Atualização

Mood disturbance and pregnancy: pros and cons of pharmacologic treatment

Transtornos do humor e gravidez: prós e contras do tratamento farmacológico

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Abstract The management of psychiatric disturbances during pregnancy, particularly depression and bipolar disorders, is complex. This article reviews the existing data regarding the impact of an untreated psychiatric illness on the infant's development. In addition, the potential risks to the fetus due to prenatal exposure to different psychotropic agents, including antidepressants, mood stabilizers, antipsychotics, and benzodiazepines, are summarized. Moreover, this article emphasizes that no decision is risk-free, and the ultimate goal is to reduce the exposure to both the illness and the potential teratogenic effects of the treatment. Therefore, clinicians should seek a treatment strategy, which poses the least risk for both mother and infant.

Keywords Depression. Bipolar disorder. Pregnancy. Therapeutics. Psychotropic drugs.

Resumo O manejo de distúrbios psiquiátricos durante a gestação, particularmente de quadros depressivos e de transtornos bipolares, é uma tarefa complexa. Este artigo revisa o conhecimento atual sobre o possível impacto dos transtornos de humor não-tratados sobre o desenvolvimento fetal. Também são reexaminados os possíveis riscos de teratogenicidade associados ao uso dos diversos antidepressivos, estabilizadores de humor, antipsicóticos e benzodiazepínicos durante a gestação. Dá-se ênfase ao fato de que nenhuma decisão clínica é isenta de risco. Desse modo, psiquiatras e demais profissionais atuantes na área de saúde mental devem buscar uma estratégia terapêutica que reduza ao máximo o risco de exposição da/do mãe/feto ao transtorno psíquico, bem como aos possíveis efeitos teratogênicos dos psicofármacos utilizados.

Descritores Depressão. Transtorno bipolar. Gestação. Terapêutica. Psicofármacos.

Introduction

Some limited data have encouraged most women and health professionals to consider pregnancy protective against the onset or recurrence of psychiatric disturbances.[1] On the other hand, there is evidence of a higher risk for mood disorders in women during childbearing years,[2] with peak prevalence occurring between ages 25 and 44 years.[3] This fact may suggest a substantial number of new-onsets or recurrences of psychiatric disturbances during pregnancy. In addition, some studies and case reports have already shown a significant prevalence of psychiatric disorders during pregnancy,[4,5] particularly an increased risk for relapse in psychiatric patients who discontinue medication.[6,7]

Although many physicians prescribe psychotropic drugs to women during pregnancy, the Food and Drug Administration (FDA) has not specifically tested or approved any of these drugs for that purpose.[8-10] Therefore, the real challenge for psychiatrists is to balance the risk of exposure to the potential teratogenic effects of psychotropic drugs versus the impact that an untreated illness may cause on the obstetric outcome and infant development.[11-12]

Use of psychotropic drug during pregnancy: weighing the risks

Some women who are currently taking psychiatric medication may ask about the risks and benefits of maintaining the medication versus discontinuing the treatment. The putative

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impact of an untreated psychiatric disturbance has also been raised as an important issue in several studies and during reproductive psychiatry consultations.[9,13] Clinicians and patients must know that no decision is risk-free, and the ultimate goal is to limit the exposure to either the illness or treatment, and help the patients to decide which path of exposure poses the least risk.[9,12]

Risks of exposure to illness

The impact of a mood disorder (new onset or recurrence) during pregnancy has been systematically assessed. Factors that may produce an increased risk for depression duringpregnancyinclude: (1) priorhistoryof depression;14 (2) younger age;[15] (3) lack of social support;[16] and (4) the presence of marital conflicts and ambivalence about the pregnancy.[17] In addition, prospective data and review studies[18,19] regarding the outcome of untreated depression during pregnancy have suggested a significant increase in the risk for having low birth weight, preterm delivery and small-for-gestational-age infants.

Other adverse conditions that are more likely to occur include: (1) poor maternal self-care and nutrition; (2) higher exposure to alcohol, tobacco, and street drugs; and (3) suicidal behavior. Therefore, prenatal exposure to an untreated maternal mental illness may constitute the first adverse life event for a child.[12]

Unplanned pregnancy is not unusual among women with diagnosis of bipolar disorder,[11] and the common tendency to discontinue treatment abruptly in this situation may be deleterious. Recently Viguera et al[7] assessed 101 women with diagnosis of bipolar disorder (DSM-IV), and compared the outcome of lithium discontinuation during pregnancy and postpartum (n=42) with the outcome of nonpregnant bipolar subjects (n=59) who discontinued medication. The similar recurrence risks (52% and 58%, respectively) observed within 40 weeks after stopping lithium suggest that pregnancy is unlikely to exert a significant protective or risk-enhancing effect. In addition, the recurrence rates were much higher postpartum as opposed to the equivalent period for nonpregnant women (weeks 41–64). Thus, the use of lithium prophylaxis in late pregnancy or immediately after delivery has been encouraged and deserves further investigation.[20-21] Viguera et al also suggested that the risk for postpartum recurrence of bipolar illness is greater after rapid (less than 2 weeks) discontinuation of lithium therapy during pregnancy.[22]

Risks of exposure to psychotropic drugs

The risk for using psychiatric medication during pregnancy include: (1) morphologic teratogenicity (the increased risk for congenital malformations); (2) neonatal toxicity (due to direct contact to the fetus via circulatory, respiratory, or gastrointestinal routes); and (3) behavioral teratogenicity (defined as the potential for longer term neurobehavioral sequelae).[9,12]

All psychotropic medications studied may cross the placenta barrier with different patterns of passage.[23] Overall, the outcome of fetal exposure to the majority of psychotropic drugs demonstrates that most of these agents exhibit a low risk for morphologic teratogenicity.[24-27] Most data, however, are still insufficient, and can scarcely exclude the risk for major malformations, while the risk for minor malformations and neurobehavioral sequelae is even less defined.

Antidepressants

Both prospective and retrospective studies have examined the risk for malformations after first trimester exposure to tricyclic antidepressants (TCAs).[28-30] More than 400 cases of first trimester exposure to TCAs were pooled and examined, and this analysis showed no association with morphologic teratogenicity.[31] Although TCAs were examined as a drug class (versus a more individualized analysis), neither single study nor a series of studies supports an increased risk for congenital malformations after early exposure to these drugs.[9] Nevertheless, several case reports have suggested that the use of TCAs may cause certain perinatal symptoms, including jitteriness, irritability, functional bowel obstruction, and urinary retention.[32]

Existing information regarding the exposure to other antidepressants during pregnancy is based mostly on fluoxetine data, including postmarketing surveillance register (Eli Lilly and Co. 1996),[9] and some prospective data.[33] Data from approximately 1,100 fluoxetine exposed children showed no increased risk for congenital malformation compared to the general population. Chambers et al[34] studied 228 women exposed to fluoxetine and a control group (n=254) exposed to nonteratogenic agents. Although no higher rates of major malformations were noted among children exposed to fluoxetine, the study described a greater occurrence of minor abnormalities, along with a greater frequency of admissions to special care nurseries. Methodological difficulties, however, restrict the interpretation of these findings. For example, the study design did not distinguish the effects of exposure to depression from drug exposure. In addition, some raters were not blind to maternal treatment status.

Cohen et al recently reviewed some obstetrical and neonatal records of 64 newborns with histories of early and late fluoxetine exposure during pregnancy.[24] This study was not designed as a controlled study of the incidence of congenital malformations associated with exposure to fluoxetine, but to examine the relative impact of fluoxetine exposure during pregnancy as a function of exposure timing (i.e. early versus late). Several characteristics were investigated such as dose and duration of fluoxetine exposure, exposure timing — early versus late —, the use of other psychotropic drugs during pregnancy, and delivery at tertiary versus community hospitals. Outcome variables included 5-minute APGAR scores, admission to Special Care Nursery (SCN) for any length of time, and timing of discharge from the hospital (with or without the mother). The results have demonstrated no differences between the early and late exposed infants with respect to gestational age at delivery, birth weight, APGAR

scores or timing of maternal-infant discharge. Later trimester exposure to fluoxetine was associated with a greater frequency of admission of infants to SCN (18.9% versus 9.1%) and newborn complications (e.g. transient tachycardia and/or tachypnea, agitation, infant jittery) — 30.2% versus 9.1% —, compared to those with early trimester exposure to the medication. It is important to note that the study was retrospective in nature with a relatively small number of cases. In addition, the authors were unable to control relevant factors including the severity and duration of depression during pregnancy, prenatal exposure to psychotropic and nonpsychotropic drugs, and the potential biases of clinicians and institutions with which mothers-newborns were affiliated. As a result of the latter, different rates of SCN admissions under the same neonatal circumstances may have occurred.

Nulman et al[35] noted no differences in global IQ, language development, or behavioral development in children (up to 4 years of age) prenatally exposed to TCAs (n=80) and fluoxetine (n=55) compared with a nonexposed control group (n=54).

To date, few data exist regarding safety of using other selective serotonin reuptake inhibitors (SRRIs) during pregnancy, such as paroxetine, fluvoxamine, or sertraline hydrochloride. Kulin et al[36] have examined the occurrence of major malformations in 267 children prenatally exposed to different SSRIs (fluvoxamine, paroxetine, and sertraline) compared with 267 controls. There were no differences between the groups regarding the occurrence of major malformations, miscarriages, stillbirths or prematurity. Birth weights of exposed children and controls were similar when they were compared. Kent & Laidlaw[37] studied the occurrence of transient neonatal difficulties after prenatal exposure to sertraline, and reported no clinically significant abnormalities. Ericson et al[38] investigated delivery outcome in 375 women after the use of citalopram during pregnancy, and reported no increase in congenital abnormalities.

Overall, there is no evidence that the exposure to TCAs or SSRIs (as a class) increases the risk of major physical malformations, significant neonatal complications, or long-term impairments in neurobehavioral development.

Mood stabilizers

Lithium

The first reports from the International Register of Lithium Babies described significant rates of cardiovascular malformations in infants prenatally exposed to lithium, particularly Ebstein's anomaly.[39] This malformation is characterized by right ventricular hypoplasia and congenital downward displacement of the tricuspid valve into the right ventricle. The Register had methodological limitations with an inherent bias toward overreporting of adverse outcome. Thus, a 10-to-20-fold increase in risk for Ebstein's anomaly was described, compared to the estimated risk for the general population (1/20,000). However, a more recent review showed a smaller relative risk for this congenital malformation while using lithium (1/2,000 to 1/1,000 or between 0.05% to 0.1%), which also represents a relatively small absolute risk.[40] To the current knowledge, there is only one study in which the impact of exposure to lithium therapy during pregnancy on long-term neurobehavioral development was examined. The findings of that study revealed no significant behavioral problems.[41]

Anticonvulsants

Carbamazepine exposure during pregnancy (first semester) is associated with a two-fold increase in risk for major malformations, particularly spina bifida (at a rate of 1%).[42] The occurrence of "anticonvulsant face" (mid-face hypoplasia with short nose with anteverted nostrils and long upper lip) has also been described in newborns exposed to carbamazepine during pregnancy. The use of valproic acid during pregnancy has been associated with craniofacial abnormalities, heart defects, deficiency of long bones and digits and syndactyly.[43] The estimate risk for neural tube defects ranges from 3% to 6%. In addition, case reports suggest an increased frequency of autism after first trimester exposure to valproic acid.[44]

The combination of two or more anticonvulsants appears to increase the risk for congenital malformations, perhaps due to higher maternal plasma drug levels.[45] Existing data are not definitive with respect to teratogenic risks associated with new anticonvulsants (e.g. lamotrigine and topiramate).

Antipsychotics

A meta-analysis describing teratogenic risk associated with several psychotropic drugs, including antipsychotics, noted a higher risk for congenital malformations after first trimester exposure to low potency neuroleptic agents.[31] Conversely, a small retrospective study found no association between fetal exposure to haloperidol and resultant congenital deformations.[46] Definitive studies on congenital malformations associated with prenatal exposure to atypical antipsychotic drugs (e.g. risperidone, olanzapine, clozapine) are lacking. There were no abnormalities reported among 7 infants prenatally exposed to risperidone.[47] Also, there have been sparse case reports of clozapine use during pregnancy (in schizophrenic patients),[48] with no congenital malformations observed. The occurrence of long-term behavioral sequelae associated with prenatal exposure to antipsychotics remains unclear.[9]

Benzodiazepines

There are a large number of benzodiazepines available in the market but data on potential teratogenicity is quite limited, restricted mostly to the oldest ones.

Hartz et al[49] found no evidence of birth defects in infants prenatally exposed to chlordiazepoxide. Preliminary studies have shown an increased risk for oral clefts due to prenatal exposure to diazepam.[50] Recently, a meta-analysis study suggested, on the basis of pooled data from case-control studies, that there was a significant increased risk for oral cleft defects

over the general population, although the absolute risk remained remarkably small.[51] A follow-up study of 276 newborn infants after a first trimester exposure to alprazolam found no evidence of increased malformations compared to the general population.[52] A limited surveillance study revealed 3 birth defects among 19 pregnant women exposed to clonazepan.[53] Finally, there are no consistent data supporting a significant impact of prenatal exposure to benzodiazepines on neurobehavioral development.[9]

General recommendations

Formulation of treatment guidelines for psychotropic agents during pregnancy is complex, and may include: (1) the severity of underlying psychiatric disorder; (2) available data regarding reproductive safety of a medication; and (3) the willingness of patients to tolerate symptoms in an effort to avoid drug exposure and/or further breastfeeding.[54]

Different situations must be taken into account:

Pre-pregnancy consultation for women who are currently taking medications

The American Academy of Pediatrics[55] recommends the daily consumption of 400 μg of folic acid when planning to start a pregnancy, to minimize certain risks for birth defects. Clinicians should investigate any evidence of seasonal variation in previous episodes of illness to better plan the timing for contraception and subsequent childbirth. The clinician should document the discussion and education of the prospective parents about the patient's severity of illness, potential adverse effects for the fetus and the neonate while maintaining or discontinuing psychotropic medication, and the potential use and efficacy of nonpharmacologic treatments (e.g., psychotherapy). Ultimately, clinicians must work collaboratively with patients and their partners to come with the safest decision based on available information and patients' wishes.

Unplanned conception during treatment with psychotropic medications

Over 50% of pregnancies are unplanned. Usually, at the point of knowledge of conception, it is likely that the fetus has already been exposed (8 to 9 weeks gestation). Therefore, abrupt discontinuation of medication cannot reverse this early exposure and may result in a higher risk for relapse or withdrawal symptoms.[56] The clinicians should always discuss risks and benefits of discontinuing medication. Women with history of depression and long intervening periods of well being may opt for discontinuing medication, although a recurrence of symptoms during pregnancy may occur in more than 50% of the cases; the risk for postpartum mood disturbance also increases.

A fetal cardiac ultrasound at week 18–20 for women with a first trimester exposure to lithium during an unplanned pregnancy is recommended. Lithium maintenance throughout pregnancy and delivery should be considered for women with more severe bipolar disorder.[57] Of note, the reintroduction of lithium after discontinuation during the first trimester does not appear to be as protective against relapses as lithium maintenance throughout the pregnancy.

In the case of lithium discontinuation, clinicians should consider the use of antipsychotics and/or benzodiazepines in the event of a clinical deterioration. It is not recommended to switch from lithium therapy to anticonvulsants without previous history of successful treatment with these agents. Pregnancy is not the appropriate time to try out novel treatments.[56]

Conclusions

The use of the current FDA classification for teratogenic risks does not provide practitioners with accurate information. In fact, the FDA subcommittee is actively working on this issue, and the current classification may be replaced by narrative statements that summarize and interpret available data regarding teratogenic risks.[55]

On the other hand, clinicians should be encouraged to use psychotropic medication during pregnancy when the potential risk for the fetus from drug exposure is outweighed by the risk of an untreated maternal psychiatric disturbance. Coordinated care involving the patient and her partner, obstetrician and psychiatrist is essential, as it is careful medical record documentation.

Finally, other issues not addressed in this review must be discussed during pre-pregnancy and prenatal psychiatric consultations, such as (1) prophylactic treatment strategies for women at high risk for postpartum mental disease exacerbation, and (2) evaluation of risks/benefits of different psychotropic drugs for women who wish to breastfeed.

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References

1. Zajieck E. Psychiatric problems during pregnancy. In: Wolkind S, Zajieck E, editors. Pregnancy: A Psychological and Social Study. London: Academic Press; 1981. p. 57-73.
2. Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB. Sex and Depression in the National Comorbidity Survey. I: Lifetime prevalence, chronicity and recurrence. J Affect Disord 1993;29:85-96.
3. Burke KC, Burke JD Jr, Rae DS, Regier DA. Comparing Age at onset of major depression and other psychiatric disorders by birth cohorts in five US community populations. Arch Gen Psychiatry 1991;48:789-95.
4. Brandt KR, Mackenzie TB. Obsessive-compulsive disorder exacerbated during pregnancy: a case report. Int J Psychiatry Med 1987;17:361-6.

5. Suppes T, Baldessarini RJ, Faedda GL, Tohen M. Risk of recurrence following discontinuation of lithium treatment in bipolar disorder. Arch Gen Psychiatry 1991;48:1082-8.
6. Cohen LS, Robertson LM, Goldstein J, Sichel DA, Grush LR, Weinstock LS. Impact of pregnancy on risk of relapse of MDD. In: 150th Annual Meeting Syllabus and Proceedings Summary; Washington (DC): American Psychiatric Association; 1997. p. 23-4.
7. Viguera AC, Nonacs R, Cohen LS, Tondo L, Murray A, Baldessarini RJ. Risk of recurrence of bipolar disorder in pregnant and nonpregnant women after discontinuing lithium maintenance. Am J Psychiatry 2000;157:179-84.
8. Cohen LS, Rosenbaum JF, Heller VH. Psychotropic drug use in pregnancy. In: Gelenberg AJ, Bassuk EL, Schoonover SC, editors. The Practitioner's Guide to Psychoactive Drugs. New York: Plenum Medical Book Company; 1991. p. 389-405.
9. Cohen LS, Rosembaum JF. Psychotropic drug use during Pregnancy: weighing the risks. J Clin Psychiatry 1998;59(suppl 2):18-28.
10. Kasilo O, Romero M, Bonati M, Tognoni G. Information on drug use in pregnancy from the Viewpoint Regional Drug Information Center. Eur J Clin Pharmacol 1988;35:447-53.
11. Cohen LS, Heller VL, Rosembaum JR. Treatment guidelines for psychotropic drug use in pregnancy. Psychosomatics 1989;30:25-33.
12. Stowe ZN. Psychopharmacology during pregnancy and lactation: determining infant exposure. In: 153rd Annual Meeting Syllabus and Proceedings. Chicago (IL): American Psychiatric Association; 2000. p. 253.
13. Istvan J. Stress, anxiety, and birth outcomes: a critical review of the evidence. Psychol Bull 1986;100:331-48.
14. O'Hara MW. Postpartum Depression: causes and consequences. New York: Springer-Verlag; 1995. p. 168-94.
15. Frank E, Kupfer DJ, Perel JM. Three-year outcomes for maintenance therapies in recurrent depression. Arch Gen Psychiatry 1990;47:1093-9.
16. Murray D, Cox JL, Chapman G, Jones P. Childbirth: life event or start of a long-term difficulty? Br J Psychiatry 1995;166:595-600.
17. Kumar R, Robson KM. A prospective study of emotional disorders in childbearing women. Br J Psychiatry 1984;144:35-47.
18. Steer RA, Scholl TO, Hediger ML, Fischer RL. Self-reported depression and negative pregnancy outcomes. J Clin Epidemiol 1992;45:1093-9.
19. Orr ST, Miller CA. Maternal depressive symptoms and the risk of poor pregnancy outcome. Review of the literature and preliminary findings. Epidemiol Rev 1995;17:165-71.
20. Austin MP. Puerperal affective psychosis: is there a case for lithium prophylaxis? Br J Psychiatry 1992;161:692-4.
21. Cohen LS, Sichel DA, Robertson LM, Heckscher E, Rosembaum JF. Postpartum prophylaxis for women with bipolar disorder. Am J Psychiatry 1995;152:1641-5.
22. Viguera AC, Nonacs R, Cohen LS. Risks of discontinuing maintenance treatment in pregnant women with bipolar disorder. In: 150th Annual Meeting New Research Program and Abstracts, Washington (DC): American Psychiatric Association; 1997. p. 97-8.
23. Pacifici GM, Nottoli R. Placental transfer of drugs administered to the mother. Clin Pharmacokinet 1995;28:235-69.
24. Cohen LS, Heller VL, Bailey JW, Grush L, Ablon S, Bouffard SM. Birth Outcomes Following Prenatal Exposure to Fluoxetine. Biol Psychiatry 2001;48:996-1000.
25. Kuessenberg EV, Knox JD. Imipramine in pregnancy. Br Med J 1972;2:292.
26. Rosenberg L, Mitchell AA, Parsells JL, Pashayan H, Louik C, Shapiro S. Lack of relation of oral clefts to diazepam use during pregnancy. N Engl J Med 1983;309:1282-5.
27. Edlund MJ, Craig TJ. Antipsychotic drug use and birth defects: an epidemiologic reassessment. Compr Psychiatry 1984;25:32-7.
28. Idanpaan-Heikkila J, Saxen L. Possible teratogenicity of imipramine-chloroyramine. Lancet 1973;2:282-4.
29. Crombie DL, Pinsent RJ, Fleming D. Imipramine in pregnancy. Br Med J 1972;1:745.
30. Rachelefsky GS, Flynt JW Jr, Ebbin AJ, Wilson MG, Banister P, Dafoe C, et al. Possible teratogenicity of tricyclic antidepressants. Lancet 1972;1:838-9.
31. Altshuler LL, Cohen L, Szuba MP, Burt VK, Gitlin M, Mintz J. Pharmacologic management of psychiatric illness during pregnancy: dilemmas and guidelines. Am J Psychiatry 1996;153:592-606.
32. Eggermont E. Withdrawal symptoms in neonates associated with maternal imipramine therapy. Lancet 1973;2:680.
33. Pastuszak A, Schick-Boschetto B, Zuber C, Feldkamp M, Pinelli M, Sihn S, et al. Pregnancy outcome following first-trimester exposure to fluoxetine. JAMA 1993;269:2246-8.
34. Chambers CD, Johnson KA, Dick LM, Felix RJ, Jones KL. Birth outcomes in pregnant women taking fluoxetine. N Engl J Med 1996;335:1010-5.
35. Nulman I, Rovet J, Stewart DE, Wolpin J, Gardner HA, Theis JG, et al. Neurodevelopment of children exposed in utero to antidepressant drugs. N Engl J Med 1997;336:258-62.
36. Kulin Na, Pastuszak A, Sage SR, Schick-Boschetto B, Spivey G, Feldkamp M, et al. Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors: a prospective controlled multicenter study. JAMA 1998;279:609-10.
37. Kent LS, Laidlaw JD. Suspected congenital sertraline dependence. Br J Psychiatry 1995;167:412-3.
38. Ericson A, Kallen B, Wiholm B. Delivery outcome after the use of antidepressants in early pregnancy. Eur J Pharmacol 1999;55:503-8.
39. Schou M, Goldfield MD, Weinstein MR, Villeneuve A. Lithium and pregnancy. I. Report from the Register of Lithium Babies. Br Med J 1973;2:135-6.
40. Cohen LS, Friedman JM, Jefferson JW, Johnson EM, Weiner ML. A reevaluation of risk in utero exposure to lithium. JAMA 1994;271:1485.
41. Schou M. What happened later to the lithium babies? A follow up study of children born without malformations. Acta Psychiatr Scand 1976;54:193-7.
42. Rosa FW. Spina Bifida in infants of women treated with carbamazepine during pregnancy. N Engl J Med 1991;324:674-7.
43. Martinez-Frias ML. Clinical manifestation of prenatal exposure to valproic acid using case reports and epidemiologic information. Am J Med Genet 1990;37:277-82.
44. Williams PG, Hersh JH. A male with fetal syndrome and autism. Dev Med Child Neurol 1997;39:632-4.
45. Koch S, Losche G, Jager-Roman E. Major and minor birth malformations and antiepileptic drugs. Neurology 1992;42(suppl 5):83-8.
46. Hanson G, Oakley G. Haloperidol and limb deformity. JAMA 1975;231:26.
47. Mackay FJ, Pearce WGL, Freemantle SN, Mann RD. The safety of risperidone: a Post-Marketing Study of 7684 patients. Human Psychopharmacol Clin Exp 1998;13:413-8.
48. Waldman M, Safferman A. Pregnancy and clozapine. Am J Psychiatry 1993;150:168-9.
49. Hartz SC, Heinonen OP, Shapiro S, Siskind V, Slone D. Antenatal Exposure to meprobamate and chlordiazepoxide in relation to malformations, mental development, and childhood mortality. N Engl J Med 1975;292:726-8.
50. Saxen I, Saxen L. Association between maternal intake of diazepam and oral clefts. Lancet 1975;2:498.
51. Dolovich LR, Addis A, Vaillancourt JMR, Power JDB, Koren G, Einarson TR. Benzodiazepines use in pregnancy and major malformations or oral cleft: meta-analysis of cohort and case-control studies. BMJ 1998;317:839-43.
52. St Clair SM, Schirmer RG. First trimester exposure to alprazolam. Obstet Gynecol 1992;80:843-6.
53. Rosa FW, Baum C. Computerized on-line pharmaceutical surveillance system (COMPASS) teratology. Reprod Toxicol 1993;7:639-40.
54. Altshuler LL, Hendrick V, Cohen LS. Course of mood and anxiety disorders during pregnancy and the postpartum period. J Clin Psychiatry 1998;59(suppl 2):29-33.

55. American Academy of Pediatrics. Committee on drugs. Use of Psychoactive medication during pregnancy and possible effects on the fetus and newborn. Pediatrics 2000;105:880-7.
56. Baugh CL, Stowe ZN. Treatment Issues during pregnancy and lactation. CNS Spectrums 1999;4:34-9.
57. Cohen LS. Maternal exposure to lithium. Presented at the human teratogens Conference-Environmental factors which causes birth defects. Boston: Harvard Medical School; May 2000.

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