OUTCOMES OF INFANTS EXPOSED TO MULTIPLE ANTIDEPRESSANTS DURING PREGNANCY: RESULTS OF A COHORT STUDY

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ABSTRACT

Background
A single study has been published documenting an increased risk for adverse pregnancy outcomes following use of more than one antidepressant during pregnancy.

Objective
To examine whether multiple antidepressant use is associated with increased rates of major malformations, spontaneous abortions (SA), therapeutic abortions (TA), stillbirths, preterm birth, low birth weight, small for gestational age (SGA) and admission to the neonatal intensive care unit (NICU).

Methods
Information from the Motherisk Program's prospectively collected database of 1243 women with gestational exposure to antidepressants. We compared pregnancy outcomes of 89 women exposed to >1 antidepressants, 89 taking one antidepressant, and 89 women not exposed to antidepressants (n= 267). Women were matched for maternal age, smoking and alcohol use. Groups were compared using odds ratios and ANOVA.

Results
11/89 (12%) took 3 and 78 (88%) took 2 antidepressants. There were no statistically significant differences in any of the outcomes analyzed among the 3 groups except for a lower mean gestational age at birth in the multi-antidepressant group (0.9 week, P=0.036). There were 9 admissions to NICU from the antidepressant groups and 3 from the non-exposed group; but this did not reach statistical significance.

Conclusions
There is a small risk of preterm delivery that is associated with exposure to antidepressant therapy, although the clinical relevance remains to be determined.

Key Words: *Antidepressants, pregnancy, preterm delivery, Motherisk Program*

In the past five years, epidemiologic studies, including a meta-analysis[1], two large case control studies[2,3] and most recently, a large cohort study[4], have established that overall there is no increase in the rates of major malformations in infants exposed to selective serotonin reuptake inhibitor (SSRI) antidepressants and other antidepressants during pregnancy. Other studies have also been published documenting a slight increased risk for spontaneous abortions[5] and an increase in the rates of preterm births (approximately 1 week preterm).[6] In addition, well defined self-limiting symptoms of abrupt discontinuation have been identified in newborn infants, although there is no definitive estimate as to their frequency.[7] Several reports, including results from a registry by the manufacturer, suggested that the risk of cardiovascular defects in infants whose mothers had used paroxetine is 1%-2%.[8-10] However, in 2008, a study documented the largest number of exposures to paroxetine (N=1170) during the first trimester of pregnancy, reporting no difference in the rates of cardiovascular defects between paroxetine exposed and unexposed infants, when compared to the rate of cardiovascular defects in the population.[11]

To our knowledge there is only one other published study analyzing outcomes following use of more than one antidepressant during pregnancy. However, the authors did not examine outcomes other than malformations, and reported an increased risk for septal defects, but not for other malformations, including other cardiovascular defects. The prevalence of septal heart defects was 0.5% (2315/493,113) among unexposed children, 0.9% (12/1370) among children whose mothers were prescribed any SSRI, and 2.1% (4/193) among children whose mothers were prescribed more than one type of SSRI.[12]

The objective of this study was to examine infant outcomes of women who were exposed to more than one antidepressant during the course of their pregnancy.

METHODS

The Motherisk Program at the Hospital for Sick Children in Toronto, Canada is a Teratology Information Service. It provides evidence-based information on the safety and/ or risks associated with exposures to drugs, chemicals, radiations and infectious diseases during pregnancy and lactation to pregnant women, lactating mothers and their health care providers. Women call for information regarding the safety of a drug, usually early in gestation, most often following recognition of the pregnancy. During the initial telephone contact, demographics, medical and obstetrical histories as well as details of drug and concurrent exposures are recorded on a standardized questionnaire. Details include duration, timing in pregnancy, dose, frequency and indication for drug use. At the follow up interview, gestational findings, fetal outcomes and neonatal health are documented on a structured form by telephone with each mother, following a detailed explanation of the study and with her consent. The details are then, with the mother's permission, corroborated with a report from the physician caring for the baby.

We used this method to ascertain pregnancy outcomes of women who called the Motherisk Program between 1992 and 2007 regarding the use of antidepressants during pregnancy. These details were entered into an electronic database which when completed, totaled 1245 women exposed to antidepressants and 1245 non-exposed women. For this study, we separated the women who had been exposed to more than one antidepressant during pregnancy. We compared their data with those from an equal number of women who were exposed to a single antidepressant and a third group not exposed to any antidepressants, who had called Motherisk for information regarding non-teratogenic drugs such as acetaminophen. The three groups were matched for maternal age (±2 years), smoking and alcohol use. We also matched for time of call to Motherisk, as this is critical when calculating the incidence of miscarriages (SA). This is important because the observed proportion of pregnancies ending in loss is highly dependent on the gestational age at which pregnancies are recognized, as well as how the losses are identified. Thus, all three groups of women were pregnant at the time of enrollment in the study and had not yet miscarried.

Outcomes of interest were major malformations, spontaneous abortion, therapeutic abortion, stillbirth, preterm birth, small for gestational age, gestational age at birth and birth weight. The latter two were compared across groups using ANOVA. All other outcomes were compared using odds ratios. A level of $P \leq 0.05$ was considered significant for all statistical tests. This study was approved the Research Ethics Board at The Hospital for Sick Children in Toronto, Canada.

RESULTS

Out of 1245 women, 89 (10%) were exposed to more than one antidepressant during pregnancy. Of these women, 78 (88%) took two different antidepressants and 11 (12%) took three. There were 32 different combinations of drugs taken by those women who took 2 antidepressants (Table 1A), and 8 different combinations by the women who took 3 antidepressants (Table 1B). A large number of the women took more than one antidepressant concomitantly (n=66, 74%), while the remainder (n=23, 26%) took a single antidepressant at a time, but switched to a different one at a later stage in the same pregnancy. All of the women reported that they were treated exclusively for depression and/or anxiety, with none reporting any other psychiatric diagnosis and none taking other psychotropic drugs during pregnancy, such as anti-psychotics or lithium. All of the women took the drug(s) in the first trimester.

TABLE 1A Exposure to two different antidepressants (n=78)

n	Drug 1	Drug 2
5	bupropion	citalopram
1	bupropion	fluoxetine
1	bupropion	mirtazapine
1	bupropion	nefazadone
1	bupropion	paroxetine
1	bupropion	sertraline
7	bupropion	venlafaxine
2	citalopram	fluoxetine
1	citalopram	mirtazapine
1	citalopram	paroxetine
1	citalopram	sertraline
5	citalopram	trazodone
2	citalopram	venlafaxine
1	citalopram	mirtazapine
2	fluoxetine	fluvoxamine
2	fluoxetine	mirtazapine
6	fluoxetine	nefazadone
1	fluoxetine	paroxetine
3	fluoxetine	trazodone
1	fluoxetine	venlafaxine
1	fluvoxamine	trazodone
3	mirtazapine	sertraline
1	mirtazapine	venlafaxine
3	mirtazapine	venlafaxine
2	nefazadone	paroxetine
1	nefazadone	sertraline
4	paroxetine	trazodone
2	paroxetine	venlafaxine
7	sertraline	trazodone
2	fluoxetine	venlafaxine
4	sertraline	venlafaxine
3	trazodone	venlafaxine
32	combinations	

TABLE 1B Exposure to three different antidepressants (n=11)

n	Drug 1	Drug 2	Drug 3
1	bupropion	citalopram	fluvoxamine
3	bupropion	citalopram	trazodone
1	bupropion	citalopram	venlafaxine
1	bupropion	fluoxetine	trazodone
1	bupropion	mirtazapine	paroxetine
1	bupropion	paroxetine	venlafaxine
1	fluoxetine	paroxetine	trazodone
2	fluoxetine	sertraline	trazodone
8	combinations		

Table 2 presents pregnancy outcomes that were measured as discrete events and Table 3 presents those measured as continuous variables. The only statistically significant result was gestational age, which was lower by 0.9 week in the multiple antidepressant group (P=0.032). There were also numerically more infants admitted to NICU in both single and multiple antidepressant groups, 9 in each of the antidepressant groups compared to 3 in the non-exposed group, although this did not reach statistical significance (Fisher's Exact P=0.077 between the multi-antidepressant and no antidepressant groups). Birth weight was numerically lower in the multi-antidepressant group, although the difference was only 172 gm and did not reach statistical significance (P=0.19). Finally, there were more preterm births (<37 weeks GA) in both antidepressant groups, but again, the differences were not statistically different (Table 2).

TABLE 2 Pregnancy outcomes following exposure to multiple/single and no antidepressants (n =89 in each group)

Outcome	Antidepressant Exposure			OR (Single)	OR (None)
	Multiple	Single	None	(95% CI)	(95% CI)
SA*	8	7	8	1.16 (0.40-3.34)	1.00 (0.36-2.79)
TA*	2	3	2	0.66 (0.11-4.04)	1.00 (0.14-7.26)
Fetal death†	3	1	1	3.08 (0.31-30.26)	3.08 (0.31-30.26)
Live birth*	76	78	78	0.82 (0.35-1.95)	0.82 (0.35-1.95)
Malformation†	2	3	2	1.03 (0.14-7.48)	0.68 (0.11-4.16)
Preterm (GA<37 weeks)	11	9	4	1.30 (0.50-3.33)	3.13 (0.95-10.31)
SGA†	2	2	3	1.03 (0.14-7.48)	0.68 (0.11-4.16)
NICU‡	9	9	3	1.03 (0.39-2.75)	3.36 (0.87-12.92)

*denominator = all exposures; †denominator = all live births; GA = gestational age; SA = spontaneous abortion; SGA = small for gestational age; TA = therapeutic abortion

TABLE 3 Pregnancy outcomes (continuous) following exposure to multiple/single and no antidepressants

Outcome	Antidepressant Exposure (n=89/group)			P-value*
	Multiple	Single	None	
Gestational age at birth (weeks)	38.4±2.3	38.8±2.6	39.3±1.7	0.036
Birth weight mean SD	3291±648	3408±692	3463±577	0.190

*ANOVA. Gestational age differs significantly between Multiple and None using Tukey's post hoc test; others=NS

DISCUSSION

To our knowledge, this is only the second study to report on outcome of infants exposed to more than one antidepressant during pregnancy, either concomitantly or intermittently. We did not find an increase risk for any type of heart defect in our study, unlike the Danish study previously described.[12] The major limitation of that study was that the information came from a database which recorded redeemed prescriptions, with very little other maternal information. Most notably, they did not verify whether the women actually took the drug and did not state whether the women took the antidepressant concomitantly or intermittently. In addition, using this type of data to document psychotropic drug exposure in pregnancy is a flawed methodology, as it has been documented that women and health care providers are more afraid of psychotropics than of other classes of drugs. Consequently, the woman may elect not to take the antidepressant, even after filling the prescription.[13] In addition, if some of these women were anxious/depressed enough to require two antidepressants, they probably sought more prenatal diagnostic testing than other women and consequently more cardiovascular heart defects would have been diagnosed (i.e., detection bias).[14]

The main strength of our model is the personal interview with the woman, which includes a detailed history. Our pregnancy registry is designed specifically for collecting pregnancy outcome data. Consequently, we are able to collect details of alcohol, tobacco and concurrent drug use, as well as other important potential confounders of pregnancy outcomes. Importantly, because all of the women called when they were in early pregnancy and the details of their pregnancy and drug exposure were recorded at that time, the possibility of a recall bias is eliminated or reduced substantially.

The main limitation of this study is the sample size at 89 is relatively small, and there was inadequate power to achieve statistical significance for the observed results. With our sample size, we would be able to detect a 5.4-fold difference in overall malformation rates and a 12-fold increase in cardiac malformations. However, it is the largest sample size to date with data to control for potentially important confounders, and to examine potential adverse effects of taking more one than one antidepressant during pregnancy.

The only statistically significant result was gestational age at time of birth, which was almost one week earlier in both single and multiple antidepressant groups, compared to the non-exposed women (p=0.036). It is debatable if this difference is clinically important. However, this same observation has been reported in other studies with the same difference. Women had delivered their babies approximately one week earlier than women who were not taking an antidepressant.[15] Another group conducted a population-based study where most of the women (98.5%), who had depressive symptoms and were not taking an antidepressant reported that the risk of preterm delivery increased with increasing severity of depression. However, they also suggested this risk appeared to be exacerbated by low educational level, a history of fertility problems and the presence of obesity and stressful events.[16]

Another difference which did not achieve statistical significance was the number of admissions to NICU - 9 in both single and multiple antidepressant groups compared to only 3 in the non-exposed group. However, some of these admissions were because of hospital policy,

to allow closer observation of infants exposed prenatally to antidepressants, not necessarily because they had a problem. It was reassuring to note that none of the infants stayed in the NICU for more than 3-4 days and that there were no differences in length of stay between neonates whose mothers were taking one antidepressant at the time of delivery, to those who were taking two or three. In addition, none of the mothers mentioned any long-term withdrawal effects from the multiple antidepressant exposure prior to delivery in their infants. This confirms the results of our findings from another study we conducted to examine the incidence of poor neonatal adaptation in infants whose mothers took an antidepressant prior to delivery. We compared paroxetine (n=57), venlafaxine (n= 97) and a non-exposed group (n= 64) and did not find a statistically significant difference in the incidence of poor neonatal adaptation syndrome (PNAS) among the three groups (p=0.54). In addition, we did not find a correlation in either the incidence or severity of PNAS when related to the dose of antidepressant a mother was taking prior to delivery, confirming results of a previous Motherisk study.[17]

Severity of depression is most likely a confounding factor, consequently another important limitation was not having a confirmed psychiatric diagnosis or severity of depression, as these were self reports with no confirmation from the attending physician. Ideally, we should have had a fourth group of women who were depressed and unexposed to antidepressants. However, due to the nature of our service, we do not have access to such a group. Women who call Motherisk do so with inquiries regarding the safety of an antidepressant that they had been taking prior to becoming pregnant. We also did not measure Socioeconomic Status (SES) and differences which may have impacted our findings. What we do know from previous research is that all women who called the Motherisk Program have a higher SES, and are more motivated to do the "right thing," and use less alcohol and tobacco than the general population.[13]

In summary, taking more than one antidepressant during pregnancy does not appear to increase the risk of birth defects, miscarriages, low birth weight or delivery of infants small for gestational age. There does appear to be an increased risk for preterm delivery, (<37 weeks GA), with women giving birth approximately one week earlier than women not exposed to antidepressants. Currently, we do not have a definitive answer as to whether this is the result of the antidepressant, depressive symptoms or a combination of both. If a pregnant woman requires treatment with an antidepressant, this additional information may be of help for her to make an evidence-based decision together with her physician regarding pharmacological treatment.

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