Risks / Safety of Psychotropic Medication use during Pregnancy

Adrienne Einarson
Assistant Director, The Motherisk Program
The Hospital for Sick Children, Toronto, Ontario

ABSTRACT

Psychiatric disorders are relatively common among women of childbearing age, who may be prescribed psychotropic drugs. There remains a high level of anxiety regarding their safety among patients and healthcare providers alike, most likely because of the conflicting studies that have been published in the literature and warnings from government organizations.

Consequently, treating a psychiatric disorder during pregnancy with pharmacotherapy, is a complex decision making process, which has to be made between the pregnant woman and her health care provider. The objective of this brief review is to discuss the current models for studying the use of drugs in pregnancy and to provide current information on the safety/risk of psychotropic drugs used in pregnancy. The body of evidence in the literature to date suggests that psychotropic drugs as a group are relatively safe to take during pregnancy and women and their health care providers should not be unduly concerned if a woman requires treatment. Optimal control of the psychiatric disorder should be maintained during pregnancy, the post partum period and thereafter. All pregnancies where a mother has a serious psychiatric disorder should be considered high risk and the mother and fetus must be carefully monitored.

Current Models to Study Safety of Drugs in Pregnancy

In the absence of randomized controlled trials, which are not ethical to conduct in pregnant women, there are currently a number of models used to study the safety of drugs in pregnancy.

***Case reports*:** These are considered a signal generator as they identify a potential problem, thus allowing a formal investigation if warranted.

***Case series*:** In a case series, there can be several cases with be up to hundreds or more. The main limitation of a case series is that there is no comparator group, so the results cannot be compared to a group representing the population.

Prospective, comparative cohort studies: In this model, used frequently by teratogen information services, exposures of interest are identified and a prospective follow up of women are enrolled in the study, usually in the first trimester when organogenesis is occurring. Following birth of the baby, pregnancy outcomes are obtained and compared with other women who were not exposed to drug in question or a teratogen and if possible a disease matched group.

Case control studies: These are retrospective studies where the outcome is known and the group is compared to another group who had the same outcome (in this area of study, the offspring were born with the same birth defects). The two groups are then matched on important variables and a search is conducted for evidence of exposure. This methodology is often used in teratology studies, because far fewer cases are required to find rare birth defects, compared to prospective comparative cohorts.

Meta-analysis: This is a very useful method when studying drug use in pregnancy, as most observational pregnancy outcome studies have small sample sizes. This is a way of combining results across different studies, enlarging the sample size, so as to make a more definitive statement regarding safety/risk of the drug. A literature search is conducted by a minimum of two individuals, using all available data bases. Case-control and cohort studies are both accepted for analysis, as well as abstracts presented at scientific meetings, as long as the subjects were similar. The inclusion and exclusion process is carried out by the reviewers, who independently evaluate the articles for acceptance into the study. If necessary, a third reviewer may act as an adjudicator for any unresolved disputes. The reviewers then extract the data from the included studies into 2x2 tables and the data is analyzed.

Administrative Data Base Studies

Databases are not typically set up for pharmacoepidemiologic research as they are primarily developed for various administrative claims payment. For this reason, important data is often missing, especially for studies of drug use and pregnancy outcomes. However, they often contain large numbers of individuals with important information, so have been increasingly used in research, most frequently to conduct post marketing surveillance. Some registries are driven by pharmaceutical companies (often compelled by national or international drug licensing agencies) and provide data on pregnancy outcome related to the sponsor's own product. Others are organized by independent research groups and they can be more useful as comparative data is used. The major strength of these registries is that often they will contain prospective data, although some do report on retrospective data, they often contain large numbers of exposed women and can be run for several years.

Prescription data base studies: Compiled with data from prescriptions that have been filled by the patient. The main strength of this method is the very large sample sizes.

National birth registries: Some countries, mostly in Europe, operate registries where the mother and child pairs are entered after birth and are followed up prospectively. When practicing evidence-based medicine, in the absence of randomized controlled trials (RCT's) which is Level 1, all of these

methodologies loosely fit into the category Level II-2: "Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group." [1]

Summary

In summary, studying the effects of drug use in pregnancy is a complicated process. Due to the ethical issues surrounding pregnancy, an RCT is unlikely to be conducted. All of the models we are using have their limitations, such as small sample size, retrospective bias, inability to know exactly if the women took the medication in pregnancy and other missing data. However, this does not mean that the data collected is not valuable and useful to provide evidence-based information. Consequently, it is of great importance when translating results, to point out the limitations of each study and how it may affect the results. For best evidence, a combination of these different types of observational studies will assist women and their health-care provider to make an informed decision as to whether or not to take a particular drug during pregnancy. Any decision to take a psychotropic drug in pregnancy should be made between the woman and her health care provider after weighing the risks and benefits of the treatment.

APPENDIX

TABLE 1 – ANTIDEPRESSANTS

AUTHOR	STUDY
[2]Altshuler et al	**Tricyclics:** 3 prospective 10 retrospective studies <700 cases. No increased risk for birth defects. *Am J Psychiatry 1996*
[3]Einarson et al	**Newer antidepressants:** Meta-analysis. No increased risk for birth defects. *Pharmacoepidemiol Drug Saf 2005*
[4]Alwan et al	**SSRI's:** National Birth Defects Prevention Study. No overall increased risk for birth defects. *N Engl J Med. 2007*
[6]Berard et al	**SSRI's:** No increased risk for birth defects. *BJOG 2008*
[7]Einarson et al	**Paroxetine:** n= 1170 No increased risk for cardiovascular malformations. *Am J Psychiatry June 2008*
[8]Lennestal et al [9]Einarson et al	**Venlafaxine:** n= 732 No increased risk for birth defects. *J Clin Psychopharmacology 2007* n=150 *Am J Psychiatry 2001*
[10]Einarson et al	**Trazodone/nefazodone**: n= 150 *Can J Psychiatry 2003*

[11]Chan et al [12]Cole et al	**Bupropion**: n =136 No increased birth defects. *Am J Obs Gynecol 2005* n= 1213 - No increased risk. *Pharmacoepidemiology Drug Saf*
[13]Chambers et al	**SSRI's:** The risk for PPHN was approximately 6-12 per 1000 (1% of infants exposed) *New England Journal of Medicine 2006*
[14]Hemels et al	**Newer antidepressants:** Meta-analysis - small increased risk for spontaneous abortions. *Ann Pharmacother 2005*
[15]Levinson et al [16]Maschi et al	**SSRI's:** PNAS 30 % rates of occurrence. *Arch Pediatr Adolesc 2006* 10% rate of occurrence. *BJOG 2007*
[17]Nulman et al [18]Nulman et al	**Tricyclics/SSRI's:** Long-term neurobehavioural studies. No difference between exposed and unexposed children in early and throughout pregnancy. *N Engl J Med 1997-62* *Am J Psychiatry 2002*
[8]Lennestal et al [16]Maschi et al	**Mixed antidepressants:** Significantly increased risk for preterm births (OR 1.6) *J Clin Psychopharmacology* *BJOG 2007*

TABLE 2 – ANTIPSYCHOTICS

AUTHOR	STUDY
[19]Slone et al [20]Diav-Citrin et al	**Conventional antipsychotics:** n =1309 No differences in rates of congenital malformations, perinatal mortality rate, birth weight as compared to the population. *Am J Obstet Gynecol July 1977* n= 215 women exposed to haloperidol No increased risk for birth defects *J Clin Psychiatry 2005*
[21]Manufacturers Registry McKenna et al	**Atypical antipsychotics:** Olanzapine = 242 Clozapine =523 Quetiapine= 446 Risperidone= 250 Prospective comparative study. 151 women followed up exposed to these drugs: Olanzapine = 60 Risperidone **=**49 Quetiapine =36 Clozapine = 6 No increase risk for birth defects, small increased risk for low birth weight. *J Clinical Psychiatry April 2005*
[22]Yeager et al	**Atypical antipsychotics: Case reports** Clozapine **=**74. Olanzepine = 69 Quetiapine=3 Risperidone =12 No increase risk for birth defects *Am J Psych 2006*

[23]Coppola et al	**Risperidone:** (n= 68/713 cases) prospectively reported No increase risk for major malformations or other adverse outcomes. *Drug Saf 2007*
[24]Newman et al	**Typical:** (n=45) Higher incidence of low birth weight and small for GA. Atypical (n= 25) higher birth weight and large for GA. *Br J Psychiatry May 2008*
[25]Reis et al	**Typical and atypical:** (n =570) Increased risk for major malformations, no pattern of defects. OR1.52 *J Clin Psychopharmacol 2008 June*

TABLE 3 - ANTIEPILEPTIC DRUGS

AUTHOR	STUDY
[26]Nulman et al	**Phenytoin:** Fetal hydantoin syndrome, higher overall rates of malformations, approx. 10%. *Drugs 1999*
[27]Wyszynski et al	**Valproic acid:** (monotherapy) Study found overall rate of malformations (10.7%) NTD (2.9%) *Neurology 2005*
[28]Genton et al.	**Valproic acid:** The potential for lower IQ has also been documented. *Drug Saf 2006*
[26]Nulman et al	**Carbamazepine:** NTD (1%) no increase risk for adverse neurodevelopmental effect. *Drugs 1999*
[29]Holmes et al	**Lamotrigine:** Has been associated in one pregnancy registry with an increased risk for major malformations. However, this trend has not been observed in other registries. *Neurology May 2008*
	Vigabatrin: No published data in humans
[30]Yerby MS	**Topiramate:** 28 cases from clinical trials and 87 cases from postmarketing survey. 3 malformations reported but no specific details. *Epilepsia 2003*
[31]Hunt et al	**Topiramate**: 178/203 live births, oral clefts 11 times background rate with polytherapy. 4/78 males had hypospadias. *Neurology Jul 2008*
[32]Montouris G	**Gabapentin:** Pregnancy outcomes of 39 women, no major malformations. *Epilepsy Behav June 2003*

TABLE 4 – MISCELLANEOUS

AUTHOR	STUDY
[33]Jacobson et al	**Lithium:** 150 women followed up, one child with Ebstein's Anomaly. *Lancet 1992*
[34]Cohen et al	**Lithium:** A review identified 30 babies who were exposed to lithium during gestation. A substantial number of adverse effects in the neonatal period, most babies made a full recovery. *JAMA 1994*
[35]Dolovitch et al	**Benzodiazepines:** There was a significant increased risk for major malformations or oral cleft alone. OR =1.79 (1.13-2.82) *BMJ 1998 Sep*
[36]Czeizel et al	**Benzodiazepines:** Hungarian study with 469 mothers treated with chlordiazepoxide during early pregnancy. There was no increase in the rate of any specific congenital malformation type. *Neurotoxicol Teratol 2004 Jul-Aug*
[37]Wikner et al	**Benzodiazepines**: 1st trimester exposure. (1944 cases) Increased risk for preterm birth and low birth weight, but no increased risk for orofacial clefts or other major malformations. *Pharmacoepidemiol Drug Saf Nov 2007*
[38]Diav-Citrin et al	**Zopiclone:** 40 cases published + 30 cases unpublished with 1 major malformation. *Am J Perinatol 1999*

Corresponding Author: ***einarson@sickkids.on.ca***

REFERENCES

1. Einarson A. Studying the safety of drugs in pregnancy: and the gold standard is…Journal of Clinical Pharmacology and Pharmacoepidemiology 2008; volume 1(number 1) p-3-8.
2. 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 May;153(5):592-606.
3. Einarson TR, Einarson A. Newer antidepressants in pregnancy and rates of major malformations: a meta-analysis of prospective comparative studies. Pharmacoepidemiol Drug Saf 2005 Dec;14(12):823-7.
4. Alwan S, Reefhuis J, Rasmussen SA, Olney RS, Friedman JM. Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. National Birth Defects Prevention Study. N Engl J Med 2007 Jun 28;356(26):2684-92.
5. Louik C, Lin AE, Werler MM, Hernández-Díaz S, Mitchell AA. First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. N Engl J Med 2007 Jun 28;356(26):2675-83.

6. Ramos E, St-André M, Rey E, Oraichi D, Bérard A. Duration of antidepressant use during pregnancy and risk of major congenital malformations. Br J Psychiatry 2008 May; 192(5):344-50.
7. Einarson A, Pistelli A, DeSantis M, Malm H, Paulus WD, Panchaud A, Kennedy D, Einarson TR, Koren G. Evaluation of the risk of congenital cardiovascular defects associated with use of paroxetine during pregnancy. Am J Psychiatry 2008 Jun;165(6):749-52.
8. Lennestål R, Källén B. Delivery outcome in relation to maternal use of some recently introduced antidepressants. J Clin Psychopharmacol 2007 Dec;27(6):607-13.
9. Einarson A, Fatoye B, Sarkar M, Lavigne SV, Brochu J, Chambers C, Mastroiacovo P, Addis A, Matsui D, Schuler L, Einarson TR, Koren G. Pregnancy outcome following gestational exposure to venlafaxine: a multicenter prospective controlled study. Am J Psychiatry 2001 Oct;158(10):1728-30.
10. Einarson A, Bonari L, Voyer-Lavigne S, Addis A, Matsui D, Johnson Y, Koren G. A multicentre prospective controlled study to determine the safety of trazodone and nefazodone use during pregnancy. Can J Psychiatry 2003 Mar;48(2):106-10.
11. Chun-Fai-Chan B, Koren G, Fayez I, Kalra S, Voyer-Lavigne S, Boshier A, Shakir S, Einarson A. Pregnancy outcome of women exposed to bupropion during pregnancy: a prospective comparative study. Am J Obstet Gynecol 2005 Mar;192(3):932-6.
12. Cole JA, Modell JG, Haight BR, Cosmatos IS, Stoler JM, Walker AM. Bupropion in pregnancy and the prevalence of congenital malformations. Pharmacoepidemiol Drug Saf 2007 May;16(5):474-84.
13. Chambers CD, Hernandez-Diaz S, Van Marter LJ, Werler MM, Louik C, Jones KL, Mitchell AA. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. N Engl J Med 2006 Feb 9;354(6):579-87.
14. Hemels ME, Einarson A, Koren G, Lanctôt KL, Einarson TR. Antidepressant use during pregnancy and the rates of spontaneous abortions: a meta-analysis. Ann Pharmacother 2005 May;39(5):803-9.
15. Levinson-Castiel R, Merlob P, Linder N, Sirota L, Klinger G. Neonatal abstinence syndrome after in utero exposure to selective serotonin reuptake inhibitors in term infants. Arch Pediatr Adolesc Med 2006 Feb; 160:173-6.
16. Maschi S, Clavenna A, Campi R, Schiavetti B, Bernat M, Bonati M. Neonatal outcome following pregnancy exposure to antidepressants: a prospective controlled cohort study. BJOG 2008 Jan;115(2):283-9.
17. Nulman I, Rovet J, Stewart DE, Wolpin J, Gardner HA, Theis JG, Kulin N, Koren G. Neurodevelopment of children exposed in utero to antidepressant drugs. N Engl J Med 1997 Jan 23;336(4):258-62.
18. Nulman I, Rovet J, Stewart DE, Wolpin J, Pace-Asciak P, Shuhaiber S, Koren G. Child development following exposure to tricyclic antidepressants or fluoxetine throughout fetal life: a prospective, controlled study. Am J Psychiatry 2002 Nov;159(11):1889-95.
19. Slone D, Siskind V, Heinonen OP, Monson RR, Kaufman DW, Shapiro S. Antenatalexposure to the phenothiazines in relation to congenital malformations, perinatalmortality rate, birth weight and intelligence quotient score. Am J Obstet Gynecol 1977;128:486-488.
20. Diav-Citrin O, Shechtman S, Ornoy S, Arnon J, Schaefer C, Garbis H, Clementi M, Ornoy A. Safety of haloperidol and penfluridol in pregnancy: a multicenter, prospective, controlled study. J Clin Psychiatry 2005;66:317-322.
21. McKenna K, Koren G, Tetelbaum M, Wilton L, Shakir S, Diav-Citrin O, Levinson A, Zipursky RB, Einarson A. Pregnancy outcome of women using atypical antipsychotic drugs: a prospective comparative study. J Clin Psychiatry 2005;66:444-449.
22. Yaeger D, Smith HG, Altshuler LL. Atypical antipsychotics in the treatment ofschizophrenia during pregnancy and the postpartum. Am J Psychiatry 2006 Dec; 163(12):2064-70.

23. Coppola D, Russo LJ, Kwarta RF, Jr., Varughese R, Schmider J. Evaluating the postmarketing experience of risperidone use during pregnancy: pregnancy and neonatal outcomes. Drug Saf 2007;30(3):247-64.
24. Newham JJ, Thomas SH, MacRitchie K, McElhatton PR, McAllister-Williams RH. Birthweight of infants after maternal exposure to typical and atypical antipsychotics: prospective comparison study. Br J Psychiatry. 2008 May;192(5):333-7. Erratum in: Br J Psychiatry. 2008 Jun;192(6):477.
25. Reis M, Källén B. Maternal use of antipsychotics in early pregnancy and deliveryoutcome. J Clin Psychopharmacol 2008 Jun;28(3):279-88.
26. Nulman I, Laslo D, Koren G. Treatment of epilepsy in pregnancy 1999. Drugs Apr;57(4):535-44.
27. Wyszynski DF, Nambisan M, Surve T, Alsdorf RM, Smith CR, Holmes LB. Antiepileptic Drug Pregnancy Registry. Increased rate of major malformations in offspring exposed to valproate during pregnancy. Neurology 2005 Mar 22;64(6):961-5.
28. Genton P, Semah F, Trinka E. Valproic acid in epilepsy: pregnancy-related issues. Drug Saf. 2006;29(1):1-21.
29. Holmes LB, Baldwin EJ, Smith CR, Habecker E, Glassman L, Wong SL, Wyszynski DF. Increased frequency of isolated cleft palate in infants exposed to lamotrigine during pregnancy. Neurology 2008 May 27; 70(22 Pt 2):2152-8.
30. Yerby MS. Clinical care of pregnant women with epilepsy: neural tube defects and folic acid supplementation. Epilepsia 2003; 44 Suppl 3:33-40.
31. Hunt S, Russell A, Smithson WH, Parsons L, Robertson I, Waddell R, Irwin B, Morrison PJ, Morrow J, Craig J. UK Epilepsy and Pregnancy Register. Topiramate in pregnancy: preliminary experience from the UK Epilepsy and Pregnancy Register. Neurology 2008 Jul 22;71(4):272-
32. Montouris G. Gabapentin exposure in human pregnancy: results from the Gabapentin Pregnancy Registry. Epilepsy Behav 2003 Jun; 4(3):310-7.
33. Jacobson SJ, Jones K, Johnson K, Ceolin L, Kaur P, Sahn D, Donnenfeld AE, Rieder M, Santelli R, Smythe J. Prospective multicentre study of pregnancy outcome after lithium exposure during first trimester. Lancet 1992 Feb 29; 339(8792):530-3.
34. Cohen LS, Friedman JM, Jefferson JW, Johnson EM, Weiner ML. A re-evaluation of risk of in utero exposure to lithium. JAMA 1994 Jan 12; 271(2):146-50.
35. Dolovich LR, Addis A, Vaillancourt JM, Power JD, Koren G, Einarson TR. Benzodiazepine use in pregnancy and major malformations or oral cleft: meta-analysis of cohort and case-control studies. BMJ 1998 Sep 26; 317(7162):839-43.
36. Czeizel AE, Rockenbauer M, Sørensen HT, Olsen J. A population-based case-control study of oral chlordiazepoxide use during pregnancy and risk of congenital abnormalities. Neurotoxicol Teratol 2004 Jul-Aug; 26(4):593-8.
37. Wikner BN, Stiller CO, Bergman U, Asker C, Källén B. Use of benzodiazepines and benzodiazepine receptor agonists during pregnancy: neonatal outcome and congenital malformations. Pharmacoepidemiol Drug Saf 2007 Nov;16(11):1203-10.
38. Diav-Citrin O, Okotore B, Lucarelli K, Koren G. Zopiclone use during pregnancy. Can Fam Physician 2000 Jan; 46:63-4.