Drugs 2005; 65 (9): 1193-1206
0012-6667/05/0009-1193/$39.95/0

Use of Antipsychotics in the Management of Schizophrenia during Pregnancy

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Abstract

The rapid development of pharmacotherapy has resulted in a growing clinical importance for the treatment of the increasing number of women with schizophrenia during pregnancy. An evolving database on reproductive health safety factors for women with schizophrenia has begun to be of assistance in optimising clinical benefits for women with childbearing potential.

Given the prevalence of antipsychotic use during pregnancy in women with schizophrenia, it is important for the clinician to have a prepared approach to the administration of these agents. In general, the use of psychotropic medication during pregnancy is indicated when risk to the fetus from exposure to this medication is outweighed by the risks of untreated psychiatric illness in the mother. The preponderance of evidence from registries to large health surveys indicate that treatment with antipsychotic medication confers either no or a small nonspecific risk for organ malformations.

According to the relevant literature published on the safety of antipsychotic medication during pregnancy, the findings are encouraging; however, the currently available data are very limited. Until there are more controlled prospective data on the impact of drugs on fetal and later development, the clinician will continue to work in a state of potential uncertainty, weighing partially estimated risks against managing individual clinical problems. The aim for the clinician should be to provide the best information available regarding the scope of possible risks associated with the treatment of schizophrenia during pregnancy. On the basis of the available data, generalisation is impossible and recommendations should be made on a drug-by-drug basis. The risks and benefits must always be carefully weighed for each patient on an individual basis. Only a woman who is well enough to acknowledge her pregnancy and her mental illness can effectively weigh the relative and partially unknown risks of treatment with antipsychotic medication against the highly probable risks of illness exacerbation if untreated.

The availability of effective treatment, the emphasis on rehabilitation and community-based care for psychotic patients have all led to an increase in fertility rates among women with schizophrenia compared with former decades. However, pregnancy complicates the treatment of women with psychoses. Contrary to former opinion, pregnancy is considered to be a critical life period with specific psychological stressors. Epidemiological studies[1,2] and clinical experiences support a precipitating effect of childbirth in affective psychoses[3,4] as well as schizophrenia.[1,2] Data indicate that untreated women with psychoses do not improve during pregnancy nor to those receiving treatment require smaller doses of maintenance medication while pregnant. In a recent survey[5] significant changes in antipsychotic drug use during pregnancy were reported. In 1989, 2.7% of all appointments at a Motherisk Program clinic were related to the use of antipsychotic medication. In 2001, 7.4% of appointments were regarding antipsychotics. This 170% increase was due to an increase in appointments for prescription of atypical antipsychotics as the number of appointments for conventional antipsychotics remained relatively constant. Since the introduction of atypical antipsychotics, more women requiring antipsychotic drug therapy have been planning to or become pregnant.

Numerous studies have clearly indicated that antipsychotic medications readily diffuse across the placenta.[6,7] Therefore, the treatment of pregnant women with schizophrenia must always take into consideration the effect of that treatment on the fetus. Many clinicians may be reluctant to prescribe antipsychotic medication because of the potential for adverse effects on the fetus, and most women are naturally concerned about the risk of exposing a fetus to medication. However, untreated psychiatric illness in the mother represents a risk to fetal as well as maternal health. The challenge is to minimise unnecessary medication exposure to the fetus while maintaining health in the mother. This is a difficult decision that involves patients and their partners working collaboratively with their physician.

Our knowledge of the risks to the fetus from *in utero* exposure to psychotropic medication is incomplete. There is the possibility of spontaneous abortion, structural malformations, carcinogenesis, intrauterine growth retardation, immediate neonatal effects, withdrawal symptoms and behavioural toxicity.[8] The number of prospective controlled trials of women with schizophrenia treated with various

antipsychotic medications is small. Few data are available in this area and the risks vary greatly among individual agents.

In this article factors of concern regarding exposure risks are reviewed in order to elaborate practical treatment guidelines for schizophrenia during pregnancy. A MEDLINE search of the literature was used (PubMed: 1950s–2004, key terms: phenothiazines, haloperidol, clozapine, olanzapine, risperidone, quetiapine, amisulpride, ziprasidone, aripiprazole – pregnancy – schizophrenia) and the relevant data were evaluated while emphasising the findings concerning the new atypical antipsychotics. A review of pregnancy-related risks of other psychotropic drugs is beyond the scope of this article. The focus is on the risks of antipsychotic medication as the first-line treatment of schizophrenia and this article does not deal with the risks of mood stabilisers, antidepressants, anxiolytics, etc., as often-used additive medication.

When considering the management of schizophrenia during pregnancy, various types of risk must be taken into account (see sections 1 and 2).

1. Risks of medication: (i) organ malformation (teratogenicity); (ii) perinatal syndromes (neonatal toxicity); and (iii) postnatal behavioural sequelae (behavioural toxicity).
2. Risks of no treatment and/or medication discontinuation.

1. Risks of Medication

1.1 Organ Malformation (Teratogenicity)

The period of primary concern for organ formation is the first 12 weeks of gestation. A drug is considered teratogenic if exposure during this time window increases the risk for congenital malformation compared with the general population. The accurate assessment of the rate of malformations secondary to antipsychotics is complicated by the fact that the definitive rate of malformations in infants of untreated women with schizophrenia is not firmly established. In a large survey among 746 children of women with schizophrenia, Bennedsen et al.[9] compared the risk of congenital malformations with the risk among 56 106 children in the general population. A small increase of malformations was found in infants of mothers with schizophrenia, but there was no difference between children of women with schizophrenia who gave birth before (no antipsychotic exposure) or after their first admission to a psychiatric department. There is other evidence that suggest that children born to women with psychoses may have an increased risk of malformations independent of antipsychotic exposure.[10,11]

There are limited data regarding fetal outcome for women with schizophrenia treated with antipsychotics during pregnancy.[12] For obvious ethical reasons antipsychotics are not tested in women who are pregnant. Most data are derived from large epidemiological studies of women who were exposed to antipsychotic agents during pregnancy. The antipsychotic agents that have been most thoroughly studied in pregnancy are the phenothiazines and haloperidol.

Sobel[13] studied 52 women with psychoses exposed to chlorpromazine during pregnancy compared with a control group of 110 untreated women from the same patient population. The surprising finding was that the rate of fetal damage was similar in both groups, but this rate was still approximately twice that seen in the general population.

1.1.1 Phenothiazines

Rieder et al.[14] found no significant correlation between maternal ingestion of phenothiazines and fetal deaths. In their case-controlled study of 117 pregnant women with schizophrenia, there was less of a correlation between medication use and fetal death than between factors such as severity of schizophrenia and fetal deaths.

Re-analysis of the data from previous studies called attention to a nonsignificant trend toward increased anomalies after phenothiazine exposure during weeks 4 through 10.[15] A meta-analysis[12] that pooled data from all available studies of first-trimester phenothiazine exposure on a total of 74 337 live births found a small increase in relative risk. The rate of congenital anomalies in phenothiazine-exposed offspring was 2.4% compared with about 2.0% in the general population.

However, no specific organ malformation associated with phenothiazine exposure has been consistently identified. None of these studies specified dosages used by patients; since most were using phenothiazines for obstetric conditions (hyperemesis) rather than for psychotic disorders, the average doses were probably lower than standard antipsychotic regimens.

1.1.2 Haloperidol

There are few studies that have investigated the effect of prenatal exposure to high-potency antipsychotics such as haloperidol.[16] However, a large number of women have been exposed to haloperidol as it had been the first choice medication for more than 10 years prior to the emergence of atypical antipsychotics. Specific teratogenic effects have not been picked up by registries or health surveys. A retrospective study of 100 women who received haloperidol while pregnant revealed no notable effect on the sex ratio of the offspring, birth weight, intrauterine or neonatal survival, fecundity or duration of gestation compared with women not taking antipsychotics.[17] However, a case report[18] described a newborn with reduction deformity of limbs whose mother's nausea was treated with haloperidol 1.5 mg/day during the limb-sensitive organogenetic period. Kopelman et al.[19] described a neonate with severe limb malformations following maternal use of haloperidol 15 mg/day during the first 7 weeks of gestation, but the neonate was also exposed *in utero* to methylphenidate and phenytoin. However, other retrospective studies failed to demonstrate an association between fetal malformations and *in utero* exposure to haloperidol given to treat maternal hyperemetic symptoms.[20,21]

Godet and Marie-Cardine[21] studied 199 children born to women with schizophrenia who were exposed to antipsychotic medication during pregnancy. A minimal increase in the risk of malformations was seen in the study: 2.5% of the children had malformations. They observed 4 malformations among 89 children exposed *in utero* to at least one antipsychotic agent during the first trimester and 3 malformations among 29 children exposed *in utero* to haloperidol. However, there was a lack of significant correlation between the risk of malformation and antipsychotic treatment.[21] This information needs to weighed against the few case reports where causality has not been established.

1.1.3 Atypical Antipsychotics

Compared with traditional antipsychotics, less is known about the risks associated with prenatal exposure to atypical antipsychotics. Atypical antipsychotics have some advantages over traditional antipsychotics in that they are only very rarely associated with extrapyramidal effects and most of them have only minimal influence on serum prolactin levels,[22] except two of the new antipsychotics (risperidone, amisulpride), which induce hyperprolactinaemia.

Koren et al.[23] have shown low folate intake in patients with schizophrenia receiving atypical antipsychotics. The mean bodyweight was 84.2kg and 63% of the female patients were obese (body mass index >27 kg/m^2).[23] Mean serum folate was significantly lower than in general hospital patients, increasing the risk for neural tube defects.

Clozapine

Some clinical follow-up studies of pregnant women with psychotic disorders who were treated with clozapine have yielded no evidence of any

causal connection between administration of clozapine and the occurrence of fetal malformations.[22,24,25] Several published case reports and case series[26-30] collectively suggest no definitive association between clozapine exposure and congenital anomalies in either animals or humans; however, the extent to which these animal data can be extrapolated to humans is unclear. Tényi and Trixler[25] reported on six pregnancies of four women with schizophrenia (one pregnancy each in three women and three pregnancies in one woman) who required clozapine treatment during pregnancy; in none of the pregnancies were any adverse effects experienced by either the women or their infants. However, in a review, Dev and Krupp[31] reported on 61 children born to 59 women who received clozapine treatment during pregnancy. Fifty-one of the children were healthy, five had congenital malformations and five had perinatal syndromes. The mothers of some of the children with congenital malformations had taken other drugs during pregnancy and these drugs could have played some part in causing fetal damage.[31] The Novartis Pharmacovigilance Service has reported on nearly 200 cases with an incidence of malformations of 6%. However, these reports must be considered with caution since they represent only the pregnancies reported spontaneously to the company, and other pregnancies associated with clozapine are, therefore, not considered.[32]

Olanzapine

Data from a case registry of olanzapine exposures during pregnancy have been provisionally reported by Goldstein et al.[33] Outcomes were available from 23 prospectively ascertained olanzapine-exposed pregnancies and there were an additional 11 retrospectively ascertained cases of pregnancy. Spontaneous abortion occurred in 13%, stillbirth in 5%, major malformation in 0% and prematurity in 5%. An expanded description in the Lilly Worldwide Pharmacovigilance Safety Database includes pregnancy outcome data[34] for 144 prospectively reported cases. Among these, 102 (70.8%) resulted in normal births, 12 (8.3%) led to spontaneous abortions, 6 (4.2%) to premature deliveries and 3 (2.1%) stillbirths occurred. The reported data are all within the range of normal historical control rates.[35-37] Major malformations were registered in six cases (4.2%). In one case the mother also used cannabis, alcohol, nicotine and ecstasy, and in another three cases the mothers were also taking concomitant psychotropic medication (benzodiazepines, paroxetine, valproic acid [sodium valproate]). There are several case reports of healthy infants born without complications despite prenatal exposure to olanzapine.[38-41]

Risperidone

There are very limited data on the safety of risperidone use during human pregnancy. Recently, Ratnayake and Libretto[42] reported on two women with schizophrenia who were treated with risperidone 4 and 6 mg/day before and throughout pregnancy and during the nursing period. No organ malformation at birth and no developmental abnormalities have been found in the children after the age of 2 years. These case reports support the findings of a postmarketing study of 7684 patients who were prescribed risperidone.[43] Nine women took risperidone during ten pregnancies and, of these ten pregnancies, there were seven live births and three therapeutic terminations. There were no abnormalities reported among the seven live infants exposed to risperidone *in utero*. However, no far-reaching consequences can be drawn on the basis of this small amount of data.

Quetiapine

Two reports were found in the literature concerning the use of quetiapine during human pregnancy. Tényi et al.[44] reported on a patient who was treated with quetiapine during her entire pregnancy without complications. The patient had been taking quetiapine 300mg twice daily at conception; the dose was reduced at the twentieth week of pregnancy to

Table I. US FDA classification system for administration of drugs during pregnancy (modified from the Food and Drug Administration[46])

Category	Interpretation
A	Controlled studies in pregnant women have failed to demonstrate a risk to the fetus. If this drug is used during pregnancy, the possibility of fetal harm appears remote. However, studies cannot rule out the possibility of harm, the drug should be used during pregnancy only if clearly needed
B	Reproduction studies in animals show no risk. However, there are no adequate and well controlled studies in pregnant women. OR animal studies have shown an adverse effect, while studies in pregnant women have not shown increases of risk. Because the studies in humans cannot rule out the possibility of harm, the drug should be used only if clearly needed
C	Animal reproduction studies have shown an adverse effect, or have not been done; there are no adequate and well controlled studies in humans, and the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks
D	There is positive evidence of human fetal risk, but the benefits from the use of the drug may be acceptable despite its potential risks. The patient should be apprised of the potential hazard to the fetus
X	Studies in humans and animals have demonstrated fetal abnormalities and the risk of the use of the drug clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant

200mg and 2 weeks later to 150mg. Taylor et al.[45] reported on a patient whose pregnancy was confirmed after 2 weeks of quetiapine 300 mg/day treatment. At week 21 the dose was reduced to 200 mg/day until 4 weeks before the estimated date for delivery, when her quetiapine dose was reduced by 50 mg/day each week. The patient remained in remission throughout pregnancy and no problems were observed in the first month postpartum.

Amisulpride, Ziprasidone and Aripiprazole

No published human data have been found for amisulpride, ziprasidone and aripiprazole.

Current Status

Notably, among antipsychotics only clozapine is a class B drug in the US FDA Classification System,[46] indicating no known evidence of risk in humans when administered during pregnancy (table I). All other antipsychotics are classified as group C drugs, indicating risks cannot be ruled out.[46,47] According to the review of Dev and Krupp[31] this distinction in favour of clozapine seems unjustified. No antipsychotic medication has been approved for use during pregnancy and the risks of infant exposure must be weighed against the risks of untreated maternal illness.

1.2 Perinatal Syndromes (Neonatal Toxicity)

Perinatal syndromes refer to a range of behavioural and physical symptoms observed in the immediate neonatal period that can be attributed to drug exposure near the time of birth. Although transient neonatal distress syndromes associated with exposure to or withdrawal from antidepressants, benzodiazepines and mood stabilisers have been documented in case reports,[12] there are only a few case reports of neonatal toxicity or perinatal syndromes associated with antipsychotic use during pregnancy.

Case reports[48,49] and case series (12 psychiatrically ill women receiving antipsychotic medication during the final trimester)[50] have reported symptoms, including motor restlessness, tremor, hypertonicity, abnormal movements and difficulty with oral feeding in infants born to women taking traditional antipsychotics, particularly phenothiazines, during pregnancy. The symptoms reported were mostly transient and resolved within days,[51,52] but some of them lasted for up to 10 months after birth. A long-lasting effect of drug exposure cannot be ruled out.

Several days of abnormal apathy was reported in a newborn whose mother received up to 1800mg of chlorpromazine daily until delivery.[53] In another report, cholestatic jaundice in a newborn during the first 2 weeks after birth was attributed to maternal

ingestion of chlorpromazine during the last trimester.[54]

In a review,[31] five children were described who developed perinatal syndromes out of 61 children who were born to women treated with clozapine during pregnancy; however, some of the mothers had taken other medications. There were two cases of new-onset or worsening gestational diabetes mellitus with shoulder dystocia,[26,30] and reports that the accumulation of clozapine in fetal serum may increase the risk of floppy infant syndrome[27] and neonatal seizures.[28]

1.3 Postnatal Behavioural Sequelae (Behavioural Toxicity)

Behavioral toxicity refers to the potential of *in utero* exposure to psychotropic medication to cause long-term neurobehavioural sequelae. This question is complicated by genetic and environmental factors that also contribute to the outcome. Some data from animal studies have demonstrated that changes in neurotransmitter function and behaviour occur after prenatal exposure to psychotropic agents, such as chlorpromazine and haloperidol.[55-57] It remains to be determined what consequence these findings have for humans.

Data regarding the neurobehavioural effects of prenatal exposure to antipsychotics are limited. Without continuous follow-up it is impossible to estimate the neurobehavioural effects in children exposed *in utero* to antipsychotics.[58] After follow-up until the age of 5 years, uncontrolled studies on children born to mothers maintained throughout pregnancy and postpartum on an average chlorpromazine dosage of 50–150 mg/day[15] found no differences in behavioural and intellectual functioning between children who were exposed to the typical antipsychotic *in utero* compared with children without such exposure. In a case control study,[59] the behaviour at school of 68 children exposed *in utero* to typical antipsychotics (phenothiazines, haloperidol) during the second half of pregnancy was evaluated. The statistical analysis did not reveal any significant difference in behaviour between the exposed children and children not exposed *in utero* to antipsychotics.

2. No Treatment and/or Medication Discontinuation

The potential risks of not treating the pregnant woman include the possibility of harm to herself or the fetus during psychotic episodes.[11,60] A growing number of studies have demonstrated high rates of relapse when medication is discontinued in patients with schizophrenia.[61-63] Reviews by Baldessarini and Viguera[64] and Gilbert et al.[65] reported that patients with schizophrenia are at greatest risk of relapse within the first 3 months of medication discontinuation. It is estimated that 65% of women with schizophrenia who do not maintain medication will relapse during a pregnancy.[66] The rate of antipsychotic withdrawal is also important. If medication is tapered over <2 weeks, relapse rates are 5- to 6-fold higher than those observed when medication are tapered over 2 months. Thus, the decision to stop antipsychotic treatment when women with schizophrenia become pregnant or plan to conceive becomes that much more difficult. Physicians must, therefore, inform patients of the high likelihood of relapse and the risks associated with a decompensation as well as of the incomplete information available regarding risks or benefits of treatment with antipsychotic medication. Risks of alcohol use, smoking, nutritional problems, stress and potential relationship problems related to psychosis should be discussed. Physicians must weigh the benefits of controlling severe psychiatric illness in their pregnant patients versus the possible risks to the mother and the fetus from continuing treatment.[67-69]

Wadhwa et al.[70] investigated the consequences of maternal stress and related factors in pregnancy on the length of fetal gestation, fetal growth and

brain development. Their findings support a significant role for maternal prenatal stress in the aetiology of prematurity-related outcomes and suggest that these effects are partially mediated by the maternal-fetal neuroendocrine axis, particularly by placental corticotropin-releasing hormone. Their findings also provide preliminary evidence that the influence of prenatal stress on the developing fetus may persist after birth.

Psychiatric illness during pregnancy may also affect maternal self-care and attention to prenatal care. Suicidality or impulsivity associated with psychotic states present clinical risks. Pregnant women with psychoses have been found to be more likely to smoke or use alcohol or illegal drugs.[71] Psychosis during the postpartum period may also affect maternal-infant attachment and, thereby, affect later infant development. Children of hospitalised mothers with schizophrenia are rarely successfully reared by their mother and, therefore, their early infant attachment environment is very disrupted and not comparable with that of children reared by healthy mothers. There are data indicating that children of mothers with schizophrenia are more likely to display behavioural problems and exhibit disruptions in motor, cognitive and emotional development.[72]

3. Treatment Guidelines

On the basis of the currently available data, making generalised recommendations is very difficult. We have attempted to order the information provided into three groups of recommendations for women with schizophrenia who: (i) wish become pregnant; (ii) have become pregnant and (iii) have a first-ever episode of schizophrenia during pregnancy

3.1 Women with Schizophrenia Who Wish to Become Pregnant

When possible, decisions regarding the use of psychotropic medications during pregnancy should be made before a woman conceives. This is not always possible for women with new-onset illness during pregnancy and for women who inadvertently conceive. Pregnancy counselling of women with schizophrenia is important but should be done in such a way that it does not further complicate the common reluctance to use antipsychotic medication. Most pregnancies in mothers with schizophrenia will be unplanned, so encouraging early disclosure of pregnancy should be standard treatment recommendation. Pregnancy counselling may be especially important among sexually active women with psychoses who may unexpectedly place themselves at risk of pregnancy during prepsychotic periods with loss of control.

In addition to the objective information, which provides estimates of risk, there is important subjective information, such as a woman's attitude toward the use of psychiatric medication during pregnancy, which must be evaluated. Women place different values on the relative risks involved for themselves and their fetuses. All of these factors must be weighed in the setting of a patient's psychiatric history and her current symptoms. Psychotic women might not consistently recognise that they are pregnant and, therefore, cannot make informed choices regarding whether to continue with the pregnancy and how to make the healthiest choices for themselves.

With most psychotropics, decisions about often unknown relative risks must be balanced on an individualised basis in light of potential benefits and likely morbidity or mortality associated with untreated or differently treated forms of psychopathology. Specific risk factors that had been delineated for definitive antipsychotic use are: denial of pregnancy or psychotic experience of pregnancy; delusions that interfere with health maintenance; and risk of suicide or exposure to violence occurring when psychosis triggers partner or family rejection because of pregnancy. It is of further importance to

note the base rate for major congenital malformations (2–4%) in the general population when assessing relative risks during medication exposures.[73,74] Moreover, the possibility exists that some forms of severe psychopathology may themselves confer some elevation of risk for complications during pregnancy, regardless of psychotropic drug use.[72,75,76]

3.2 Women with Schizophrenia Who Have Become Pregnant

The most appropriate treatment algorithms for women with schizophrenia who have become pregnant depend on the severity of the disorder. Close monitoring during pregnancy is very important to allow prompt detection and treatment of recurrent illness. When medication is indicated, an attempt should be made to choose the safest option, a decision based on the available reproductive safety data and the woman's history of medication response. This may involve switching from an agent with relatively less reproductive safety data. When possible, this switch should take place before the woman attempts to conceive, to confirm her stability in response to the medication.

In contrast, patients with chronic psychosis, particularly those with histories of repeated relapses, are best maintained on antipsychotics before and during pregnancy. This approach has the advantage that fetal drug exposure may be limited when the low dosage is used and the need for intermittent administration of higher dosages to treat a psychotic relapse may be avoided. Therapeutic drug monitoring could be helpful for finding the optimal dosage, particularly considering the altered metabolic capacity for many drugs in pregnancy. Ideally, chronically psychotic, difficult to treat women should be maintained on monotherapy with the medication that has been most effective for them.

Data regarding the effect of drug discontinuation on the well-being of patients with psychiatric illness have revealed substantial risk. This has prompted reassessment of guidelines for women who become pregnant while being treated with antipsychotics, as well as for women who develop a new-onset psychiatric disorder during pregnancy. The decision to accept the higher than average relative risk and small absolute risk for teratogenesis associated with certain antipsychotics may be justified by the need for drug treatment to ensure stable maternal mental health during pregnancy.[12]

The recommendation that, if use of an antipsychotic with a high propensity to cause extrapyramidal symptoms is necessary during pregnancy, treatment be discontinued 5–10 days before delivery in order to minimise the chances of the neonate experiencing extrapyramidal symptoms has been re-evaluated.[12] As the risk for decompensation is high with drug discontinuation,[63,75] and postpartum decompensation can frequently occur,[7,69,77] cessation of medication before delivery puts both the mother and newborn at risk.

Women with refractory illness who have failed multiple medication trials and have ultimately been stabilised on a particular regimen are likely to do well if they remain on that regimen during pregnancy rather than risk relapse by switching to another medication. While there is little definitive evidence for the safety of some of the newer atypical antipsychotics, there is no information on the effect of combination therapy often used when women are hospitalised for acute decompensation. There is insufficient information to justify recommending switching medication. When more than one medication has been required, attempts should be made to simplify the regimen as much as possible without compromising maternal stability.

Attention must also be paid to medication dosages during pregnancy. There is an intuitive impulse to decrease medication usage during pregnancy. However, for many drugs, there appears to be no clear dosage-response relationship to risk during

pregnancy.[47] Therefore, many women can be undertreated and placed at an increased risk for relapse if medication dosages are decreased.[63,75] Although risks cannot be quantified absolutely, the importance of weighing up the various treatment options and relative risks with women faced with this decision cannot be overstated.[50,69]

Some of the atypical antipsychotics cause various degrees of weight gain, which increases the risk for neural tube defects in the infants of overweight women.[78,79] Because many pregnancies in women with schizophrenia are unplanned it is likely that pregnancy may be first detected beyond the first postconceptional month, after the neural tube defect has formed. Hence, it makes clinical sense to perform diagnostic tests to rule out neural tube defects among the fetuses of these patients, including using detailed level 2 ultrasound and maternal α-fetoprotein tests. It is conceivable to supplement overweight women taking atypical antipsychotics with high doses of folate (e.g. 4 mg/day), which is recommended in other high-risk populations (e.g. those with previous infants with neural tube defects, with diabetes mellitus and taking antiepileptics).[23]

3.3 Women with First-Episode Schizophrenia during Pregnancy

Psychosis during pregnancy should be considered an obstetric and medical emergency. Symptoms may place a woman at increased risk for dangerous or impulsive behaviour, and can interfere with her ability to obtain appropriate prenatal care.[60]

Risks for adverse pregnancy outcome are most likely to be substantially less during second and third trimester exposures, after the completion of organogenesis, although the absence of extensive case registry data with most compounds limits the certainty with which conclusions about safety can be drawn. In general, avoidance of antipsychotic agents in the first trimester is recommended but, if this is not possible, keeping doses low and brief to minimise exposure is wise.

A meta-analysis[12] noted a higher risk of congenital malformations after first trimester exposure to low-potency antipsychotics. In view of the potential for the development of maternal hypotension with aliphatic phenothiazines and thioridazine,[68] and the possible increased risk of fetal malformation with phenothiazines,[12] it is preferable to use high-potency agents as first-line management for psychotic disorders during pregnancy. The choice of medication for pregnant women with psychosis would be determined by the risks of adverse effects. High-potency typical antipsychotics are advantageous as they have lower rates of orthostatic hypotension and also have some safety data in the use by psychotic women.

The growing number of experiences of safe use of atypical antipsychotics during pregnancy can encourage clinicians to promote such treatment. However, because of the limited data available regarding the safety of the newer antipsychotic agents,[37] it is difficult to make decisions on the use of clozapine, olanzapine or risperidone in the treatment of pregnant psychotic women. The decision is much more difficult when considering the other atypical antipsychotics such as quetiapine with only two published case reports, or amisulpride, ziprasidone and aripiprazole without available human data. The data reported regarding clozapine indicate that, in certain instances, its beneficial effect to the mother may outweigh any risk to the infant. However, clozapine has not been systematically studied in pregnancy and its use is far too limited to determine whether it has any unique advantage or disadvantage in terms of fetal development.[68] The large recorded case registry with olanzapine describes a relatively low risk for adverse events in comparison with base rates for spontaneous malformations, premature deliveries or spontaneous abortions; therefore, it seems a promising agent in the treatment of pregnant wo-

men with psychoses. However, there is a substantial need for the collection of more data about the risks of atypical antipsychotics in pregnancy.[47]

Nonpharmacological treatment strategies should always be explored. These options may limit the need for medication during pregnancy. Nonpharmacological therapy, such as individual psychotherapy, therapy for the patient's family and partner, social casework and hospitalisation in a supportive, structured milieu, should usually be attempted before, and concomitantly applied beside, drug therapy to alleviate the symptoms of a major psychiatric disorder.[62]

Finally, we suggest extension of the recommendations for bipolar patients of Llewelyn et al.[80] to include all women of reproductive age with psychosis. These include: (i) documentation of birth control method; (ii) discussion of risks for drug exposure; (iii) motivation for proper nutrition and exercise; (iv) omission of alcohol, nicotine or caffeine >300 mg/day; (v) exploration of the use of nutritional/herbal supplements, and information about the lack of data for their use during pregnancy; and (vi) exploring plans for pregnancy and emphasising the importance of pre-pregnancy consultation. This consultation should include education about the risk of psychiatric illness in the offspring, detailed data about the patient's illness course and response to treatment, and a treatment plan for managing a relapse during pregnancy and the postpartum period.

4. Conclusions

The introduction of several new pharmacotherapies has resulted in renewed optimism about the prognosis and treatment outcome for women with schizophrenia, as well as having raised new questions about reproductive safety issues. A complex inter-relationship exists between pharmacological, neuroendocrine, genetic and other health issues in distinct clinical populations. This complicates conclusions regarding possible adverse effects of some pharmacological agents on reproductive functions. Progress on their disclosure creates a basis for better understanding of these effects. An emerging database on reproductive health safety factors for women with schizophrenia has been even more useful in maximising clinical benefits while realistically calculating medication adverse effects for women with childbearing potential.

It is crucial for the clinician to have a prepared approach to the administration of psychotropic agents, given the prevalence of psychotropic drug use during pregnancy in those with schizophrenia. Careful medical record documentation is helpful in a difficult decision-making process. In general, the use of psychotropic medication during pregnancy is indicated when the risk to the fetus from exposure is outweighed by the risks of untreated psychiatric illness in the mother. For some women, the decision to accept a modest increase in teratogenic risk may be appropriate in comparison with the need to maintain stable maternal health during pregnancy. In addition, more data are emerging regarding a possible adverse effect of untreated psychiatric illness on fetal development, and this must also be included in the equation. Objectively, any risk from antipsychotic medication is most likely to be small and potentially clinically insignificant compared with the definitive risk to children of mothers with schizophrenia secondary to genetic and lifestyle risks (smoking, alcohol, illegal drugs), and these risks are well established and outweigh any potential risks of antipsychotics. Education of women needs to put these relative risks into perspective.

Although most published data on antipsychotic medication during pregnancy are encouraging, the currently available data are very limited. Until there are more controlled prospective data on the impact of drugs on fetal and later development, the clinician will continue to act in a state of potential uncertainty, weighing partially calculated risks against managing individual clinical dilemmas. Therefore, it is

important for any clinician who is treating a pregnant woman with antipsychotics to report on his/her experiences systematically in order to build up a broad database. The goal for the clinician caring for women who are pregnant or planning to conceive should be to provide the best information available regarding the spectrum of risks associated with either indicating or retaining antipsychotic treatment during pregnancy. Any decisions made are always very personal and unique for a given individual.

Acknowledgements

No sources of funding were used to assist in the preparation of this manuscript. The authors have no conflicts of interest that are directly relevant to the content of this review.

References

1. Stevens BC. Psychoses associated with childbirth: a demographic survey since the development of community care. Soc Sci Med 1971; 5: 527-9
2. Trixler M, Gáti Á, Tényi T. Risks associated with childbearing in schizophrenia. Acta Psychiatr Belg 1995; 95: 159-62
3. Bratfos O, Haug JI. Puerperal mental disorders in manic-depressive females. Acta Psychiatr Scand 1966; 42: 285-8
4. Reich T, Winokur G. Postpartum psychoses in patients with manic-depressive disease. J Nerv Ment Dis 1970; 151: 60-4
5. McKenna K, Einarson A, Levinson A, et al. Significant changes in antipsychotic drug use during pregnancy. Vet Hum Toxicol 2004; 46: 44-6
6. Reynolds R. The effects on the infant of psychotropic drugs used in pregnancy. In: Krauer B, Krauer F, Hytten FE, et al., editors. Drugs in pregnancy: maternal drug handling, fetal drug exposure. London: Academic Press, 1984: 131-50
7. Goldberg HL, Nissim R. Psychotropic drugs in pregnancy and lactation. Int J Psychiatr Med 1994; 24: 129-49
8. Lewis P. Drug usage in pregnancy. In: Lewis P, editor. Clinical pharmacology in obstetrics. Boston (MA): Wright-PSG, 1983
9. Bennedsen BE, Mortensen PB, Olesen AV, et al. Congenital malformations, stillbirths, and infant deaths among children of women with schizophrenia. Arch Gen Psychiatry 2001; 58: 674-9
10. Sitland-Marken P, Rickman LA, Wells BG, et al. Management of acute mania in pregnancy. J Clin Psychopharmacol 1989; 9: 78-87
11. Mortola J. The use of psychotropic agents in pregnancy and lactation. Psychiatr Clin North Am 1989; 12: 69-87
12. Altshuler LL, Cohen L, Szuba MP, et al. Pharmacologic management of psychiatric illness during pregnancy: dilemmas and guidelines. Am J Psychiatry 1996; 153: 592-606
13. Sobel DE. Fetal damage due to ECT, insulin coma, chlorpromazine or reserpine. Arch Gen Psychiatry 1960; 2: 606-11
14. Rieder O, Rosenthal D, Wender P, et al. The off-spring of schizophrenics: fetal and neonatal death. Arch Gen Psychiatry 1975; 32: 200-11
15. Edlund MJ, Craig TJ. Antipsychotic drug use and birth defects: an epidemiologic reassessment. Compr Psychiatry 1984; 25: 32-8
16. Ayd FJ. Haloperidol: 15 years of clinical experience. Dis Nerv Syst 1972; 33: 459-69
17. Guze BH, Guze PA. Psychotropic medication use during pregnancy. West J Med 1989; 151: 296-8
18. Dieulangard P, Coignet J, Vidal JC. Sur un cas d'ectrophocomélie peut-être d'origine médicamenteuse. Bull Féd Gynécol Obstét 1966; 18: 85-7
19. Kopelman AE, McCullar FW, Heggeness L. Limb malformations following maternal use of haloperidol. JAMA 1975; 231: 62-4
20. Hanson JW, Oakley Jr GP. Haloperidol and limb deformity [letter]. JAMA 1975; 231: 26
21. Godet PF, Marie-Cardine M. Neuroleptiques, schizophrenie et grossesse: etude epidemiologique et teratologique. Encephale 1991; 17: 543-7
22. Lieberman J, Safferman AZ. Clinical profile of clozapine: adverse reactions and agranulocytosis. In: Jones LY, editor. Clozapine in treatment resistant schizophrenia: a scientific update. London: Royal Society of Medicine, 1992
23. Koren G, Cohn T, Chitayat D, et al. Use of atypical antipsychotics during pregnancy and the risk of neural tube defects in infants. Am J Psychiatry 2002; 159: 136-7
24. Dickson RA, Edwards A. Clozapine and fertility. Am J Psychiatry 1997; 154: 582-3
25. Tényi T, Trixler M. Clozapine in the treatment of pregnant schizophrenic women. Psychiatria Danubina 1998; 10: 15-8
26. Dickson RA, Hogg L. Pregnancy of a patient treated with clozapine. Psychiatr Serv 1998; 49: 1081-3
27. DiMichele V, Ramenghi LA, Sabatino G. Clozapine and lorazepam administration in pregnancy [letter]. Eur Psychiatry 1996; 11: 214
28. Stones SC, Sommi Jr RW, Rasken PA, et al. Clozapine use in two full-term pregnancies [letter]. J Clin Psychiatry 1997; 58: 364-5
29. Tényi T, Trixler M, Vereczkey G, et al. Use of clozapine during pregnancy [in Hungarian]. Orv Hetil 1994; 135: 1967-9
30. Waldman MD, Safferman AZ. Pregnancy and clozapine [letter]. Am J Psychiatry 1993; 150: 168-9
31. Dev V, Krupp P. The side-effects and safety of clozapine. Rev Contemp Pharmacother 1995; 6: 197-208
32. Nguyen HN, Lalonde P. Clozapine et grossesse. Encephale 2003; 29: 119-24
33. Goldstein DJ, Corbin LA, Fung MC. Olanzapine-exposed pregnancies and lactation: early experience. J Clin Psychopharmacol 2000; 20: 399-403
34. Lilly Research Laboratories, Lilly Corporate Center. Written correspondence at 2004 Mar 10. Indianapolis (IN): Eli Lilly & Company, 2004. (Data on file)
35. McDonald AD. Maternal health and congenital defect: a prospective investigation. N Engl J Med 1958; 258: 767-73

36. Kerly M. Reproductive and perinatal epidemiology. Boca Raton (FL): CRC Press, 1999: 69
37. Patton SW, Misri S, Corral MR, et al. Antipsychotic medication during pregnancy and lactation in women with schizophrenia: evaluating the risk. Can J Psychiatry 2002; 47: 9559-65
38. Nagy A, Tényi T, Lénárd K, et al. Olanzapine and pregnancy [in Hungarian]. Orv Hetil 2001; 142: 137-8
39. Kirchheiner J, Berghofer A, Bolk-Weischedel D. Healthy outcome under olanzapine treatment in a pregnant woman. Pharmacopsychiatry 2000; 33: 78-80
40. Neumann NU, Frasch K. Olanzapine and pregnancy: 2 case reports [in German]. Nervenarzt 2001; 72: 876-8
41. Littrell KH, Johnson CG, Peabody CD, et al. Antipsychotics during pregnancy [letter]. Am J Psychiatry 2000; 157: 1342
42. Ratnayake T, Libretto SE. No complications with risperidone treatment before and throughout pregnancy and during the nursing period. J Clin Psychiatry 2002; 63: 76-7
43. MacKay FJ, Wilton GL, Pearce SN, et al. The safety of risperidone a post-marketing study on 7684 patients. Hum Psychopharmacol Clin Exp 1998; 13: 413-8
44. Tényi T, Trixler M, Keresztes ZS. Quetiapine and pregnancy [letter]. Am J Psychiatry 2002; 159: 674
45. Taylor TM, O'Toole MS, Ohlsen RI, et al. Safety of quetiapine during pregnancy [letter]. Am J Psychiatry 2003; 160: 588-9
46. Food and Drug Administration. Labeling and prescription drug advertising: content and format for labeling for human prescription drugs. Fed Regist 1979; 44: 37434-67
47. Ernst CL, Goldberg JF. The reproductive safety profile of mood stabilizers, atypical antipsychotics, and broad-spectrum psychotropics. J Clin Psychiatry 2002; 63 Suppl. 4: 42-55
48. Hill RM, Desmond MM, Kay JK. Extrapyramidal dysfunction in an infant of a schizophrenic mother. J Pediatr 1966; 69: 589-95
49. Tamer A, McKey R, Arias D, et al. Phenothiazine induced extrapyramidal dysfunction in the neonate. J Pediatr 1969; 75: 479-80
50. Auerbach JG, Hans SL, Marcus J, et al. Maternal psychotropic medication and neonatal behavior. Neurotoxicol Teratol 1992; 14: 399-406
51. Rayburn WF, Andresen BD. Principles of perinatal pharmacology. In: Rayburn WF, Zuspan FP, editors. Drug therapy in obstetrics and gynecology. Norwalk (CT): Appleton, Century, Crofts, 1982: 1-8
52. Desmond MM, Rudolph AJ, Hill RM, et al. Behavior alterations in infants born to mothers on psychoactive medication during pregnancy. In: Farrel G, editor. Congenital mental retardation. Austin (TX): University of Texas Press, 1967: 235-44
53. Hammond JE, Toseland PA. Placental transfer of chlorpromazine. Arch Dis Child 1970; 45: 139-40
54. L'Hirondel J, Venzia R, Russelot P, et al. Ictere neonatal á la chlorpromazine. Arch Franc Péd 1968; 25: 1171-7
55. Clark CVH, Gorman D, Vernadakis A. Effects of prenatal administration of psychotropic drugs on behavior of developing rats. Dev Psychobiol 1970; 3: 225-35
56. Golub M, Kornetsky C. Seizure susceptibility and avoidance conditioning in adult rats treated prenatally with chlorpromazine. Dev Psychobiol 1974; 7: 79-88
57. Spear IP, Shalaby IA, Brick J. Chronic administration of haloperidol during development: behavioral and psychopharmacological effects. Psychopharmacology (Berl) 1980; 70: 47-58
58. Kris EB. Children of mothers maintained on pharmacotherapy during pregnancy and postpartum. Curr Ther Res 1965; 7: 785-9
59. Stika L, Elisova K, Honzakova L, et al. Effects of drug administration in pregnancy on children's school behaviour. Pharm Weekbl Sci 1990; 12: 252-5
60. Pearson KH, Nonacs R, Cohen LS. Practical guidelines for the treatment of psychiatric disorders during pregnancy. In: Pearson KH, Sonawalla SB, Rosenbaum JF, editors. Women's health and psychiatry. Philadelphia (PA): Lippincott Williams & Wilkins, 2002: 115-25
61. Viguera AC, Baldessarini RJ, Hegarty JD, et al. Clinical risk following abrupt and gradual withdrawal of maintenance neuroleptic treatment. Arch Gen Psychiatry 1997; 54: 49-55
62. Dencker SJ, Malm U, Lepp M. Schizophrenic relapse after drug withdrawal is predictable. Acta Psychiatr Scand 1986; 73: 181-5
63. Carpenter Jr WT, Hanlon TE, Heinrichs DW, et al. Continuous versus targeted medication in schizophrenic outpatients: outcome results. Am J Psychiatry 1990; 147: 1138-48
64. Baldessarini RJ, Viguera AC. Neuroleptic withdrawal in schizophrenic patients. Arch Gen Psychiatry 1995; 52: 189-92
65. Gilbert PL, Harris MJ, McAdams LA, et al. Neuroleptic withdrawal in schizophrenic patients: a review of the literature. Arch Gen Psychiatry 1995; 52: 173-88
66. Casiano ME, Hawkins DR. Major mental illness and childbearing: a role for the consultation-liaison psychiatrist in obstetrics. Psychiatr Clin North Am 1987; 10: 37-51
67. Miller LJ. Clinical strategies for the use of psychotropic drugs during pregnancy. Psychiatry Med 1991; 9: 275-98
68. Bernstein JG. Psychotropic drugs in pregnancy and lactation. In: Bernstein JG, editor. Handbook of drug therapy in psychiatry. 3rd ed. St Louis (MO): Mosby-Year Book Inc., 1995: 397-412
69. Trixler M, Tényi T. Antipsychotic use in pregnancy: what are the best treatment options? Drug Saf 1997; 16: 403-10
70. Wadhwa PD, Sandman CA, Garite TJ. The neurobiology of stress in human pregnancy: implications for prematurity and development of the fetal central nervous system. In: Russell JA, Douglas AJ, Windle RJ, et al., editors. The maternal brain: neurobiological and neuroendocrine adaptation and disorders in pregnancy and post partum. Amsterdam: Elsevier, 2001: 131-42
71. Zuckerman B, Amaro H, Bauchner H, et al. Depressive symptoms during pregnancy: relationship to poor health behaviors. Am J Obstet Gynecol 1989; 160: 1107-11
72. Weinberg M, Tronick E. The impact of maternal psychiatric illness on infant development. J Clin Psychiatry 1998; 59: 63-71
73. Codero JF, Oakley GP. Drug exposure during pregnancy: some epidemiologic considerations. Clin Obstet Gynecol 1983; 26: 418-28
74. Stowe ZN, Nemeroff CB. Psychopharmacology during pregnancy and lactation. In: Schatzberg AF, Nemeroff CB, editors.

Textbook of psychopharmacology. Washington, DC: American Psychiatric Press, 1998: 979-96
75. Spielvogel A, Wile J. Treatment and outcomes of psychotic patients during pregnancy and childbirth. Birth 1992; 19: 131-7
76. Hendrick V, Altshuler L, Cohen L, et al. Evaluation of mental health and depression during pregnancy: position paper. Psychopharmacol Bull 1998; 34: 297-9
77. Cohen LS. Psychotropic drug use in pregnancy. Hosp Community Psychiatry 1989; 40: 566-7
78. Werler MM, Louik C, Shapiro S, et al. Pre-pregnancy weight in relation to risk of neural tube defects. JAMA 1996; 275: 1089-92
79. Shaw GM, Velie EM, Schaffer D. Risk of neural tube defect-affected pregnancies among obese women. JAMA 1996; 275: 1093-6
80. Llewellyn A, Stove ZN, Strader Jr JR. The use of lithium and management of women with bipolar disorder during pregnancy and lactation. J Clin Psychiatry 1998; 59 Suppl. 6: 57-64

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