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Sedatives in pregnancy and psychiatric outcomes in offspring

Evidence is reassuring, but risk-benefit discussions with patients should reflect broader safety profile

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Anxiety and insomnia are among the most common conditions during pregnancy, yet treating them with drugs confronts clinicians with a difficult dilemma: leaving maternal illness untreated may compete with uncertainty about the consequences of fetal drug exposure. Benzodiazepines and Z-hypnotics are prescribed to approximately 2% of pregnant women worldwide, but existing evidence on their long term neurodevelopmental safety has been limited in scope and methodological rigour.[1,2] A linked large nationwide cohort study by Cho and colleagues offers qualified reassurance to clinicians and pregnant women facing this decision on the question of psychiatric and neurodevelopment effects in children (doi:10.1136/bmj-2025-0888671).[3]

Using South Korea's National Health Information Database—which includes claims data for the entire population with universal health coverage and direct linkage between mothers and their children—the authors followed nearly 3.8 million liveborn children for up to 13 years.[4] Those exposed to benzodiazepines or Z-hypnotics in utero were compared with unexposed children and with a "past user" group—children of mothers who had used these drugs before but not during pregnancy. After propensity score overlap weighting and sibling controlled analysis, prenatal exposure was not associated with any psychiatric disorder in offspring (hazard ratio 0.99, 95% confidence interval (CI) 0.94 to 1.04). Twelve specific disorders spanning neurodevelopmental and general psychiatric categories were assessed, with no excess risk detected for any one.

The study methods attempted to overcome problems seen in previous work. Earlier research often tackled confounding by indication only in sensitivity analyses rather than as part of the primary study design.[5] The past user comparator group tackles this directly, as these mothers share the same indication but stopped treatment before conception. Sibling controlled designs have been advocated as a more robust approach to disentangle drug effects from underlying maternal illness.[6] In the study by Cho and colleagues, the comparison with past users showed slightly attenuated but still elevated hazard ratios, whereas the sibling controlled analysis was decisive: the association was no longer apparent. The value of this study lies in the systematic triangulation of propensity weighted analysis, past user comparison, and sibling design—a combination that reduces the residual confounding that has limited earlier work.

Although reassuring, the findings call for careful rather than uncritical interpretation. Sibling controlled estimates for benzodiazepines (hazard ratio 0.98, 95% CI 0.93 to 1.03) and Z-hypnotics (1.12, 0.94 to 1.33) were consistent with the overall null finding; the wider interval for Z-hypnotics reflects fewer exposed pregnancies, as the two drug classes differ in patterns of use, patients' characteristics, and duration of treatment. Point estimates in certain subgroups remained modestly elevated: late pregnancy exposure (benzodiazepines: hazard ratio 1.27, 95% CI 0.95 to 1.71; Z-hypnotics: 1.81, 0.57 to 5.74) and Z-hypnotic use of 30 days or more (1.31, 0.96 to 1.78). These findings do not constitute evidence of harm, given the imprecision of the estimates, but they warrant prospective attention.

The authors acknowledge limitations including potential exposure misclassification and variable follow-up duration; and several additional limitations merit consideration. This study covers psychiatric diagnoses among liveborn offspring and cannot be taken as establishing overall perinatal safety—it does not inform risks of pregnancy loss, congenital malformations, or neonatal outcomes that also influence treatment decisions. Reassurance should therefore remain outcome specific rather than global. The sibling design cannot account for confounders varying between pregnancies and may amplify bias from non-shared factors such as changes in severity of maternal illness or psychosocial circumstances between pregnancies, which could partly explain the protective associations observed for certain outcomes such as schizophrenia spectrum disorder, eating disorders, and attention deficit-hyperactivity disorder in the sibling analysis.[7] Outcome validity also warrants scrutiny, as diagnoses were based on a single recorded code, and the validity of claims based algorithms for neurodevelopmental disorders in young children is an important consideration.[8] Follow-up into adulthood will be needed to evaluate late onset outcomes such as schizophrenia and personality disorders.

For the clinician counselling a pregnant woman with anxiety or insomnia, this study provides meaningful reassurance regarding the association between these drugs and psychiatric outcomes in children. The weight of evidence—from three converging analytical strategies across 12 psychiatric outcomes—does not support an association between benzodiazepine or Z-hypnotic use in pregnancy and psychiatric disorders in offspring, consistent with earlier sibling controlled work on autism and attention deficit-hyperactivity disorder.[9,10] This does not mean that sedatives should be prescribed without caution. Non-drug interventions, particularly cognitive behavioural therapy for insomnia, remain first line.[11,12] When drug treatment is necessary, clinicians should be mindful of signals around prolonged use and late pregnancy exposure. The risk-benefit discussion should extend to the broader safety profile

in pregnancy; evidence on miscarriage, for instance, remains inconclusive,[13] and this uncertainty may weigh heavily on patients' decision making. Clinicians must also weigh the harms of untreated maternal psychiatric illness, including adverse birth outcomes, impaired fetal neurodevelopment, and increased risk of postpartum depression.[14 -16]

Comprehensive, longitudinal national databases are increasingly providing the large scale evidence that randomised trials in pregnancy cannot ethically deliver. The systematic triangulation of propensity weighted analysis, past user comparison, and sibling design demonstrated in this study by Cho and colleagues offers a compelling example of how observational research can generate reliable estimates of prenatal drug safety.

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