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Gestational Exposure to Benzodiazepines, 1:
The Risk of Spontaneous Abortion Examined Through the Prism of Research Design

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Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

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ABSTRACT

A recent, large, case-control study found that, after adjusting for measured confounds, early gestational exposure to benzodiazepines was associated with a nearly doubled odds of spontaneous abortion. The risks differed little between pregnancies exposed to short- and long-acting benzodiazepines. The risks were elevated for all benzodiazepines for which data were adequate for analysis. The risks were higher with higher daily doses. These findings indicate that early gestational exposure to benzodiazepines is a marker for the risk of spontaneous abortion. These findings are *not* evidence for a cause-effect relationship because analyses in studies such as this can adjust for only measured confounds; therefore, unmeasured, inadequately measured, and unknown confounds will continue to contaminate the interpretation of findings. It follows, therefore, that replication of the study with the same study design using data extracted from other databases will serve no purpose. So, innovative research designs should be considered, such as the examination of risk associated with benzodiazepine exposure in the year before pregnancy, examination of risk in previously unexposed pregnancies, examination of risk in discordant sibling pairs, and examination of risk associated with paternal exposure. Such research designs have the potential to indirectly partially address unmeasured and unknown confounds, including those related to genetics and the family environment.

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Women who are unwell during pregnancy may not always be able to avoid the use of medications that are meant to treat their illness. For this reason, some pregnant women may receive antidepressants to treat depression and anxiety disorders, or antipsychotics to treat psychosis, or benzodiazepines to treat anxiety, or insomnia related to pregnancy, medical conditions, or neuropsychiatric disorders.

Some but not all studies have associated early gestational exposure to antidepressant drugs with an increased risk of spontaneous abortion.[1] This article critically examines, from the perspective of research design, a recent case-control study of the risk of spontaneous abortion after gestational exposure to benzodiazepines.[2]

Spontaneous Abortion in Pregnancies Exposed to Benzodiazepines

During pregnancy, about 1%–5% of women have been reported to receive benzodiazepines or other sedative/hypnotic drugs.[2–4] Benzodiazepine exposure during pregnancy has been associated with a higher risk of spontaneous abortion.[5,6] In the most recent study on the subject, Sheehy et al[2] reexamined the risk of spontaneous abortion following early gestational exposure to benzodiazepines.

These authors[2] described a nested case-control conducted within the prospective, population-based Quebec Pregnancy Cohort (n = 442,066), Canada. Cases (age, 15–45 years) comprised pregnancies (n = 27,149; 6.1%) that ended in a spontaneous abortion. Each case was randomly matched, based on gestational age and calendar year, with up to 5 unexposed controls (n = 134,305). Cases and controls were selected only if they had had no first trimester exposure to a known teratogen, no past or current epilepsy, no previous use of benzodiazepines, and no (current) planned or induced abortion.

The mean age of the sample was 24 years. Spontaneous abortion was defined as pregnancy loss between weeks 6 and 19, both inclusive. Incident benzodiazepine exposure was examined in cases and controls. Exposure was defined as at least 1 filled prescription for a benzodiazepine drug during or overlapping the period between the first day of the last menstrual period and the date of spontaneous abortion.

There were 1,163 exposed pregnancies, among which 97% had been exposed to only 1 benzodiazepine and 77% had only 1 prescription filled. The commonest benzodiazepines prescribed were lorazepam (45%) and clonazepam (23%). The median duration of benzodiazepine use was 15 days.

Analyses were adjusted for sociodemographic, pregnancy-related, illness-related, treatment-related, and other confounding variables, including anxiety and mood disorders before pregnancy.

Important findings from the study are presented in Table 1. In summary, the authors found that early gestational exposure to benzodiazepines was associated with an increased risk of spontaneous abortion. The risk was elevated with short- as well as with long-acting benzodiazepines.

Table 1. Important Findings From a Study on the Risk of Spontaneous Abortion Associated With Early Gestational Benzodiazepine Exposure[2]

1. There was higher benzodiazepine exposure, early in gestation, in cases relative to controls (1.4% vs 0.6%, respectively). The association between spontaneous abortion and early gestation benzodiazepine exposure was statistically significant (OR, 1.85; 95% CI, 1.61–2.12).
2. The risks differed little in pregnancies exposed to short-acting benzodiazepines (n = 284; OR, 1.81; 95% CI, 1.55–2.12) and those exposed to long-acting benzodiazepines (n = 98; OR, 1.73; 95% CI, 1.31–2.28).
3. Risks were elevated for all benzodiazepines for which data were adequate for analysis, with ORs ranging from 1.48 to 3.43.
4. The risks increased in a daily dose-dependent fashion.

Abbreviations: CI = confidence interval, OR = odds ratio.

The risk was elevated with all benzodiazepines, considered individually. The risk was elevated in a daily dose-dependent fashion.

Limitations

Information for the analyses was drawn from different databases, not collected prospectively by the investigators. So this information was limited by the accuracy and completeness of the recordings. In consequence, for example, whereas the authors could adjust their analyses for diagnoses of alcohol, tobacco, and other substance use disorders, they would not have been able to capture and adjust for unreported, subthreshold use of these substances and problem use that escaped medical attention.

More importantly, there was plenty of indication from the baseline data that the case pregnancies were more disadvantaged in terms of medical and psychiatric illness, substance use disorders, medication use, and (absence of) folic acid use. Whereas these identified variables were adjusted for in the analyses, they could also have been markers for other adversities that remained unmeasured or inadequately measured. These adversities include exposure to and response to stress, the consequences of risk-taking behaviors, and the consequences of unhealthy lifestyle behaviors associated with the indication for the use of the medications. Very specifically, no effort by the authors could adjust for the greater severity of illness that necessitated benzodiazepine use in the case pregnancies. That is, confounding by indication remains an elephant in the room.

An added point is that of unknown confounds. As an example, unknown genetic variables that predispose to spontaneous abortion may have been unbalanced between cases and controls. Such variables may be linked to psychiatric diagnoses and the need for benzodiazepine use, explaining the imbalance between the groups.

What Are Future Lines of Study?

Observational studies can never confirm causal associations between an exposure and an outcome; randomized controlled trials are needed for this. Therefore, at best, this study[2] suggests that benzodiazepine exposure during pregnancy is a marker for the risk of spontaneous abortion. This signal should therefore be studied in designs that use innovative ways of addressing confounding by indication. Possibilities are outlined below.

Propensity score matching can be conducted so that known risk factors are well balanced between case and control groups. A limitation, however, is that propensity score matching cannot match for inadequately measured, unmeasured, and unknown risk factors. However, such matching as a prelude to analysis could be better than the absence of matching.[7]

Analysis can examine whether benzodiazepine exposure in the year before pregnancy (but not during pregnancy) is associated with increased risk of spontaneous abortion to the same extent as benzodiazepine exposure during pregnancy. Such analyses have been conducted in other regards, such as to examine whether antidepressant use increases the risk of hip fracture in the elderly.[8] Such analyses could indicate whether the risk runs with the exposure or with the individual.

The risk of spontaneous abortion in previously unexposed pregnancies can be compared between cases and controls. Sibling pair analyses in pregnancies exposed vs unexposed to benzodiazepines can be conducted, as has already been done in the context of child internalizing problems.[9] Such analyses have the potential to identify the contribution of unknown confounds, including shared environmental, familial, and genetic confounds.[10]

The effect of paternal exposure to benzodiazepines during pregnancy can be studied as a way of addressing unmeasured and unknown environmental confounds. This has already been done in the context of gestational antidepressant exposure and the risk of autism spectrum disorder in the offspring.[11]

Additional Note

The authors also examined the risk of spontaneous abortion associated with different antidepressant categories, and with antipsychotic drugs, as well. Risks were elevated for all analyses with adequate data for analysis. This does not mean that antidepressant and antipsychotic drugs increase the risk of spontaneous abortion because all the limitations expressed for the benzodiazepine analyses apply equally to the antidepressant and antipsychotic drug analyses.

Parting Notes

Replicatory studies, that is studies extracting information from other databases but using the same methods as the present study,[2] will serve no purpose because the limitations will remain the same. Studies on very young children that demonstrate that verbal abilities increase as the number of teeth increase will always obtain the same finding no matter how often they are performed; the replications cannot prove that verbal abilities depend on teeth. Confounding needs to be addressed, not replicated.

The critical analysis presented in this article is not an endorsement for the use of benzodiazepines during pregnancy. Medications should be used during pregnancy only when the benefits clearly outweigh the risks, and decision-making should be shared between the mother and the prescriber.

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