Acta Neurol. Belg., 2010, **110**, 163-167

The effects of benzodiazepines in pregnancy

Marcel Leppée PhD[1], Josip Culig PhD[1,2], Mirela Eric MSc[3], Sinisa Sijanovic PhD[4]

[1]Department od Pharmacoepidemiology, Andrija Stampar Institute of Public Health, 10000 Zagreb, Croatia; [2]Department of Pharmacology, School of Medicine, Josip Juraj Strossmayer University, 31000 Osijek, Croatia; [3]Department of Anatomy, School of Medicine, University of Novi Sad, 21000 Novi Sad, Serbia; [4]Department of Obstetrics and Gynecology, Clinical Hospital Osijek, 31000 Osijek, Croatia

Abstract

Objectives: The objectives of the study were to assess the prevalence of anxiolytic use in pregnancy, the rate of congenital malformations in neonates at in utero exposure to these agents, and the possible association of congenital malformations with the use of these drugs in pregnancy.

Method: The study was conducted as cross-sectional study. The study was performed at university departments of gynecology and obstetrics in four Zagreb hospitals and included 893 pregnant women. Main outcome measures were pathological defects and congenital malformations.

Results: The main anatomic group N drugs (nervous system) was predominated by the use of the benzodiazepine anxiolytic diazepam (FDA group D), which increased with gestational age. Diazepam was used by 74 (8.3%), 127 (14.2%) and 212 (23.7%) women in the first, second and third trimester, respectively. Diazepam ranked second among twenty most frequently prescribed drugs in pregnancy. It was taken by 303 (33.9%) pregnant women, while congenital cardiovascular malformations were recorded in three children and genitourinary malformations in three children too.

Conclusions: The high utilization of diazepam in pregnancy that is not supported by professional guidelines is an issue of serious concern. In spite of some study limitations, its results pointed to inappropriate and even potentially harmful use of drugs in pregnant women from Zagreb, thus calling for upgrading the quality of therapy in this vulnerable period of life. In our opinion, other measures appear to be a more appropriate therapeutic modality than medicamentous therapy in many cases.

Key words: anxiolytics, pregnancy, diazepam, benzodiazepines

Introduction

Pregnancy is a period in which attention should be paid to the use of medication in particular because drugs can exert dual adverse effects in pregnant women. Drugs can threaten maternal health and influence the course of pregnancy, and may also exert adverse effects on the fetus by reaching it via placental route and influencing its growth and development. As a great proportion of pregnancies have not been planned, maternal exposure to the adverse effects of medication may occur while still being unaware of pregnancy (1, 2).

Every child as a unique person is characterized by his/her own response and sensitivity to the drug used by the mother. The cause of variable fetal response remains unknown. Different pregnant women may take the same drug at the same dosage and over the same period of time, while their fetuses/infants will differ in their response to it (3, 4). The use of drugs in pregnancy has come into focus of interest after thalidomide tragedy that upset the public worldwide in the 1960s. Thalidomide, a sedative and hypnotic, largely advertised as being safe for use in pregnancy, resulted in the birth of some 10,000 neonates with phocomelia, i.e. absence of the proximal portion of limbs (5-9). Drugs prescribed to pregnant women should primarily treat maternal disease. Pregnancy is associated with some specific pharmacokinetic features because the drug that is not intended for the fetus reaches fetus via placental route. During pregnancy, major changes occur at the level of drug distribution and elimination. Controlled studies of drug use in pregnancy cannot be performed for ethical reasons; therefore data can only be obtained from animal experiments, general databases, professional literature, and individual reports on sporadic use of drugs in pregnancy (10). Many data are categorized as 'probable' for being based on epidemiological retrospective studies. Animal experiments provide data on structural teratogenicity, yet limited by the fact that none of the animal species resembles humans to such an extent that the results can be

extrapolated to humans with certainty. Therefore, decision on the maternal benefits outweighing the potential risk for the fetus lies on the physician. The imperative of modern medicine is rational pharmacotherapy for pregnant women relying on scientific medical determinants and supported by economic resources. Depression, anxiety disorders, anorexia nervosa and bulimia, all indications for anxiolytic and antidepressant use, are common disorders in women of childbearing age. Nevertheless, the use of anxiolytics and antidepressants during gestation remains a controversial issue. Given that 50% of pregnancies are unplanned, the safety of anxiolytics and antidepressants during the first trimester of pregnancy, a critical period for fetal development, has become a major public health concern (11). Psychotropic medication is used by a growing number of women of reproductive age. Although necessary in some cases, in many others non-pharmacological treatments offer valid alternatives for pregnant women. The noxious effects of antidepressants and anxiolytics urge the physician to look for other solutions. The efficacy of alternative treatment is enhanced by early detection that requires monitoring for mood disorders from the earliest stages of pregnancy, and multidisciplinary professional care (12). Considering the relatively high utilization of anxiolytics in pregnancy and early postpartum period, the aim of the study was to assess the prevalence of their use and their influence on the occurrence of congenital malformations.

Methods and materials

The study was performed over a one-month period (May 1-31, 2004) at university departments of gynecology and obstetrics in four Zagreb hospitals: Zagreb University Hospital Center, Sestre milosrdnice University Hospital, Merkur University Hospital and Sveti Duh General Hospital. The study was conducted according to the Clinical Epidemiological Research Plan and in line with the valid By-Law on Clinical Trials and Good Clinical Practice (Official Gazette No. 121/03), including full respect of all Helsinki Declaration provisions and recommendations of the World Medical Association of Physicians Performing Biomedical Research in Humans. The the study included all women who gave birth in that month (893 women). No woman has refused to take part in the survey. The study was approved by independent Ethics Committee of the School of Medicine and four Zagreb hospitals. Study subjects were first analyzed according to age structure, residence and level of education. A simple structured standardized questionnaire consisting of two parts, i.e. mother interview and medical records, was used in the study. Data were collected from the following sources: questionnaires for pregnant women administered by the physician during hospitalization; detailed physical examination of newborns to establish the presence of major or minor malformations, performed by trained pediatrician according to standard protocol; and pathologic examination of fetuses performed by trained pathologists according to standard protocol. Drugs were classified into four groups as follows: drugs initiated before and continued in pregnancy; drugs initiated in pregnancy; drugs taken between hospital admission and delivery; and drugs taken in puerperium. As clinical therapeutic trials in pregnant women are strictly limited by the existent ethical principles, epidemiological methods were employed in the study. The trial was designed as a cross-sectional study to measure exposure of pregnant women to a particular drug and their health status, and to determine the rate of malformations and pathologic conditions in children born to mothers with and without exposure to a particular drug. The study was carried out by use of the questionnaire distributed to study subjects during pregnancy and puerperium, which could be perceived as a methodological limitation of the study because the possible recollection bias as well as the impact of educational level and personality on the validity of their answers could not be excluded. For this reason, a part of the study was performed by exploration of hospital records. In addition, the possible seasonal effects on study results could not be ruled out either. In international studies, data have been increasingly derived from computer databases on prescription drugs, thus minimizing the possible errors and pointing to the need of establishing as soon as possible the computer healthcare system for full transparency of healthcare indicators in Croatia. The present study investigated utilization of drugs from the subgroup of anxiolytics (N05B) that account for the majority of utilization within the main therapeutic group of psycholeptics (N05). A representative sample playing a major role in epidemiological studies was used. Pregnant women hospitalized at maternity wards were included in the study. The questionnaire was strictly focused on the facts that are directly relevant for drug use. Results were processed by use of appropriate statistical methods. The drugs reported to have been used by study women in pregnancy were classified according to safety in pregnancy into five Food and Drug Administration (FDA) categories.

Student's t-test and Chi-square test with a significance level of $p \leq 0.05$ were used when appropriate for the evaluation of the results. All analysis were

performed with SigmaStat 3.0 for Windows (SPSS Science software products, Chicago, IL, U.S.).

Results

Study results showed 96.2% of women from Zagreb to have taken at least one drug in pregnancy. Every pregnant woman took a mean of 2.6 drugs in pregnancy. When the whole period of observation starting immediately before pregnancy and continuing to pregnancy and early postpartum period was considered, every woman took a mean of 5.1 drugs, which is comparable with the European mean value.

Analysis of the drugs taken by pregnant women in pregnancy showed the benzodiazepine anxiolytic diazepam to predominate among the main group N drugs (nervous system) according to the Anatomic-Therapeutic-Chemical (ATC) classification. The use of diazepam increased with gestational age; it was used by 74 (8.3%), 127 (14.2%) and 212 (23.7%) women in the first, second and third trimester, respectively, while 54 women used it immediately before delivery. Of other benzodiazepines, only one pregnant woman took alprazolam in third trimester (Table 1). These two anxiolytics belong to D class according to FDA classification. Diazepam was the second of twenty most frequently prescribed drugs in pregnancy, used by 303 (33.9%) pregnant women.

Congenital malformations were recorded in 26 (2.9%) newborns, mostly involving cardiovascular system (n = 9; 34.6% of the total number of malformations), followed by genitourinary system (n = 5; 19.2%), head and neck region, musculoskeletal system, etc. In the group of women that gave birth to neonates with congenital malformations of the cardiovascular system, one woman had been taking diazepam throughout pregnancy, and the other two only in third trimester. Neonates with genitourinary system malformations were born to five women, three of them having taken diazepam, i.e. two in the first and third trimester, and one throughout pregnancy.

Table 1

Diazepam use in a series of 893 pregnant women according to the gestational age

Period	Diazepam	
	n	%
Before and during pregnancy	1	0.1
First trimester	74	8.3
Second trimeste	127	14.2
Third trimester	212	23.7
Maternity ward	54	6.0
Puerperium	14	1.6

No congenital malformations other than cardiovascular and genitourinary system malformations were present in children born to mothers having used diazepam in pregnancy.

These malformations were noted in six cases (2.0%), three of the cardiovascular system and the same number of the genitourinary system. Four of them were exposed to diazepam during the first trimester, two of them were exposed during the second trimester and all six fetuses were exposed to diazepam during the third trimester when the functional defects are more common. In Table 2 are shown other medications taken during pregnancy.

Table 2

Associated medications in cases of congenital malformations with respect to period of medication use

	Congenital malformation	Trimester			Associated medications
		I.	II.	III.	
	Cardiovascular system	+	+	+	atenolol (belongs to D class), dydrogesterone, ritodrin, cephalexin, combination of oxytetracycline and nystatin
2.				+	vitamins and minerals
3.				+	vitamins and minerals
4.	Genitourinary system	+	+	+	analgetic, iron, vitamins and minerals
5.		+		+	hepatrombin, iron, vitamins and minerals
6.		+		+	

Discussion

Anxiety disorders are the most prevalent of all psychiatric disorders, especially among women, 30% of whom have an anxiety disorder at some time during their lives (13). Pregnancy is a period of great emotional change for the woman, producing increased stress and anxiety and does not have a clear impact on the natural history of anxiety disorders, although there is an apparent risk of susceptibility in the postpartum period (14). Medication may be required for the treatment of anxiety disorders at this time. The teratogenic risks, perinatal toxicity and effects on the neurobehavioral development of newborns associated with exposure to these medications through the placenta or breastfeeding need to be carefully assessed before starting psychopharmacological treatment in pregnant or lactating women (15). Patients on maintenance pharmacotherapy for these disorders show high rates of relapse with medication discontinuation. On comparison with similar studies carried out in other countries, the use of drugs in pregnancy was found to be lower in Croatia than in most of these countries. The mean number of drugs taken during pregnancy is 13.6 in France, 7.8 in Germany, 4.2 in the Netherlands and 3.8 in the USA; in Croatia, the mean number of drugs taken during pregnancy was 2.6, which is equal to the mean number recorded in Denmark. Studies on drug utilization in pregnancy indicate 80%-99% of pregnant women to take drugs, 4 to 7 on an average (16). Most of these drugs can cross the placenta and exert harmful effects on the embryo and fetus. The subgroup of anxiolytics (N05B) was the second most commonly used group of drugs taken in pregnancy, immediately following the group of vitamins. Benzodiazepines that are too frequently prescribed accounted for total utilization of anxiolytics (17). The very large doses of diazepam used for self-poisoning during pregnancy did not increase the rate of congenital abnormalities in the offspring (18). Because of their favorable safety profile, benzodiazepine anxiolytics have become the most frequently prescribed drugs, immediately following analgesics-antipyretics. Benzodiazepines are not recommended by FDA (class D) either, except for some extreme cases where maternal benefits outweigh fetal risk (19). Most authors agree that they should be avoided, in first trimester in particular (cleft lip and cleft palate), and should only be prescribed in lowest dosage and for a very short period of time (20). A meta-analysis performed by Altshuler et al. (21) noted that the increased risk of cleft lip and palate associated with use of benzodiazepines was real, but small (less than 1%, compared with 0.06% in the general population) (22). A recent meta-analysis (2000) of 13 studies showed no increased risk of BZ-induced malformations from cohort studies and slight increased risk from case-controlled studies (23). Such malformations were not registered in our study. But malformations of cardiovascular system were registered in three women (3/303; 1.0%) as well as malformations of genitourinary system. Four women were taking diazepam during the first trimester. Women which gave birth to neonates with cardiovascular and genitourinary malformations and had been taking diazepam in some periods or throughout pregnancy, also had been taking some other medications: atenolol (belongs to D class), dydrogesterone, ritodrin, cephalexin, analgesics, hepatrombin, iron, vitamins and minerals, and combination of oxytetracycline and nystatin. It is interesting that all six women which gave birth with malformations, have been taking benzodiazepines during third trimester. There is possible a relation between use of diazepam and congenital malformation. With respect to the polypragmasia, it is difficult to determine impact of each drug to malformation. Most studies suggest that physicians may often under-prescribe or discontinue antidepressants and anxiolytics at the time of conception and during pregnancy. On the other hand, discontinuation of antidepressant and anxiolytic use during pregnancy was also recently associated with maternal relapse of depression and withdrawal symptoms, which is not optimal for the mother and her fetus. At this time, it appears important to take into account all evidence-based data to evaluate the risks and benefits of using anxiolytics and antidepressants during gestation in order to help mothers make the best choice for themselves, and their infants (24).

Cognitive behavior therapy has been shown to be an effective treatment modality in many of these disorders, and it may be a reasonable option for patients who wish to discontinue medications during pregnancy (25). However, if medication is required, pregnant women should be prescribed the lowest dosage of the drug with the highest safety profile according to FDA classification for the minimal period of time (26). Though no controlled studies have ever been done in pregnant women to truly prove their safety, it appears that most, but not all, current psychotropic drugs appear fairly safe for use in pregnancy (27).

Acknowledgements

We would thank all monitors participating to collect data for this study, and all physicians collaborating of hospital structures involved into the study: university

departments of gynecology and obstetrics in four Zagreb hospitals: Zagreb University Hospital Center, Sestre milosrdnice University Hospital, Merkur University Hospital and Sveti Duh General Hospital.

We have not received any financial support.

REFERENCES

1. Austin MP, Mitchell PB. Psychotropic medications in pregnant women: treatment dilemmas. Med J Aust. 1998;169:428-31.
2. Bérard A, Ramos E. Antidepressants and pregnancy: risks and benefits for the mother and child. Medecine Sciences, 2007;23:957-60.
3. Briggs GG, Freeman RK, Yaffe SJ. Drugs in pregnancy and lactation, 5th ed., Baltimore, Williams and Wilkins, 1998.
4. Campagne DM. Fact: antidepressants and anxiolytics are not safe during pregnancy. Eur J Obstet Gynecol Reprod Biol. 2007;135:145-8.
5. Chaudhuri G, Giacoia GP, Yaffe SY. Drug development for pregnancy. In: "Drug development for women". Ragavan VV, ed. John Wiley and Sons, Chichester: 1998: 213-34.
6. Dolovich LR, Addis A, Vaillancourt RJ, Power BJ, Koren G. *et al*. Benzodiazepine use in pregnancy and major malformations or oral cleft: meta-analysis of cohort and case-control studies. BMJ. 1998;317: 839-43.
7. Erić M. Research of teratogenic effects of medicines on embryo. MS thesis. School of Medicine, University of Novi Sad, Novi Sad, 2004.
8. Culig J, Leppée M, Stimac D, Kuvacic I, Pulanic-Klepac T. *et al*. Cross-sectional study of drug use in pregnancy. Lijec vjesn. 2007;129:253-9.
9. Eric M, Sabo A. Teratogenicity of antibacterial agents. Coll Antropol. 2008;32:919-25.
10. Freedman MJ, Polifka EJ. The effects of drugs on the fetus and nursing infant: a handbook for health care professionals. Johns Hopkins University Press, Baltimore; 1996.
11. Freedman MJ, Polifka EJ. Teratogenic effects of drugs: a resource for clinicians. Johns Hopkins University Press, Baltimore; 2000.
12. Freeman MP, Hibbeln JR, Wisner KL, Watchman M, Gelenberg AJ. An open trial of omega-3 fatty acids for depression in pregnancy. Acta Neuropsychiatrica. 2006;18:21-4.
13. Regier DA, Narrow WE, Rae DS. The epidemiology of anxiety disorders: the Epidemiologic Catchment Area (ECA) experience. J Psychiatr Res, 1990;2: 3-14.
14. 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.
15. Rubinchik MS, Kablinger SA, Gardner SJ. Medications for panic disorder and generalized anxiety disorder during pregnancy. Primary Care Companion to The Journal of Clinical Psychiatry, 2005;7:100-5.
16. Tognoni G, Liberati A, Pello L, Sasanelli F, Spagnoli A. Drug utilization studies and epidemiology. Rev Epidemiol Sante Publique. 1983;31:59-71.
17. Gentile S. The safety of newer antidepressants in pregnancy and breastfeeding. Drug Saf, 2005;28: 137-52.
18. Gidai J, Acs N, Banhidy F, Czeizel AE. No association found between use of very large doses of diazepam by 112 pregnant women for a suicide attempt and congenital abnormalities in their offspring. Toxicol Ind Health. 2008;24:29-39.
19. Koren G. Maternal-fetal toxicology: a clinician's guide. 3rd ed. Marcel Dekker, New York: 2001.
20. Leppée M. Drugs in pregnancy. PhD thesis. School of Medicine, Josip Juraj Strossmayer University, Osijek; 2008.
21. Altshuler LL, Cohen L, Szuba MP. *et al*. Pharmacologic management of psychiatric illness during pregnancy: dilemmas and guidelines. Am J Psychiatry. 1996;153:592-606
22. Rubinchik SM, Kablinger AS, Gardner JS. Medication for panic disorder and generalized anxiety disorder during pregnancy. Prim Care Companion J Clin Psychiytry. 2005;7:100-5.
23. Addis A, Dolovich LR., Einarson TR., Koren G, Motherisk. Meta-analysis, Canadian Health Network. March 2000.
24. McGrath C, Buist A, Norman TR. Treatment of anxiety during pregnancy: effects of psychotropic drug treatment on the developing fetus. Drug Saf. 1999;20:171-86.
25. Nesse RM, Zamorski MA. Anxiety disorders in primary care. In: Knesper DJ, Riba MB, Schwenk TL, eds. Primary care psychiatry. Saunders, Philadelphia; 1997:132-62.
26. Shepard TH. Teratogenicity of therapeutic agents. Curr Probl Pediatr. 1979;10:1-42.
27. Goldberg HL. Psychotropic drugs in pregnancy and lactation. Int J Psychiatry Med. 1994;24:129-47.

M. Leppée
Department of Pharmacoepidemiology,
Andrija Stampar Institute of Public Health Zagreb,
Mirogojska 16, 10000 Zagreb, Croatia
e-mail: marcel.leppee@stampar.hr