MOTHERISK *UPDATE*

Can we use anxiolytics during pregnancy without anxiety?

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abstract

QUESTION One of my patients suffers from anxiety and was using lorazepam to treat it. When she became pregnant, she stopped the medication immediately, but now she is worried about the potential effect on the baby because she was using the drug just after conception. Is this class of drugs safe during pregnancy? What should she do if she needs antianxiety treatment during the rest of her pregnancy?

ANSWER Evidence to date from cohort studies did not identify a notable association between use of benzodiazepines and increased risk of major malformations, including oral cleft. In contrast, data from case-control studies show a slightly increased risk of oral cleft. Hence, level 2 ultrasonography is recommended to rule out visible forms of cleft lip. Using benzodiazepines late in pregnancy could cause withdrawal syndrome in newborns.

résumé

QUESTION Une de mes patientes souffre d'anxiété et elle utilisait du lorazepam comme pharmacothérapie. Lorsqu'elle est devenue enceinte, elle a cessé immédiatement la médication, mais elle s'inquiète maintenant des effets possibles sur l'enfant parce qu'elle prenait ce médicament juste après la conception. Cette catégorie de médicament est-elle sans danger durant la grossesse? Que devrait-elle faire si elle a besoin d'un traitement contre l'anxiété durant le reste de sa grossesse?

RÉPONSE Les données probantes actuellement disponibles, tirées d'études par cohortes, n'ont pas relevé de rapport notoire entre le recours aux benzodiazépines et un risque accru de malformations majeures, notamment le bec-de-lièvre. Par ailleurs, des données tirées d'études cas témoins indiquent un risque légèrement plus élevé de bec-de-lièvre. Par conséquent, il est recommandé de procéder à une échographie de niveau 2 pour éliminer la possibilité de formes visibles de bec-de-lièvre. L'usage de benzodiazépines tard durant la grossesse pourrait causer des symptômes de sevrage chez les nouveau-nés.

Benzodiazepines (BZDs) are commonly used for anxiety and insomnia, even by pregnant women. A recent study found that 2% of pregnant women in the United States who were receiving Medicaid benefits filled one or more prescriptions for BZDs during pregnancy.[1] An international drug use study has shown that BZDs account for the greatest number (85%) of psychotropic agents used during pregnancy.[2] Because about half of pregnancies are unplanned,[3] many women could inadvertently expose fetuses to BZDs during the first trimester.

Antepartum exposure to BZDs has been associated with teratogenic effects (facial cleft, skeletal anomalies) in some animal studies[4,5] but not others.[6-7] Risk for cleft palate in the general population is approximately 0.06%.[8] Early human case-control studies suggested that maternal exposure to BZDs increases risk of fetal cleft lip and cleft palate.[9,10] Subsequent reports have implicated BZDs in other major malformations,[11-13] abnormal neurodevelopment,[11,14,15] and an irreproducible congenital benzodiazepine syndrome similar to fetal alcohol syndrome.[11,16-17]

Unfortunately, these studies were not designed to control for confounding factors that could influence results. Several prospective cohort studies involving hundreds of women using BZDs during pregnancy and an equal number of controls failed to show increased risk of malformations after BZD use during the first trimester.

The contradictory results mentioned above have led to considerable controversy surrounding use of BZDs during pregnancy. Nevertheless, it seemed clear that, even if it existed, the risk of malformations in newborns exposed to BZDs during the first trimester was marginal. To investigate this issue, Motherisk conducted a meta-analysis of all data on exposure to BZDs during the first trimester.[18]

Do you have questions about the safety of drugs, chemicals, radiation, or infections in women who are pregnant or breastfeeding? We invite you to submit them by fax to (416) 813-7562; they will be addressed in future Motherisk Updates. Published Motherisk Updates are available on the College of Family Physicians of Canada website (www.cfpc.ca). Some articles are published in *The Motherisk Newsletter* and Motherisk website (www.motherisk.org) also.

Motherisk's meta-analysis

Motherisk considered 13 studies that examined major malformations, 11 that examined oral cleft alone, and three that examined other specific malformations. Exposure was

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Table 1. Association between prenatal exposure to benzodiazepines and major malformations

STUDIES	MALFORMED EXPOSED	MALFORMED NOT EXPOSED	ODDS RATIO (95% CONFIDENCE INTERVAL)
COHORT			
Milkovich and van den Berg[13]	5/86	10/229	1.35 (0.45-4.07)
Crombie et al[20]	3/300	382/19 143	0.75 (0.24-2.35)
Hartz et al[21]	11/257	2129/46 233	0.90 (0.49-1.66)
Kullander and Kallen[22]	2/89	198/5664	0.63 (0.16-2.60)
Laegreid et al[14]	1/17	1/29	1.75 (0.10-29.92)
Pastuszak et al[23]	1/106	3/115	0.36 (0.04-3.47)
Ornoy et al[24]	9/335	10/363	0.97 (0.39-2.43)
Combined effect			0.90 (0.61-1.35)
CASE-CONTROL			
Greenberg et al[25]	36/60	800/1612	1.52 (0.9-2.58)
Bracken and Holford[26]	39/72	1331/4266	2.61 (1.63-4.16)
Noya[27]	1/24	0/24	3.13 (0.12-80.68)
Laegreid et al[17]	8/10	10/68	23.20 (4.29-125.55)
Combined effect			3.01 (1.32-6.84)

Table 2. Association between prenatal exposure to benzodiazepines and oral cleft

STUDIES	MALFORMED EXPOSED	MALFORMED NOT EXPOSED	ODDS RATIO (95% CONFIDENCE INTERVAL)
COHORT			
Shiono and Mills[28]	1/854	31/32 395	1.22 (0.17-8.89)
Bergman[1]	0/1354	62/102 985	1.21 (0.17-8.71)
Ornoy et al[24]	0/335	0/363	1.08 (0.07-17.39)
Combined effect			1.19 (0.34-4.15)
CASE-CONTROL			
Safra and Oakley[12]	7/16	42/262	4.07 (1.44- 11.54)
Saxen and Saxen[9]	27/40	511/1044	2.17 (1.11-4.24)
Rosenberg et al[29]	13/67	590/3011	0.99 (0.54-1.82)
Rodriguez et al[31]	8/61	442/7990	2.58 (1.22-5.45)
Czeizel[30]	48/91	1153/2311	1.12 (0.74-1.71)
Laegreid et al[17]	2/10	4/68	4.00 (0.63-25.43)
Combined effect			1.79 (1.13-2.82)

ascertained mainly through interviewing the mothers (61%), and outcome was confirmed mainly through examination by a physician, records (44%), or malformation registries (30%). Various BZDs were used or prescribed, although 48% of the studies examined use of chlorodiazepoxide or diazepam only.

Data pooled from seven cohort studies did not show an association between fetal exposure to BZDs during pregnancy and major malformations (**Table 1**). A combination of four case-control studies, however, showed that major malformations were associated with use of BZDs during pregnancy (**Table 1**). Data pooled from three cohort studies showed no association between fetal exposure to BZDs during pregnancy and oral cleft (**Table 2**), but analysis of six case-control studies produced a significant odds ratio for oral cleft.

Discussion

Data from cohort studies showed no significant association between BZDs during the first trimester and either major malformations or oral cleft alone. Data from case-control studies, however, showed a small but significant increased risk for these outcomes. This finding might reflect the substantially higher sensitivity of case-control studies for examining risk of specific malformations.

Tests of heterogeneity also showed that the cohort studies were homogeneous for both major malformations and oral cleft, whereas the case-control studies for oral cleft were heterogeneous, which decreases the reliability of the marginally significant results. Even when a "worst case scenario" is assumed, BZDs do not seem to be major human teratogens but, because some cases of cleft lip can be visualized by fetal ultrasound, level 2 ultrasonography should be used to rule out this malformation.

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