Psychotropics in pregnancy: weighing the risks

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Received November 5, 2004

With increase in the use of newer psychotropics, there is a growing concern in relation to the teratogenicity. Unfortunately, it is not possible to carry out prospective studies in pregnant women and as a result physicians caring for such patients have to rely on case reports, case series, and retrospective studies. Available evidence shows that the safety of psychotropics in pregnancy is still unresolved and the decision to prescribe psychotropics in pregnancy should be taken in the light of severity of mental disease, and drugs should be prescribed only when the potential risk to the foetus from exposure is outweighed by the risk of untreated maternal disorder. In this review we discussed the current evidence of the teratogenic risks with psychotropic drugs commonly used to treat psychiatric disorders and also focused on decision making in such patients.

Key words Depression - pregnancy - psychosis - psychotropics

Female reproductive health safety has become a growing focus of concern amidst the expanding psychotropic pharmacopoeia. There are large numbers of studies demonstrating high rates of relapse when medications are discontinued in patients suffering from mood disorders, schizophrenia and anxiety disorders. The decision to stop drugs when women with these disorders become pregnant or plan to conceive becomes more difficult. Physicians caring for such patients face the challenge of minimizing the risk to the foetus, at the same time limiting the impact of maternal morbidity on the mother. Patients and their clinicians also face the reality that decisions either to use or not to use psychotropic medications can be associated with complications. Deciding what constitutes reasonable risk during pregnancy requires shared responsibility but the ultimate decision rests with the informed patient. For obvious ethical reasons, it is not possible to conduct randomized placebo-controlled studies on medication safety in pregnant women. Accordingly, most information about the reproductive safety of drugs derives from case reports, case series, and retrospective studies. Very few studies involve prospective design. Knowledge regarding the risks of prenatal exposure to psychotropic medications remains far from complete. The current understanding of the teratogenic risks with drugs commonly used to treat psychiatric disorders are reviewed.

Psychotropics and risks to offspring

All psychotropic medications diffuse across the placenta, which exposes the foetus to some degree of risk. Usually, the effects of
psychopharmacological therapies have exclusively been discussed in the context of their risk during the first trimester, when organ formation occurs. However, it has been noted that psychotropics are harmful even after the organogenesis, as intrauterine exposure during the 2nd and 3rd trimester can lead to postnatal complications. Accordingly the risks can be divided into teratogenicity, obstetrical complications, perinatal syndromes, and long-term postnatal behavioural sequelae. The baseline incidence of congenital malformations has been reported to be 2.0 to 2.5 per cent. A medication is considered teratogenic when prenatal exposure is associated with a significant increase in the risk of congenital physical deformities over the baseline risk. Obstetrical complications include preterm delivery, low birth weight, and delivery complications such as low Apgar scores or behavioural effects requiring intensive care. Perinatal syndromes include physical and behavioural symptoms noticed shortly after birth (such as jitteriness). These consequences are putatively related to drug use at or near birth and have limited duration. Postnatal behavioural sequelae include long-term neurobehavioural abnormalities in children who were exposed to psychotropics in utero.

**Potential risks of pharmacotherapy in pregnancy**

No psychotropic drug has been approved by the US Food and Drug Administration (FDA) for use during pregnancy. To guide physicians about the reproductive safety of various prescription drugs, the FDA has established a system that classifies medications into 5 risk categories (A, B, C, D, and X), based on data derived from human and animal studies. Category A medications are designated as safe for use during pregnancy (no psychotropics have this rating), while category X drugs are contraindicated by having demonstrated foetal risks that outweigh any benefit to the patient. Drugs in categories B to D are considered to have intermediate risks, which are greatest in category D. Most psychotropic drugs are classified as category C agent for which adequate human studies are lacking and foetal effects are seen in animal studies, or even the animal studies may also be insufficient; thus the foetal risks cannot be ruled out. Mood stabilizers like lithium, valproate and carbamazepine are classified as category ‘D’ drugs. This classification system is often ambiguous, inaccurate, and misleading. Psychiatrists must rely on other sources of information when recommending the use of psychotropic medications during pregnancy.

**Psychotic disorders and pregnancy**

Evidence from literature shows that various psychiatric illnesses are associated with poor pregnancy outcome (Table I).

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Schizophrenia</td>
<td>There is a significantly increased risk for stillbirth, infant death, preterm delivery, low birth weight and small for gestational age among offsprings of women with schizophrenia, with highest risk for those women who are in an episode of schizophrenia</td>
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<tr>
<td>Bipolar disorder</td>
<td>(i) Women with bipolar disorder are at high risk for symptom exacerbation during the immediate postpartum period and (ii) recurrence rates within the first 3 to 6 postpartum months are above 60 per cent (range 67 to 82%)</td>
</tr>
<tr>
<td>Depression</td>
<td>(i) Depression is associated with preterm labour and low birth weight. (ii) the risk persists even after control for confounding variables such as socioeconomic status, maternal weight gain, and health habits during pregnancy and (iii) women with history of major depression are at approximately 25 per cent risk for relapse of depression after childbirth (postpartum depression)</td>
</tr>
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prevalence rates of cigarette smoking, alcohol use, drug use, and low socio-economic status, all of which were strongly associated with low birth weight, preterm birth, and perinatal death. In another large population based cohort study, Nilsson et al found significantly increased risks for still birth, infant death, preterm delivery, low birth weight and small for gestational age among offspring of women with schizophrenia, with highest risk for those women who were in an episode of schizophrenia. The risk of adverse outcome remained significantly high in women with an episode of schizophrenia, even after controlling for other confounding factors. A metaanalysis of case controlled studies done to evaluate the effect of schizophrenia on pregnancy outcome showed that there was evidence of a small but significantly increased risk for low birth weight and poor neonatal condition in infants born to patients with schizophrenia. Based on above information it can be concluded that women with schizophrenia are at increased risk for poor obstetrical outcomes and that many other factors may contribute to this. Continuation or discontinuation of antipsychotics during pregnancy should be addressed in this background.

Bipolar disorders: Pregnancy has been found to be a time of substantial risk for relapse of affective disorders, particularly following discontinuation of ongoing mood-stabilizing treatment. To some extent, the risks for recurrence may be predicted by the history of illness or severity, as well as by a history of prolonged wellness or proven ability to tolerate long periods without mood-stabilizing treatment. Women with bipolar disorder are also at a high risk for symptom exacerbation during the immediate postpartum period. Although quantitative specification of that risk has been inconsistent, in recent studies recurrence rates within the first 3 to 6 postpartum months were well above 60 per cent (range, 67 to 82%), perhaps reflecting more reliable diagnosis and greater interest in the problem. Bipolar disorder is also closely associated with postpartum psychosis and several studies have demonstrated that many women presenting with postpartum psychosis later develop bipolar disorder. Any decision regarding continuation or discontinuation of drugs should be weighed with the risk.

Depressive disorders: Women with history of depressive episode in the past may relapse during pregnancy or the postpartum period. Depression during pregnancy can present risks to the mother and foetus, such as inadequate maternal weight gain and, in the extreme, suicidality. Many studies have reported an association between maternal anxiety/stress during pregnancy and negative pregnancy outcomes, such as preterm labour and low birth weight infants, even after control for confounding variables such as socio-economic status, maternal weight gain, and health habits during pregnancy. A few studies have evaluated the impact of maternal major depression on pregnancy outcomes and found a significant relationship between depression and preeclampsia and a greater risk of low birth weight infants and preterm delivery. Further, a woman with a history of major depression is at approximately 25 per cent risk for relapse of depression after childbirth (postpartum depression). Psychotherapeutic interventions like individual psychotherapy, and counselling can help treat depression during pregnancy and the postpartum period. If a woman continue to remain depressed despite nonpharmacologic interventions or if depression is associated with significant morbidity, antidepressant medications should be considered.

Effects of psychotropics on pregnancy

Antipsychotics

Typical antipsychotics – There are no adequate reports or well controlled studies for use of high potency antipsychotics in pregnancy. However, use of haloperidol in the first trimester has not shown an excess of birth defects. These data suggest that there is no increased risk of congenital malformations associated with first trimester exposure to haloperidol and other high potency antipsychotics.

Low potency antipsychotics such as chlorpromazine are usually avoided because of side effects, such as hypotension, and their probable association with a slightly increased risk for malformations. Altshuler et al carried out a metaanalysis of data (74,337 live births) on outcome following first trimester phenothiazines exposure in...
an effort to assess evidence of overall increased risk. The results showed that with the baseline incidence of congenital anomalies estimated at 2 per cent, phenothiazines use increased the risk to 2.4 per cent, conferring an additional risk of 4 in 1,000. They also reported that there was no specific organ malformation following foetal exposure to phenothiazines.

Atypical antipsychotics – The newer atypical antipsychotics are becoming first-line treatment for many people with schizophrenia because these do not have some of the side effects of the older medications and appear to result in better acute and long-term responses. Usually it is suggested that pregnant women who require treatment with antipsychotics and are on an atypical agent, should switch to one of the older drugs. But, some patients do not respond to treatment with typical antipsychotics but respond only to an atypical agent. There are sparse data on the reproductive safety of the currently available newer compounds.

Clozapine – Clozapine is the only antipsychotic belonging to category B of FDA classification. The data available on its use in pregnancy are only in the form of case reports, case series and occasional review. Waldman & Safferman32 reported at least 15 normal births following maternal exposure to clozapine in pregnancy and several other authors also observed no definitive association between maternal exposure and congenital anomalies in either animals or humans33-38. On the other hand, Dev and Knapp99 revealed 5 congenital malformations and 5 perinatal syndromes in 61 children exposed to clozapine. Various associations reported with maternal exposure are floppy infant syndrome39, neonatal seizures40, new onset or worsening of gestational diabetes mellitus with shoulder dystocia32,34, decreased variability of foetal heart rate40, intrauterine growth retardation (IUGR) with oligohydrominous and intrauterine death41 and gastroesopahgeal reflux disease42. But many of these findings have been complicated by the concomitant use of drugs, malnutrition or family history of diabetes mellitus.

Olanzapine – Studies done in rodents have not revealed any evidence of teratogenicity with olanzapine despite the use of doses higher than those used clinically. Less than 20 per cent of the maternal dose of olanzapine crosses the human placenta. Goldstein et al43 reported data of pregnancies exposed to olanzapine. Outcomes were available from 23 prospectively ascertained olanzapine-exposed pregnancies. Normal birth without complications occurred in 16 cases, spontaneous abortion occurred in 3, stillbirth in 1, prematurity in 1, postmaturity in 2 cases with one of them developing perinatal complications in the form of meconium aspiration after caesarean section, and no major malformation in any case. The rates of complications were less than or comparable to the range of base rates for general population. Data from a case registry of olanzapine included data of 96 prospectively reported cases. Among these, 69 resulted in normal births; 12 in spontaneous abortions; 2 led to premature deliveries, 3 stillbirths, 1 case with major malformations, and 2 cases with unspecified outcomes. Perinatal complications were observed in 7 cases44. Levinson et al45 found 8 live births with no malformations, 1 spontaneous abortion, and one stillbirth. Various other case reported also reported of healthy infants born without complications despite prenatal exposure to olanzapine46-51. With respect to the postnatal long term effects, Gati et al52 did not find any postnatal behavioural sequelae in children up to the age of 6 to10 yr.

Risperidone – There is very limited information on the use of risperidone in pregnancy. Animal studies in rats have shown increased incidence of pup deaths and stillbirth with use of risperidone during pregnancy45. Rosengarten and Quartermain45 reported impaired learning and disrupted short term retention in adulthood (2 months) with use of risperidone in dam during pregnancy. In humans, case reports with use of risperidone in pregnancy suggested agenesis of corpus callosum54; 9 live births with no malformation and 2 spontaneous abortions45; oligohydraminos55; and no abnormality in two cases56.

Ziprasidone – Use of ziprasidone during pregnancy in animals at doses similar to human therapeutic doses has shown evidence of developmental delays, possible teratogenic effects
(cardiac, renal and skeletal), and increased still births\textsuperscript{54}. Human studies are lacking.

Quetiapine – Animal studies on use of quetiapine in pregnancy has shown some evidence of delay in skeletal ossifications, reduced foetal weight, and increased foetal and pup deaths\textsuperscript{54}. We could come across only two studies on use of quetiapine in human pregnancy. Tenyi \textit{et al}\textsuperscript{57} reported no abnormality during the pregnancy, delivery and in the postnatal period after using quetiapine throughout the pregnancy. Levinson \textit{et al}\textsuperscript{45} found three live births with no malformations and one stillbirth.

Aripiprazole – In animal studies aripiprazole has shown developmental toxicity, including possible teratogenic effects in rats and rabbits. The main effects were delayed skeletal ossification and decreased foetal weight with 3 to 10 times the maximum recommended human dose\textsuperscript{58}.

\textbf{Lithium and pregnancy}

Since the last four decades there has been concern about an association between prenatal exposure to lithium and risk for major congenital anomalies. Reports from an early International Register of Lithium Babies, based on a voluntary physician reporting system, described an excess of cardiovascular malformations, particularly Ebstein’s anomaly\textsuperscript{59-61}. The risk for this malformation in infants with first trimester lithium exposure was initially proposed to be 400 times higher than the background baseline\textsuperscript{59-62}. Later, based on a pooled analysis of the data, Cohen \textit{et al} estimated the risk for Ebstein’s anomaly following first trimester exposure to be between 1/1000 (0.1%) and 1/2000 (0.05%) births\textsuperscript{62}. Although the estimated risk of Ebstein’s anomaly in lithium exposed infants is 10 to 20 times higher than in the general population, the absolute risk is small (0.05 to 0.1%), and lithium remains the safest mood stabilizer for use during pregnancy\textsuperscript{62}. Other congenital abnormalities reported include large for gestational age infants\textsuperscript{63}, anencephaly\textsuperscript{64} and oromandibular-limb hypogenesis\textsuperscript{65}. Additional risks from exposure to lithium during labour and delivery include muscular hypotonia with impaired breathing and cyanosis in new born, often referred to as “floppy baby” syndrome\textsuperscript{66-68}. Isolated cases of neonatal hypothyroidism, nephrogenic diabetes insipidus, and polyhydramnios have also been described\textsuperscript{1,68,69}. Based on these reports of toxicity in infants born to lithium - treated mothers, some groups have recommended discontinuing lithium several days or weeks prior to delivery to minimize the risk of neonatal toxicity\textsuperscript{63,67,69,70}. However, there is a low incidence of neonatal toxicity with lithium exposure, and this practice of discontinuing lithium carries significant risk, since it withdraws treatment from patients precisely as they are about to enter the postpartum period. Limited information is available regarding behavioural outcomes of children exposed to lithium in utero, but follow up of children (for 3.5 - 5 yr) exposed to lithium during pregnancy showed no evidence of significant behavioural problems\textsuperscript{70,71}. The small sample, however, precludes conclusions about lithium exposure and long term neurobehavioural sequelae.

\textbf{Anticonvulsants and pregnancy}

Compared with lithium, anticonvulsants pose a much more serious teratogenic risk. All commonly used older anticonvulsants have been associated with teratogenicity and the risk for major birth defects in infants born to women receiving anticonvulsants is twice that of general population\textsuperscript{72}. Though most information about the reproductive safety of anticonvulsants have been derived from patients with epilepsy rather than bipolar disorder, recent findings suggest that exposure to certain anticonvulsants, rather than the presence of a seizure disorder, is the relevant variable\textsuperscript{73}. Factors that may increase the risk for teratogenesis include high maternal serum anticonvulsant levels and exposure to more than a single anticonvulsant\textsuperscript{73,74}.

\textit{Carbamazepine}: First trimester exposure to carbamazepine associated risk of neural tube defects is estimated to be about 1.0 per cent\textsuperscript{75}. Infants exposed to carbamazepine prenatally are also at increased risk for craniofacial abnormalities, microcephaly, growth retardation, spina bifida, cardiac abnormalities, fingernail hypoplasia and developmental delay\textsuperscript{73,75}. In controlled studies it has been found that carbamazepine exposure during pregnancy and
neonatal period does not lead to significant cognitive dysfunction in childhood\textsuperscript{76}. Neonatal exposure to carbamazepine has also been found to be associated with transient hepatic toxicity (cholestatic hepatitis and direct hyperbilirubinaemia) in neonates exposed to the drug during pregnancy\textsuperscript{77,78}. It is not known whether the new derivative, oxcarbazepine, is associated with similar foetal risks\textsuperscript{79}.

Most experts feel that carbamazepine should be used during pregnancy only if other options are not available. If used, it should be remembered that carbamazepine can cause foetal vitamin K deficiency. Since adequate levels of vitamin K are necessary for normal mid-facial growth and for the functioning of clotting factors, carbamazepine exposure in utero could increase the risk of neonatal bleeding and mid-facial abnormalities. Most experts recommend administering 20 mg/day of oral vitamin K in the last month of pregnancy in women taking carbamazepine\textsuperscript{80,81}.

Valproate: Valproic acid and its various derivatives and preparations, including divalproex, are teratogens, with rates of neural tube defects in the range of 1.0 to 5.0 per cent, or about a two-to ten fold increase in risk above the general population base rates of about 0.5 per cent\textsuperscript{82,83}. These risks are of particular concern because formation of the neural tube occurs within the first month of gestation, often before the pregnancy has been diagnosed. The neural tube defect found in exposed infants is more likely to be lumbosacral rather than anencephalic, which suggests a drug effect on neural crest closure\textsuperscript{84}. Prenatal exposure to valproate has also been associated with characteristic craniofacial abnormalities, and other central nervous system (CNS) structural abnormalities including hydrocephalus, cardiovascular malformations, limb defects, genital anomalies, intrauterine growth retardation\textsuperscript{72,73,82,83,85}. Valproate use near the time of delivery is associated with neonatal complications like heart rate decelerations\textsuperscript{86}, liver toxicity\textsuperscript{87}, hypoglycaemia\textsuperscript{88}, reductions in neonatal fibrinogen levels\textsuperscript{89} and withdrawal symptoms of irritability, jitteriness, feeding difficulties, and abnormal tone\textsuperscript{85}.

Lamotrigine: The obstetrical outcome information is maintained by the International Lamotrigine Pregnancy Registry. Cunnington et al\textsuperscript{90} reported that out of the 414 first trimester exposure to lamotrigine only, 12 offspring (2.9 per cent) had major birth defects which are similar to that in general population. They found higher rate of major birth defects (12.5 %) in 88 first trimester exposure to lamotrigine along with valproate\textsuperscript{90}. In another followup study of 23 infants, no neurobehavioural teratogenic effects of lamotrigine were seen on development at 12 months of age\textsuperscript{91}. The clearance rate of lamotrigine during pregnancy has also generated significant attention due to its increased use and the characteristics metabolic pathway. In many studies a significant increase has been found in the clearance rate during pregnancy\textsuperscript{82,93}.

Topiramate: Animal studies have demonstrated craniofacial and skeletal abnormalities\textsuperscript{54}. No data regarding possible teratogenic effects of topiramate in humans are available.

Gabapentin: Animal studies have demonstrated delayed bone ossification, hydronephrosis and increased rates of hydroureter\textsuperscript{54}. No information is available regarding its possible teratogenic effects in humans.

Antidepressants and pregnancy

Tricyclic antidepressants (TCAs): Prenatal use of tricyclic antidepressants in humans does not appear to increase the risk of congenital anomalies\textsuperscript{94,95}, although when used near the time of delivery these medications may produce transient neonatal toxicity or withdrawal symptoms in the form of lethargy, hypotonia, and anticholinergic effects, such as constipation, tachycardia, and urinary retention\textsuperscript{94,31,96}. The anticholinergic symptoms of functional bowel obstruction and urinary retention in the newborn have also been reported. Nortriptyline and desipramine are preferable to other tricyclic antidepressants during pregnancy because of their lower likelihood of anticholinergic and hypotensive side effects\textsuperscript{97}. Only two studies have evaluated the long term behavioural changes in children exposed to tricyclic agents during pregnancy. In one study, the children had normal
motor skills and behavioural development till the last evaluation at 3 yr of age\textsuperscript{98}. The other study evaluated 55 children who were prenatally exposed to fluoxetine, 80 children exposed to tricyclic antidepressants and 84 unexposed children and found no significant differences in global IQ, language development, temperament, mood, distractibility, or behaviour in children up to the age of 7\textsuperscript{99}. 

**Selective serotonin reuptake inhibitors (SSRI):** Most of information available on prenatal antidepressant exposures is for fluoxetine. Neither retrospective nor prospective studies have found a greater risk of miscarriage or major congenital malformations with fluoxetine\textsuperscript{99-103}. A study of prenatal exposures to sertraline, paroxetine, and fluvoxamine found the rates of major malformations and preterm labour to be no higher than those of nonexposed subjects\textsuperscript{104}. Third trimester use of fluoxetine has been linked with higher rates of perinatal complications (tachypnoea, jitteriness, premature delivery) in some\textsuperscript{99,100,103}, but not in all studies\textsuperscript{99,100,103}. A large prospective study that used the Swedish Birth Registry with 969 cases of prenatal exposure to antidepressants, including citalopram (375 cases), paroxetine (122 cases), sertraline (33 cases), and fluoxetine (16 cases) reported rates of perinatal complications and congenital malformations comparable to population norms\textsuperscript{99}. One study evaluated the long term sequelae of exposure to fluoxetine during pregnancy and found no effect on cognition, language development, or the treatment of pre-school and early-school children\textsuperscript{105}.

In a recent meta-analysis of prospective comparative study\textsuperscript{106}, the relative risk of major malformation with newer antidepressants (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, reboxetine, venlafaxine, nefazodone, trazadone, mirtazapine and bupropion) was found to be 1.01 (95\%CI: 0.57-1.80). The study concluded that as a group, the newer antidepressants are not associated with an increased risk of major malformations above the baseline of 1-3 per cent in the population\textsuperscript{106}.

**Monoamine oxidase inhibitors (MAOIs):** A study on 21 prenatal exposures to monoamine oxidase inhibitors (MAOIs)\textsuperscript{107} found a relative risk of 3.4 for congenital malformations. In contrast, a case report of phenelzine use throughout pregnancy described a healthy outcome for the patient and her infant\textsuperscript{108}. Nevertheless, MAOIs are best avoided in pregnant women because of the risk of hypertensive crisis.

**Venlafaxine:** Only two studies have evaluated use of venlafaxine in pregnancy. In one study, venlafaxine was used in 150 women and incidence of major malformations was similar to the expected rate of 1-3 per cent\textsuperscript{109}. In the second study, 10 subjects who received venlafaxine during pregnancy gave birth to healthy babies\textsuperscript{110}.

**Mirtazapine:** A small case series (N= 7) of mirtazapine use in pregnancy found no perinatal complications or congenital malformations in the infants\textsuperscript{111}. In another study, eight women received mirtazapine alone or in combination with some other drugs during pregnancy: there were no major malformation in 7 cases and spontaneous abortion was noted in only one pregnancy exposed to mirtazapine, alprazolam, diazepam and trifluperazine\textsuperscript{110}.

**Nefazodone and trazadone:** Einarson et al\textsuperscript{112} evaluated the effect of prenatal exposure to nefazone and trazadone, and found no significant difference in the number of major congenital malformation. The nefazone and trazadone group and other antidepressant group had more number of spontaneous abortions compared to non teratogen group but the difference was not statistically significant, and further the rate of spontaneous abortions was in the expected range of general population\textsuperscript{112}.

**Bupropion:** Chun-Fai-Chan et al\textsuperscript{113} studied 136 women exposed to bupropion during the first trimester of pregnancy. There were 105 live births with no major malformations, 20 spontaneous abortions, 10 therapeutic abortions, 1 stillbirth, and 1 neonatal death. There were no statistically significant differences between bupropion group, other antidepressant group and non-teratogen group, except for significantly more spontaneous abortions in the bupropion group\textsuperscript{113}.
Benzodiazepines and pregnancy

Benzodiazepines are used commonly as adjunctive medications for mood stabilization or for anxiety, agitation, and sleep problems. All major classes of benzodiazepine compounds diffuse readily across the placenta to the foetus. The risk of malformation is greatest when the foetus is exposed between two and eight weeks after conception. If the drugs are administered at or near term, they may cause foetal dependence and eventual withdrawal symptoms. The issue of use of benzodiazepines in pregnancy has been discussed in much detail by Iqbal et al.\textsuperscript{114} and here we would discuss only the salient issues.

Diazepam: Although occasional reports have associated the therapeutic use of diazepam with congenital malformation, the bulk of the evidence indicates that the use of diazepam during gestation has no adverse effects on the child’s development.\textsuperscript{114}

Clonazepam: Clonazepam use during pregnancy has been associated with congenital heart disease, ventral septal defect, hip dislocation, uteropelvic junction obstruction, bilateral inguinal hernia, undescended testicle, paralytic ileus of the small bowel, cyanosis, lethargy, hypotonia and apnoea.\textsuperscript{114} But in most cases clonazepam was used along with other antiepileptics like phenytoin and barbiturates. In a large study of 10,698 infants with congenital anomalies, maternal use of clonazepam during pregnancy was not significantly represented.\textsuperscript{115} Use of clonazepam during lactation leads to apnoea, cyanosis, hypotonia, and excessive periodic breathing and central nervous system depression.

Lorazepam: Exposure to lorazepam has been linked to anal atresia and neonatal withdrawal symptoms, such as low Apgar scores, depressed respiration, hypothermia, poor suckling and jaundice. The neonatal withdrawal symptoms can be severe because of shorter half life. So, whenever possible lorazepam should be avoided during pregnancy.\textsuperscript{114}

Alprazolam: Use of alprazolam in pregnancy does not increase the risk of major malformations. It has been linked with malformations like cleft lip, inguinal hernia, hypospadias, cryptorchidism, tracheoesophageal fistula, patent ductus arteriosus, microcephaly, strabismus, congenital hip dislocation, fused lacrimal duct, Down’s syndrome, cat’s eye with Pierre Robin syndrome, pyloric stenosis, umbilical hernia, ankle inversion, lipomeningocele, neonatal withdrawal syndrome. Whenever possible, its use should be avoided in first trimester.\textsuperscript{114}

Management of psychotic disorders during pregnancy

The process of counselling a pregnant and psychiatrically symptomatic woman regarding the use of medication during pregnancy is complex and delicate. Concerns regarding potential for foetal complications as well as for the women’s decompensations must be addressed. Maternal self-esteem may be closely linked to the sense of not causing harm to the foetus, and the patient’s fears of adverse foetal outcomes that could be attributed to her decision to accept pharmacologic treatment may interfere with the desire to take care of herself. Clinicians and patients must make collaborative decisions, weighing the risks of foetal exposure to medication against the risks of untreated psychiatric disorder. Use of medications during pregnancy should vary as a function of severity of illness. If the decision to treat with medications is made, an attempt should be made to use the lowest effective dose for the shortest period of time, to minimize foetal drug exposure. However, it is to be remembered that pregnant patients may require higher doses of medications during pregnancy, compared to pregravid doses, in order to adequately treat symptoms. This difference in dose is secondary to altered pharmacokinetics and metabolism of drugs during pregnancy. While focusing on psychotropic medications, clinicians should not ignore other risk factors for poor perinatal outcome, such as obesity, smoking, and the use of alcohol or other substances of abuse. Healthy behaviour, including adherence to a prenatal vitamin regimen and a schedule of prenatal care visits and maintenance of a healthy diet must be supported (Table II).

Schizophrenia & psychosis: Acute psychosis in pregnancy is a medical and obstetrical emergency, as
it may prevent women from obtaining proper prenatal care. Disorganization or denial may lead to impulsive and other dangerous behaviours that place mother and foetus at risk. New onset psychosis calls for a differential diagnostic evaluation comparable to that performed with nongravid patients.

If a woman has no prior history of psychosis and develops mild psychotic symptoms during pregnancy, antipsychotics should be used as needed and histories of chronic psychosis — best maintained with antipsychotics before and during pregnancy.

**Bipolar disorder**

*Mild to moderate bipolar disorder:* (i) Pradual taper and discontinuation of mood stabilizer before pregnancy (or at positive documentation of pregnancy) and (ii) maintain drug-free in first trimester if possible; maintain low threshold for re-introduction of mood stabilizer

*Severe bipolar disorder:* Consider continuation of mood stabilizer in the first trimester and throughout pregnancy

**Depression**

(i) Mild depressive symptoms - non pharmacological strategies to be used and (ii) severe depression, including diminished oral intake, suicidality and presence of psychotic symptoms - pharmacological intervention is warranted in pregnant women with severe depression.

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**Table II. Treatment options for various psychiatric disorders**

| General principles | (i) Plan pregnancy; (ii) consider the pregnancy as “high risk pregnancy”; (iii) use the lowest effective dose for the shortest period of time necessary; (iv) while focusing on psychotropic medications, clinicians should not ignore other risk factors for poor perinatal outcome, such as obesity, smoking, and the use of alcohol or other substances of abuse and (v) healthy behaviour, including adherence to a prenatal vitamin regimen and to a schedule of prenatal care visits and maintenance of a healthy diet must be supported |
| Schizophrenia | (i) Patients who have prior history of psychosis and develop mild psychotic symptoms during pregnancy - antipsychotics should be used as needed and (ii) histories of chronic psychosis – best maintained with antipsychotics before and during pregnancy |
| Bipolar disorder | Mild to moderate bipolar disorder: (i) Pradual taper and discontinuation of mood stabilizer before pregnancy (or at positive documentation of pregnancy) and (ii) maintain drug-free in first trimester if possible; maintain low threshold for re-introduction of mood stabilizer |
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**Table II:** Treatment options for various psychiatric disorders

**General principles**

1. Plan pregnancy;
2. Consider the pregnancy as “high risk pregnancy”;
3. Use the lowest effective dose for the shortest period of time necessary;
4. While focusing on psychotropic medications, clinicians should not ignore other risk factors for poor perinatal outcome, such as obesity, smoking, and the use of alcohol or other substances of abuse and
5. Healthy behaviour, including adherence to a prenatal vitamin regimen and to a schedule of prenatal care visits and maintenance of a healthy diet must be supported.

**Schizophrenia**

1. Patients who have prior history of psychosis and develop mild psychotic symptoms during pregnancy - antipsychotics should be used as needed and

**Bipolar disorder**

*Mild to moderate bipolar disorder:* (i) Pradual taper and discontinuation of mood stabilizer before pregnancy (or at positive documentation of pregnancy) and (ii) maintain drug-free in first trimester if possible; maintain low threshold for re-introduction of mood stabilizer

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**Depression**

1. Mild depressive symptoms - non pharmacological strategies to be used and
2. Severe depression, including diminished oral intake, suicidality and presence of psychotic symptoms - pharmacological intervention is warranted in pregnant women with severe depression.

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**Bipolar disorders:** Managing the illness of pregnant women with bipolar disorders is very challenging. All decisions regarding the continuation or initiation of treatment during pregnancy must take into account:

1. The highly variable but often poorly quantified risks of foetal exposure to drugs
2. The substantial risks to the patient, foetus, and family from untreated illness in the mother; and
3. High risk of relapse associated with discontinuation of maintenance treatment, particularly if it is abrupt. Each of these risks should be discussed openly with the patient and her spouse.

Important factors to consider in the prepregnancy treatment planning phase for women with bipolar disorder are the illness history and the acceptability and estimated safety of specific clinical interventions, which may be pharmacologic or non pharmacologic. Specific considerations include the frequency and severity of previous episodes, past and current levels of functioning or impairment, past and recent duration of clinical stability with and without medication, the nature of prodromal symptoms that have been characteristic of impending relapse, and average...
time to recovery following re-introduction of treatment. In the assessment process, it is useful to assess previous medication trials, responses rate, adverse effects, and effect of discontinuation of treatment. While focusing on psychotropic medications, clinicians should not ignore other risk factors for poor perinatal outcome.

In the past, abrupt discontinuation of lithium or other ongoing psychotropic treatments was a common practice, to avoid liability associated with foetal exposure to potential teratogens. However, a more appropriate approach is to consider risks more broadly, including the high risks of recurrence that can follow discontinuation of lithium or other mood stabilizers. For women with bipolar disorder who have a history of multiple and frequent recurrences of mania or bipolar depression, several options can be considered. Some patients may choose to discontinue a mood stabilizer prior to conception. An alternative strategy is to continue treatment until pregnancy is verified, and then gradually taper off the mood stabilizer. Since uteroplacental circulation is not established until approximately 2 wk post-conception and the early risk of foetal exposure is minimal. The advantages of this strategy are that it minimizes foetal exposure to drugs and extends the protective treatment up to the time of conception, which may be particularly prudent for older patients, who may require more time to conceive. However, this strategy may lead to relatively abrupt treatment discontinuation, thereby placing the patient at increased risk for relapse. For women who tolerate discontinuation of maintenance treatment, the decision when to restart the treatment depends on the clinician and the patient. Some patients and clinicians may prefer to wait for the initial symptoms to appear before restarting medication; others may prefer to limit risk of a major recurrence by restarting treatment after the first trimester of pregnancy. Recent data suggest that pregnant women with bipolar disorder who remain well throughout pregnancy may have a lower risk for postpartum relapse than those who become ill during pregnancy. For women with severe forms of bipolar disorder, for example, multiple severe episodes and, especially with history psychotic symptoms and suicidal attempts maintenance treatment with a mood stabilizer before and during pregnancy may be the safest option. In such situation lowest effective dose of a medication must be used, and agents with the least teratogenic potential should be selected in preference to those that pose a higher risk. In certain cases of refractory illness, one may decide to use a medication for which information regarding reproductive safety is sparse. For instance, a woman with severe bipolar disorders who has responded only to a newer anticonvulsant, or to an antipsychotic agent for which reproductive safety data are unknown, one may be forced to continue this medication during pregnancy rather than risk relapse by discontinuing or switching to another agent.

For women taking mood stabilizers during pregnancy prenatal screening with a high resolution ultrasound and foetal echocardiography is recommended at or about weeks 16 to 18 of gestation to screen for cardiac anomalies. The possibility of foetal neural tube defects should be evaluated with maternal serum alpha foetoprotein (MSAFP) and ultrasonography. In addition, 4 mg daily of folic acid is recommended before conception and in the first trimester for women receiving anticonvulsants, even though it is unknown whether supplemental folic acid can attenuate the risk of neural tube defects in the setting of anticonvulsant exposure.

Unfortunately about 50 per cent of pregnancies in women with bipolar disorders are unplanned. In many instances, recognition of pregnancy occurs during or after the peak risk period for some agents. Discontinuation of the medication at that point may place the woman’s clinical well-being at risk and confer minimal benefit. The patient’s stability, duration of pregnancy, psychotropic agent, and treatment preferences should be considered in finalizing the treatment plan. Some experts advise decreasing the dose of lithium at the onset of labour to avoid toxicity associated with the rapid reduction of vascular volume at delivery. Vigilant monitoring of symptoms and serum lithium levels are required to avoid relapse or toxicity during delivery and the immediate postpartum period. In patients on valproate, when pregnancy is recognized late, the
mood stabilizer may have to be discontinued abruptly, and the abrupt discontinuation enhances the risk for illness relapse. Adjunctive (antipsychotic) medication may be used to assist in mood stabilization while valproate is tapered, but the efficacy of this approach has not been established.

**Depressive disorders:** Discontinuation of an antidepressant prior to conception is the safest approach for women who are stable and, from the past history appear to remain well for least several months without taking the medications. Another reasonable approach is to continue antidepressants until conception is confirmed as by that time developing embryo will receive minimal medication exposure since the uteroplacental circulation does not form until 10-12 days postconception. It is important to keep in mind that short term discontinuation of an antidepressant may produce withdrawal symptoms and is associated with a 75% per cent risk of relapse during pregnancy. Each case must be evaluated on an individual basis by taking into account the number and severity of previous episodes and the time to relapse after previous attempts at medication discontinuation. For women with histories of rapid and severe relapses after medication discontinuation, antidepressants need to be maintained throughout the pregnancy. Women who are pregnant or attempting to conceive should be encouraged to initiate psychotherapy if they are not already obtaining it. Interpersonal psychotherapy has been found to be effective in pregnancy.

Management of depression during pregnancy depends on severity of the disorder. Mild depressive symptoms during pregnancy may improve with non pharmacological treatments. Pharmacological intervention is warranted in pregnant women with severe depression, including diminished oral intake, suicidality and presence of psychotic symptoms.

**Prescribing benzodiazepine in pregnancy**

As a general rule, exposure to any type of benzodiazepine during the first three months of pregnancy should be avoided. However, its use during pregnancy is not absolutely contraindicated. To avoid the potential risk of congenital defects, physicians should use the benzodiazepines that have long safety records and should prescribe a benzodiazepine as monotherapy at the lowest effective dosage for the shortest possible duration. Also, high peak concentrations of the drugs should be avoided by dividing the daily dosage into at least two doses. Finally, the best means of monitoring the safety and efficacy of therapy should be determined. For many anxiety disorders, non pharmacological treatment such as behavioural techniques, relaxation techniques, relaxation exercises, psychotherapy, and avoidance of caffeine may be effective during pregnancy and lactation, and should be attempted before pharmacologic management.

**Conclusion**

From the literature it is evident that the safety of psychotropics in pregnancy is still unresolved. The decision to prescribe psychotropics in pregnancy should be taken in the light of severity of mental disease and drugs should be prescribed only when the potential risk to the foetus from exposure to medication is outweighed by the risk of untreated maternal disorder. The choice of drug should depend on the balance between safety and efficacy profile. Whenever patient is on psychotropics, close and intensive monitoring should be done. Women with history of chronic psychosis or who develop acute psychosis during pregnancy should be treated with antipsychotic medications. Despite reports of complications in neonates exposed to antipsychotics during labour and delivery, the rationale for discontinuation of antipsychotics just prior to delivery is lacking. Among all the available antipsychotics the evidence for relative safety is highest for high potency antipsychotics.

Experts agree that acute and maintenance management of bipolar disorder requires somatic prophylaxis. Unfortunately, a number of the medications used to treat acute mania and prophylaxis of bipolar disorders are associated with structural teratogenicity. On the other hand, there is scant evidence of enduring neurobehavioral teratogenicity associated with these agents, although the data are extremely limited. Among the mood stabilizers, lithium should be considered a first-line
treatment option in pregnancy. Reproductive safety data on the newer mood-stabilizing agents remain limited, and these agents should preferably be avoided. An algorithm of treatment options should depend on the severity of illness and the individual patient’s unique treatment needs.

Management of depression during pregnancy depends on severity of the disorder. Mild depressive symptoms during pregnancy may improve with non pharmacological treatments. Women who develop mild depression during pregnancy should be encouraged to initiate psychotherapy. Pharmacological intervention should be considered in pregnant women with severe depression, including diminished oral intake, suicidality and presence of psychotic symptoms. There is data to support the use of certain antidepressants, including fluoxetine and the tricyclic antidepressants. Data on the other SSRI antidepressants is gradually accumulating and is encouraging. If pharmacological intervention is required, among all the antidepressants SSRIs, preferably fluoxetine should be used.

There is an urgent need for more research in this area to provide information on usage of psychotropics in pregnancy. In India, there is sparse literature on this issue and there is a need for setting up a pregnancy register to generate appropriate data.

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