Clinical and Practical **Psychopharmacology**

Safety of Pregabalin in Pregnancy

Chittaranjan Andrade, MD

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.

Department of Psychopharmacology, National Institute of Mental Health and Neurosciences, Bangalore, India (candrade@psychiatrist.com).

ABSTRACT

In different parts of the world, pregabalin is an approved treatment for neuropathic pain syndromes, fibromyalgia, partial-onset seizures, and generalized anxiety disorder. Few studies have examined the safety of pregabalin exposure during pregnancy. Among 4 studies identified through a PubMed search conducted in September 2018, one small study (exposed n = 30) recorded a major malformation rate of 3.3%, which was similar to that in unexposed controls. Another small study (exposed n = 30) recorded increased rates of spontaneous abortion (23.3%), preterm birth (25.0%), and major malformations (7.7%), none of which reached statistical significance even in unadjusted analyses. A third study (exposed n = 116) identified a significantly increased rate of major malformations (6.0%) but no increase in the rates of other adverse birth outcomes. The fourth and largest study (exposed n = 477 and n = 174; 2 datasets), which also presented the best statistical analysis, found no increase in the major malformation risk associated with pregabalin exposure. A subjective conclusion is that there is no clear signal that pregabalin exposure during pregnancy is associated with adverse gestational outcomes; however, this conclusion is limited by the consideration that all analyses were underpowered. Pregabalin use in pregnancy is therefore best restricted to circumstances in which the risk-benefit ratio is clearly favorable, and then, only after shared decision-making.

J Clin Psychiatry 2018;79(5):18f12568

To cite: Andrade C. Safety of pregabalin in pregnancy. *J Clin Psychiatry.* 2018;79(5):18f12568.

To share: https://doi.org/10.4088/JCP.18f12568

Pregabalin is a drug that has been approved for different indications across the world, including the treatment of pain syndromes such as postherpetic neuralgia,[1] painful diabetic peripheral neuropathy,[1] spinal cord injury,[2] and fibromyalgia[1]; as adjunctive treatment for partial onset seizures[3]; and for generalized anxiety disorder.[4] Sometimes, a woman receiving pregabalin may wish to become pregnant or may discover that she is pregnant, or the drug may be considered for a woman who plans pregnancy or is already pregnant. So how safe is pregabalin during pregnancy?

Earlier articles in this column examined gestational outcomes associated with antiepileptic drug exposure during pregnancy[5–7]; however, pregabalin was not included in these articles, nor were gestational outcome data for the drug available in recent meta-analyses and pregnancy registry database analyses.[8–11] Animal studies on pregabalin exposure during pregnancy have shown inconsistent effects on morphological and developmental outcomes.[12–14] This article therefore summarizes recent research in the field,[15–18] identified through a PubMed search conducted on September 7, 2018, using the search terms *pregabalin* and *pregnancy*, and through a hand search of the reference lists of identified articles.

Veiby et al

These authors[15] assessed the risks of fetal growth restriction and birth defects in children gestationally exposed to antiepileptic drugs. The data were drawn from a Norwegian birth registry. Only 30 children had been exposed to pregabalin, and only 1 of these had a major congenital malformation. The malformation rate, 3.3%, was similar to that in unexposed controls (2.9%).

Winterfeld et al

These authors[16] described a prospective observational cohort study that compared pregnancy outcomes in women exposed to pregabalin (median dose, 150 mg/d; n = 164) with those of matched controls (n = 656) who had not been exposed to medications known to be teratogenic or to any antiepileptic drugs. About 61% of women continued pregabalin beyond week 6 of gestation, and 33% continued it beyond week 7. About 13% of women were on antiepileptic drug polytherapy. The data were drawn from teratology information services and pharmacovigilance centers in 7 countries.

After conditions due to chromosomal disorders were excluded and when first trimester exposure in pregabalin (n = 116) vs control (n = 580) groups was considered, pregabalin was found to be associated with a higher risk of major birth defects (6.0% vs 2.1%; odds ratio [OR], 3.0; 95% confidence interval [CI], 1.2–7.9). However, the risk was not dose-dependent.

Pregabalin was associated with a lower live birth rate (71.9% vs 85.2%) because of a higher rate of elective (9.8% vs 5.0%) as well as medically indicated (5.5% vs 1.8%) termination of pregnancy. However, pregabalin exposure was not associated with an increased hazard of spontaneous abortion, nor did it influence birthweight, gestational age at birth, or the

rate of preterm birth. Neonatal complications, reported in 5 of 13 newborns who had been exposed to pregabalin until delivery, could plausibly have been due to competing risks.

In summary, this study suggested that pregabalin may be teratogenic; however, pregabalin did not appear to adversely influence other gestational outcomes.

Patorno et al

These authors[17] examined data from a US health care service. They compared women exposed to pregabalin during the first trimester with women unexposed to anticonvulsants and used propensity score fine stratification to adjust for over 50 potential confounders. The analyses were replicated on data drawn from another health care database. Finally, pooled estimates were calculated using data from the 2 databases and the Winterfeld et al[16] study.

In analyses of the first dataset, first trimester exposure to pregabalin (median dose, 150 mg/d; n = 477) was associated with a 5.9% rate of major congenital malformations relative to a 3.3% rate in unexposed infants (n = 1,322,955). The relative risk (RR) was 1.80 (95% CI, 1.26–2.58), reducing to nonsignificance after propensity score adjustment (RR, 1.16; 95% CI, 0.81–1.67). The RRs were nonsignificant in all analyses restricted to pregabalin monotherapy (n = 353). The results were similar in sensitivity analyses.

In analyses of the second dataset, relative to unexposed infants (n = 427,304), the adjusted RR for major congenital malformations in 174 pregabalin-exposed infants (dosing not specified) was 1.03 (95% CI, 0.56–1.90), and the RR in infants exposed to pregabalin monotherapy (n = 118) was 1.26 (95% CI, 0.64–2.49).

In the pooled analyses, the RR for major malformations was 1.33 (95% CI, 0.83–2.15) for any use of pregabalin and 1.02 (95% CI, 0.69–1.51) for use of pregabalin in monotherapy.

In summary, in this study, all 3 sets of analysis found no signal for teratogenicity associated with gestational exposure to pregabalin.

Mostacci et al

These authors,[18] drawing data for 2009–2011 from regional registries in Italy, identified 30 pregnancies that had been exposed to pregabalin. Of these pregnancies, 7 (23%) were terminated by choice. Exposed and unexposed pregnancies were compared for several gestational outcomes in analyses unadjusted for confounding variables.

The rate of spontaneous abortion in exposed vs unexposed pregnancies was 23.3% vs 11.3%, respectively (OR, 2.39; 95% CI, 0.87–5.75). The rate of preterm birth was 25% vs 14% (OR, 2.05; 95% CI, 0.48–6.76). The rate of smallness for gestational age was 6.3% vs 7.0% (OR, 0.88; 95% CI, 0.12–6.70). One (7.7%) major malformation was recorded among 13 newborns who had had first trimester exposure to pregabalin.

In summary, relative to unexposed pregnancies, exposure to pregabalin was associated with increased (crude, unadjusted) odds of many adverse outcomes; however, none of these were statistically significant.

Comments

A limitation of the Winterfeld et al[16] study, which suggested that pregabalin is teratogenic, is that it was not population-based, as was the Patorno et al[17] study. Furthermore, there were substantial differences between exposed and unexposed pregnancies, and the adjusted analyses may not have been able to account for all the differences. Residual confounding may have explained the single adverse outcome identified.

The reassuring findings of the new analyses from Patorno et al[17] should be tempered by the observation that they were based on small numbers of exposed pregnancies; additionally, exposure trimester and dose-dependent analyses were not described.

The analysis of Mostacci et al[18] may have been underpowered to identify significantly increased risks, but the increased rates of adverse outcomes reported were crude, and analyses adjusting for confounding variables were not presented.

Conclusions

The available data do not identify a signal for adverse gestational outcomes associated with pregabalin exposure during pregnancy. However, this conclusion is subjective and is based on a very small number of studies and a very small number of exposed pregnancies. Prudence dictates that the use of pregabalin during pregnancy should be restricted to situations in which the risk-benefit ratio is clearly favorable, and then, only through a shared decision-making process.

Published online: October 2, 2018.

REFERENCES

1. Arnold LM, McCarberg BH, Clair AG, et al. Dose-response of pregabalin for diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia. *Postgrad Med*. 2017;129(8):921–933.
2. Cardenas DD, Nieshoff EC, Suda K, et al. A randomized trial of pregabalin in patients with neuropathic pain due to spinal cord injury. *Neurology*. 2013;80(6):533–539.
3. Pulman J, Hemming K, Marson AG. Pregabalin add-on for drug-resistant partial epilepsy. *Cochrane Database Syst Rev*. 2014;(3):CD005612.
4. Frampton JE. Pregabalin: a review of its use in adults with generalized anxiety disorder. *CNS Drugs*. 2014;28(9):835–854.
5. Andrade C. Valproate in pregnancy: recent research and regulatory responses. *J Clin Psychiatry*. 2018;79(3):18f12351.
6. Andrade C. Adverse pregnancy outcomes associated with gestational exposure to antiepileptic drugs. *J Clin Psychiatry*. 2018;79(4):18f12467.
7. Andrade C. Major congenital malformations associated with exposure to antiepileptic drugs during pregnancy. *J Clin Psychiatry*. 2018;79(4):18f12449.
8. Weston J, Bromley R, Jackson CF, et al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. *Cochrane Database Syst Rev*. 2016;11:CD010224.
9. Veroniki AA, Cogo E, Rios P, et al. Comparative safety of anti-epileptic drugs during pregnancy: a systematic review and network meta-analysis of congenital malformations and prenatal outcomes. *BMC Med*. 2017;15(1):95.
10. Veroniki AA, Rios P, Cogo E, et al. Comparative safety of antiepileptic drugs for neurological development in children exposed during pregnancy and breast feeding: a systematic review and network meta-analysis. *BMJ Open*. 2017;7(7):e017248.
11. Tomson T, Battino D, Bonizzoni E, et al; EURAP Study Group. Comparative risk of major

congenital malformations with eight different antiepileptic drugs: a prospective cohort study of the EURAP registry. *Lancet Neurol*. 2018;17(6):530–538.
12. Morse DC, Henck JW, Bailey SA. Developmental toxicity studies with pregabalin in rats: significance of alterations in skull bone morphology. *Birth Defects Res B Dev Reprod Toxicol*. 2016;107(2):94–107.
13. Morse DC. Embryo-fetal developmental toxicity studies with pregabalin in mice and rabbits. *Birth Defects Res B Dev Reprod Toxicol*. 2016;107(2):85–93.
14. Singh KP, Gupta K. Teratogenic effects of third-generation antiepileptic drug, pregabalin: an in vivo study. *Curr Drug Saf*. 2018;13(2):113–121.
15. Veiby G, Daltveit AK, Engelsen BA, et al. Fetal growth restriction and birth defects with newer and older antiepileptic drugs during pregnancy. *J Neurol*. 2014;261(3):579–588.
16. Winterfeld U, Merlob P, Baud D, et al. Pregnancy outcome following maternal exposure to pregabalin may call for concern. *Neurology*. 2016;86(24):2251–2257.
17. Patorno E, Bateman BT, Huybrechts KF, et al. Pregabalin use early in pregnancy and the risk of major congenital malformations. *Neurology*. 2017;88(21):2020–2025.
18. Mostacci B, Poluzzi E, D'Alessandro R, et al; ESPEA Study Group. Adverse pregnancy outcomes in women exposed to gabapentin and pregabalin: data from a population-based study [published correction appears in *J Neurol Neurosurg Psychiatry*. 2018;89(5):e1]. *J Neurol Neurosurg Psychiatry*. 2018;89(2):223–224.