (6) (7).

Investigations of the developmental impact of prenatal psychiatric illness are incomplete without consideration of the potential influence of psychotropic pharmacotherapy. Some human and animal studies indicate that *in utero* exposure to selective serotonin reuptake inhibitors (SSRIs) may contribute to poor perinatal outcomes (8) (9) (10) (11), and adverse offspring neurobehavioral development including altered hypothalamic-pituitary-adrenal (HPA) axis regulation and pain sensitivity in humans (12) (13), and elevated fear and anxiety in rodents (14). Offspring neurodevelopment following prenatal exposure to atypical antidepressants and antipsychotics has not been formally studied, yet both classes of agents have been associated with pregnancy complications that may be relevant to neurodevelopment. Similar to the SSRI fluoxetine (15) (9), one study suggests that bupropion may be associated with a higher rate of spontaneous abortion (16). Similarly, the use of atypical antipsychotics during pregnancy has been linked to both low (17) (18) and high (19) birth weight, each of which has long–term health implications.

Identification of the biological mechanisms mediating associations between prenatal distress, medication exposure, and child outcomes has proven complex. One potential pathway conveying offspring vulnerability is variation in uterine or umbilical blood flow (UBF) (20) (21). Briefly, during pregnancy, placental trophoblastic cells invade the uterine wall and migrate the entire length of the maternal spiral arteries. Remodeling of these high resistance arteries results in low resistance and high flow circulation in the intervillous space, optimizing oxygen and nutrient delivery to the fetus (22). Doppler ultrasound of the two uterine and one umbilical arteries allows for the characterization of vascular flow and resistance, making it possible to infer information about blood flow on the maternal and fetal sides of the placenta. When the placental microcirculation is impeded, this leads to higher measures of velocimetry, identified in the pulsatility and resistance indices in uterine and umbilical arteries (PI and RI, respectively).

There is widespread assertion that depression and anxiety–associated reductions in UBF may be a pathway by which maternal distress is 'transduced' to the fetus, affecting neurodevelopmental outcomes (20) (23). Previous UBF studies have demonstrated a decrease in flow associated with maternal anxiety (24) (25), though there are discordant data

[1]Throughout the paper, we use 'distress' as an umbrella term to encompass anxiety, depression, and stressful life events because (1) these syndromes/experiences are highly comorbid/co–occurring;(2) to date, the literature on prenatal influences on child outcomes lacks specificity with respect to unique associations between maternal mood and child outcomes.

(26) (27) (28). Importantly, substantial methodological differences across these investigations impede definitive conclusions: 1) gestational timing of Doppler assessment; 2) method of symptom assessment (self–report vs. clinician-rated; in-person vs. phone interview); 3) proximity of symptom assessment to UBF assessment; 4) UBF indices reported (uterine versus umbilical artery; highest versus mean resistance value; right versus left uterine artery (though the two do not differ in clinical importance and the mean is a common index in the obstetrical literature; 5) multiple sonographers without inter–reliability assessments; and 6) limited control for potential confounds (i.e., smoking, parity, obstetrical complications, medications).

With respect to psychotropic medications and UBF, serotonin is a uterine vasoconstrictor; in animal studies, fluoxetine administration is associated with a transient decrease in UBF (29) and direct injection of serotonin into the uterine vasculature was found to reduce blood flow acutely by 20% (29). Finally, dopamine infusion has been shown to reduce UBF in sheep (Fishburne et al 1980). Animal models also have demonstrated that dopamine antagonists are associated with risk for hypertension and other manifestations of vasoconstriction (30).

To date, there is no investigation of UBF in relation to both maternal mood and psychotropic medication use, though the potential overlap in the pathophysiological mechanisms of alterations in UBF related to neuropsychiatric illness and its treatment, and the ecological validity of such an approach, are clear. For this study, we hypothesized that pregnant women undergoing psychiatric care are likely to show significant reductions in UBF (based on their elevated vulnerability for experiencing psychological distress and use of psychiatric medications), and that the assessment of UBF in a well–characterized, high–risk sample of pregnant women undergoing psychiatric care would provide a novel support for the hypothesis that UBF is a mediator for vulnerability in the offspring. Consistent with the prior UBF reports, as well as data showing high co–morbidity of these syndromes of ‘distress’ (31), we did not have unique predictions for anxiety or depressive symptoms. To respond to the methodological weaknesses in the existing studies, the present study includes: all of the UBF indices, a single sonographer, symptom ratings concurrent with the Doppler study, and detailed longitudinal information on maternal symptoms, medication use, and other potential confounds.

Methods and Materials

Overview

The study was conducted at the Women’s Mental Health Program (WMHP) at the Emory University School of Medicine. Women with lifetime histories of mental illness (SCID) participating in a longitudinal investigation of the impact of perinatal maternal stress on child neurobehavioral outcomes (P50 MH 77928) were screened for inclusion in the current analysis. Participants were enrolled prior to 16 weeks gestation, and evaluated at 4–6 week intervals through 26 weeks postpartum. At approximately 25 weeks gestation, women underwent an ultrasound examination of uterine and umbilical artery blood flow between 1600–1700 hours. All mood and medication results were coded with a HIPAA compliant identifier and entered into a centralized database. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The study was reviewed and approved by the Emory University Institutional Review Board. Informed consent of the participants was obtained after the nature of the procedures had been fully explained.

Participants

Pregnant women between the ages of 18–45 were referred to a tertiary care program providing treatment to pregnant women with histories of mental illness. Referral sources

included obstetrical and mental health care providers. Women were excluded from participation if they were: suicidal or homicidal, evidencing psychotic symptoms, carried a primary diagnosis of a psychotic disorder, or had an active eating or substance use disorder within 6 months prior to conception.

Psychosocial and obstetric covariates

Information on women's age, parity, gravidity, race/ethnicity, smoking, body mass index (BMI), education, marital status, and whether pregnancy was planned and/or desired was obtained at the study enrollment.

Maternal diagnosis and symptoms of depression and anxiety

At enrollment, lifetime diagnoses were established using the Structured Clinical Interview for Diagnosis (SCID)(32). Approximately every 4–6 weeks, participants completed the self-rated Beck Depression Inventory (BDI) (33). In addition, a research interviewer masked to treatment status administered the 17-item Structured Interview Guide (34) for the Hamilton Rating Scale for Depression (35) (HRSD–17) and the Hamilton Rating Scale of Anxiety (HRSA) (36). A BDI was collected at the time of the Doppler UBF assessment. Quarterly inter-rater reliability assessments were conducted throughout the study to maintain kappa statistics > 0.8 on all clinician-administered instruments.

Medication use

At enrollment and all follow up visits, study psychiatrists (ZNS, DJN) interviewed participants to document all exposures to medications and tobacco, and any changes in treatment. Medications were categorized as: (1) serotonergic antidepressants including SSRIs and SNRIs, (2) bupropion, (3) lamotrigine, (4) atypical antipsychotics, (5), benzodiazepines, and (6) cardiovascular medications, i.e., antihypertensives and antithrombotics.

Doppler ultrasound

All UBF examinations were performed by the same board certified maternal fetal medicine specialist (JHK) using a Seimens Sequoia 2-D and Doppler Ultrasound (Malvern, Pennsylvania) or a GE Voluson E8 (Milwaukee, WI) and a 3.5 Mhz curvilinear transabdominal probe. Gestational age was estimated to the nearest day by ultrasound–determined fetal biometry using software installed by Hadlock charts of biparietal diameter. Waveforms later were analyzed by the same operator (JHK) masked to psychiatric symptom data, lifetime diagnosis, and treatment status. The main branch of the uterine artery was identified at its junction with the internal iliac artery using color Doppler ultrasound; from here blood flow velocity waveforms were obtained. Waveforms were recorded from both uterine arteries, and umbilical artery in standard fashion. The artery resistance measures included: left and right uterine artery RI, the sum and the maximum of the two uterine RIs, and the umbilical artery RI. The pulsatility measures included: left and right uterine artery PI, the sum and the maximum of the two uterine PIs, and the umbilical artery PI.

Data Analysis

Descriptive analysis was performed to summarize the characteristics of the study population. We assessed acute, proximal, and chronic exposures across a variety of domains, including (1) maternal depression at the time of the UBF assessment (acute BDI); (2) maternal depression and anxiety within two weeks of the UBF assessment (proximal HRSD–17, HRSA); (3) maternal depression and anxiety between conception and the UBF assessment (adjusted to a standard 25–week duration) as represented by Area Under the Curve (AUC) calculation from serial symptom ratings using the trapezoidal method (chronic BDI, HRSD–

17, HRSA); 4) medication exposure by medication class at the time of the UBF assessment as determined by clinician interview on that day (acute medication); and (5) weeks of exposure by medication class from conception to the UBF assessment (adjusted to a standard 25–week duration) as determined by clinician assessments during serial study visits (chronic medication).

Initial bivariate hypothesis testing utilized Pearson correlational analysis and Wilcoxon tests. Pearson correlation coefficients were computed to assess the associations of each UBF outcome variable with each depression and anxiety measure (acute, proximal, or chronic), and each chronic medication exposure operationalized as number of weeks exposed. Wilcoxon tests were used to compare each outcome variable between subjects with and without acute medication exposure.

Multiple linear regression models were used to assess concurrently the impact of exposure to maternal depression and a pharmacological agent upon UBF indices. The same models were repeated for exposure to maternal anxiety, which replaced the depression indices. The first set of regressions modeled the effect of acute exposures to maternal depression (acute BDI score) and a pharmacological exposure of interest (serotonergic antidepressant or bupropion) on each UBF measure while adjusting for confounders. Candidate confounders included BMI, maternal age, gravidity (1 vs others), parity (0 vs others), maternal education level, the number of marriages for the mother (1 vs others), whether the pregnancy was planned, and whether the pregnancy was desired. Backward model selection based on Akaike Information Criterion (AIC) (37) was used to choose the final model in the regression analysis for each UBF outcome variable, where the acute BDI score and acute pharmacological exposure of interest (i.e., serotonergic antidepressant or bupropion) were always retained in the model. The multiple linear regression analyses were then repeated to assess the effect of chronic (between conception and date of the UBF) exposures including chronic depression (AUC for BDI) and chronic pharmacological exposure of interest (number of weeks exposed to a serotonergic antidepressant or bupropion) while adjusting for confounders. In the regression analyses with depression exposure replaced by anxiety, the anxiety variables were proximal HRSA and chronic HRSA, respectively.

Results

One hundred and one women (n=101) completed the Doppler assessment at 24.8 weeks gestation (range was 22–28 weeks) though due to difficulties with equipment and/or fetal position, there were missing values for the various UBF indices. Specifically, for the resistance indices, 0–11 women had one or more missing values; for the pulsatility indices, the range was 25–28 women. (See Table 1 for descriptive information on the study sample.) A limited number of subjects (n=15) had one of three medical complications of pregnancy (gestational diabetes, oligo– or polyhydramnios, hyperemesis gravidarum) or endorsed tobacco use/exposure. Medication use is reported in Table 2. The range and variability of scores on each psychiatric symptom index (see Table 3) indicate that a portion of participants were experiencing moderate depression (average 3rd quartile scores on the acute BDI and the proximal HRSD–17: 12 and 11.8, respectively, range 0–28 and 1–37, respectively), and mild proximal anxiety (HRSA) (3rd quartile score = 11, range 1–23).

Average values for RI and PI are given in table 4. At 25 weeks gestation, a PI of .89 has been reported to be at the 50th percentile (38). Criterion for an abnormal RI — that is, one that can predict a medically–compromised pregnancy outcome such as preeclampsia and growth restriction — has varied from a single cutoff (e.g., RI > 0.58) to a percentile cutoff value (e.g., 75th, 90th, 95th) (22). In this study, 21.8% and 16.0% of women had an RI > 0.58 RI for the left and right uterine arteries, respectively.

Bivariate analyses of UBF and depression or anxiety

There were no significant associations between the acute, proximal, and chronic measures of maternal depression (BDI, HRSD-17) or anxiety (HRSA) and blood flow indices. Stratified analysis excluding participants who smoked or had any of three identified complications of pregnancy did not alter these results.

Bivariate analyses of UBF and pharmacologic exposure

Significant associations between UBF measures and pharmacological exposure were limited (see Tables 5–6). No UBF indices were associated with acute or chronic exposure to lamotrigine or benzodiazepines. Chronic medication exposure revealed the following positive UBF associations: 1) serotonergic antidepressant with right uterine artery PI; 2) bupropion with umbilical and left uterine artery RI; and 3) cardiovascular medication with umbilical artery RI. Excluding participants who smoked or had an obstetrical complication produced little difference in the findings except that the association between serotonergic antidepressant exposure and right uterine artery PI was no longer significant and a significant relation between atypical antipsychotic exposure and umbilical artery RI emerged.

Significant associations between acute pharmacological exposure and UBF measures were also limited (cf. Table 6). Women with acute bupropion exposure had higher RIs in the left uterine artery and in the sum of the uterine artery values (t= 0.10, p = .01 and t =0.13, p =. 03), and those who had smoked within 24 hours of the assessment had higher umbilical artery RIs (t = 0.25, p = .02). Surprisingly, acute exposure to a serotonergic antidepressant was associated with a lower RI in the left uterine artery (t = − 0.06, p = .03). Excluding participants who smoked or had a pregnancy complication eliminated the finding with a serotonergic antidepressant while the differences associated with bupropion exposure remained significant (data not shown).

Multivariate analyses of UBF in relation to depression and pharmacological exposure

In a series of multiple regression analyses, we examined the effects on UBF of both exposures — psychiatric symptoms and medication use — in the context of each other while also controlling for other potential confounds (see statistical approach, above). The first set of regression analyses, using acute depression and acute serotonergic antidepressant as principal independent variables, showed an adjusted effect of serotonergic antidepressant use associated with a lower left uterine artery RI (p =.04, n= 93); the BDI score was not significant. Removal of subjects who smoked or had pregnancy complications made this finding insignificant, and no others emerged. The regression analyses of chronic depression and chronic serotonergic antidepressant exposure also yielded no significant findings.

The regression analyses using depression and bupropion exposure as principal independent variables, acute and then chronic exposure, yielded the following findings: both acute and chronic bupropion exposure were associated with higher left uterine artery RI (p =.034, n= 92; p =.048, n= 90, respectively) and higher umbilical artery RI (p =.018, n= 81; p =.012, n= 79, respectively). In these analyses, there were no significant effects of BDI on UBF indices. These results remained statistically significant following removal of participants who smoked or had pregnancy complications (data not shown).

Multivariate analyses of UBF in relation to anxiety and pharmacological exposure

Regression analyses, using proximal anxiety and acute serotonergic medication as principal independent variables, showed similar results to those based on maternal depression: an adjusted effect of acute serotonergic antidepressant use associated with a lower left uterine artery RI (p =.032, n= 77) (data not shown); the proximal anxiety score was not significant.

The regression analyses of chronic anxiety and chronic serotonergic medication exposure as independent variables yielded no significant findings, similar to the model using depression.

Regression analyses using anxiety and bupropion exposure as principal independent variables mirrored those using depression (data not shown): both acute and chronic bupropion exposure were associated with higher left uterine artery RI (p =.027, n= 77; p =.042, n= 89, respectively) and higher umbilical artery RI (p =.008, n= 67; p =.013, n= 78, respectively). There were no significant effects of the anxiety variables.

Discussion

Burgeoning research collectively known as the Fetal Origins of Adult Disease (3,39) has provided the background for the hypothesis that maternal distress during pregnancy may influence perinatal development and outcomes via mood–based constriction in uterine and/or umbilical blood flow (20,23). Focusing on a sample of 2nd trimester pregnant women highly vulnerable to significant mood dysregulation, our study found no significant association between depression or anxiety and reductions in uterine or umbilical blood flow. However, our report provides the first human evidence that bupropion use may be associated with a reduction in UBF.

Using acute, proximal and chronic assessments of maternal prenatal depression and anxiety, we found no association with any of the indices used to measure uterine and umbilical blood flow. Since the original study by Teixeira et al. (24), the effect estimates of any associations between prenatal mood and UBF have been quite small, particularly following adjustments for confounds (28,40). Of the seven published reports on UBF and maternal prenatal mood (26,28,40,41,42), only two (24) (25) have strong positive findings. The absence of an association between prenatal maternal distress and UBF indices now includes similar results on a sample of women with psychiatric histories. The predominantly negative findings regarding UBF as a conduit of maternal distress to the developing fetus underscores the need for further investigation of the maternal/fetal/placental interface to discover insights into the pathways of these earliest influences on development (43).

We did not find significant associations between serotonergic antidepressant use and reduced UBF. The one significant finding between chronic serotonergic antidepressant use and a higher PI in the right artery, in the context of multiple comparisons, was no longer significant once women with pregnancy complications were removed from analyses. The one other significant relation was an inverse association between acute serotonergic antidepressant exposure and the left uterine artery RI. In contrast to the animal studies on the vasoconstrictive effects of fluoxetine (29,44), our results are consistent with a recent report showing no differences in 3rd trimester uterine and umbilical PI between women taking SSRIs versus no psychiatric medication use (45).

Chronic and acute use of bupropion was associated with reduced UBF. Because bupropion is used as an aide to smoking cessation, its cardiovascular and hemodynamic effects has been subject to investigation. In a study using standardized laboratory stressors, bupropion treated adults showed greater total peripheral resistance increases compared to controls (46) while a report of smokers who had recently quit showed that bupropion use was associated with maintenance of physiological arousal (i.e., in blood pressure heart rate, plasma epinephrine and norepinephrine) between stressor and rest periods whereas controls had lower physiologic activity (47). An *in vitro* study of human cardiac tissue found that bupropion exerts indirect sympathetic activation in the myocardium, possibly via catecholamine release (48). Animal models of acute bupropion injection indicate that it leads to an increase in systemic vascular resistance index (49,50). To our knowledge, the

vasoconstrictive effects of bupropion have not been studied in human pregnancy or animal models of pregnancy.

Chronic use of atypical antipsychotics and nicotine exposure also were associated with increased uterine RIs, though, unexpectedly, the effect for antipsychotics only emerged once women using tobacco were removed from analyses. With respect to the data on atypical antipsychotics, in animal studies of dopamine receptors, blocked receptor activity is associated with hypertension (30), though we do not know of any investigations of this effect in pregnancy. These findings are relevant for research on schizophrenia: 1) higher rates of obstetrical complications in women with schizophrenia may be related to the use of antipsychotics and an associated reduction in UBF; 2) fetal hypoxia has been identified as a risk factor for schizophrenia and variation in UBF, whether related to psychotropic medications and/or smoking, may be a variable to consider in this association.

While intriguing, these results on psychotropic medication effects require replication. Moreover, nearly 80% of the women had normal RI indices (based on the 0.58 cut off). However, consistent with the Fetal Origins of Adult Disease model, the clinical relevance of these results lies in the potential for psychotropic medication use to cause subtle variation in oxygen and nutrient delivery to the fetus and thereby influence neurobehavioral development.

It is estimated that 6.6% of women are prescribed an antidepressant during pregnancy (51), and rates of prenatal antipsychotic exposure remain unknown, underscoring the critical need to examine potential effects of psychotropic medications on maternal and fetal perinatal well being. Disentangling the impact of prenatal exposure to maternal psychiatric symptoms versus psychotropic agents is a critical challenge fueling on–going debate.

Strengths of this paper include a well–characterized, relatively homogenous clinical sample of pregnant women with carefully documented psychiatric histories, enabling us to ask the clinically–relevant question of the effects on UBF of prenatal mood and psychotropic medication use, *in the context of considering the other factor as well*. A single maternal fetal medicine specialist (JK), masked to participant psychiatric symptoms and psychotropic medication use, performed and interpreted all of the Doppler flow velocity wave forms, minimizing error introduced by coder variability. In response to inconsistent results in prior studies that were based on different indices for measuring blood flow and variability in the way maternal prenatal mood was assessed, we included all of the possible blood flow indices, as well as acute and chronic measures of mood symptoms based on self report and in–person interview.

This study has some limitations. This study was conducted with a clinical sample and thus the results may only generalize to that population. There was no objective verification of psychotropic medication use, though prior reports show a high correlation between self–report and verified data on medication use during pregnancy (52). Prior papers on UBF in relation to maternal mood, as well as more general papers on UBF during pregnancy, do not include data on women's cardiovascular functioning, as we did not in this study, though such information might be useful.

Mounting evidence indicates that a child's developmental trajectory can be shifted in the direction of risk as early as the prenatal period, and in relation to factors that affect the fetal environment, such as pregnant women's psychiatric symptom profile and the associated biological alterations. Data presented in this paper, and consistent with other reports, suggest that, contrary to a popular hypothesis, depressed or anxiety–based reductions in UBF are not a pathway by which risk is conferred during prenatal development. However, our findings suggest the possibility that psychotropic medication use during pregnancy, specifically

bupropion, may be associated with reductions in UBF, which could affect fetal neurobehavioral development and/or birth outcomes. These results need to be replicated prior to formal inclusion in the risk/benefit assessment for psychotropic therapy during pregnancy.

Acknowledgments

The authors gratefully acknowledge the women who participated in this study and the community obstetrical practices in the Atlanta area for their assistance. This study was supported by the Translational Research Center in Behavioral Sciences (TRCBS) (P50 MH077928) and the National Alliance for Research on Schizophrenia and Depression award.

References

1. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry. 2010; 167:748–751. [PubMed: 20595427]
2. Insel TR, Wang PS. Rethinking mental illness. JAMA. 2010; 303:1970–1971. [PubMed: 20483974]
3. Bale TL, Baram TZ, Brown AS, Goldstein JM, Insel TR, et al. Early life programming and neurodevelopmental disorders. Biol Psychiatry. 2010; 68:314–319. [PubMed: 20674602]
4. Talge NM, Neal C, Glover V. Antenatal maternal stress and long-term effects on child neurodevelopment: how and why? J Child Psychol Psychiatry. 2007; 48:245–261. [PubMed: 17355398]
5. Charil A, Laplante DP, Vaillancourt C, King S. Prenatal stress and brain development. Brain Res Rev. 2010; 65:56–79. [PubMed: 20550950]
6. Newport DJ, Stowe ZN, Nemeroff CB. Parental depression: animal models of an adverse life event. Am J Psychiatry. 2002; 159:1265–1283. [PubMed: 12153816]
7. Weinstock M. The potential influence of maternal stress hormones on development and mental health of the offspring. Brain Behav Immun. 2005; 19:296–308. [PubMed: 15944068]
8. Oberlander TF, Bonaguro RJ, Misri S, Papsdorf M, Ross CJ, et al. Infant serotonin transporter (SLC6A4) promoter genotype is associated with adverse neonatal outcomes after prenatal exposure to serotonin reuptake inhibitor medications. Mol Psychiatry. 2008; 13:65–73. [PubMed: 17519929]
9. Bauer S, Monk C, Ansorge M, Gyamfi C, Myers M. Impact of antenatal selective serotonin reuptake inhibitor exposure on pregnancy outcomes in mice. Am J Obstet Gynecol. 2010; 203:375 e371–374. [PubMed: 20541736]
10. Broy P, Berard A. Gestational exposure to antidepressants and the risk of spontaneous abortion: a review. Curr Drug Deliv. 2010; 7:76–92. [PubMed: 19863482]
11. Suri R, Altshuler L, Hellemann G, Burt VK, Aquino A, et al. Effects of antenatal depression and antidepressant treatment on gestational age at birth and risk of preterm birth. Am J Psychiatry. 2007; 164:1206–1213. [PubMed: 17671283]
12. Oberlander TF, Grunau RE, Fitzgerald C, Ellwood A-L, Misri S, et al. Prolonged prenatal psychotropic medication exposure alters neonatal acute pain response. Pediatric Research. 2002; 51:443–453. [PubMed: 11919328]
13. Oberlander TF, Grunau R, Mayes L, Riggs W, Rurak D, et al. Hypothalamic-pituitary-adrenal (HPA) axis function in 3-month old infants with prenatal selective serotonin reuptake inhibitor (SSRI) antidepressant exposure. Early Hum Dev. 2008; 84:689–697. [PubMed: 18639992]
14. Ansorge MS, Morelli E, Gingrich JA. Inhibition of serotonin but not norepinephrine transport during development produces delayed, persistent perturbations of emotional behaviors in mice. J Neurosci. 2008; 28:199–207. [PubMed: 18171937]
15. Kulin NA, Pastuszak A, Sage SR, Schick–Boschetto B, Spivey G, et al. Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors. Journal of the American Medical Association. 1998; 279:609–610. [PubMed: 9486756]

16. Chun-Fai-Chan B, Koren G, Fayez I, Kalra S, Voyer-Lavigne S, et al. Pregnancy outcome of women exposed to bupropion during pregnancy: a prospective comparative study. Am J Obstet Gynecol. 2005; 192:932–936. [PubMed: 15746694]
17. Newport DJ, Calamaras MR, DeVane CL, Donovan J, Beach AJ, et al. Atypical antipsychotic administration during late pregnancy: placental passage and obstetrical outcomes. Am J Psychiatry. 2007; 164:1214–1220. [PubMed: 17671284]
18. McKenna K, Koren G, Tetelbaum M, Wilton L, Shakir S, et al. Pregnancy outcome of women using atypical antipsychotic drugs: a prospective comparative study. J Clin Psychiatry. 2005; 66:444–449. quiz 546. [PubMed: 15816786]
19. Newham JJ, Thomas SH, MacRitchie K, McElhatton PR, McAllister-Williams RH. Birth weight of infants after maternal exposure to typical and atypical antipsychotics: prospective comparison study. Br J Psychiatry. 2008; 192:333–337. [PubMed: 18450655]
20. Glover V, Teixeira J, Gitau R, Fisk NM. Mechanisms by which maternal mood in pregnancy may affect the fetus. Contemporary Reviews in Obstetrics & Gynecology. 1999; 11:155–160.
21. Wadhwa PD, Culhane JF, Rauh V, Barve SS. Stress and preterm birth: neuroendocrine, immune/inflammatory, and vascular mechanisms. Matern Child Health J. 2001; 5:119–125. [PubMed: 11573837]
22. Sciscione AC, Hayes EJ. Uterine artery Doppler flow studies in obstetric practice. Am J Obstet Gynecol. 2009; 201:121–126. [PubMed: 19646563]
23. Wadhwa PD, Glynn L, Hobel CJ, Garite TJ, Porto M, et al. Behavioral perinatology: biobehavioral processes in human fetal development. Regul Pept. 2002; 108:149–157. [PubMed: 12220739]
24. Teixeira JMA, Fisk NM, Glover V. Association between maternal anxiety in pregnancy and increased uterine artery resistance index: Cohort based study. British Medical Journal. 1999; 318:153–157. [PubMed: 9888905]
25. Sjostrom K, Valentin L, Thelin T, Marsal K. Maternal anxiety in late pregnancy and fetal hemodynamics. European Journal of Obstetrics & Gynecology and Reproductive Biology. 1997; 74:149–155. [PubMed: 9306108]
26. Kent A, Hughes P, Ormerod L, Jones G, Thilaganathan B. Uterine artery resistance and anxiety in the second trimester of pregnancy. Ultrasound in Obstetrics & Gynecology. 2002; 19:177–179. [PubMed: 11876811]
27. Harville EW, Savitz DA, Dole N, Herring AH, Thorp JM, et al. Stress and placental resistance measured by Doppler ultrasound in early and mid-pregnancy. Ultrasound Obstet Gynecol. 2008; 32:23–30. [PubMed: 18546420]
28. Mendelson T, DiPietro JA, Costigan KA, Chen P, Henderson JL. Associations of maternal psychological factors with umbilical and uterine blood flow. J Psychosom Obstet Gynaecol. 2011; 32:3–9. [PubMed: 21219117]
29. Morrison JL, Chien C, Riggs KW, Gruber N, Rurak D. Effect of maternal fluoxetine administration on uterine blood flow, fetal blood gas status, and growth. Pediatr Res. 2002; 51:433–442. [PubMed: 11919327]
30. Wang X, Villar VA, Armando I, Eisner GM, Felder RA, et al. Dopamine, kidney, and hypertension: studies in dopamine receptor knockout mice. Pediatr Nephrol. 2008; 23:2131–2146. [PubMed: 18615257]
31. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005; 62:593–602. [PubMed: 15939837]
32. First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured clinical interview for DSM–IV axis I disorders–non-patient edition. Biometrics Research Department/NYSPI; 1997.
33. Beck AT, Rial WY, Rickels K. Short form of depression inventory: Cross–validation. Psychological Reports. 1974; 34:1184–1186. [PubMed: 4424377]
34. Williams JB. A structured interview guide for the Hamilton Depression Rating Scale. Arch Gen Psychiatry. 1988; 45:742–747. [PubMed: 3395203]
35. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960; 23:56–62. [PubMed: 14399272]

36. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol. 1959; 32:50–55. [PubMed: 13638508]
37. Akaike, H. Automatic Control, IEEE Transactions on 19. 1974. A new look at the statistical model identification.
38. Gomez O, Figueras F, Fernandez S, Bennasar M, Martinez JM, et al. Reference ranges for uterine artery mean pulsatility index at 11–41 weeks of gestation. Ultrasound Obstet Gynecol. 2008; 32:128–132. [PubMed: 18457355]
39. Seckl JR. Physiologic programming of the fetus. Clinics in Perinatology. 1998; 25:939–962. [PubMed: 9891623]
40. Harville EW, Savitz DA, Dole N, Thorp JM Jr, Herring AH. Psychological and biological markers of stress and bacterial vaginosis in pregnant women. Bjog. 2007; 114:216–223. [PubMed: 17305894]
41. Maina G, Saracco P, Giolito MR, Danelon D, Bogetto F, et al. Impact of maternal psychological distress on fetal weight, prematurity and intrauterine growth retardation. J Affect Disord. 2008; 111:214–220. [PubMed: 18394713]
42. Vythilingum B, Geerts L, Fincham D, Roos A, Faure S, et al. Association between antenatal distress and uterine artery pulsatility index. Arch Womens Ment Health. 2010; 13:359–364. [PubMed: 20119861]
43. Glover V. Annual Research Review: Prenatal stress and the origins of psychopathology: an evolutionary perspective. J Child Psychol Psychiatry. 2011; 52:356–367. [PubMed: 21250994]
44. Morrison JL, Riggs KW, Chien C, Gruber N, McMillen IC, et al. Chronic maternal fluoxetine infusion in pregnant sheep: effects on the maternal and fetal hypothalamic-pituitary-adrenal axes. Pediatr Res. 2004; 56:40–46. [PubMed: 15128928]
45. Rurak D, Lim K, Sanders A, Brain U, Riggs W, et al. Third Trimester Fetal Heart Rate and Doppler Middle Cerebral Artery Blood Flow Velocity Characteristics during prenatal Selective Serotonin Reuptake Inhibitor (SSRI) exposure. Pediatr Res. 2011
46. Straneva-Meuse PA, Light KC, Allen MT, Golding M, Girdler SS. Bupropion and paroxetine differentially influence cardiovascular and neuroendocrine responses to stress in depressed patients. J Affect Disord. 2004; 79:51–61. [PubMed: 15023480]
47. Kotlyar M, Brauer LH, al'absi M, Adson DE, Robiner W, et al. Effect of bupropion on physiological measures of stress in smokers during nicotine withdrawal. Pharmacol Biochem Behav. 2006; 83:370–379. [PubMed: 16581115]
48. Cremers B, Schmidt KI, Maack C, Schafers HJ, Bohm M. Catecholamine release in human heart by bupropion. Eur J Pharmacol. 2003; 467:169–171. [PubMed: 12706471]
49. Paganelli MO, Martins LC, Chaud MV, Ferreira-Melo SE, Sabha M, et al. Hemodynamic effects of a combination of bupropion and nicotine in anesthetized dogs. Cardiovasc Toxicol. 2006; 6:63–68. [PubMed: 16845183]
50. Paganelli MO, Tanus-Santos JE, Sabha M, do Prado JF, Chaud MV, et al. Hemodynamic effects of bupropion in anesthetized dogs. Eur J Pharmacol. 2006; 530:124–127. [PubMed: 16376873]
51. Andrade SE, Raebel MA, Brown J, Lane K, Livingston J, et al. Use of antidepressant medications during pregnancy: a multisite study. Am J Obstet Gynecol. 2008; 198:194, e191–195. [PubMed: 17905176]
52. Newport DJ, Brennan PA, Green P, Ilardi D, Whitfield TH, et al. Maternal depression and medication exposure during pregnancy: comparison of maternal retrospective recall to prospective documentation. BJOG. 2008; 115:681–688. [PubMed: 18410650]

Table 1

Demographic and clinical characteristics of study sample (n=101).

Characteristic	Mean (SD) or n (%)
Age (years)	32.6 (4.9)
Race	
White non–Hispanic	91 (90.0%)
Asian	1 (1%)
African American	7 (7%)
White Hispanic	2 (2%)
Education (in years)	16.4 (1.9)
Currently married	87 (87%)
Pregnancy planned	70 (69%)
Pregnancy desired	82 (81%)
UBF assessment (in gestational weeks)	24.8 (1.2)
Gravidity	2.3 (1.4)
Parity	0.68 (0.8)
Preconception BMI (n=100[1])	25.8 (6.9)
Smoking	18 (18%)
Pregnancy complication: Gestational diabetes (n=70[1])	6 (9%)
Pregnancy complication: oligo– or polyhydramnios Hydramnios (n=66[1])	5 (8%)
Pregnancy complication: Hyperemesis gravidarum (n=66[1])	4 (6%)
Major Depressive Episode proximal (within 2 weeks of UBF assessment) (n=80[1])	11(14%)[2]
Lifetime diagnoses (SCID)	
Major Depressive Disorder	64 (63%)
Bipolar Disorder	19 (19%)
Anxiety Disorders	60 (59%)
Psychotic Disorders	0 (0%)
No Psychiatric Disorder	7 (0.7%)

[1]Sample size for variables with missing data

[2]SCID evaluation for major depressive episode within proximal (2 week window) of the UBF assessment was completed for 80 subjects.

Table 2

Percentage of subjects with acute and chronic pharmacologic exposure during pregnancy

Medication	Percentage of Subjects Exposed	
	Acute[1]	Chronic[1]
Serotonergic Antidepressant	66%	72%
Bupropion	12%	13%
Benzodiazepines	14%	21%
Lamotrigine	8%	10%
Atypical antipsychotics	13%	17%
Nicotine	6%	18%
Cardiovascular Medications[2]	11%	15%

[1] Percentage with chronic exposure represents proportion who were exposed to an agent within the class at any time between conception and the date of the UBF assessment. Percent with acute exposure represents proportion who were exposed to an agent within the class with 24 hours of the UBF assessment.

[2] Medications with cardiovascular (CV) effects include antihypertensives and antithrombotics.

Table 3

Psychiatric symptoms during pregnancy: acute, proximal and chronic assessments

Symptom Scale[1]	Symptom Ratings Mean (SD) & [Range]		
	Acute[2]	Proximal[2]	Chronic[2]
BDI	7.5 (7.1) [0 – 37]	8.4 (8.0) [0 – 37]	252.5 (192.3) [0 – 1051]
HRSD-17		9.0 (5.4) [0 – 28]	255 (119.2) [26.8 – 660.5]
HRSA		7.8 (4.6) [0 – 23]	232.8 (110.9) [22.4 – 593.9]

[1]BDI = Beck Depression Inventory; HRSD-17 = Hamilton Rating Scale for Depression (17-item); HRSA = Hamilton Rating Scale for Anxiety;

[2]Acute – symptom rating collected on the data of the UBF assessment; Proximal – symptom rating collected within two weeks of the UBF assessment; Chronic – area under the curve calculated for serial symptom ratings across pregnancy from conception until the UBF assessment adjusted to a standard 25-week duration.

Table 4

Summary of Uterine Blood Flow (UBF) Measurements

	Resistance Index[1]					Pulsatility Index[2]				
	Umbilical Artery	Uterine Arteries				Umbilical Artery	Uterine Arteries			
		Left Artery	Right Artery	Sum	Max		Left Artery	Right Artery	Sum	Max
(n)	90	101	100	100	100	72	76	76	74	74
Min	0.41	0.19	0.11	0.37	0.19	0.01	0.04	0.11	0.45	0.25
Mean	0.69	0.46	0.43	0.88	0.52	0.99	0.68	0.65	1.33	0.85
SD	0.31	0.13	0.17	0.23	0.16	0.26	0.31	0.38	0.51	0.36
Max	3.00	0.74	1.33	1.92	1.33	1.81	1.41	1.83	2.61	1.83

[1]For the resistance index, data were missing for n = 0–11 participants.

[2]For the pulsatility index, data were missing for n = 25–28 participants.

Table 5

Chronic Pharmacologic Exposure and Uterine Blood Flow (UBF): Results of Pearson Correlational Analysis between Number of Weeks Exposed and UBF Measurement Highlighting Significant Associations

Pharmacologic Exposure[1]	Resistance Index					Pulsatility Index				
	Umbilical Artery	Uterine Arteries				Umbilical Artery	Uterine Arteries			
		Left Artery	Right Artery	Sum	Max		Left Artery	Right Artery	Sum	Max
All Participants										
Serotonergic Antidepressants								*r*=.27 *p*=.017 (n=75)		
Bupropion	*r*=.27 *p*=.012 (n=87)	*r*=.24 *p*=.018 (n=98)								
Atypical Antipsychotics										
Cardiovascular Medications	*r*=.30 *p*=.005 (n=87)									
Excluding Participants with Obstetrical Complications[2] or Tobacco Use										
Serotonergic Antidepressants										
Bupropion	*r*=.38 *p*=.002 (n=62)	*r*=.26 *p*=.029 (n=69)		*r*=.28 *p*=.022 (n=68)						
Atypical Antipsychotics	*r*=.27 *p*=.031 (n=62)[3]									
Cardiovascular Medications	*r*=.36 *p*=.0004 (n=62)									

[1] There were no statistically significant associations between any UBF measures and chronic (weeks of) exposure to benzodiazepines or lamotrigine. Consequently, those medication classes are omitted from the table.

[2] Obstetrical complications omitted from secondary stratified analysis include gestational diabetes, oligohydramnios, polyhydramnios, and hyperemesis gravidarum.

[3] This sample size reflects n=6 women smokers taking antipsychotics who were removed from analyses.

Table 6

Acute Pharmacologic Exposure and Uterine Blood Flow (UBF): Results of Wilcoxon Tests Highlighting Significant Associations

Pharmacologic Exposure[1]	Resistance Index					Pulsatility Index				
	Umbilical Artery	Uterine Arteries				Umbilical Artery	Uterine Arteries			
		Left Artery	Right Artery	Sum	Max		Left Artery	Right Artery	Sum	Max
Serotonergic Antidepressants										
Exposed		M=.44 (n=65)								
Not Exposed		M=.50 (n=34)								
Test Result		*p*=.033								
Bupropion										
Exposed		M=.54 (n=12)		M=.99 (n=12)						
Not Exposed		M=.45 (n=86)		M=.87 (n=85)						
Test Result		*p*=.011		*p*=.050						
Tobacco (Nicotine)										
Exposed	M=.92 (n=6)									
Not Exposed	M=.67 (n=84)									
Test Result	*p*=.017									

[1]There were no statistically significant associations between any UBF measures and acute exposure to atypical antipsychotics, benzodiazepines, lamotrigine, or cardiovascular medications. Consequently, those medication classes are omitted from the table.