Clinical Utilization of Atypical Antipsychotics in Pregnancy and Lactation

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OBJECTIVE: To analyze the available literature regarding the safety of atypical antipsychotics in pregnancy and lactation in order to recommend evidence-based strategies for pharmacologic management of psychosis in these conditions.

DATA SOURCES: We summarized the results from articles identified via MEDLINE/PubMed/TOXNET (1993–January 31, 2004), using the key terms pregnancy, lactation, breast-feeding, human milk, psychotropic drugs, atypical antipsychotics, olanzapine, quetiapine, risperidone, clozapine, ziprasidone, and aripiprazole.

STUDY SELECTION AND DATA EXTRACTION: Retrospective studies, clinical observations, and case reports regarding the 6 atypical antipsychotics mentioned above were selected and analyzed. Extensive manual review of pertinent journals and textbooks was also performed.

DATA SYNTHESIS: Reviewed studies show that olanzapine and clozapine apparently do not increase the teratogenic risk if administered to pregnant women, while evidence on quetiapine, risperidone, aripiprazole, and ziprasidone is still limited. In contrast, available information is not able to exclude unwanted serious effects associated with the use of all atypical antipsychotics on mother–infant dyads. Furthermore, more than a few studies suggest increased hyperglycemic risk for pregnant women related to atypical antipsychotic therapy during gestation. Finally, published evidence about the effects on long-term infant neurodevelopment of drug exposure through both placenta and breast milk is represented only by sporadic case reports.

CONCLUSIONS: It is well known that potential consequences of an untreated psychotic episode may be severe and may lead to the mother attempting suicide and/or infanticide. For these reasons, clinicians need to help mothers weigh both fetal and neonatal risks of exposure to drugs against the potential risk they and their infant may incur if the psychiatric illness is not treated. On the other hand, atypical antipsychotics in pregnancy and breast-feeding do not show evident advantages in safety when compared with typical neuroleptic agents. Therefore, we suggest that the most relevant parameters for selecting the best clinical option for pregnant and breast-feeding women with schizophrenia and related disorders remain strongly related to 3 main points: (1) cautious evaluation of the risk/benefit ratio of fetal and neonatal drug exposure, (2) degree of severity of maternal psychiatric illness, and (3) careful preliminary choice of drugs characterized by a balanced safety/efficacy profile.

KEY WORDS: aripiprazole, atypical antipsychotics, breast-feeding, clozapine, olanzapine, pregnancy, quetiapine, risperidone, teratogenic risk, ziprasidone.


Atypical antipsychotics have been extensively and effectively used in the treatment of schizophrenia, particularly in the long-term management of both positive and negative symptoms, because most unwanted effects of typical neuroleptics were found to be less frequent with atypical agents. However, psychopharmacologic management of atypical antipsychotic drugs still represents a controversial clinical and ethical aspect of treating pregnant and breast-feeding women with mental disorders.
While all atypical antipsychotics have been identified by the American Academy of Pediatrics and the Food and Drug Administration as pregnancy category C (except for clozapine, identified as category B), most existing information about the outcomes of pregnant women exposed to these medications is derived from small, selected case registries reported by either industry or tertiary academic centers. However, all psychotropic drugs cross the placental barrier.

Concentrations of drug metabolite are higher in fetal than in maternal circulation due to difficulties in transport back to maternal circulation, as well as to the fetus's lower ability to metabolize medications and its lower glomerular filtration rate. In addition, specific drug exposure during the first versus second or third trimester may also vary in relation to the developmental period of organogenesis, as well as to windows of greater/lesser risk for breakthrough psychopathology. In fact, the possibility exists that some forms of serious psychopathology may themselves confer some increase of risk of complication during pregnancy, regardless of psychotic drug use.

The necessity of starting psychopharmacologic treatment during the weeks following delivery may also be considered: the incidence of post-partum psychosis in all women is estimated at 0.1–0.2%. Psychotropic medications are excreted in breast milk, but several factors affect the passage of drugs into breast milk. They include administration route, absorption rate, half-life, and time of peak serum concentration, dissociation constant, volume of distribution, molecular size, degree of ionization, pH of plasma and milk, solubility of drugs in water and lipids, and greater binding to plasma protein than to milk protein. The amount of drug received by the infant depends on multiple aspects as well. The most relevant factors are milk yield, composition of milk, concentrations of drugs in the milk, which breast is being suckled, and how well the breast was emptied during the previous feeding. Nevertheless, the consequences on the child's neurobehavioral development after exposure to antipsychotics during breast-feeding are still unclear.

Therefore, the first aim of this review is to analyze the available literature regarding the safety of atypical antipsychotics in pregnancy and breast-feeding. The second is to suggest potential strategies for psychopharmacologic treatment of psychosis in these conditions, reducing as much as possible both the iatrogenic risks for the mother and the teratogenic and neurodevelopmental risks for the infant.

Data Sources

I conducted a MEDLINE/PubMed/TOXNET search from 1993 to April 20, 2004, with the following key words: pregnancy, lactation, breast-feeding, human milk, psychotropic drugs, atypical antipsychotics, clozapine, olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole. Resulting articles were cross-referenced for other relevant articles not identified by the electronic search. Prospective studies, significant clinical observations, and case reports were primarily selected and analyzed. Extensive manual review of pertinent journals and textbooks was also performed.

Results

OLANZAPINE

Pregnancy Outcomes and Perinatal Adverse Events

To evaluate intrauterine exposure effects to olanzapine, Goldstein et al. ascertained all prospectively and retrospectively collected pregnancy reports as a registry in the Lilly Worldwide Pharmacovigilance Safety Database. Twenty-three prospectively identified pregnancies (in which infants were exposed to medications at daily dosages ranging from 5 to 25 mg) showed rates of spontaneous abortion, stillbirth, and prematurity all within the range of normal historic control rates. This study also documented fetal abnormalities and perinatal unwanted reactions, as well as gestational complications. Abnormalities and perinatal unwanted reactions were represented by one case of unilateral dysplastic kidney, one case of Down syndrome, and one case of sudden infant death syndrome at 2 months. Gestational complications consisted of 2 cases of gestational diabetes development in women with no family or personal history of glucose intolerance. Onset of gestational diabetes complicated by hypertension and preeclampsia while taking olanzapine throughout pregnancy was also observed in 2 other women, with and without a family history of diabetes, respectively. A further investigation, including 96 prospectively identified cases, expanded the description of the Lilly Pharmacovigilance Registry (see Table 1 for the description of pregnancy outcomes). However, there have

| Table 1. Known Outcomes of Pregnancies Exposed to Olanzapine, Risperidone, and Clozapine Compared with Pregnancy Outcomes in General Healthy Populations |
|----------------------|------------------|-------------------|------------------|
|                      | Olanzapine (N = 96) | Risperidone (N = 11) | Clozapine (N = 176) |
| Healthy offspring    | 69 (71.9)         | 7 (63.6)          | 94 (53.4)         |
| Spontaneous abortions| 12 (12.5)         | 0 (0)             | 15 (8.5)          |
| Elective terminations| 3 (27.3)          | 27 (15.4)         | N/A               |
| Premature deliveries  | 2 (2.1)           | (3.7)             |                   |
| Stillbirths           | 3 (3.1)           | (2.0)             |                   |
| Major/minor fetal malformations plus perinatal complications | 8 (8.3) | 1 (9.1) | 18 (10.2) |
| Unscheduled outcomes  | 2 (2.1)           | 22 (12.5)         |                   |

N/A = not available.
*Pooled data from reviewed epidemiologic studies.
†One case due to known abnormalities (mother taking clozapine 25 mg/day plus lithium).
‡Ranging from low glucose levels to malformations.
been several descriptions of healthy infants born without complications despite prenatal exposure to medication.25–29

Breast-Feeding

Among 21 reports of breast-fed infants exposed to olanzapine,20,30 5 showed adverse events including jaundice, sedation, cardiomegaly, and heart murmur; shaking, poor sucking; and lethargy; protruded tongue; and rash, diarrhea, and sleeping disorders. The fifth infant could not roll from back to front at age 7 months, but had a normal developmental profile by age 11 months. However, no definitive conclusions were made regarding the role of olanzapine in contributing to these events. One report focused on the case of a pregnant woman with recurrent paranoid schizophrenia.39 The patient was treated with olanzapine from the 18th gestational week until delivery and during breast-feeding. No adverse effects occurred during pregnancy, and the outcome was healthy. After delivery, plasma concentration of medication in the infant was 1/3 of maternal concentrations; during breast-feeding, this relatively high value decreased to undetectable concentrations, and the infant showed normal neurodevelopment during short-term observation. Milk/plasma ratio and relative dose for suckling infants whose mother ingested olanzapine while breast-feeding (determined by HPLC39) are shown in Table 2.32,36 All 12 infants included in the studies experienced no adverse reactions.

QUETIAPINE

Pregnancy Outcomes and Perinatal Adverse Events

Tényi et al.37 reported the case of a 38-year-old woman who had been treated for schizophrenia since 1988. After a period of outpatient treatment with zuclopenthixol, her medication had been changed to quetiapine 300 mg twice daily. Pregnancy was discovered at week 17; she had been taking quetiapine when her child was conceived. At the 20th week of pregnancy, the dosage of quetiapine was reduced to 200 mg twice daily; from week 22, she was taking only 150 mg twice daily because her psychiatric symptoms had improved significantly. The patient was in remission during her pregnancy, and at week 38, she gave birth to a healthy boy. Because the patient continued taking her medication, breast-feeding was not introduced. The son’s development was intact during the first 6 months of life.

Taylor et al.38 reported the case of a woman treated with risperidone 4 mg/day, then quetiapine 50–300 mg/day throughout pregnancy without complications. The third case of prenatal exposure to quetiapine has been recently described in a woman who developed psychotic features early during her first pregnancy.39 A pharmacologic approach with thioridazine 100 mg/day plus clordemetildiazepam 1 mg/day was suspended because of lack of efficacy after 4 weeks, as well as successive treatment with haloperidol at a daily dose of 3 mg. Thus, treatment with quetiapine plus clordemetildiazepam was started, at daily doses of 200 and 1 mg, respectively. Quetiapine was reduced to 50 mg/day during month 9 of gestation, and both medications were stopped 10 days before uncomplicated vaginal delivery of a healthy infant.

Breast-Feeding

No literature data are available regarding the secretion of quetiapine in human milk. A 24-year-old woman, with bipolar disorder and treated with 25–50 mg/day of quetiapine throughout her pregnancy, had a normal delivery; the infant, breast-feeding while the mother continued to take the drug, showed no anomalies during the first 6 weeks of life.40

RISPERIDONE

Pregnancy Outcomes and Perinatal Adverse Events

A postmarketing study of 7684 patients who were prescribed risperidone also included 9 women who had taken risperidone during 10 pregnancies (Table 1).21 Nevertheless, one case of agenesis of corpus callosum has been reported.22 Two other babies exposed in utero to a daily dose of risperidone of 4 and 6 mg/day, respectively, showed normal neurodevelopment during the first year of life.41

Breast-Feeding

Hill et al.34 calculated risperidone and its active metabolite milk/plasma ratios and the estimated infant dose exposure during breast-feeding (Table 2); however, the emerging value was measured to be well below the “attention critical” concentration of many medications during lactation (in fact, it is recommended for safe breast-feeding that the ratio of infant dose exposure to maternal dose not be greater than 10%42).

To quantify the amount of risperidone and its active metabolite transferred into breast milk, Ilett et al.35 recently evaluated 3 women treated with this drug. Two patients breastfed their infants; the third woman experienced risperidone-induced galactorrhea. Neither the drug nor its metabolite was detected in the infants, and no adverse reactions were noted.

<table>
<thead>
<tr>
<th>Drug/Metabolite</th>
<th>Maternal Daily Dose (mg)</th>
<th>Total Sample Size (n)</th>
<th>Milk/Plasma Ratio</th>
<th>Relative Infant Dose (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>5–25</td>
<td>12</td>
<td>0.10–0.84</td>
<td>0.22–2.5</td>
</tr>
<tr>
<td>Risperidone</td>
<td>1.5–6</td>
<td>4</td>
<td>0.10–0.42</td>
<td>0.42</td>
</tr>
<tr>
<td>9-OH risperidone</td>
<td>1.5–6</td>
<td>4</td>
<td>0.24–0.50</td>
<td>2.3–4.7†</td>
</tr>
<tr>
<td>Clozapine</td>
<td>50–100</td>
<td>1</td>
<td>from 4.32</td>
<td>1.2</td>
</tr>
</tbody>
</table>

†On basis of weight-adjusted maternal daily dosage.
§Resulting from combination of risperidone and its metabolite (risperidone equivalents).
CLOzapine

Pregnancy Outcomes and Perinatal Adverse Events

Several case reports suggest no definitive association between clozapine exposure and congenital anomalies in either animals or humans.60,61,64 Dev and Krupp63 reported information regarding the course and outcome of pregnancy in 104 infants born by 102 patients treated with clozapine (some of the mothers had taken other medications during the pregnancy). Another report briefly analyzed 72 outcomes of 84 pregnancies with medication24 (Table 1). Nevertheless, several investigations described both nonmetabolic and metabolic complications in pregnant women exposed to clozapine. A pregnant schizophrenic patient treated with clozapine 100 mg/day during pregnancy experienced a slight decrease of hemoglobin and leukocytosis, but no therapeutic intervention was needed.42 Recently, Mendhekar et al.46 described intrauterine fetal death in a woman exposed to low-dose (75 mg/day) clozapine during pregnancy. In addition, there were 4 case reports of new-onset or worsening gestational diabetes with shoulder dystocia.47,48 It has also been suggested that the accumulation of clozapine in fetal serum may increase the risk of floppy infant syndrome,50 neonatal seizures,51,52 and gastroesophageal reflux disease.53 Finally, the potential for clozapine-induced agranulocytosis warrants monitoring of white blood cell levels in newborns.20

Breast-Feeding

Relatively high concentrations of clozapine have been found in breast milk; the authors attributed this to the higher lipid concentrations of breast milk in combination with the lipophilic properties of drug.42 There have been reports indicating that babies experienced sedation, agranulocytosis,53,49 and cardiovascular instability54 when mothers took clozapine during the period they were breast-feeding. Table 2 shows the clozapine milk/plasma ratio and relative dose for suckling infants exposed to medication through human milk.

ZIPRsidoNE

Pregnancy Outcomes and Perinatal Adverse Events

Developmental delays, possible teratogenic effects, and increased stillbirths have been described in animal studies, at equivalent human doses of ziprasidone. Nevertheless, data from human studies are lacking.20

Breast-Feeding

There is no published information regarding newborn exposure to ziprasidone from human milk.

AriPiPrazoLE

Pregnancy Outcomes and Perinatal Adverse Events

In animal studies, aripiprazole demonstrated development toxicity, including possible teratogenic effects, in rats and rabbits.55 The main effects were delayed skeletal ossification (at doses of 10 and 30 mg/kg/day, 3 and 10 times the maximum recommended human dose, respectively) and decreased fetal weight (at a dose of 30 mg/kg/day).

Breast-Feeding

Aripiprazole is excreted in rat’s milk during lactation. It is not known whether the drug or its metabolites are also excreted in human milk.56

Discussion

EPIDEMIOLOGIC BACKGROUND

Women with schizophrenia have sexual practices similar to those of demographically matched control subjects with respect to frequency of sex and the age at which they become sexually active. Nevertheless, they have a greater risk of unplanned pregnancy.57,58 On the other hand, it is well known that infants born to women with schizophrenia have increased risk of preterm delivery, low birth weight, and small size for gestational age.49 In a population-based cohort study, the estimated risk of adverse pregnancy outcomes (including increased risk of stillbirths) was generally double for women with an episode of schizophrenia during pregnancy compared with women in the control group.41 These parameters for poor obstetrical outcomes are strongly associated with increased infant morbidity, mortality, and neurodevelopmental impairment.

PREGNANCY

Reviewed studies suggest that both olanzapine and clozapine apparently do not increase fetal teratogenic risk, while literature regarding quetiapine, risperidone, ziprasidone, and aripiprazole is either partial or absent. Moreover, the rate of spontaneous abortions in women exposed to olanzapine and clozapine during pregnancy is not higher than the rate exhibited by general healthy populations.15,17 Nevertheless, both olanzapine14,18,19 and clozapine47,48 increase the risk of hyperglycemia in pregnant women. In addition, several investigations have found that treatment with both olanzapine and clozapine, as well as quetiapine, is associated with increased risk for developing weight gain and for glucose intolerance, including type 2 diabetes mellitus and ketoacidosis, as in the general psychiatric population.62,64 While data on risperidone and aripiprazole are still controversial,52,56,66 ziprasidone has also been correlated with weight gain.67,68 Both weight gain and glucose intolerance carry augmented possibility for poor obstetrical outcomes. Maternal diabetes during pregnancy actually places the developing infant at higher risk for perinatal mortality, prematurity, congenital abnormalities (eg, neural tube defects), macrosomia (which can lead to shoulder dystocia and cesarean section), and developing diabetes in the future.50 Recently, gestational glucose intolerance has also been associated with long-term increased risk of maternal malignant neoplasm, particularly malignant neoplasm of the breast.69 In addition, women affected by
schizophrenia who take atypical antipsychotics have a higher risk of neural tube defects in their babies because of the associated low intake of folate and obesity.78

On the other hand, 2 reviews reported that patients with schizophrenia are at a high risk of relapse within the first 3 months after antipsychotic withdrawal and reach maximal risk within 12 months.71,72 Thus, stopping medications during pregnancy or the post-partum period, especially abruptly, places the mother at high risk for relapse of psychotic symptoms. These potentially serious ramifications of discontinuing medication, as well as the known potential risk of medication exposure during infant development, need to be discussed carefully with the mother, who may also be informed about the usefulness of a dietary consultation and folate supplements both before conception and during pregnancy.78 Hence, in clinical practice, pharmacologic treatment (with monotherapy at the lowest possible dose) would have to be limited to situations in which exposure to the drugs has less risk for the fetus than the risk presented by untreated illness for the mother.87,73,74

BREAST-FEEDING

Owing to scant literature data, at present, I am unable to recommend breast-feeding for women taking antipsychotic agents, as the safety evaluation of these drugs for suckling infants is derived from only a few anecdotal reports. When mothers are breast-feeding, it would appear especially prudent to avoid clozapine because of its clear tendency to accumulate in infant serum.80

CONCLUSION

Available evidence shows that the safety of atypical antipsychotics in pregnancy and lactation is still an unresolved question. At present, these compounds do not demonstrate evident advantages in these 2 conditions when compared with typical neuroleptic agents, such as chlorpromazine.75-77 To obtain more significant information, the routine use of a pregnancy register (and the creation of an analogous breast-fed infants register)89 may be strongly promoted, even if it is difficult to record essential data, such as the degree of maternal adherence. Given these situations, I suggest that the principal parameters in selecting the best clinical option of whether to initiate drug therapy in a pregnant woman affected by schizophrenia and/or related disorders remain strongly related to 3 main points: (1) degree of severity of mental disease, (2) a cautious evaluation of the risk/benefits ratio of fetal and neonatal drug exposure, and (3) a careful preliminary choice of drugs characterized by a balanced safety/efficacy profile.

Summary

The ideal management of women with schizophrenia and related disorders during pregnancy and the post-partum period involves achieving an optimal balance between minimizing fetal and neonatal exposure to the deleterious influences of both neuroleptic drugs and untreated psychotic symptoms. During the last few years, atypical antipsychotics have been used extensively in the treatment of schizophrenia. However, psychopharmacologic management of atypical antipsychotic drugs still represents a controversial clinical and ethical aspect of treating pregnant and breast-feeding women with mental disorders.

Olanzapine and clozapine do not apparently increase the fetal teratogenic risk or the rate of spontaneous abortion, although both medications have been associated with increased risk of developing glucose intolerance and weight gain during gestation. On the other hand, literature evidence regarding teratogenic risk associated with the use of quetiapine, risperidone, ziprasidone, and aripiprazole is limited or absent. Both weight gain and glucose intolerance carry increased risk for poor obstetrical outcomes and serious long-term maternal complications. In addition, the safety evaluation of atypical antipsychotics for suckling infants is derived from only a few anecdotal reports. At present, these compounds do not demonstrate any evident advantages in safety in these 2 conditions when compared with typical neuroleptic agents.

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El objetivo de la revisión ha sido el de analizar los datos de la literatura acerca de la seguridad de los antipsicóticos atípicos durante el embarazo y la lactancia para recomendar estrategias basadas en la evidencia para la gestión farmacológica de la psicosis en esta condición fisiológica.

FUENTES DE INFORMACIÓN: Se han resumido los resultados de los artículos identificados a través de MEDLINE/PubMed/TOKNET desde el 1 de enero de 1993 hasta el 31 de enero de 2004, usando los siguientes términos: embarazo, lactancia, leche humana, fármacos psicótropos, antipsicóticos atípicos, olanzapina, quetiapina, risperidona, clozapina, ziprasidona, y aripiprazol.

SELECCIÓN DE FUENTES DE INFORMACIÓN Y METODOLOGÍA DE EXTRACCIÓN DE INFORMACIÓN: Los estudios retrospectivos, observaciones clínicas, y casos clínicos referidos a los 6 antipsicóticos atípicos ya mencionados han sido seleccionados y analizados. Asimismo, se ha realizado una revisión manual extensiva de las revistas pertinentes y de libros de texto.

SÍNTESIS: Los estudios revisados han mostrado que, aparentemente, olanzapina y clozapina no aumentan el riesgo teratógeno si se administran a mujeres embarazadas, mientras que la literatura acerca de quetiapina, risperidona, aripiprazol, y ziprasidona es aún limitada. Por el contrario, la información disponible no permite de excluir efectos adversos graves asociados al uso de todos los antipsicóticos atípicos en el duod madrehijo sea en el parto que durante el período postparto. Además solo algunos estudios sugieren un aumento del riesgo de hiperplasia en las embarazadas que han tomado antipsicóticos atípicos durante el embarazo. Finalmente, las evidencias de la literatura sobre los efectos a largo plazo de la exposición al fármaco, ya sea a través de la placenta o de la leche materna, en el desarrollo neurológico del niño se refieren solo a casos clínicos esporádicos.

CONCLUSIONES: Es bien conocido que las consecuencias del no tratar un episodio psicótico pueden ser graves y pueden llevar a la madre a un tentativo de suicidio o al infanticidio. Por estos motivos, los médicos necesitan tratar a las madres sopesando el riesgo fetal y neonatal debido a la exposición al fármaco contra el riesgo potencial en el que madre e hijo pueden incurrir si su enfermedad mental no se trata. Por otro lado, los antipsicóticos atípicos durante el embarazo y la lactancia no muestran ventajas evidentes de seguridad en comparación con los agentes neurolepticos. Por lo tanto, I que los parámetros más relevantes para seleccionar la mejor opción clínica entre tratar o no con fármacos mujeres con esquizofrenia o con transtornos similares, embarazadas o que dan de mamar a sus hijos son los siguientes: (1) una evaluación prudente de la relación beneficio/riesgo debido a la exposición neonatal al fármaco, (2) el grado de severidad de la enfermedad mental de la madre, y (3) una atenta selección preliminar de los fármacos caracterizados por un equilibrado perfil de seguridad y de eficacia.