

TREATMENT OF SCHIZOPHRENIA IN PREGNANCY AND POSTPARTUM

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ABSTRACT

Background

The prime age of onset for schizophrenia in women is during the childbearing years from ages 25-35. 50-60% of these women will become pregnant; fifty percent of these pregnancies will be unplanned or unwanted. Discontinuation of medication will likely lead to a relapse of the illness during pregnancy or postpartum. Although research on the safety of psychotropic medication during pregnancy and breastfeeding is limited, it is still necessary to make treatment recommendations based on the accumulated information of the best available studies.

Objectives

To give an overview of what is known about the risks/benefits of antipsychotic medications during pregnancy and postpartum and make treatment recommendations for pregnant schizophrenic women.

Methods

A review was done on Pubmed, Medline and Cochrane to locate any studies or articles addressing the safety and efficacy of antipsychotic medication use in pregnancy and during breastfeeding and treatment planning for pregnant schizophrenic women.

Results

The majority of antipsychotic medications used to treat schizophrenia appear to be relatively safe for use during pregnancy and breastfeeding.

Conclusions

There appears to be greater risk for the mother and the fetus/infant in not treating schizophrenia during pregnancy and postpartum. Recommendations are made about the treatment of schizophrenic women in order to achieve the best outcome for mother and baby.

Key Words: *Schizophrenia, pregnancy, breastfeeding, antipsychotic medication*

The prime onset for schizophrenia in women is during the childbearing years from ages 25-35.¹ Fertility may be reduced in schizophrenic women, partly related to the illness itself and partly as a side effect of typical antipsychotic medications.^{2,3}

Currently, with better care and increased use of atypical (second generation) antipsychotics, 50-60% will become pregnant; fifty percent of these pregnancies will be unplanned or unwanted as

women with chronic schizophrenia may be poor at family planning and are at high risk of being sexually assaulted. These women are more likely to be unmarried and have fewer social supports. As such, they are at greater risk of being deemed incompetent to mother and having the added burden of having to give up their children. Good preventative health care of schizophrenic women with the potential to become pregnant should,

therefore, begin with attention to contraception use with the aim of avoiding unwanted pregnancies.

For those women who choose to become pregnant or wish to keep their pregnancies, care involves comprehensive intervention including personal and social supports and psychopharmacology. Assessing the effects of psychotropic drugs during pregnancy is not an easy task.⁴ Due to ethical issues, no studies of medication during pregnancy meet the gold standard of randomized, placebo-controlled, double-blind, crossover trials. Few studies control for age of the patient, previous pregnancy loss, dosages, timing of administration, multiple drug use or substance abuse. Many studies base their findings on the fact that the women were given a prescription for a medication without proving that the patient has actually taken it.

Given the limitations of the research, it is still necessary to make recommendations based on the accumulated information of the best available studies on the safety of antipsychotic medication during pregnancy or breastfeeding. In evaluating any negative effects of taking medication during pregnancy concerns include: whether there is an increased risk of miscarriage; the risks of major malformations in the baby; any problems during labour; difficulties for the neonate; safety during breastfeeding; and the occurrence of long-term problems in the child. In determining whether a drug is teratogenic, the defect must either have a distinctive pattern (such as the limb problems that occurred with thalidomide) or occur at a rate greater than 3%, the general rate of defects found in newborns.

Any of these concerns must be weighed against the risks of stopping medication during pregnancy. Discontinuation of medication, will likely lead to illness relapse. Reviews of relevant studies⁵⁻⁸ have concluded that, over follow-up periods of up to 2 years, relapse of illness in those patients who have withdrawn from antipsychotics occurs in around 50%, while for people who have continued on medication it is about 15%. In other words, for those patients stopping antipsychotic medication the risk of relapse is 2–3 times greater than it would have been if they had stayed on it, and the risk of relapse is greater with abrupt

discontinuation compared with a gradual withdrawal.

Schizophrenia has been associated with multiple obstetrical complications including low APGAR scores, prematurity, low birth weights, small for gestational age babies, stillbirth and death.^{2,9} It is unclear whether these outcomes are due to the illness itself or problems that might occur during the pregnancy. Women with schizophrenia may fail to attend prenatal appointments, eat poorly, smoke more and abuse alcohol or illegal drugs. Therefore, discontinuing medication in pregnant schizophrenic women increases the risk to the fetus and the mother.

ANTIPSYCHOTICS

Typical Teratogenesis

Although a meta-analysis by Altshuler et al¹⁰ found a rate of congenital malformations of 2-2.4% infants exposed to typical antipsychotics, there was no specific pattern of abnormality and the rates detected were below the normal 3% rate in the general population. Einarson¹¹ and Einarson & Boskovic¹² summarized the findings of multiple studies and found no increase in teratogenesis in women taking piperidyl phenothiazines (thioridazine), piperazines (fluphenazine, perphenazine), phenothiazines (chlorpromazine, promethazine), piperazine phenothiazines (trifluoperazine), butyrophenones (haloperidol), thioxanthenes (flupenthixol), dibenzoxazepines or diphenylbutylpiperidines.

Labour and Delivery

It is difficult to differentiate between the effects of the medications versus the effects of the illness itself. Diav-Citrin et al¹³ found an increased risk of prematurity and low birth weight in infants exposed to haloperidol or penfluridol during pregnancy. Newham et al¹⁴ found that those exposed to typical antipsychotics during pregnancy had a significantly lower mean birth weight and a higher incidence of small for gestational age infants than the reference group. However, Lin et al¹⁵ concluded that the risks for low birth weight and small for gestational age babies among women with schizophrenia did not differ regardless of exposure to antipsychotics

although there was an increased risk of preterm birth (OR=2.46), after adjusting for potential confounders.

Effects on the Neonate

Some typical antipsychotics such as chlorpromazine, flupenthixol and fluphenazine have been associated with a risk of neonatal withdrawal and extrapyramidal signs that may last for weeks to months.¹⁶ The use of promethazine in late pregnancy could induce respiratory distress in the newborn and impaired platelet aggregation in the mother and the newborn.¹¹ Kohen et al¹⁷ has described a rare syndrome in the neonate consisting of respiratory distress, difficulty feeding, floppy infant syndrome, hypertonicity, sluggish primitive reflexes, extrapyramidal symptoms, tremor, abnormal movements, irritability and agitation which generally resolve within days.

Johnson et al¹⁸ reported that infants exposed to antipsychotic drugs during pregnancy demonstrated 10% poorer motor skills at 6 months. Their findings were limited to 22 cases of which 20 were also taking antidepressants, anxiolytics and/or hypnotics. The motor skills scores were significantly associated with the maternal psychiatric history. It was also not clear whether or not these effects were transient.

Long-Term Effects

Intelligence quotients at age four were not found to be different in children exposed to antipsychotics during the first four months of pregnancy as compared to children of controls.¹⁹ No differences have been found in behavior, socialization or cognition in nine and ten year olds who were exposed to chlorpromazine in utero.^{20,21}

ATYPICAL

Miscarriage

There are two case reports of pregnancy loss due to high neural tube defects in women taking aripiprazole.²² In 23 cases of women taking olanzapine, Goldstein et al²³, found rates of miscarriage (13%) to be in the normal range. Einarson et al¹² reported an 8.8% risk of miscarriage in 57 reported cases of women taking ziprasidone.

Teratogenesis

Although limited information is available on clozapine, olanzapine, quetiapine and risperidone, there is no conclusive evidence of an increased risk of teratogenesis.^{24,25} In a prospective comparative study of 110 pregnant women on atypical antipsychotics no increased risk or specific patterns of major congenital malformations were detected.²⁶ Aripiprazole, ziprasidone and paliperidone (a metabolite of risperidone) are the newest atypical antipsychotics. Only a few case reports have been published but none of these have shown any excess in specific malformations.

There may, however, be an indirect risk; the use of atypicals during pregnancy may lead to weight gain that, in turn, can increase the risk for neural tube defects, hypertension, pre-eclampsia and gestational diabetes.^{27,28} Pregnancy can impair glucose tolerance from the second trimester onwards, and several cases of gestational diabetes associated with the use of clozapine, olanzapine and other atypical antipsychotics during that time have been reported.^{29,30}

Labour and Delivery

A prospective study by McKenna et al²⁶ concluded that exposure to atypical antipsychotics during pregnancy did not cause an increased risk for adverse pregnancy outcomes. Schizophrenia itself has been associated with an increased risk of placental abruption, preterm delivery, low birth weight, stillbirth and neonatal death.

Effects on the Neonate

Newham et al¹⁴ found that infants exposed to atypical antipsychotics had a significantly higher incidence of large for gestational age (LGA) babies than both comparison groups and a mean birth weight significantly heavier than those exposed to typical antipsychotics. Newham et al¹⁴ found that infants exposed to atypicals had a significantly higher risk of being large for gestational age than either controls or infants whose mothers had taken typical antipsychotics. Yaeger et al²⁵ have also described an increased risk of hypoglycaemia and macrosomia resulting in shoulder dystocia and associated birth injuries such as fractures and nerve palsies. The weight gain and possible gestational diabetes induced by

atypicals increase the risk of macrosomia, hypoglycemia, shoulder dystocia and associated birth injuries.²⁴

In contrast, McKenna et al²⁶ found a 10% risk of low birthweight babies in those exposed to second generation antipsychotics as opposed to 2% in unexposed women. Newport et al³¹ found tendencies toward higher rates of low birth weight and neonatal intensive care admissions in infants exposed to olanzapine.

Long-Term Effects

Normal development has been reported in the offspring of women taking atypical antipsychotics in pregnancy who have been followed for lengths of time ranging from six months to five years.²⁴

OTHER MEDICATIONS

There are a variety of other medications that may be used in the treatment of schizophrenics. Anticholinergics have been little researched but may be teratogenic and are best avoided in pregnancy.¹⁷ Antidepressants may cause a small increase in miscarriage risk but do not appear to cause an increase in major malformations. There is some risk of the infant experiencing a neonatal syndrome that tends to be short-lived with no permanent negative consequences.⁴

Information on the effects of minor tranquilizers ranges from some case reports to a few prospective studies. No increases in malformations have been reported with lorazepam, clonazepam, alprazolam, triazolam or flurazepam.⁴ Withdrawal syndromes may be seen after use of clonazepam, alprazolam, and lorazepam. Lorazepam used in late pregnancy may lead to respiratory distress, decreased APGARS, problems with temperature regulation and poor feeding.³² No malformations or delivery problems have been reported with zopiclone use but low birth weight, preterm deliveries and small for gestational age babies have been found after the use of zopidem.³³

POSTPARTUM

The risk for relapse in women with schizophrenia during the first three months postpartum is approximately 24%.³⁴ Women who become

psychotic during this time present a possible danger to themselves or their infants due to delusional ideation, disorganization or lack of responsiveness to the infant. This may interfere with bonding or present a risk to the infant either due to direct physical harm or neglect.

The main concern about taking medication in the postpartum is the possible effect on the breastfeeding infant. Typical antipsychotics are excreted in breast milk at the rate of less than 3% of maternal levels.³⁵ Although there have been some reports of drowsiness and lethargy, the majority of the reports have not found any adverse events.¹¹ Less than 5% of atypical antipsychotics are found in breast milk³⁵ and no negative effects on the infants have been reported for the majority of the atypicals. Clozapine has been associated with sedation, decreased sucking reflex, restlessness and irritability, seizures and cardiac instability in the breastfed infant.³⁶

PRINCIPLES OF TREATMENT

Prior to Pregnancy

If a woman with schizophrenia is planning a pregnancy her psychiatric history and response to treatment should be carefully reviewed in order to evaluate the risk of discontinuing medication. If the woman has been stable for many years on very small doses of an antipsychotic medication it might be possible to discontinue it however, generally, it may be more risky to discontinue than to continue medications. A discussion should be held with her (ideally with her partner) about her personal risk if the medication is discontinued, the limitations of the research and the current evidence concerning the safety of antipsychotics in pregnancy. This discussion should be documented in the chart.

If the woman decides to stop her medication, a schedule for gradual discontinuation should be drawn up and she should be followed very closely during the pregnancy. Supporting persons should be enlisted to watch for any early signs of decompensation.

If the woman who agrees to continue medication is taking an antipsychotic with a propensity to increase prolactin secretion, the plasma prolactin level should be measured. If significantly increased, this may interfere with

fertility and changing medication should be considered.

Less is known about the safety of atypical versus typical antipsychotics. As well, if the woman has elevated risk factors for type 2 diabetes mellitus, atypical antipsychotics are best avoided. However, if the atypical antipsychotic being used is the only medication that stabilizes the patient, it is safer to maintain this medication and watch for possible side effects during pregnancy. In the case of clozapine, concerns about the potential for relapse usually outweigh any concerns about its dysglycaemic effect.⁹ Similarly, if a woman has been taking depot antipsychotic medication it should be continued if the risk of recurrence is high.

During Pregnancy

The therapist should first consider whether psychological interventions such as some type of psychotherapy would be effective. There is, unfortunately a dearth of good studies to document the effectiveness of psychotherapy to treat psychiatric illness during pregnancy.³⁷ As with any pregnancy, women with schizophrenia should take prenatal vitamins plus a daily supplement of 5mg folate to decrease the risk of neural tube defects.

If the patient continues to take antipsychotic medication, prescribe it in the lowest effective dose and give in divided doses. Dosages often need to be increased later in pregnancy as there are further changes in weight, metabolism, excretion and lean/fat ratios.³⁸ The patient should avoid diuretics and low-salt diets. Polypharmacy should be avoided. If the woman is taking an atypical antipsychotic, regular screening for gestational diabetes is essential and attempts should be made to avoid excessive weight gain. Depot antipsychotic medication should not be initiated in pregnancy because of the lack of flexibility in dosing.

Regular follow-up is essential, both to assess physical well-being and watch for any signs of deterioration in her mental health. Pre-natal classes are important to help prepare for childbirth. Preliminary assessment of capacity to care for a newborn should begin. Parenting classes could start for those who capacity is questionable.

Support systems for after the baby is born should be established.

The psychiatrist should work closely with the obstetrician to ensure that the patient is not advised to discontinue medication and proper monitoring is done during the pregnancy.

In late pregnancy, ultrasound monitoring of women who have been taking atypical antipsychotics can determine fetal size and determine whether vaginal delivery is advisable.

Post-Delivery

The paediatrician or neonatologist should be alerted to the fact the woman has been taking antipsychotic medication. If the mother was taking typical antipsychotics during pregnancy, the newborn should be monitored for extrapyramidal side effects for several days. The occurrence of a neonatal syndrome should be treated symptomatically. If the mother was taking clozapine, the infant's neutrophil count should be checked.

Postpartum

Schizophrenic women may need lots of support during the postpartum period. Close follow-up is required to watch for any return of psychotic symptoms or inattention to the infant which may put it at risk. As there is a high risk of decompensation and return of schizophrenic symptoms postpartum, medication should be continued or re-introduced. If the woman requires admission, ideally it should be in a mother-baby unit in which she can continue to care for her baby.

Assessment of their competency to care for the newborn should be carried out. Children's services may be required to offer support to the mother. Parenting classes may be required to help the woman be attentive to their infant's needs. Breastfeeding is possible while taking antipsychotics. Mothers may assume that, to be perfectly safe, they should avoid taking medication until they finish breastfeeding. Once again, it is important to clarify with them the possible risks of not treating a major psychiatric illness during this time. These include: poor infant care; rejection of the infant; poor parental relationships; suicide; infanticide; long term

failure to bond with the child; guilt; delayed infant development; and failure to thrive.

All the antipsychotic medications pass into breast milk but in levels much lower than in the mother. Drug excretion into the breast milk of less than 10% of the maternal dose is unlikely to lead to dose-related adverse events in the infant.³⁹ Monitor the baby for alertness. Avoid polypharmacy and use the lowest effective dose. It is best to avoid breastfeeding when taking clozapine.

SUMMARY

Although fertility used to be low for schizophrenic women, current multimodal treatment is allowing more women to become pregnant. Discontinuing medication during pregnancy can cause deterioration in the mother's mental health which can increase risks of poor prenatal care, placental abruption, preterm delivery, low birth weight, stillbirth and neonatal death. Attention to contraception can protect women against unwanted pregnancy. For those who choose to pursue a pregnancy, knowledge about the risk/benefits of medication and provision of adequate psychosocial supports both during pregnancy and postpartum can promote the best outcome for mother and child.

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