# Pregnancy Outcome of Women Using Atypical Antipsychotic Drugs: A Prospective Comparative Study

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***Background:*** A substantial number of women of childbearing age suffer from schizophrenia and other mental illnesses that require the use of antipsychotic drugs. Atypical antipsychotics have been on the market since the mid-1990s, and to date there are no prospective comparative studies regarding use during pregnancy.

***Objectives:*** (1) To determine whether atypical antipsychotics increase the rate of major malformations above the 1% to 3% baseline risk seen in the general population. (2) To examine rates of spontaneous and therapeutic abortions, rates of stillbirths, birth weight, and gestational age at birth.

***Method:*** The cohort was composed of pregnant women who contacted the Motherisk Program in Canada or the Israeli Teratogen Information Service in Israel and women who were recruited from the Drug Safety Research Unit database in England. Women who had been exposed to atypical antipsychotics were matched to a comparison group of pregnant women who had not been exposed to these agents.

***Results:*** Data were obtained on 151 pregnancy outcomes that included exposure to olanzapine (N = 60), risperidone (N = 49), quetiapine (N = 36), and clozapine (N = 6). Among women exposed to an atypical antipsychotic, there were 110 live births (72.8%), 22 spontaneous abortions (14.5%), 15 therapeutic abortions (9.9%), and 4 stillbirths (2.6%). Among babies of women in this group, there was 1 major malformation (0.9%), and the mean ± SD birth weight was 3341 ± 685 g. There were no statistically significant differences in any of the pregnancy outcomes of interest between the exposed and comparison groups, with the exceptions of the rate of low birth weight, which was 10% in exposed babies compared with 2% in the comparison group (p = .05), and the rate of therapeutic abortions (p = .003).

***Conclusion:*** These results suggest that atypical antipsychotics do not appear to be associated with an increased risk for major malformations.

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Atypical antipsychotics (clozapine, olanzapine, risperidone, and quetiapine) are used primarily for the treatment of psychotic disorders such as schizophrenia; however, they are being used increasingly for the treatment of other psychiatric disorders. The incidence of schizophrenia in the general population ranges from 0.04 to 0.58 per 1000.[1] Its prevalence is equal across the sexes and is seen in all cultures and socioeconomic classes, with the peak age at onset for women from 25 to 35 years. For women, this age range is in the peak childbearing years; hence, it can be expected that women with schizophrenia will become pregnant.

In the past, fertility in women with schizophrenia has been documented as lower than in the general population,[2–4] with studies showing that approximately 60% of women with psychosis are mothers.[5] The conventional antipsychotics used to treat schizophrenia until the last decade caused hyperprolactinemia, which often resulted in infertility, whereas the newer, atypical antipsychotics are less likely to cause this lowering of fertility. The one exception is risperidone, which has been shown to increase prolactin levels.[6] As a result, more women requiring antipsychotic drug therapy may be more likely to become pregnant.

While the older, conventional antipsychotics often caused reversible amenorrhea, there have been several case reports of unplanned pregnancies in patients who were switched from a conventional to an atypical antipsy-

chotic.[7–9] Women with psychotic illnesses are likely to have more unplanned pregnancies than women without a psychotic illness.[10] This may result in delayed prenatal care and risky behavior such as alcohol consumption that may have been avoided if the woman had been aware of the pregnancy. These pregnancies are also more likely to be unwanted and result in termination.[11,12] In addition, these women are more likely to have less knowledge about birth control and reproductive issues, are less likely to use contraception, and are more likely to have unplanned sex.[13]

Women with schizophrenia are very likely to experience a relapse if they discontinue antipsychotic medication[14] and are also more likely to have difficulties with parenting and may lose custody of their children.[15] Consequently, it is particularly important that their mental health is stable if they are about to become a parent.

Schizophrenia has been linked to a number of adverse pregnancy outcomes. A meta-analysis published in 1996 found an increased risk for low birth weight, pregnancy and delivery complications, and poor neonatal health.[16] Recently, an epidemiologic study showed an increased risk for preterm delivery (relative risk [RR] = 1.46, 95% CI = 1.19 to 1.79), low birth weight (RR = 1.57, 95% CI = 1.36 to 1.82), and small for gestational age (RR = 1.43, 95% CI = 1.17 to 1.53) in women with schizophrenia.[17] A British study published in 2003 showed no increased risk for obstetric complications but an increased risk for stillbirth (OR = 4.03, 95% CI = 1.14 to 4.25) in infants of mothers with psychosis.[18] Obstetric complications have also been identified as a possible risk factor for later development of schizophrenia.[19]

All of the atypical antipsychotics have been shown to cause considerable weight gain.[20] Obesity in pregnancy has been associated with many risks to both the mother and the baby. Obese women are more likely to have preexisting hypertension and diabetes or to develop these conditions during pregnancy.[21–24] All of these conditions are associated with their own risks to the pregnancy.

Although atypical antipsychotics have been on the market since the mid-1990s, currently, there are no prospective comparative studies examining the safety of these drugs during pregnancy. Animal studies have shown no teratogenic or embryotoxic effects, and, although human data are limited, there are a number of spontaneous reports from the manufacturers. The manufacturer of olanzapine reported both prospective (144) and retrospective (98) pregnancy outcomes up until 2001 with no increase above baseline in the rates of major malformations or other abnormal outcomes (Ken Hornbuckle, D.V.M.; Eli Lilly Canada Inc; Toronto, Ontario, Canada; written communication; March 2005). The manufacturer of clozapine reported that their worldwide safety database contains 523 cases of pregnancy with exposure to clozapine since product launch. They reported 22 unspecified malformations (Sven Schellberg, Dr.Med.; Novartis; Montreal, Quebec, Canada; written communication; March 2005). The manufacturer of quetiapine reported that through March 4, 2005, there were 446 reports of pregnancy exposure (prospective and retrospective) in an international database; of these, 151 (34%) had outcomes reported. Among these, there were 8 reports of congenital anomaly. There was no pattern among the types of congenital anomalies (each was different). In 7 of the 8 reports, there were other medications also taken during the pregnancy, and many of the reports provided incomplete information (Patricia Fontana, B.Sc., B.Pharm.; AstraZeneca Canada; Missisauga, Ontario, Canada; written communication; March 2005). The manufacturer of risperidone reported they had approximately 250 spontaneous reports, prospective and retrospective, regarding both pregnancy and lactation. In many cases, the outcome of the pregnancy was unknown. Of the known outcomes, there were 8 reports of malformations with no pattern of defects (Paul Percheson, M.D.; Janssen-Ortho Inc; Toronto, Ontario, Canada; written communication; March 2005). It must be noted that spontaneous reports to drug companies have an inherent bias and cannot be regarded as definitive information. It should also be noted that we had no data on the newer drugs such as ziprasidone or aripiprazole, as these drugs were not available at the time our study was in progress.

The primary objective of this study was to determine whether exposure to an atypical antipsychotic medication during the first trimester of pregnancy is associated with an increased risk for major malformations above the baseline risk of 1% to 3% seen in the general population. The secondary objectives included determining the rates of spontaneous abortions and therapeutic abortions, birth weight, gestational age at delivery, neonatal complications following third-trimester exposure, method of delivery, weight gain, pre-pregnancy body mass index (BMI), and rates of diabetes and pregnancy-induced hypertension.

## METHOD

The Motherisk Program at The Hospital for Sick Children in Toronto, Ontario, Canada, is a counseling service that provides pregnant and breastfeeding women and health care providers with evidence-based information on the safety and risks of exposures to prescription and over-the-counter medications, natural health products, chemicals, radiation, and infectious agents. Women were enrolled in the study when they contacted the line for information on the atypical antipsychotic that they were currently taking during pregnancy. They were given information about the study, and, if they agreed to participate, oral consent was given over the phone. This study was approved by The Hospital for Sick Children Research Ethics Board. The group in Jerusalem, Israel (Israeli Teratogen Information Service), is a service similar to Motherisk (a

teratology information service), and the women were enrolled in the same fashion. The Drug Safety Research Unit in Southampton, England, is an independent medical charity that conducts Prescription-Event Monitoring studies to monitor the safety of recently marketed medicines prescribed under the conditions of general practice in England. This monitoring is carried out in a prospective manner, so the practitioner is not approached before a decision to treat a patient has been made and a prescription dispensed. Women who were identified as having taken an atypical antipsychotic within 3 months of pregnancy or during pregnancy were followed up prospectively. This was achieved by sending each general practitioner a detailed questionnaire with questions regarding drug history and pregnancy outcome. The information collected was similar to the data gathered by the other 2 centers.

In the case of the teratogen information centers, telephone contact was made 3 to 4 months after the expected date of confinement to assess the outcome of pregnancy. Information about possible medical and psychiatric complications and any additional exposures was obtained. Once the questionnaire was completed, permission was requested to receive a report from the physician primarily caring for the infant (family doctor/pediatrician). The researchers sent a letter to the infant's physician asking for corroboration of the maternal report on the health of the infant.

For analysis, a comparison group of women was followed throughout their pregnancies. Each exposed woman identified through the Motherisk Program was matched to a subsequent woman who contacted the Motherisk Program regarding exposure to a non-teratogenic agent. Non-teratogenic exposures included cold medications, hair dyes, antibiotics, acetaminophen, antacids, antihistamines, etc. Women were matched for maternal age plus or minus 2 years and gestational age at time of call plus or minus 2 weeks. Women who reported a psychiatric diagnosis or psychotropic medication use were excluded from the comparison group. Cases obtained from Jerusalem were matched to callers from the Motherisk Program in Toronto in the same manner, and cases from the Drug Safety Research Unit were matched with similar women in their database. The comparison women were followed through their pregnancies in the same manner as the exposed women, by recording details of maternal history, exposures during the pregnancy, pregnancy outcome, and health of the baby.

Each drug was examined individually and as a part of the total combined group. Demographic data were compared between the exposed and nonexposed groups, using a $\chi^2$ test to compare the following values: ethnic background, living arrangements, highest level of education completed, occupational status, patient-reported diagnosis, status of vitamin use during the pregnancy, smoking status, alcohol use, and whether the pregnancy was planned.

The primary outcome of interest was the presence or absence of a major congenital malformation. The exposed and nonexposed groups were compared using $\chi^2$ analysis.

Secondary outcomes of interest included a range of maternal conditions and neonatal health outcomes. All categorical data were compared using $\chi^2$ analysis or Fisher exact test. Categorical outcomes of interest included pregnancy outcome defined as spontaneous abortion, elective abortion, stillbirth, or live birth; method of delivery; presence/absence of neonatal distress following third-trimester exposure; presence of maternal diabetes; and presence of maternal hypertension. All continuous data were compared between the groups with the Student t test when the data had normal distribution and with the Mann-Whitney U test when a nonparametric test was required. Numerical data included birth weight, gestational age at delivery, and maternal pre-pregnancy weight, height, weight gain, and pre-pregnancy BMI.

## RESULTS

We were able to ascertain the pregnancy outcomes of 151 women in 3 different centers, all of whom took an atypical antipsychotic in the first trimester. They included women exposed to olanzapine (N = 60), risperidone (N = 49), quetiapine (N = 36), and clozapine (N = 6). We were also able to determine in detail the maternal characteristics of 105 of the exposed women and 105 of the comparison group who contacted the Motherisk Program. We were unable to obtain this information from the Israeli Teratogen Information Service or from the Drug Safety Research Unit, as these questions are not routinely asked in these centers.

The exposed group had higher rates of factors known to increase the risk for a negative pregnancy outcome. Thirty-nine exposed women (57%) reported the pregnancy as being unplanned, compared with 22 (23%) of the comparison women ($p < .001$). In both groups, 31% of women with an unplanned pregnancy used birth control. Significantly more exposed women than comparison women did not take vitamins, either folic acid or a multivitamin, at any point during their pregnancy (15% vs. 2%, $p = .005$). Similar numbers of exposed and comparison women reported alcohol consumption during the pregnancy (14 [14%] vs. 12 [12%], $p = .83$). Five (36%) out of the 14 exposed women who reported drinking alcohol during the pregnancy reported binge or heavy drinking, whereas only 1 (8%) of 12 comparison women reported binge or heavy drinking ($p = .17$). Significantly more exposed women than comparison women reported smoking during their pregnancy (38% vs. 13%, $p < .001$). Exposed women were also more likely to have a lower level of education and were less likely to work during the pregnancy (Table 1).

A number of women required polytherapy to achieve adequate control of their symptoms. Seventeen women

**Table 1. Maternal Characteristics of the Motherisk Cohort of Women Exposed to an Atypical Antipsychotic or a Non-Teratogenic Agent[a]**

| Characteristic | Atypical Antipsychotic (N = 105) | Non-Teratogenic Agent (N = 105) | p Value |
|---|---|---|---|
| Unplanned pregnancy | 39 (57) | 22 (23) | < .001[b] |
| Vitamin use | | | .005[b] |
| Yes | 64 (85) | 94 (98) | |
| No | 11 (15) | 2 (2) | |
| Reported alcohol use | | | .834 |
| Yes | 14 (14) | 12 (12) | |
| No | 87 (86) | 89 (88) | |
| Level of alcohol consumption | | | .17 |
| Heavy/binge | 5 (36) | 1 (8) | |
| Casual | 9 (64) | 11 (92) | |
| Reported smoking | | | < .001[b] |
| Yes | 38 (38) | 13 (13) | |
| No | 63 (62) | 88 (87) | |
| Ethnic background | | | .05[b] |
| White | 50 (76) | 82 (83) | |
| Asian | 7 (11) | 11 (11) | |
| Black | 1 (2) | 2 (2) | |
| Other | 8 (12) | 4 (4) | |
| Living arrangements | | | .06 |
| With parents | 2 (3) | 3 (3) | |
| Single | 11 (17) | 5 (5) | |
| Separated/divorced | 2 (3) | 1 (1) | |
| Married | 51 (77) | 92 (91) | |
| Occupation | | | < .001[b] |
| Unemployed | 22 (33) | 3 (3) | |
| Homemaker | 22 (33) | 20 (20) | |
| Student | 3 (5) | 3 (3) | |
| Work part-time | 6 (9) | 14 (14) | |
| Work full-time | 13 (20) | 61 (60) | |
| Education | | | < .001[b] |
| Public school | 13 (20) | 4 (4) | |
| High school | 18 (27) | 20 (20) | |
| College/university | 32 (48) | 58 (58) | |
| Postgraduate | 3 (5) | 19 (19) | |
| Diabetes | | | .99 |
| Yes | 6 (8) | 6 (6) | |
| No | 72 (92) | 87 (94) | |
| Hypertension | | | .30 |
| Yes | 1 (1) | 5 (5) | |
| No | 77 (99) | 88 (95) | |
| Body mass index (pre-pregnancy), kg/m$^2$ | | | |
| N | 58 | 91 | |
| Median (25%–75% quartile) | 27.80 (22.96–32.77) | 22.92 (20.52–27.37) | < .001[b] |
| Minimum | 16 | 16 | |
| Maximum | 45 | 39 | |

[a]Values are shown as N (%) unless otherwise noted. Total numbers of women vary among the characteristics due to missing data.
[b]Statistically significant.

(16%) also took a conventional antipsychotic, 60 (57%) also took an antidepressant, and 18 (17%) were taking an antiepileptic drug, of which 13 used valproic acid, 4 used carbamazepine, 3 used lamotrigine, and 1 each used gabapentin and topiramate. Thirty-six women (34%) also took a benzodiazepine, of which the most commonly used was lorazepam, with 14 women taking it. In addition, 5 women used diazepam, 4 clonazepam, 2 temazepam, and 1 alprazolam. Six women (6%) took lithium at some point during their pregnancy, and 5 of the 6 women discontinued lithium after the pregnancy was confirmed. No major malformations were reported in any of the babies that were exposed to antiepileptics, benzodiazepines, or lithium.

Patients reported their diagnoses as follows: 29% depression, 24% schizophrenia, 18% bipolar disorder, 2% schizoaffective, 7% psychotic episode, 5% psychotic depression, 2% obsessive-compulsive disorder, 1% posttraumatic stress disorder, and 1% schizophreniform disorder. Some women had more than 1 diagnosis, and some women were unsure of their diagnosis.

During the pregnancy, there was no statistical difference in rates of hospitalization for medical reasons, diabetes, or hypertension between exposed and nonexposed women. The median pre-pregnancy weight of exposed women was significantly greater than that of nonexposed women. Exposed women also had a greater mean BMI, with the mean within the obese range. Fifty-two percent of exposed women had a BMI > 27, compared with 29% of the comparison women (p = .008). Women taking antipsychotic therapy tended to gain more weight than comparison women, although the difference did not reach statistical significance. Analysis of BMI by drug revealed that of all 4 drugs, women taking quetiapine had the highest BMI.

Significantly more women taking antipsychotics chose to terminate their pregnancy (9.9% vs. 1.3%; p = .003), and there was a higher rate of spontaneous abortions in the exposed group (14.5% vs. 8.6%), although this was not statistically significant. The mean gestational age at birth was not different between the 2 groups; 10 babies (13%) born to exposed women were premature (gestational age < 37 weeks), and 7 babies (8%) born to comparison women were premature (p = .36) (gestational age data were missing for some respondents). Of the 10 premature babies born to exposed women, 4 were born at less than 35 weeks gestational age. The mean birth weight was not statistically different between the exposed and comparison groups. However, 10% of exposed babies were low birth weight, whereas only 2% of comparison babies were low birth weight (p = .05). There was no difference in the rates of babies with low birth weight or premature births between the different drugs (Table 2).

The rates of major malformations in the exposed and comparison groups were not statistically different, 1 (0.9%) in the exposed group versus 2 (1.5%) in the comparison group. In the exposed group, the malformations were observed in the baby of a woman exposed to olanzapine and consisted of multiple anomalies including midline defects: cleft lip, encephalocele, and aqueductal stenosis. In the comparison group, the malformations were right kidney double system.

There was no statistical difference in the rates of reported complications during labor. Similarly, there was no statistical difference in the rates of neonatal complications between the 2 groups.

**Table 2. Comparison of Pregnancy Outcome Between Women Exposed to Atypical Antipsychotics and Non-Teratogenic Agents**

| Outcome | Atypical Antipsychotic (N = 151) | Non-Teratogenic Agent (N = 151) | p Value |
|---|---|---|---|
| Live birth, N | 110 | 135 | < .001 |
| Spontaneous abortion, N (%) | 22 (14.5) | 13 (8.6) | .15 |
| Stillbirth, N (%) | 4 (2.6) | 4 (2.6) | 1.0 |
| Therapeutic abortion, N (%) | 15 (9.9) | 2 (1.3) | .003 |
| Major malformation, N (%) | 1 (0.9) | 2 (1.5) | 1.0 |
| Birth weight, mean (SD), g | 3341 (685) | 3411 (534) | .38 |
| Gestational age at birth, mean (SD), wk | 39 (1) | 39 (1) | 1.0 |

## DISCUSSION

To our knowledge, this is the first prospective comparative study documenting pregnancy outcomes of women taking atypical antipsychotics. All of the women were exposed in the first trimester, and 48 were exposed throughout pregnancy. However, it must be noted that this study did not attempt to evaluate the potential long-term neurobehavioral effects of these drugs on the offspring.

There were many differences in the maternal characteristics between the women who were taking antipsychotics and the women who were a part of the comparison group. One of the main differences was that the comparison women were more likely to have planned their pregnancies, which may explain why more exposed women terminated their pregnancies. Fewer exposed women took vitamin supplements, and more smoked cigarettes and consumed alcohol. They were also more likely to be single, be unemployed, and have completed a lower level of education. Overall, the median birth weight was not different between the 2 groups; however, 10% of the exposed babies were low birth weight compared with 2% of the comparison group. This could be due to the lifestyle differences between the 2 groups of women.

There is a selection bias in studying women that contact the counseling services. In general, they tend to be middle to upper middle class women. This may explain some of the demographic differences between the exposed and comparison group that, in turn, may have resulted in better pregnancy outcomes for the comparison group. In addition, the group of women requiring antipsychotic medication during their pregnancy who contacted these types of services may not be representative of the general population of women who require antipsychotics. The women who contacted the program may be higher functioning since they had the motivation to call the program and seek advice about their pregnancy and were willing to participate in the study. Other women with schizophrenia may be too suspicious to participate in a study that asks many personal details. This potential selection bias may increase the likelihood of having a positive pregnancy outcome. As such, the results of this study may only be applicable to women who have similar characteristics. On the other hand, our data may have fewer confounders due to the selected sample and may be more appropriate to evaluate the effects of these drugs.

Women in the study were taking antipsychotics for a wide range of psychiatric disorders, not just for schizophrenia, and as a result there was a wide range of doses. Some women required polytherapy to control their psychiatric condition. Some of these medications are known teratogens (e.g., antiepileptics increase the risk for neural tube defects [NTDs][25]). If we had detected a difference in the rates of major malformations, multivariate analysis would have been required to determine what factors had the most influence on the increase in risk.

A substantial number of the women were also taking antidepressants[26] or benzodiazepines[27] in the third trimester of pregnancy, and these medications have been reported to cause neonatal complications. However, there were no such cases of neonatal complications in our cohort of babies, although it would be prudent to monitor babies closely after birth who have been exposed to combinations of these drugs, to allow for prompt identification and treatment of any potential complications.

In our study, women taking olanzapine did not have a significantly higher mean BMI than the comparison group, but the quetiapine group had a significantly higher BMI than the comparison group, despite the fact that quetiapine had been marketed as a weight-neutral drug. It is possible, as this study was observational, that women who had gained weight while taking other medications or who were already obese may have been prescribed quetiapine in an attempt to minimize their weight gain. Obesity in pregnancy is associated with many risks; however, we did not detect an increase in the rates of cesarean section delivery, gestational diabetes, or pregnancy-induced hypertension in women who took atypical antipsychotics, which may have been expected. One malformation in the exposed group did include an NTD, but it was not a simple case, as there were many other midline defects and the woman who gave birth to the baby was not obese. Previously, risks associated with obesity have been shown in large retrospective studies, and our study may not have had sufficient power to detect these risks.

The literature suggests that women with schizophrenia have a higher risk for obstetric complications than the general population[15]; however, we did not observe this finding. It may be due to the self-selection of the women participating in this study, who may not accurately represent the general population of women with schizophrenia and other disorders requiring antipsychotic medication.

The main limitation of this study is the sample size, in that it only has an 80% power to detect a 4-fold increase in the rates of major malformations, with an $\alpha$ of 0.05. Approximately 800 cases would be required in each group to

detect a 2-fold increase in relatively common malformations, and thousands would be required to detect rare defects. Another limitation is that the results may not be applicable to women suffering from psychotic illness in the general population.

As the prescribing of atypical antipsychotics increases,[28] it is important that physicians are aware of the increased potential for a woman to become pregnant while using these medications and discuss birth control options to avoid unplanned pregnancies.

For some women, including those with serious psychiatric morbidity, stopping effective medication is unreasonable and may put them and their babies at a greater risk. If a woman is successfully treated with an atypical antipsychotic, discontinuing the medication because she is pregnant is probably not necessary. Our study does provide evidence that suggests exposure does not present an increased risk for the baby or the mother. However, it must be noted that these are not definitive data regarding the teratogenic potential of these drugs. More data are needed to state whether these drugs are safe to use during pregnancy, so in the meantime the benefits and risks should be weighed carefully in each individual case.

Optimal control of the psychiatric disorder should be maintained throughout the pregnancy and the postpartum period. All pregnancies in which a woman requires an antipsychotic medication should be considered high risk because of the mother's diagnosis, and both mother and fetus should be carefully monitored throughout the pregnancy and thereafter.

*Drug names:* alprazolam (Xanax and others), aripiprazole (Abilify), carbamazepine (Carbatrol, Equetro, and others), clonazepam (Klonopin and others), clozapine (Clozaril, FazaClo, and others), diazepam (Valium and others), gabapentin (Neurontin and others), lamotrigine (Lamictal), lithium (Lithobid, Eskalith, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), temazepam (Restoril and others), topiramate (Topamax), valproic acid (Depakene and others), ziprasidone (Geodon).

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