Jefferson Journal of Psychiatry

Volume 18 | Issue 1 Article 1

January 2004

Use of Clozapine in Women of Childbearing Age: A Literature Review and Recommendations

Susan Hatters Friedman, MD
University Hospitals of Cleveland

Adit Yanjee, MD
Minneapolis VA Medical Center

Recommended Citation

Hatters Friedman, MD, Susan and Yanjee, MD, Adit (2004) "Use of Clozapine in Women of Childbearing Age: A Literature Review and Recommendations," *Jefferson Journal of Psychiatry*: Vol. 18: Iss. 1, Article 1.
DOI: https://doi.org/10.29046/JJP.018.1.001
Available at: https://jdc.jefferson.edu/jeffjpsychiatry/vol18/iss1/1

Use of Clozapine in Women of Childbearing Age: A Literature Review and Recommendations

Susan Hatters Friedman, MD,[1] and Adityanjee, M.D.[2]

Abstract

Concerns about medications in women of childbearing age include impact on fertility, pregnancy, neonatal outcome, breastfeeding, and behavioral teratogenesis. The objectives were to examine possible risks of clozapine on these parameters. PsycINFO and MEDLINE searches were performed and Novartis was contacted regarding their clozapine pregnancy registry. Since prolactin levels are not elevated with clozapine as they are with typical antipsychotics, there is not interference with fertility. Adverse pregnancy outcomes included gestational diabetes, shoulder dystocia, seizure, and mild floppy infant syndrome. Higher concentrations of clozapine were present in breast milk than in maternal blood. Despite a lack of case-control prospective data, available information raises some questions regarding the safety of clozapine in pregnancy. Suggestions for treatment are made. Reproductive counseling should be given to women starting on clozapine. Individual risk-benefit assessments must be performed. In pregnant women taking clozapine, the clinician should screen for gestational diabetes and advise against breastfeeding.

Key words: fertility, pregnancy, teratogenesis, lactation, clozapine, schizophrenia, atypical antipsychotics.

INTRODUCTION

The usual age at onset, diagnosis, and initiation of treatment for schizophrenia falls within childbearing years for women. Many female patients with chronic schizophrenia have been switched to atypical antipsychotics from typical antipsychotics due to a more favorable side effect profile. Patients with new onset schizophrenia are often started on atypical antipsychotics.

Clozapine, the gold standard antipsychotic for treatment-resistant schizophrenia, has been used as an FDA-approved medication in the United States since 1990, and longer in Europe. Among the atypical antipsychotics, it has the most extensive published information. Therefore, it was decided to inquire systematically into the issues of fertility, teratogenicity, and breastfeeding with clozapine.

[1]Chief Resident in Psychiatry, University Hospitals of Cleveland.
[2]Director, Schizophrenia Program, Minneapolis VA Medical Center.
Presentation at: International Congress of Schizophrenia Research, March, 2003; Cleveland Consultation Liaison Psychiatry Society meeting, 2001.

METHODS

In order to examine risks of clozapine use in pregnancy, including anatomic teratogenicity, perinatal syndromes, and behavioral teratogenesis (such as developmental delay or neurological sequellae), PsycINFO and MEDLINE searches were conducted. Search terms included: clozapine, atypical antipsychotics, pregnancy, teratogenesis, lactation, schizophrenia, and fertility. Case reports and review articles were critically appraised. Further references were obtained from identified articles. Additionally, Novartis was contacted regarding their clozapine pregnancy registry.

RESULTS

Fertility Information

With the exception of risperidone, atypical antipsychotics do not cause significant hyperprolactinemia [1,2]. Hyperprolactinemia secondary to typical antipsychotics leads to anovulatory cycles, amenorrhea, and infertility [1]. Clozapine is without this hyperprolactinemic side effect and there is a consequent lack of interference with fertility. Two patients who became pregnant had been taking clozapine for only two months [3,4], as they had previously been on typical antipsychotics and did not use additional contraception when switched to clozapine. Women with psychotic illnesses may become inadvertently pregnant while on atypical antipsychotics. As such, exposure during the critical period of fetal organogenesis may occur before the patient is aware that she is pregnant. In addition to resumption of the menstrual cycle, improvement in negative symptoms may lead to better social functioning, and patients may have more relationships and desire to bear children [1,3,5–8].

TERATOGENESIS AND PERINATAL SYNDROMES:

A. Case Reports from Published Literature

Six pregnancies exposed to clozapine have been reported in the US literature (Table 1) [3,6–8,9]. Dosages ranged from 50–650 mg daily; most were lower than commonly used doses. Notably, four of the six were taking other prescription medications during the pregnancy, including lithium, lorazepam, haloperidol, and metformin, which may have impacted outcome. Two of the six pregnancies were complicated by gestational diabetes and shoulder dystocia [3,6]. Another pregnancy had a larger than expected weight gain [8]. Clozapine is associated with both glucose intolerance among susceptible individuals in the non-pregnant population [10], and weight gain [11], lending credence to these associations.

An infant exposed *in utero* to clozapine had a single seizure at eight days with a negative workup and no further development of seizure disorder [9]. The infant also had evidence of gastrointestinal reflux and gastroenteritis [9], and it has been speculated that clozapine decreases esophageal motility [12]. Another infant, exposed to lorazepam and clozapine, had mild floppy infant syndrome with hypotonia

TABLE 1.

Clozapine in Pregnancy: Case Reports

Author	Dx	Age	Clozapine course before pregnancy; during pregnancy	Other meds in pregnancy (trimester)	Clozapine dose	Clinical outcome
Barnas (8)	Schiz	31	5 years; attempted discontinuation with recurrence of hallucinations	None	100 mg/d, 50 mg/d (last 9 wks)	Regular U/S. 25 kg wt gain. Infant followed to 6 mos.
Waldman (6)	SCUT	30	11 years; pregnancy noted at 6 mos; No exacerbations.	None	Unreported	Gestational diabetes in 2nd trimester. Difficulty complying with dietary. Shoulder dystocia.
Stoner (9)	SCPT	30	12 months; admitted in week 23 for psychotic sx.	lithium (1), lorazepam, haloperidol, codeine, cephalexin, metronidazole.	300–350 mg/d, some noncompliance.	Seizure at 8 days. Negative workup, gastroenteritis, possible GERD. No sequellae. Followed to 2 years.
Stoner (9)	SCUT	32	35 m; increase psychosis	lithium (1)	600–625 mg/d noncompliance	Postpartum fever.
Dickson (3)	Schiz	28	2 months: discovered DM in hosp at initiation of Clozapine therapy. Intermittent hospitalizations.	metformin (1), insulin	450 mg/d in 1st, 200–250 mg/d in 2nd, 150 mg/d last 2 mos.	Diabetes with difficult compliance, shoulder dystocia. Followed to 3 yrs with intensive community support.
Di Michele (7)	Schiz	37	2 years	lorazepam 2.5 mg 3–5 ×/d	200 mg/d, increased 3× to 300 mg/d	Benign tachypnea, transient mild floppy infant syndrome, hypotonia resolved at day 5.

that spontaneously resolved at five days [7]. Infant serum concentrations of clozapine were not noted.

B. Sandoz Pharma European Pregnancy Registry

Dev and Krupp reported 102 pregnancies in patients taking clozapine based on European data from Sandoz Pharmaceuticals [11]. Of these, there were eight spontaneous abortions, 13 elective abortions, and 22 unknown outcomes. The known outcomes of these pregnancies were 59 deliveries of 61 babies, 51 of which were "born healthy," five (8%) had malformations (of unreported character), and five had unspecified "problems during the post-natal period." Some mothers were taking other drugs during pregnancy, calling into question any relationship noted. The authors suggested that there was no "deleterious effect" on either the mother or the infant from clozapine use during pregnancy [11], though this conclusion may be questioned.

C. Novartis United States Pregnancy Registry

Novartis has investigated 48 clozapine-exposed pregnancies, 40 of which had first trimester exposure, and 12 of which continued exposure to delivery. Eight patients had elective abortions, four patients had spontaneous abortions, one had a spontaneous abortion of a fetus with multiple anomalies, and six had unknown outcomes. There were 29 deliveries, with 25 healthy babies, and three (10%) with anomalies, which included: Turner's syndrome (a chromosomal anomaly), congenital blindness, and one infant (also exposed to carbamazepine) with collarbone fracture, facial deformities, and congenital hip dislocation. One infant (3%) suffered an adverse perinatal event, which was neonatal convulsion with hypocalcemia. Novartis suggested that a causal relationship was "highly unlikely." (L. Alps, Novartis Pharmaceutical Company, personal communication) Novartis reported that a relationship between exposure to clozapine and hypotonia, sedation, and extrapyramidal system disorders could be "assumed." Because of the nature of this database, it is likely that it suffers the same over-reporting of adverse events as did the lithium registry [13–17]. However, clozapine had no specific trend of anomaly in contradistinction to lithium.

BREASTFEEDING SAFETY

The Sandoz registry included four infants breastfed by mothers taking clozapine, two without adverse outcomes. One infant developed agranulocytosis that spontaneously resolved after discontinuation of breastfeeding. The other infant was "excessively sleepy." [11]

Another patient was followed through her pregnancy and delivery at various doses of clozapine. Serum concentrations in mother and infant, and breast milk concentrations of clozapine were measured (Table 2) [8]. The mother's serum

TABLE 2.

Clozapine Concentrations in Pregnancy and Lactation

Time	Clozapine dose	Maternal plasma	Fetus/ Amniotic fluid	Breast milk
Monthly during pregnancy	100 mg/d	38–55 ng/ml	NA	NA
Last 9 weeks of pregnancy	50 mg/d	15.4 ng/ml	NA	NA
Delivery	50 mg/d	14.1 ng/ml	27 ng/ml/11.6 ng/ml	NA
1 Day after delivery	50 mg/d	14.7 ng/ml	NA	63.5 ng/ml
1 Week after delivery	100 mg/d	41.4 ng/ml	NA	115.6 ng/ml

High Performance Liquid Chromatography in one patient. Adapted from Barnas et al. (8) (1994).

concentrations reported were much lower than the suggested therapeutic window for clozapine. Accumulation did occur in fetal serum. Concentrations of clozapine in breastmilk were approximately triple that of maternal blood.

There were no case reports suggesting behavioral teratogenesis, or long-term neurobehavioral sequellae.

DISCUSSION

Concerns regarding the use of medications in women of reproductive age include impact on fertility, pregnancy, neonatal outcome, breastfeeding, and behavioral teratogenesis.

Fertility Issues

Because of normal prolactin levels, patients taking clozapine have a higher risk of unplanned pregnancy than patients taking typical antipsychotics do [1]. During clinical care, reproductive plans, contraceptive method, risks, concerns, and recommendations to plan pregnancy with consultation should be made [18]. Patients need to be informed of resumption of menses and ovulation, and of re-normalized fertility when changing to atypical antipsychotics. They should also receive genetic counseling about risks of mental illness in their offspring.

Reproductive counseling should be standard when switching to clozapine therapy in women of childbearing age. Through counseling, patients who were relatively infertile on typical antipsychotics are taught that clozapine does not protect against pregnancy. Medroxyprogesterone acetate injections are a suggested long-acting contraceptive method for those patients who are not planning pregnancy, as com-

pliance is not difficult and there is no significant interaction with other medications [19].

Pregnancy

In pregnancy, risks and benefits of treatment should be balanced against the risks of mental illness. Important factors to weigh include inability to care for self or obtain proper prenatal care, danger to self or others, degree of disorganization, unresponsiveness, or impairment in reality perception [20]. Informed consent, including discussing the risks and benefits of both treatment and alternatives, is needed [18]. For patients with severe and treatment-resistant psychosis (the appropriate candidates for clozapine), recommendations have been that antipsychotics should be used throughout pregnancy [13,21,22]. Strategically, treating throughout pregnancy would yield a lower total dose, and less polypharmacy, because patients would be less likely to become severely psychotic and require stabilization with higher doses. More specifically, control of target symptoms should be the goal of psychotropic treatment in pregnancy [18], especially symptoms including command hallucinations to harm self or baby [23,24] and lack of self care [23].

Data indicates that symptoms of schizophrenia do not improve during pregnancy, and pregnant women with schizophrenia do not require smaller doses of maintenance medications [22]. Women with schizophrenia often have significant pregnancy risk factors, including smoking [25], alcohol and substance abuse [25,26], lower socio-economic status [19,25], increased victimization by violence [26], and poor prenatal care [19,26]. A meta-analysis indicated an increased risk of obstetric complications due to schizophrenia itself [27].

Clozapine may cause an increased risk of gestational diabetes mellitus (GDM) in mothers and neonatal complications such as shoulder dystocia (due to larger infant size), similar to its risk of diabetes mellitus. Further studies may illuminate the actual risks of GDM, but current prudence would dictate counseling patients about GDM. Careful, and perhaps early, screening for GDM and complications should be recommended to obstetrical colleagues, especially as women with schizophrenia may not be sufficiently organized to pursue appropriate prenatal care. Concerns have been raised about clozapine-induced fetal agranulocytosis [28], and the risk of placental hypoperfusion with clozapine-induced hypotension. Past recommendations were to avoid drugs which caused hypotension and impaired glucose tolerance, due to the physiologic changes of pregnancy (decreased blood pressure and insulin resistance) [23]. Due to recent concerns of increased risk of neural tube defects in neonates exposed to atypical antipsychotics, folate supplementation, ultrasound and maternal alpha-fetoprotein level can also be recommended [29]. A team approach, of psychiatry, obstetrics, and pediatrics, should routinely be used to care for these women [18].

No clear pattern or trend of malformation is noted with fetal clozapine exposure. Population baseline rates of major and minor congenital anomalies are quoted at 2%–10% [13,18,30]. The calculated percentages from the current clozapine

databases (8%, 10%) are based on small sample size. (The case report sample is not averaged into the databases, in order to decrease negative reporting bias.) The multiple types of anomalies (including a chromosomal malformation, which is unlikely to be due to teratogenesis) were not conclusively linked to clozapine. These percentages are comparable to the population rates. No specific trend for major anomalies emerged with clozapine, unlike the 1960s lithium data in which a trend emerged. In addition, caution must be used in interpretation as case reports can be misleading by implying causation without statistical evidence.

Delivery

Cessation of medications prior to delivery puts both the woman and baby at undue risk from postpartum psychosis [22], as a study reported 24–36% of women with schizophrenia develop postpartum psychosis [31]. However, a lower dose of clozapine has been recommended prior to delivery to decrease concentration in the newborn, and decrease risk of subsequent perinatal syndromes [8].

Neonatal Syndromes

Specific neonatal syndromes due to the use of clozapine close to the time of delivery have not been described. While the reported hypotonia is relatively nonspecific, the seizure may have been related to the concentration of clozapine. Clozapine is metabolized through the CYP1A2 enzyme, which is not well expressed until much later in the infant [32]. Underdevelopment of fetal metabolism, which leads to increased clozapine concentrations, could lead to increased risk of seizures, which are dose-dependent adverse events [9]. Alternatively, the seizure may have been due to withdrawal, or may have been incidental. Due to the risk of agranulocytosis, neonates' white blood count should be monitored [33]. Though there is a lack of case-control prospective data, available information is guardedly encouraging, as clozapine has been used for many years and there is an absence of data indicating any teratogenic pattern or significantly higher proportion of fetal adverse outcome.

Lactation and Postpartum

Clozapine's case report showing an increased concentration in breast milk is consistent with the drug's lipophilic properties [8]. Increased levels could lead to infant complications such as agranulocytosis or neonatal seizures. As formula feeding is a safe option, breastfeeding should be advised against in patients using clozapine. American Academy of Pediatrics recommendations report that the risk of using clozapine during breastfeeding is "unknown, may be of concern." [34] The mother should be questioned about excess sedation from clozapine because it may prevent her from hearing the infant cry [24]. In addition, parenting skills may be taught to mothers with schizophrenia [35], which may improve outcome. Behavioral

teratogenesis in the child is unknown based on lack of current information, but is the most difficult aspect of teratogenesis to demonstrate.

SUMMARY

The use of clozapine in women of childbearing age requires thoughtful counseling regarding birth control and expectant management of any pregnancies exposed to the drug. There remains a limited but expanding database of pregnancies exposed to clozapine. Potential areas for concern include risks of gestational diabetes with shoulder dystocia, neonatal seizure, neonatal agranulocytosis, and sedation. Further pharmaco-epidemiologic controlled studies, such as a case-control methodology including women on typical and atypical antipsychotics, as well as a larger prospective pregnancy registry are needed, because many women of childbearing age with schizophrenia and mood disorders are now prescribed atypical antipsychotic agents.

REFERENCES

1. Dickson RA, Seeman MV, Corenblum B: Hormonal side effects in women: typical versus atypical antipsychotic treatment. J Clin Psychiatry 2000; 61: 10–15.
2. Perry RG: Prolactin and antipsychotic medications: mechanism of action. Schizophr Res 1999; 35 Suppl: S67–73.
3. Dickson RA, Hogg L: Pregnancy of a patient treated with clozapine. Psychiatr Serv 1998; 49: 1081–1083.
4. Kaplan B, Modai I, Stoler M, *et al.*: Clozapine treatment and risk of unplanned pregnancy. J Am Board of Fam Pract 1995; 8: 239–241.
5. Dickson RA, Edwards A: Clozapine and fertility. Am J Psychiatry 1997; 154: 582–583.
6. Waldman MC, Safferman AZ: Pregnancy and clozapine. Am J Psychiatry 1993; 150: 168–169.
7. Di Michele V, Ramenghi LA, Sabatino G: Clozapine and lorazepam administration in pregnancy. European Psychiatry 1996; 11: 214.
8. Barnas C, Bergant A, Hummer M, *et al.*: Clozapine concentrations in maternal and fetal plasma, amniotic fluid, and breast milk. Am J Psychiatry 1994; 151: 945.
9. Stoner SC, Sommi RW, Marken PA, *et al.*: Clozapine use in two full-term pregnancies. J Clin Psychiatry 1997; 58: 364–365.
10. Popli AA, Konicki PE, Jurjus GJ, *et al.*: Clozapine and associated diabetes mellitus. J Clin Psychiatry 1997; 58: 108–111.
11. Dev VJ, Krupp P: Adverse event profile and safety of clozapine. Reviews in Contemporary Pharmacotherapy 1995; 6: 197–208.
12. Baker RW, Chengappa KNR: Gastroesophageal reflux as a possible result of clozapine treatment. J Clin Psychiatry 1998; 59: 257.
13. Altschuler LL, Cohen L, Szuba MP, *et al.*: Pharmacologic management of psychiatric illness during pregnancy: dilemmas and guidelines. Am J Psychiatry 1996; 153: 592–596.
14. Zalzstein E, Koren G, Einarson T, *et al.*: A case-control study on the association between first trimester exposure to lithium and Ebstein's anomaly. Am J Cardiol 1990; 65: 817–818.

15. Jacobson SJ, Jones K, Johnson K, *et al.:* Prospective multicentre study of pregnancy outcome after lithium exposure during first trimester. Lancet 1992; 339: 530–533.
16. Cohen LS, Friedman JM, Jefferson JW, *et al.:* A reevaluation of risk of in utero exposure to lithium. Journal of the American Medical Association 1994; 271(2): 146–150.
17. Llewellyn A, Stowe ZN, Strader 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.
18. Gold LH: Use of psychotropic medications during pregnancy: risk management guidelines. Psychiatric Annals 2000; 30: 421–432.
19. Miller LJ: Sexuality, reproduction, and family planning in women with schizophrenia. Schizophr Bull 1997; 23: 623–635.
20. Nurnberg HG, Prudic J: Guidelines for treatment of psychosis during pregnancy. Hospital and Community Psychiatry 1984; 35: 67–71.
21. Cohen LS, Rosenbaum JF: Psychotropic drug use during pregnancy: weighing the risks. J Clin Psychiatry 1998; 59(Suppl 2): 18–28.
22. Trixler M, Tenyi T: Antipsychotic use in pregnancy. Drug Saf 1997; 16: 403–410.
23. Altschuler LL, Szuba MP: Course of psychiatric disorders in pregnancy: dilemmas in pharmacologic management. Neurol Clin 1994; 12: 613–635.
24. Miller LJ: Clinical strategies for the use of psychotropic drugs during pregnancy. Psychiatric Medicine 1991; 9: 275–298.
25. Bennedsen BE: Adverse outcome in schizophrenic women: occurrence and risk factors. Schizophr Res 1998; 33: 1–26.
26. Miller LJ, Finnerty M: Sexuality, pregnancy, and childrearing among women with schizophrenia-spectrum disorders. Psychiatr Serv 1996; 47: 502–506.
27. Sacker A, Done DJ, Crow TJ. Obstetric complications in children born to parents with schizophrenia: a meta-analysis of case-control studies. Psychol Med 1996; 26: 279–287.
28. Pinkofsky HB, Fitz-Gerald MJ, Reeves RR: Psychotropic treatment during pregnancy. Am J Psychiatry 1997; 154: 718–719.
29. 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: 136–137.
30. Rimoinn D, Connor JM, Pyeritz RE (eds): in Emery and Rimoin's Principles and Practice of Medical Genetics. New York, Churchill Livingston, 1997, p 31.
31. McNeil TF. A prospective study of postpartum psychoses in a high-risk group. 1. Clinical characteristics of the current postpartum episodes. Acta Psychiatr Scand 1986; 74: 205–216.
32. Sonnier M, Cresteil T: Delayed ontogenesis of CYP1A2 in the human liver. Eur J Biochem 1998; 251: 893–898.
33. 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.
34. American Academy of Pediatrics Committee on Drugs. Transfer of drugs and other chemicals into human milk. Pediatrics 2001; 108: 776–789.
35. Empfield MD. Pregnancy and schizophrenia. Psychiatric Annals 2000; 30: 61–66.