

MOTHERISK UPDATE

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Zopiclone use during pregnancy

ABSTRACT

QUESTION One of my patients, whom I had treated with a 2-week course of zopiclone for insomnia, conceived while using the medication. She is concerned. How should I advise her?

ANSWER Based on available, albeit limited, evidence, zopiclone does not appear to be a major human teratogen.

RÉSUMÉ

QUESTION Une de mes patientes suivait une cure de deux semaines au zopiclone pour cause d'insomnie. Elle est tombée enceinte durant cette période et elle s'inquiète. Comment puis-je la conseiller?

RÉPONSE Selon les données probantes disponibles, quoique limitées, le zopiclone ne semble pas un facteur tératogène important chez l'humain.

Zopiclone (Imovane et al), a cyclopyrrolone derivative, is a short-acting hypnotic.¹ Although structurally unrelated, it has a pharmacologic profile similar to that of benzodiazepines. Zopiclone is currently available in Canada but not in the United States.

Following oral administration, the drug is rapidly absorbed, with a bioavailability of approximately 80% and an elimination half-life that ranges from 3.5 to 6.5 hours.² Zopiclone is well tolerated and effective and is a suitable alternative to benzodiazepines for short-term treatment of insomnia.³ Rebound insomnia is substantially less frequent with zopiclone compared with hypnotic benzodiazepines. Zopiclone does not have high potential for dependence or abuse,⁴ and it has anticonvulsant, muscle relaxant, and sedative properties.

Animal reproductive studies have not shown zopiclone to have teratogenic effects.^{5,6} Human studies of pregnancy outcome following exposure to zopiclone during the first trimester of pregnancy are limited to 15 spontaneous reports to the manufacturer (Rhône-Poulenc Rorer). No congenital abnormalities were reported among women with known outcomes.

Because the safety of zopiclone in human pregnancy has not yet been studied, Motherisk recently

initiated the first prospective observational cohort study to investigate the potential teratogenic effect of zopiclone.⁷ We chose 40 pregnant women who had taken zopiclone and consulted the Motherisk Program from 1993 to 1997. Control subjects were women who contacted Motherisk for nonteratogenic exposure during pregnancy who were matched for age, cigarette smoking, and alcohol consumption with our 40 subjects. The control group had follow-up interviews similar to those of the study group. Study subjects and control women were similar with regard to gravidity, previous miscarriages and pregnancy terminations, and weight gain during pregnancy. The two groups differed in parity, with a higher proportion of women in the zopiclone group calling during their third or

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 to Dr Gideon Koren by fax at (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. This research is supported by the CIBC World Market Gundy Children's Miracle Foundation Chair in Child Health Research at the University of Toronto.

Motherisk questions are prepared by the **Motherisk Team** at the Hospital for Sick Children in Toronto and edited by **Dr G. Koren**, Professor of Pediatrics in Pharmacology, Ph University of Toronto and Chair in Child Health Research of the CIBC World Market Children's Miracle Foundation. **Dr Diav-Citrin**, **Dr Okotore**, and **Ms Lucarelli** are members of the Motherisk Team.

fourth pregnancy, and most of the control women calling during their first pregnancy.

Of the 40 women in the study group, 35 reported taking zopiclone during the first trimester and four reported taking it throughout their pregnancies. The 40 women reported various indications for zopiclone use: depression (10), insomnia (three), anxiety-depressive disorder (three), anxiety (two), bipolar disorder (two), and schizophrenia (two). Two did not know the indication, and 16 did not specify an indication.

No differences in outcome of pregnancy, delivery method, assisted deliveries, fetal distress, presence of meconium at birth, preterm deliveries, or neonatal intensive care admissions were seen between study and control groups. Newborns in the zopiclone group had a significantly lower mean birth weight (3245.9 ± 676 g) than control group newborns (3624.2 ± 536 g) ($P = .002$) and a lower gestation age (38.3 ± 2.7 weeks vs 40.0 ± 1.6 weeks) ($P = .01$).

No major malformations were found in the study group. No significant differences were found in the rate of major or minor malformations between the two groups. In each group, one infant was born with congenital hip dislocation: one required braces for 4 months (control), and one resolved after triple diapering (zopiclone).

Although our cohort of 40 women has limited power to identify an increase in teratogenic risk, lack of any serious malformations among the 31 newborns of women exposed to zopiclone during the first trimester is reassuring and suggests that the drug is not a major human teratogen. The lower birth weight and gestation age in the zopiclone group could be attributed to the disease state of the women. Previous reports have shown high rates of

prematurity and low birth weight in infants born to women with mental disorders.^{8,9}

Interestingly, only a few of the women in our cohort reported using zopiclone for the indication listed in the *Compendium of Pharmaceutical and Specialties*¹⁰: short-term treatment of insomnia. ❖

References

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