Exposure to Mirtazapine During Pregnancy: A Prospective, Comparative Study of Birth Outcomes

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Background: Mirtazapine is a novel piperazinoazepine antidepressant, unrelated to any known class of antidepressants. Currently, apart from a few case reports and case series in the literature, there are no studies evaluating the safety of this drug during pregnancy.

Objective: To determine whether mirtazapine increases the risk for major malformations in newborns when used by pregnant women.

Method: The study design was prospective, with 2 comparison groups: disease-matched pregnant women diagnosed with depression taking other antidepressants and pregnant women exposed to nonteratogens. The primary outcome was major malformations in neonates; secondary endpoints included spontaneous abortions, therapeutic abortions, gestational age at birth, and mean birth weight. Women were recruited from 5 teratogen information services in Toronto, Canada; Farmington, Conn., U.S.A.; Jerusalem, Israel; Rome, Italy; Sydney, Australia; and from the Drug Safety Research Unit in Southampton, United Kingdom. Women were recruited into the study from June 2002 to August 2005.

Results: We were able to follow 104 pregnancy outcomes in each drug group. There were 77 live births, 1 stillbirth, 20 spontaneous abortions, 6 therapeutic abortions, and 2 major malformations in the mirtazapine group. The mean ± SD birth weight was 3335 ± 654g and the mean ± SD gestational age at delivery was 38.9 ± 2.5 weeks. Most (95%) of the women took mirtazapine in the first trimester, but only 25% of the women took it throughout pregnancy. The differences among the 3 groups were in the rate of spontaneous abortions, which was higher in both antidepressant groups (19% in the mirtazapine group and 17% in the other antidepressant group) than in the nonteratogen group (11%), but none of the differences were statistically significant. The rate of preterm births (prior to 37 weeks' gestation) was also higher in the mirtazapine group (10%) and in the other antidepressant group (7%) than in the nonteratogen group (2%). The difference was statistically significant between the mirtazapine group and the nonteratogen group (p = .04).

Conclusion: Mirtazapine does not appear to increase the baseline rate of major malformations of 1% to 3%. However, the higher number of spontaneous abortions in the antidepressant groups confirms the higher rates of spontaneous abortions in pregnant women taking antidepressant medications found in previous studies.

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Mirtazapine is a novel piperazinoazepine antidepressant, chemically unrelated to any known class of psychotropic medication.[1] It increases the active levels of norepinephrine and serotonin in the synapse by blocking the presynaptic α_2-adrenergic receptors with a dual action on autoreceptors and heteroreceptors. It also blocks the postsynaptic serotonin receptors 5-HT2 and 5-HT3. Mirtazapine is indicated for various DSM-IV disorders and has been on the market for more than 10 years. It is administered in 15 to 45 mg preparations, with once-daily dosing.[2] Administration of mirtazapine to pregnant rats and rabbits in doses up to 100 mg/kg and 40 mg/kg, respectively, by the manufacturer did not increase the incidence of abnormal development in the offspring. However, pup weight and viability were decreased at term, and

preimplantation embryo loss was increased in rats. The doses used were 20 and 17 times the maximum recommended dose for humans, respectively.[1] There is a paucity of safety data on human exposure to mirtazapine in pregnancy, currently limited to a total of 16 case reports and case series.[3,4,5] However, all of these women delivered healthy newborns, with the exception of 1 newborn who had transient hyperbilirubinemia and gastroesophageal reflux disease.

A substantial number of women of child-bearing age suffer from depression. In a recent investigation[6] conducted as part of a large screening study of perinatal depression, pregnant women were assessed for demographics, depression, and treatment variables in obstetrics clinics. Because the trial was designed to establish the prevalence of antidepressant use and its association with the symptoms of depression, women who took medication before becoming pregnant were assessed in the study. Twenty-two percent of pregnant women who endorsed antidepressant use within 2 years before assessment (N = 390, or 11% of all women) continued it. Increased symptoms of depression during pregnancy were endorsed both by women who reported using antidepressant medications (52%) and by those who discontinued them (49%).[6]

We are aware that women remain hesitant to take antidepressant medications during pregnancy. Because of fear and/or lack of information, some will even discontinue their antidepressant abruptly, upon confirmation of pregnancy, which is definitely not a safe practice.[7] Recently, we published a study[8] in which one goal was to evaluate how depressed pregnant women perceived the risk of antidepressant drugs. Three hundred women were recruited; 100 were taking antidepressants during pregnancy. Two hundred women were divided into 2 equal comparison groups, each taking other drugs. In spite of being given evidence-based information that was largely reassuring, women taking antidepressants discontinued their medication at a rate of 15%, while only 4% of women taking gastric drugs and 1% of those taking antibiotics discontinued medication use. The women in all 3 groups viewed antidepressant use during pregnancy as more harmful to the newborn than use of nonpsychiatric drugs.[8]

Whether to take a medication during pregnancy is a complex decision facing women and their health care providers. In light of this complexity, and considering that at least 50% of pregnancies are unplanned, it is likely that a relatively large number of women will use an antidepressant during pregnancy, especially during the organogenesis stage.

Our primary objective in this study was to ascertain whether mirtazapine taken by pregnant women increased the baseline rate of 1% to 3% for major malformations in newborns. Secondary objectives included determining effects on spontaneous and therapeutic abortions, preterm births, gestational age at birth, and birth weight.

METHOD

This was a prospective, multicenter, comparative, observational study. The Motherisk Program at the Hospital for Sick Children in Toronto, Canada, is a teratology information service. We provide evidence-based information on the safety and risks associated with exposure to drugs, chemicals, radiation, and infectious diseases during pregnancy and lactation to pregnant women, lactating mothers, and their health care providers. The other 4 teratology information services used in this study were the Israel Teratogen Information Service (Jerusalem, Israel), the Mothersafe Program (Sydney, Australia), the Pregnancy Riskline (Farmington, Conn., U.S.A.), and the Telefono Rosso (Rome, Italy). All of these centers provide similar services and collect similar data from similar patients. Pregnant women who were exposed to mirtazapine during pregnancy and who contacted (directly or indirectly through their health care providers) 1 of the 5 participating centers were asked to participate in the study. Women were recruited into the study from June 2002 to August 2005.

Exposed women were also recruited through the Drug Safety Research Unit in Southampton, United Kingdom. This facility is an academic and independent medical charity whose work is principally concerned with the detection of side effects associated with newly marketed drugs. They monitor the safety of new medicines prescribed under the condition of general practice in England through their special technique named Prescription-Event Monitoring (PEM). This monitoring is carried out in a prospective manner. The practitioner is not approached before a decision to treat a patient has been made and a prescription dispensed. Women who were identified from the dispensed prescriptions as taking mirtazapine during pregnancy were followed up prospectively. A detailed questionnaire was sent to each prescribing general practitioner regarding drug history and pregnancy outcome, and other information similar to the data gathered by the participating teratology information services.

At the teratogen information services, eligible exposed pregnant women were prospectively enrolled in the study after oral informed consent was given over the telephone. During the initial telephone contact, demographics, medical and obstetric histories, and details of exposure and concurrent exposures were recorded on a standardized questionnaire. Details about the exposure included duration, timing in pregnancy, dose, frequency, and medical indication for drug use. Participants also were informed that they would be contacted 2 to 6 months after their expected date of delivery to assess pregnancy outcome. At this interview, gestational findings and fetal outcomes were documented on a structured form by telephone interview with

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each mother. Each mother's report was, with her permission, corroborated with the report of the physician caring for the infant.

A specific, detailed questionnaire was sent to each prescribing general practitioner regarding drug history and pregnancy outcome. The documented information is similar to the data gathered by the participating teratology information services.

The pregnancy outcomes for neonates born to the group of pregnant women exposed to mirtazapine were compared with those for 2 other groups. The first comparison group included disease-matched pregnant women taking other antidepressants, such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, or tricyclic antidepressants. The second comparison group included nondepressed women who contacted the participating centers for exposures known to be nonteratogenic, such as acetaminophen, cold medications, hair dyes, cleaning products, antacids, antibiotics, and antihistamines. The 2 comparison groups were matched with the mirtazapine group for maternal age at the time of conception (± 2 years), gestational age at the first contact (± 2 weeks), tobacco use, alcohol consumption, and chronic conditions.

The incidence of major malformations in neonates was the primary outcome of interest. Major malformation was defined as a structural abnormality that was either lethal, required treatment (medical or surgical), or was of cosmetic importance and would interfere with quality of life. We excluded chromosomal defects and genetic disorders from the primary analysis of major structural defects. Secondary outcomes of interest included rates of live births, stillbirths, spontaneous abortions, therapeutic abortions, and preterm birth (< 37 weeks gestational age), as well as mean gestational age at birth and birth weight.

All categorical endpoints for mirtazapine were compared with those for each of the 2 comparison groups using the χ^2 test or Fisher exact test when assumptions for χ^2 were not met. Categorical data of interest included incidence of major malformations, live births, spontaneous abortions, therapeutic abortions, stillbirths, and preterm deliveries. All continuous endpoints of interest, such as gestational age at birth and birth weight, were compared using the Student t test between the mirtazapine group and each of the 2 control groups. In addition, a 95% confidence interval was constructed for malformation rates using the score method.

The study protocol was approved by the Hospital for Sick Children Research Ethics Board.

RESULTS

A total of 104 pregnancy outcomes following exposure to mirtazapine were obtained from the 6 different centers, along with an equal number in each of the other 2 groups (i.e., exposed to other antidepressants or nonteratogens). Due to the matching, there were no significant differences ($p > .05$) in any of the maternal characteristics between the mirtazapine group and each of the 2 comparison groups. Overall, the mean ± SD daily dose of mirtazapine was 30 ± 12 mg. Twenty-five (24.0%) of the women took mirtazapine in combination with another antidepressant, 8 (7.7%) reported using it in combination with a benzodiazepine, and 4 (3.8%) with an anticonvulsant. No major malformations were reported in any of the newborns who were exposed to anticonvulsants or benzodiazepines.

Pregnancy outcomes in the mirtazapine-exposed group included 77 live births, 1 stillbirth, 20 spontaneous abortions, and 6 therapeutic abortions (see Table 1). Among the live births, there were 2 major malformations, which included 1 patent ductus arteriosis and 1 midline facial defect. The mean ± SD birth weight was 3335 ± 654 g, and the mean ± SD gestational age at delivery was 38.9 ± 2.5 weeks. Most (95%) of the women took mirtazapine in the first trimester, but only 25% of the women took it throughout pregnancy.

There were no statistically significant differences in the rates of major malformations between the mirtazapine group and either of the comparison groups. In the mirtazapine group, 2 major malformations were reported, for a rate of 1.9% (95% CI = 0.5% to 3.6%). In the other antidepressant group, there was 1 malformation (for a rate of 1.0%, 95% CI = 0.2% to 2.7%). The difference between rates was not significant (1.0%, 95% CI = –2.3% to 4.2%). The nonteratogen group also had 2 malformations.

We compared 3 outcomes that differed between groups. The first was the rate of live births, which was significantly higher in the nonteratogen group (88.5%) than in the mirtazapine group (74.0%, $p = .01$). This outcome was expected, because there were more spontaneous and therapeutic abortions in the mirtazapine group. On the other hand, spontaneous and therapeutic abortions were not significantly different between groups. The other significant difference was in rates of preterm births between the mirtazapine group and the nonteratogen group ($p = .04$) but not between the other antidepressant group and the nonteratogen group (see Table 1).

DISCUSSION

To our knowledge, this is the first prospective, comparative study to examine pregnancy outcomes of women who took mirtazapine during pregnancy, 99/104 (95.1%) of whom were exposed during the organogenesis period and 24/96 (25.0%) throughout pregnancy. However, we did not conduct a study examining neurodevelopmental outcomes, as the infants were too young at the time of follow-up.

Mirtazapine does not appear to be associated with an increased risk for major malformations in newborns.

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Table 1. Neonatal Outcomes in Women Exposed to Mirtazapine, Other Antidepressants, and Nonteratogens During Pregnancy (N = 104 in each group)

	Exposure			p Value	
Outcome	Mirtazapine	Other Antidepressant	Nonteratogen	Mirtazapine vs Other Antidepressants	Mirtazapine vs Nonteratogens
Live birth, N (%)	77 (74)	83 (80)	92 (88)	.41	.01[a]
Spontaneous abortion, N (%)	20 (19)	18 (17)	11 (11)	.86	.12
Therapeutic abortion, N (%)	6 (6)	3 (3)	1 (1)	.49	.12
Stillbirth, N (%)	1 (1)	0 (0)	0 (0)	.50	.50
Preterm birth (< 37 wk gestation), N (%)	10 (10)	7 (7)	2 (2)	.61	.04[a]
Gestational age at birth, mean ± SD, wk	38.9 ± 2.5	39.1 ± 1.8	39.6 ± 1.4	.60	.06
Birth weight, mean ± SD, g	3335 ± 654	3419 ± 597	3502 ± 540	.40	.08
Major malformations					
No. (%)	2 (1.9)	1 (1.0)	2 (1.9)	.50	.69
95% confidence limits	0.5%, 3.6%	0.2%, 2.7%	0.5%, 3.6%		

[a]Statistically significant χ^2 test.

This information increases the knowledge concerning the safety of antidepressants as a group during pregnancy. We recently published a meta-analysis[9] that included almost 1800 woman exposed in the first trimester to one of the newer antidepressants, which included fluoxetine, paroxetine, citalopram, sertraline, venlafaxine, trazodone, nefazodone, and bupropion. The summary relative risk was 1.01 (95% CI = 0.57 to 1.80). As a group, the newer antidepressants were not associated with an increased risk of major malformations above the baseline of 1% to 3% in the population.

In the current study the only differences in the outcomes of interest were the higher rates of spontaneous abortions and preterm births (prior to 37 weeks' gestation) in both the mirtazapine and other antidepressant group. The high rate of spontaneous abortions confirms similar findings from other antidepressant studies.[10] Recently, we published a meta-analysis[10] in which we combined prospective studies with comparison groups to examine the rates of spontaneous abortions. Of 15 potential studies, 6 cohort studies of 3567 women (1534 exposed, 2033 nonexposed) provided extractable data, and all 6 were matched on important confounders. Tests found no heterogeneity ($\chi^2 = 3.13$; p = .98), and all quality scores were adequate (> 50%). The baseline spontaneous abortion rate (95% CI) was 8.7% (7.5% to 9.9%; N = 2033). For antidepressants, the rate was 12.4% (range 10.8% to 14.1%; N = 1534), significantly increased by 3.9% (range 1.9% to 6.0%); relative risk was 1.45 (range 1.19 to 1.77; N = 3567). No differences were found among antidepressant classes. Our conclusion was that maternal exposure to antidepressants may be associated with increased risk for spontaneous abortion; however, depression itself cannot be ruled out as a cause.[11] It is also important to keep in mind that it is possible, in some cases, that a woman who was treated for depression may have decided to terminate the pregnancy but chose to report it as a miscarriage because of the guilt surrounding her decision.

It is also difficult to estimate the true rates of spontaneous abortions in the population. The consensus appears to be that spontaneous abortions occur at a rate between 15% and 20%; however, there is no real basis for these numbers. The observed proportion of pregnancies ending in loss is highly dependent on the gestational age at which pregnancies come to be recognized and how the losses are identified. Obviously, identifying pregnancy even a week earlier will make a major difference in the early period of gestation, since loss rates are highest at that point, so greater awareness and focus on pregnancy alone will inflate the reported frequency. In our study, we matched the gestational age at the time of call to control for the effects of gestational age on the spontaneous abortion rate. Results will also differ if based on a pregnancy history obtained retrospectively rather than prospectively, with early losses subject to recall errors or varying interpretation.[11] Recently, a group in the United Kingdom estimated that the incidence of spontaneous abortions in the population was 11.5% to 12.7%, which is similar to the rates in our unexposed group.[12] It is uncertain why there were more preterm births (prior to 37 weeks of gestation) in both the antidepressant groups, but this phenomenon may be due to the underlying disease.

There are limitations to this study. The most important is that we had a relatively small sample size, which had the statistical power only to detect major malformations. It had 80% power to detect a 6-fold increased risk for malformations, with an α of .05. Given our results, approximately 800 cases in each group would be required to detect a 2-fold increase in risk of relatively common malformations, and thousands would be required to detect rare defects. Furthermore, it would require 11 more studies (2500 women) having the same results to achieve statistical significance. It is therefore important that more research be done to increase sample sizes and allow examination of more infrequent outcomes.

The strengths of this type of study include a personal interview with the individual, which involved detailed

history-taking and included documentation of actual consumption of the drug during pregnancy. In addition, details were verified with the physician. Furthermore, using prospective, comparative groups is considered Level 2 evidence in evidence-based research, as such use allows comparisons between the exposed and nonexposed groups, and a disease-matched group also allows for comparisons of outcomes that may be related to the underlying illness, in this case depression.

Women who have been diagnosed with depression prior to becoming pregnant should weigh the benefits and risks carefully with their physicians before making a decision about continuing an antidepressant during pregnancy. If they do decide to discontinue, the medication should be tapered slowly to avoid abrupt discontinuation syndrome. In fact, failure to treat depression during pregnancy can have significant negative ramifications for both the mother and child. Most notably, depression during pregnancy is the most reliable predictor of postpartum depression, which can sometimes have tragic consequences.[13,14]

The issue of not treating depression during pregnancy is emerging as an important one that requires addressing. Untreated depression during pregnancy can have deleterious effects on peripartum and neonatal outcomes, such as more cesarean sections and a greater number of admissions to neonatal intensive care units. A woman who is depressed may also make other poor decisions during her pregnancy, such as drinking alcohol and not attending her obstetrician's appointments. In addition, a woman who is depressed may have difficulty bonding with her child after birth and may experience other adverse attachment behaviours.[15]

In summary, in this cohort of women exposed to mirtazapine during pregnancy, the results of this study do not suggest that there is a higher risk for major malformations in neonates above the baseline rate of 1% to 3%. The higher rates of spontaneous abortions in the 2 antidepressant-exposed groups, compared with the nonteratogenic exposed group, are similar to, although somewhat higher than, those of other antidepressant studies. Further research is required to determine causation. The higher rates of preterm births in the 2 antidepressant-exposed groups also need to be addressed further. This evidence-based information can be helpful to women and their health professionals who are making the decision regarding treatment of depression with mirtazapine during pregnancy.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa and others), fluoxetine (Prozac and others), mirtazapine (Remeron and others), paroxetine (Paxil and others), sertraline (Zoloft and others), trazodone (Desyrel and others), venlafaxine (Effexor).

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