THE EFFECTS OF ANTIDEPRESSANT MEDICATIONS ON MOTHERS AND BABIES

Sophie Grigoriadis

Women's Mood and Anxiety Clinic: Reproductive Transitions; Sunnybrook Health Sciences Centre; Sunnybrook Research Institute; Women's College Research Institute; Faculty of Medicine, University of Toronto, Canada

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ABSTRACT

Depression during pregnancy may be undertreated for a variety of reasons, one of which is concern regarding the safety of antidepressant medication. Dr. Grigoriadis leads a program of research to develop a reference guide to facilitate perinatal treatment discussions. The clinical group has published systematic reviews and meta-analyses on various potential outcomes following antidepressant exposure (i.e., congenital anomalies, spontaneous abortion, delivery outcomes, immediate neonatal outcomes and persistent pulmonary hypertension) in addition to outcomes associated with maternal depression. Some of the results of this program of research are presented together with a case example to start your thinking on the issues.

Key Words: *Pregnancy, depression, antidepressants, risk:benefit discussions, poor neonatal adaptation syndrome, persistent pulmonary hypertension of the newborn*

INTRODUCTION

This presentation will present the available research evidence on the safety of antidepressant medication use during pregnancy and the impact of depression during pregnancy. The intent is to gain an appreciation of the rigorous methodology needed to evaluate data in the perinatal domain and the confounding factors requiring consideration, as well as to become familiar with the latest meta-analytic research evidence.

The backdrop to this presentation and to the patient case includes a number of realities and factors:

- As many as 30-57% of pregnancies have been found to be unplanned,[1] increasing the possibility of fetal exposure to medication during the first trimester.
- Approximately 2-13% of women report taking an antidepressant at some point during their pregnancy.[2,3]
- The prescription rate for antidepressant medication has increased dramatically.[4,5]
- Antidepressants are more commonly used by women regardless of depression severity.[6]
- More and more women will face having to make decisions about the use of antidepressant medications during pregnancy.
- From the general depression literature we know:
  - The natural course of depression varies.[7]
  - Depression is typically a recurrent disorder: 80% of people experience more than 1 episode.[8]
  - Depression severity can increase with time and the episodes can be more resistant to treatment. [7,9]
  - The chance of recovery in the absence of treatment is about 20% in the first week following meeting diagnosis, then decreases with duration of illness. By 6 months there is less than 1% chance of recovery the following week.[10]
  - After 3 or more episodes, maintenance antidepressant therapy is recommended and for some, over their lifetime.[11]

Case
Anne is a 27-year-old woman living in Northern Ontario. She has had 3 major depressive episodes, is currently in remission, and has been taking paroxetine for over 1 year. Her previous episodes were severe. She often remained in bed, did not shower for days, and for weeks at a time had daily thoughts and an active plan on how to end her life. At her latest appointment with her psychiatrist, Anne talks about planning a pregnancy in the coming year. She is concerned about staying on her antidepressant medication as well as wanting to know about other treatment options. Her husband is also concerned about her staying on the antidepressant while pregnant and how that might harm the baby. Anne has heard lots about drugs and pregnancy in the news recently.

Previous Meta-analyses

In 2010 Grote and colleagues conducted a meta-analysis of 29 prospective U.S. and international studies "on antenatal depression and at least 1 adverse birth outcome."[12] They found a significant risk for preterm birth and low birth weight associated with depression during pregnancy. Our group[i,ii] reviewed 7 meta-analyses on the impact of antidepressant exposure (see Table 1) dating to the year 2010 while we were conducting the work and another was published in 2012. The findings were variable, with some studies focusing on specific antidepressants, while others did not. Two analyses both found an increased risk of cardiac malformation in children born of mothers who had taken paroxetine in the first trimester of their pregnancy.[13,14] Other analyses of studies with selective serotonin reuptake inhibitors (SSRIs) or antidepressants found higher rates of spontaneous abortion[15-17] and malformation.[14,16]

Given the mixed evidence, and recognizing that there were no evidence-based tools to aid the physician and the patient in risk:benefit discussions, our group set about to develop the Physician Reference Guide for the Treatment of Depression in Pregnancy with Antidepressant Medication.[iii] The guide was intended to provide useful information to support women with major depression, as about 10-16% of pregnant women meet the diagnostic criteria for a major depressive episode,[23,24] and at least 18% exhibit depressive symptoms.[25] Treatment is essential to avoid untoward effects for mother *and* infant. Unfortunately, depression during pregnancy is undertreated,[26] in part due to concerns regarding medication safety for the fetus.[27]

Outcomes that could be associated with antidepressant medication use were considered: any congenital malformation, cardiac malformation, persistent pulmonary hypertension of the newborn (PPHN), immediate neonatal outcomes, preterm birth/low gestational age, spontaneous abortion, low birth weight, Apgar score, and developmental outcomes. We also looked at the impact of depression on delivery outcomes, i.e., premature delivery, low birth weight (under 2500 g), birth weight in general, and gestational age (in weeks) and maternal/neonatal outcomes, specifically preeclampsia, breastfeeding initiation, Apgar scores at 1 and 5 minutes, and neonatal intensive care (NICU) admissions.

The creation of the guide forms part of a large program of research where we completed a systematic review and meta-analyses were possible; our methods have been published and will be briefly reviewed to highlight what needs to be considered in order to evaluate the data.[28] Please note that we attempted to evaluate non-pharmacological options but this work will not be described here. In terms of outcomes, this presentation will focus on the poor neonatal adaptation and PPHN outcomes as I had presented the others previously but I will briefly outline them.

[i] Principal Investigators: Sophie Grigoriadis, Lori Ross (2009-2011), Patricia Mousmanis (2013-2015); Co-investigators: Amy Cheung, Cindy Lee Dennis, Gideon Koren, Meir Steiner, Patricia Mousmanis (2009-2011); Collaborator: Lori Ross (2013-2015); Advisory Committee: Michael Dunn, Hiltrud Dawson, Sarah Romans, Jan Kasperski, Karen Wade, Adrienne Einarson, Sagar Parikh, Paula Ravitz, Irena Nulman, Jennifer Blake, Arthur Zaltz, Jasmine Gandhi, Jane Lowry, Alex Kiss, Diane Meschino, Alicja Fishell, Simone Vigod, Robin Harvey, Sidney Kennedy, Karen Liberman; Research Staff: Lana Mamisashvili, Lana Bradley, Allison Eady, Kim Radford, Emily VonderPorten. Research Students: Jenna MacKay, Jovana Martinovic; Research Fellow: Beverly Bouffard

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TABLE 1 Meta-analytic Evidence Circa 2012

Authors	Notes	Results
Addis 2000[18] (4 studies)	Fluoxetine during T1*	No significant malformation: OR† = 1.33 (95% CI‡ 0.49-3.58) for 2 controlled studies (NS§)
Einarson 2005[19] (7 studies)	SSRIs**, SNRIs*** and others in T1*	No significant malformation: RR††=1.01 (95% CI 0.57-1.80)
Hemels 2005[15] (6 studies)	SSRIs, TCAs, Others	Increased rate of spontaneous abortion RR=1.45 (95% CI 1.19-1.77)
Lattimore 2005[20] (9 studies)	SSRIs	Increased neonatal effects Low birth weight : OR=3.64 (95% CI 1.01-13.08) SCN/NICU Admission: OR=3.30 (95% CI 1.45-7.54) PNA: OR= 4.08 (95% CI 1.20-19.93), p=0.07 Prematurity: OR=1.85 (95% CI 0.79-4.29), p=0.13
Rahimi 2006[17] (9 studies)	SSRIs	No significant malformation (including major, cardiac and minor) Major malformations: OR=1.39 (95% CI 0.91-2.15) Cardiac malformations: OR=1.19 (95% CI 0.53-2.68) Minor malformations: OR=0.97 (95% CI 0.14-6.93) Increased rate of spontaneous abortion: OR=1.7 (95% CI 1.28–2.24)
Bar-Oz 2007[13] (7 studies)	Paroxetine during T1	Increased risk of cardiac malformation: OR = 1.72 (95% CI 1.22-2.42) No significant major malformation: OR=1.31 (95% CI 1.03-1.67)
Wurst 2010[14] (20 studies)	Paroxetine during T1	Increased risk of cardiac malformation: POR+ = 1.46 (95% CI 1.17-1.82) Increased rate of congenital defects: POR = 1.24 (95% CI 1.08-1.43)
Nikfar 2012[16] (25 studies)	SSRIs	Increased rate of spontaneous abortion: OR = 1.87 (95% CI 1.5-2.33) Increased rate of major malformations: OR = 1.272 (95% CI 1.098-1.474) No significant cardiac malformations: OR = 1.192 (95% CI 0.39-3.644) No significant minor malformations: OR = 1.36 (95% CI 0.61-3.04)

T1 = first trimester; **SSRI = selective serotonin reuptake inhibitor; ***SNRI = serotonin-norepinephrine reuptake inhibitor; †OR = odds ratio; ††RR = relative risk; ‡CI = confidence interval; §NS = not statistically significant; +POR = prevalence odds ratio; *PNA= poor neonatal adaption

METHODOLOGY OF REVIEW

The systematic literature review began with 2 independent professional librarians completing a comprehensive search[iv] of databases (e.g., EMBASE, MEDLINE, PsycINFO, and CINAHL) from their initiation up to June 2010 (to December 2012 for PPHN). English language cohort or case-control studies were included if they: contained original data reporting on outcomes following any antidepressant exposure (i.e., tricyclic antidepressants [TCAs], SSRIs, or monoamine oxidase inhibitors [MAOIs]); included a comparison/control group of pregnant women not exposed to the antidepressant medication under analysis; and included enough data to calculate an effect size, if not already provided. For studies that used the same cohort, only the most recently published paper with the largest number of specific cases was used. Two independent research staff screened the literature results and 2 independent research staff then extracted the data.

A data extraction tool was developed by the research team, based on the STROBE statement criteria.[29] Adjusted estimates and their variances were extracted directly or crude odds ratios were calculated with the available published data. Requests for raw data were sent to authors if not provided in the original publications. Using our published quality assessment tool, SAQOR,[28] 19 quality criteria within 5 categories were assessed: sample, control group, quality of exposure/outcome measure, follow-up, and distorting influences (included whether any control for confounders was present, i.e., depression, other psychotropic medications).

A High, Moderate, Low or Very Low quality rating was assigned to each study, based on the SAQOR and on a modification of the GRADE.[30] Statistical analyses involved pooling of studies of above quality threshold (high, moderate and low quality) and below quality threshold, as well as pooling of all studies.

Adjusted or unadjusted odds ratios (ORs), prevalence, or relative risks were used as estimates of ORs. We analysed the impact of antidepressant medication treatment, of depression itself, as well as of non-pharmacological interventions (will not be discussed). We did not find sufficient data to examine developmental outcomes.

[iv] Examples of keywords used: depressive/mood disorder, pregnancy/pregnancy trimesters, antidepressant drugs, PPHN, congenital malformations, premature delivery, etc.

REVIEW FINDINGS

Over 7000 abstracts were reviewed, with many duplicated between databases, for a total of 3,077. Of 738 complete articles retrieved, 80 unique articles were eligible for inclusion in the review. Our findings have been published in a number of journals.[31-35]

Based on our meta-analysis, antidepressants do not appear to be major teratogens.[31] Of note, the majority of the drugs investigated in our meta-analyses were SSRIs. Antidepressants appear to be statistically associated with cardiovascular malformations, and paroxetine may be specifically associated with cardiovascular malformations; however results were marginal and confounding cannot be ruled out.[31] Antidepressants appear to be associated with delivery outcomes that include preterm birth, lower birth weight, lower gestational age, and lower Apgar scores.[32] However, not all analyses found significant increases in these parameters, so caution needs to be taken in their interpretation. There is a need to balance the findings with consideration of *clinical* significance as it does not always equal *statistical* significance. Differences were small in magnitude, e.g., gestational age was approximately 3 days shorter, birth weight 75 grams lower, and the 1- and 5-minute Apgar scores were less than half a point lower.[32] Therefore, it is important to consider the clinical significance of these results as applied to your patient and their infant.

Poor Neonatal Adaptation Syndrome (PNAS)

In order to better understand the effect of antidepressants on neonatal outcomes, we then looked specifically at PNAS.[33] In total, 12 studies were eligible for inclusion in this meta-analysis. The result from 8 studies, pooled to examine the overall risk for PNAS, was found to be a significantly increased risk with prenatal exposure to antidepressants: OR = 5.07, 95% CI 3.25-7.90, P

< 0.0001. Nine studies showed that risk of respiratory distress was significantly increased: OR = 2.20, 95% CI 1.81-2.66, P < 0.0001. Four studies found risk of tremors significantly increased: OR = 7.89, 95% CI 3.33-18.73, P < 0.0001. Therefore, antidepressant exposure during pregnancy does appear to be associated with PNAS. Other published studies show this association as well.[36-40] In addition, respiratory distress and tremors also appear to be associated with antidepressant exposure, however PNAS signs are typically transient, with no known long-term implications to date.[33] The recommendation is therefore to maintain close monitoring of neonates and educate parents.[41]

PNAS has been described to occur in up to 30% of infants that have had serotonergic antidepressant exposure in utero.[42] Signs of PNAS can include[42,43]: respiratory distress, tremors, shaking or jitteriness, irritability, sleep disturbances, poor muscle tone, weak or absent cry, hypoglycemia, seizures.

Case

After talking with her psychiatrist and family doctor, and with the support of her husband, if Anne decides to stay on paroxetine through her pregnancy (as this is the only antidepressant she has responded to failing multiple trials and she did not respond to psychotherapy*):

At 20 weeks, should a fetal echocardiogram be recommended to Anne?

"The practicing physician, to be "on the safe side" may wish to inform the pregnant patient that detailed fetal ultrasound scanning and echocardiogram at pregnancy weeks 18-22 can detect VSD at relatively high sensitivity and specificity."[21] (VSD = ventricular septal defect.) "... fetal echocardiography should be considered for women exposed to paroxetine during early pregnancy."[22]

What if she were using fluoxetine?

In general, experts have recommended avoiding paroxetine if possible.[7, 22]

TABLE 2 PPHN as a Function of Timing of Exposure in Pregnancy

Timing of SSRI Exposure in Pregnancy	OR	95% CI	P-value	N (studies)
Early Exposure	1.23	0.58-2.60	0.584	3
At Any Time Exposure	1.55	0.79-3.04	0.202	2
Most or All of Pregnancy Exposure	3.33	1.58-7.02	0.002	2
Late Exposure	2.50	1.32-4.73	0.005	5

Persistent Pulmonary Hypertension of the Newborn (PPHN) and SSRI Exposure

Another of our meta-analyses looked at PPHN in neonates exposed to SSRIs.[34] The odds ratios in relation to the timing of fetal exposure were analyzed. All the studies were above quality threshold. Late in utero exposure to SSRIs was found to be associated with an increase in the risk for neonatal PPHN[34], see Table 2. Clinically, however, the absolute risk of PPHN after SSRI exposure in late pregnancy remains low. Sub-analyses were able to be completed for the late exposure group, taking into consideration the "study design (case-control vs. cohort), congenital malformations, and meconium aspiration".[34] None of the moderators accounted "for significant

sources of heterogeneity"; however, publication bias was identified. Correction for the bias provided the revised estimate of an odds ratio of 2.84 (95% CI 1.41-5.72, P = 0.004). The result remained significant, with a marginally higher odds ratio.

Given that 1.9 of every 1,000 liveborn infants have PPHN,[44] the number needed to treat to harm (NNTH) was calculated. For late pregnancy, from "286 to 351 women would need to be treated with an SSRI in late pregnancy to result in an average of one additional case of" PPHN.[34] For SSRIs taken in early pregnancy, 2,288 women would need to be treated for each additional infant case.

There were limitations to this meta-analysis due to insufficient research and data: study authors did not classify early vs. late exposure consistently; there was lack of control for depression itself or for underlying psychiatric conditions; studies did not all control for the same confounding factors or known risk factors for PPHN, or control for these factors in the same way; and there were variations in data sources among authors.[34] Additional confounding factors could also include use of antidepressants in patients with anxiety disorders, which of themselves have been associated with adverse birth outcomes.[45]

Case

After delivery, should Anne and her baby be kept longer in the hospital for observation?

Monitor the neonate for PPHN and PNAS in hospital, thus allowing the opportunity for immediate start of treatment if needed.[21]

Impact of Antenatal Depression

Another of our meta-analyses focused on infant outcomes for pregnant women with depression itself.[35] Modest associations were found between depression and preterm delivery and decreased breastfeeding initiation.[35]

OTHER META-ANALYSES

A few meta-analyses on the effects of perinatal antidepressants on neonates have been published in the last year.[46-49] The two analyses published in 2013 focused on the risk of malformations with fluoxetine and the others included other SSRIs; conflicting results for fluoxetine were found.[46,47] The two most recent publications looked at preterm birth and low birth weight, and found a significant association for both.[48,49] While both did find a tendency for preterm births, only Huybrechts and colleagues examined the findings according to time of exposure, i.e., in early pregnancy, any time, or in T3.[49]

CLINICAL RECOMMENDATIONS

The decision to use psychotropic drugs in pregnancy needs to balance the benefits of treatment against the risks to the pregnant woman and the fetus or child.[34,36] These agents should be used if they are clearly indicated, keeping in mind the risks of untreated illness in the mother and the potential for relapse associated with discontinuation of maintenance treatment (which we did not discuss today) as well as the risks of fetal exposure to medication. Although we did not focus on this here, keep in mind that non-pharmacological treatments should also be utilized where appropriate, and discussed in the treatment decision-making process.

Current expert and guideline recommendations summarize the following:

- Medications may be considered for management of moderate to severe depression in pregnancy.[11]
- Patients with residual symptoms, comorbid conditions (e.g., panic disorder), or at high risk of relapse may also benefit from psychotherapy.[50]

- No study has found a level or a "safe amount" of medication exposure for the fetus or neonate. "Exposure to antidepressants via breast milk", however, is considerably less than in utero.[11]
- When assessing the need for drug treatment, consider:[50]
  - Suicidal ideation and psychotic symptoms;
  - Recurrent, severe, depressive episodes;
  - Previous failed trials of psychotherapy, rapid relapse after psychotherapy termination;
  - Comorbid conditions, bipolarity;
  - Relapse following medication discontinuation.

Perinatal psychiatrists try to manage the depressed pregnant woman using a collaborative multidisciplinary approach, if possible, involving a perinatal treatment team that comprises the family physician, psychiatrist, obstetrician, paediatrician, and the patient and her family. Pharmacological and non-pharmacological treatments should also be taken into consideration within this context, keeping in mind that there is a need for the treatment team to give a consistent message to the patient and her family.

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