Paroxetine use in pregnancy and increased risk of heart defects

Evaluating the evidence

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ABSTRACT

QUESTION I have a patient who has just found out she is pregnant, and she is currently taking paroxetine for severe anxiety and depression. Owing to conflicting results from different studies, as well as my patient hearing about the lawsuit against GlaxoSmithKline, I did try her on other antidepressants; however, only paroxetine was effective, so she restarted it. Now she is pregnant and euthymic, but she is extremely worried about taking the drug. How do I explain the confusing information to her?

ANSWER There has recently been an increase in the publication of studies reporting pregnancy outcomes associated with use of antidepressants; many focus on paroxetine, often with conflicting results. However, despite these studies and the precedent-setting lawsuit in which GlaxoSmithKline was ordered to pay $2.5 million to the family of a child with a heart defect whose mother took paroxetine in the first trimester of pregnancy, the evidence that paroxetine increases the rate of cardiac malformations above the population baseline risk of 1 out of 100 pregnancies just does not exist.

RÉSUMÉ

QUESTION En 1985, je vous ai demandé conseil pour la première fois à propos d'une de mes patientes qui, ne sachant pas qu'elle était enceinte, avait pris de la tétracycline. J'étais très préoccupé, tout comme ma patiente, qui était prête à mettre un terme à sa grossesse par crainte d'avoir causé des problèmes à son bébé. Directement grâce à vos conseils, le « fœtus » est maintenant l'heureuse mère de 25 ans d'un fils en bonne santé. Votre réponse à ma question se lisait comme suit : Cette femme a été exposée à la tétracycline bien avant la formation des bourgeons dentaires; par conséquent, il n'y a pas de risque fœtal apparent. Selon vous, quels sont certains des plus importants renseignements que vous ayez fournis aux médecins de famille en pratique active au cours des 25 dernières années?

RÉPONSE Malheureusement, trop de décisions dans la prise en charge des femmes enceintes se fondent sur de l'information erronée ou une mauvaise compréhension des risques tératogènes. Il est essentiel de prendre les décisions thérapeutiques concernant les expositions durant la grossesse en faisant un juste équilibre entre les risques de ne pas traiter la maladie maternelle et les renseignements fondés sur les données probantes existants sur la sécurité fœtale.

Paroxetine is a selective serotonin reuptake inhibitor (SSRI), used for the treatment of depression and anxiety disorders. Before late 2005, the SSRI class of antidepressants, including paroxetine, was considered relatively safe to use during pregnancy, as these antidepressants had not been found to increase the risk of major malformations above the baseline of 1% to 3% found in the general population. This was based in part on a meta-analysis and 2 database studies.[1-3]

In the fall of 2005, GlaxoSmithKline published a study on its website, with findings that indicated infants exposed to paroxetine might be at higher risk of congenital malformations, in particular cardiovascular defects.[4] This study was based on outcomes of 815 infants, and the reported incidence of cardiovascular malformations (unspecified in terms of severity) was 2% compared with 1% in the comparison group. Data were later re-analyzed and adjusted to 1.5% in the exposed group.[5]

In addition, the results of a case-control study from Sweden, which also included 815 exposures to paroxetine in early pregnancy, indicated an increased risk (also 2%) of cardiovascular defects of relatively mild types after maternal use of paroxetine.[6] A further small study, published only in abstract form,[7] completed the available evidence at this time. This preliminary data led Health Canada to issue an alert, which to date has not been revised despite the increasing number of studies that have been published in the past 5 years.[8]

New studies

At Motherisk we conducted our own prospective, comparative cohort study. From teratogen information services

around the world, we collected prospectively identified cases of infants exposed to paroxetine in the first trimester of pregnancy and compared them with a nonexposed cohort. We were able to ascertain the outcomes of 1170 infants from 8 teratogen information services and reported the rate of heart defects in the paroxetine group was 0.7% versus 0.7% in the nonexposed group.[9] Last year a meta-analysis of 11 studies documented a small increased risk of heart defects associated with paroxetine use; however, not all the relevant data were included in the study and the results were not conclusive.[10] Interestingly, in the same month another group published a large cohort study and found an increased risk of heart defects associated with citalopram and sertraline but not with paroxetine.[11]

This year, to date, 2 more studies have been published, focusing on the risk of paroxetine and heart defects. One was an update from the Swedish group[12] and the other was from the Netherlands,[13] and both reported a marginally increased risk of heart defects associated with paroxetine. Both of these studies reported an odds ratio of below 2—a marginal increase in risk.[12,13]

The most recent study was published in March 2010, in which Wurst et al updated their previous meta-analysis[10] and reported similar findings. Again, some of the same studies were not included in this meta-analysis for no plausible reasons, most notably our study with almost 1200 women,[9] which would have changed the results to non-significant if it had been included—as the authors acknowledged themselves.[14] The Wurst et al paper was published with 2 opposing commentaries from experts in the field: One expert stated, "The scientific evidence does not support the conclusion that paroxetine causes cardiovascular defects."[15] The other explained, "Evidence-based literature shows consistent epidemiologic evidence that paroxetine use during pregnancy increases the risk of cardiac malformations in newborns."[16]

Conclusion

Heart defects are relatively common in the population, as approximately 1 in 100 babies will be born with one, regardless of exposure.[17] In the absence of randomized controlled trials, observational study designs (ie, case reports, case series, cohort studies, case-control and nested case-control studies, administrative database studies, and meta-analyses) are currently used to study the safety of drugs during pregnancy, all of the above possessing both strengths and limitations.[18] However, accumulated evidence from different types of studies does not suggest that paroxetine is associated with an increased risk of heart defects.

Many family physicians are called upon today to prescribe antidepressants, and, in the absence of best practice guidelines, this evidence-based information can be helpful when discussing with their pregnant and depressed patients the risks and benefits of taking paroxetine during pregnancy.

Competing interests
None declared

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MOTHERISK

Motherisk questions are prepared by the Motherisk Team at the Hospital for Sick Children in Toronto, Ont. **Ms Einarson** is Assistant Director of the Motherisk Program.

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