Epilepsy Currents
2024, Vol. 24(2) 105-107

DOI: 10.1177/15357597241227656
journals.sagepub.com/home/epi
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Caution: Benzodiazepines in Pregnancy and Risk of Adverse Perinatal Outcomes

Association Between Maternal Benzodiazepine or Z-Hypnotic Use in Early Pregnancy and the Risk of Stillbirth, Preterm Birth, and Small for Gestational Age: A Nationwide, Population-Based Cohort Study in Taiwan

Meng L, Lin C, Lin Y, Huang S, Chen Y, Shang C, Wu C, Chen L, Chan KA, Hsiao F. *Lancet Psychiatry*. 2023;10(7):499-508. doi:10.1016/S2215-0366(23)00148-7.

Background: Benzodiazepines and Z-hypnotics are commonly prescribed for anxiety and insomnia during pregnancy, but the evidence regarding potential adverse neonatal outcomes is insufficient because of poor control for confounding factors in previous studies. We therefore aimed to evaluate the association between the use of benzodiazepines or Z-hypnotics during early pregnancy and adverse neonatal outcomes (stillbirth, preterm birth, and small for gestational age). Methods: We did a nationwide, population-based cohort study in Taiwan using three data sources: Taiwan's National Birth Certificate Application database, the National Health Insurance database, and the Maternal and Child Health Database. The study cohort included all singleton pregnancies of females aged 15-50 years who gave birth between Jan 1, 2004, and Dec 31, 2018. Pregnancies without valid information were excluded. Benzodiazepine and Z-hypnotic use was defined as at least one benzodiazepine or Z-hypnotic prescription during early pregnancy (the first 20 weeks of pregnancy). The primary outcomes were stillbirth (fetal death at or after 20 weeks' gestation), preterm birth (<37 weeks' gestation), and small for gestational age (birthweight below the 10th percentile for gestational age by sex). Logistic regression models with propensity score fine stratification weighting were used to control for potential confounders and examine the association between benzodiazepines or Z-hypnotics use during early pregnancy and the risk of adverse neonatal outcomes. Odds ratios (ORs) and 95% CIs were reported. We used confounding by indication control analyses, a sibling control study, and a paternal negative control design to account for unmeasured confounders. The risk associated with exposure during late pregnancy was also assessed. Findings: Between Oct 7, 2021, and June 10, 2022, we analysed the study data. The cohort included 2 882 292 singleton pregnancies; of which, 75 655 (2·6%) of the mothers were dispensed one or more benzodiazepines or Z-hypnotics during early pregnancy. Women exposed during pregnancy were older (mean age at delivery was 31.0 years [SD 5.3] for exposed women vs 30.6 years [4.9] for unexposed women), had a higher prevalence of psychiatric disorders, and were more likely to have unhealthy lifestyle behaviours than unexposed women. Information about ethnicity was not available. Early pregnancy exposure was associated with adverse neonatal outcomes compared with non-exposure. The propensity score-weighted OR was 1.19 (95% CI 1.10-1.28) for stillbirth, 1.19 (1.16-1.23) for preterm birth, and 1.16 (1.13-1.19) for small for gestational age. After controlling for confounding by indication, there was no significant association between drug exposure and stillbirth risk; however, this attenuation was not observed for preterm birth and small for gestational age. In models with sibling controls that accounted for familial confounding and genetic factors, early exposure to benzodiazepines or Z-hypnotics was not associated with an increased risk of stillbirth and preterm birth, but it remained significantly associated with small for gestational age. The paternal negative control analyses with point estimates close to the null indicated no strong evidence of unmeasured confounding shared by the mother and the father. Substantially increased risks of stillbirth and preterm birth were observed for late pregnancy exposure. Interpretation: Benzodiazepine or Z-hypnotic use in early pregnancy is not associated with a substantial increase in the risk of stillbirth and preterm birth after accounting for unmeasured confounding factors. Clinicians should be aware of the increased risk of small for gestational age and caution should be taken when prescribing these medications during late pregnancy.

Commentary

Despite mounting data from epilepsy pregnancy registries and other observational studies examining the association of anti-seizure medications with fetal malformations, neurodevelopmental outcomes and perinatal outcomes, large gaps in this literature exist for many specific medications. Furthermore,

data on perinatal adverse outcomes including stillbirth, preterm birth, and small for gestational age (SGA) are especially sparse. Benzodiazepines are prescribed in epilepsy as continuous antiseizure medications, intermittently for seizure clusters,[1] or occasionally for anxiety symptoms, and the literature in epilepsy on perinatal outcomes for this class of medications is extremely limited. Some data exist for continuously prescribed clonazepam and clobazam from a Danish population-based study,[2] but evidence is almost nonexistent for other benzodiazepines in epilepsy, such as lorazepam and diazepam, or as needed benzodiazepines.

While it would be ideal to have more data specifically in epilepsy on perinatal outcomes with benzodiazepines, the recent Taiwanese population-based study by Meng et al[3] is an important addition to the general literature on perinatal outcomes of benzodiazepine use in pregnancy, with potential implications for epilepsy care. This well-designed study examined the association of maternal benzodiazepine or Z-hypnotic (zolpidem, zaleplon, zopiclone, eszopiclone) prescription in the first 20 weeks of pregnancy with stillbirth, preterm birth, and SGA among singleton pregnancies. In the main analysis, the unexposed group included pregnant women with no such prescriptions from 30 days prior to estimated last menstrual period through early pregnancy, and propensity score fine stratification weighting was done to control for confounders. Additional study designs were used to address different types of confounding, including: (1) to address potential confounding by indication for the prescription: control group of those who had discontinued these types of medications, and analyses restricted to those with specific, related diagnoses, (2) sibling-matched controls to address potential unmeasured confounders, and (3) paternal negative control design to evaluate for additional residual confounding. Subgroup analyses also separately examined short- and long-acting benzodiazepines and individual medications, and risks were also explored for late pregnancy or first trimester prescriptions.

Multiple key findings relevant to the epilepsy community were reported.[3] Across the various study designs, early pregnancy prescribing of benzodiazepines or Z-hypnotics (median 7 days of medication) was associated with SGA birth, with odds ratio of 1.16 in the propensity score weighted analysis and consistent estimates across other designs. The odds of SGA were elevated and of similar magnitude for benzodiazepines as a class and for lorazepam and diazepam specifically, with over 11 000 exposures to lorazepam and over 13 000 exposures to diazepam in the analyses. Also in the individual medication analyses, diazepam was associated with stillbirth in the propensity-weighted and sibling control analyses (odds ratios 1.46 and 1.52, respectively). Midazolam, with over 1000 exposures, was associated with stillbirth in the subgroup analyses (odds ratio 2.70 and 3.18 for the propensity-weighted and sibling control analyses, respectively). Finally, analyses examining late pregnancy exposure (after 20 weeks) to benzodiazepines or Z-hypnotics showed increased odds of stillbirth, preterm birth, and SGA in both propensity matched and sibling control designs, with odds ratios over 2.0 for both stillbirth and preterm birth.

Overall, these findings suggest potential increased risk of SGA from not only continuous benzodiazepine prescribing in pregnancy, but even limited benzodiazepine use in early pregnancy, given the median prescription duration of 7 days in this sample. These findings are consistent with analyses of SGA birth outcomes among smaller groups of women with epilepsy prescribed clonazepam and clobazam in the Danish population-based study of Kilic et al.[2] Together, these studies may suggest significant risk of adverse perinatal outcomes with benzodiazepines in pregnancy and potential need for closer monitoring, such as additional ultrasound monitoring for growth measurement during pregnancies exposed to benzodiazepines, and perhaps other supportive measures. Thus, benzodiazepines should potentially be added to phenobarbital, topiramate, and possibly zonisamide[4] as a group of medications warranting closer monitoring in pregnancy due to risk of SGA. Further, these brief prescriptions for diazepam or midazolam examined in the Meng et al study and found to be associated with stillbirth may be similar in overall quantity to rescue medications/cluster prevention regimens used for some epilepsy patients. Thus, rescue prescriptions may incur a previously unrecognized risk for pregnant people with epilepsy, warranting closer obstetrical monitoring.

Work by Meng et al also raises further questions about risk of medication exposure during different timeframes within pregnancy, raising concern that risk of stillbirth and preterm birth may be higher with late second trimester and third trimester exposure than early pregnancy.[3] In the North American Pregnancy Registry, adverse perinatal outcomes also appeared more likely with third trimester exposure, as risk of SGA with topiramate exposure through the third trimester was more than double the risk if topiramate was stopped before the third trimester.[4] Later in pregnancy, there is increased placental transfer and thus potential greater fetal accumulation of medications,[5] which may be particularly risky for medications with risk of adverse perinatal outcomes including stillbirth and SGA. This, together with the risks elucidated under limited prescribing duration of the benzodiazepines studied, may be reason for caution among epileptologists regarding use of benzodiazepines for cluster management during pregnancy. This poses questions for consideration about whether alternative cluster management approaches such as added doses of lower-risk continuous anti-seizure medications such as levetiracetam may be appropriate in pregnancy instead of benzodiazepines, especially for patients with seizure types that are not tonic–clonic.

Clearly, further work in this area would be ideal in epilepsy given that the overall cohort of greater than 2.5 million pregnancies included well below 1% women with epilepsy, even in the exposed group. However, it is worth noting that no future epilepsy cohort study will ever be able to include >10 000 exposures to these or other less-commonly prescribed but relevant medications in epilepsy. This study is an opportunity for the epilepsy field to consider potential risk implications and management approaches to reduce risk well before epilepsy specific–literature would provide this information. Similar

opportunities for earlier information about potential risk with medications used in epilepsy and other conditions may exist, for example via larger scale, methodologically rigorous studies on risks associated with pregabalin[6] and gabapentin[7] to complement existing data on very small numbers of exposures currently available in the epilepsy literature.[2,4] Future attention to non-epilepsy literature on this topic may be warranted, along with collaborations among different specialties to analyze perinatal outcome risk data for medications used across different indications. With regard to specific future study of adverse perinatal outcomes of benzodiazepines, more detailed dosing and duration of treatment data is needed to bring further clarity to potential risks and define implications for clinical management. In the meanwhile, epileptologists may want to consider increased caution with benzodiazepine use in pregnancy.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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