

Exposure to attention deficit hyperactivity disorder medications during pregnancy

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ABSTRACT

QUESTION An 18-year-old patient of mine, currently under treatment for attention deficit hyperactivity disorder (ADHD) with methylphenidate, just found out that she is pregnant. What are the risks for the baby when the mother uses ADHD medications during pregnancy?

ANSWER Available evidence for amphetamines suggests no increased risk of malformations with use of therapeutic doses, and inadvertent exposure during pregnancy is unlikely to be harmful. Human data for methylphenidate and atomoxetine treatment in pregnancy are very limited. Documented cases do not suggest teratogenicity, but we cannot rule out this risk with the information available.

RÉSUMÉ

QUESTION Une de mes patientes de 18 ans, actuellement traitée avec du méthylphénidate pour trouble d'hyperactivité avec déficit de l'attention (THADA), vient d'apprendre qu'elle est enceinte. Quels sont les risques pour l'enfant lorsque la mère prend des médicaments contre le THADA durant la grossesse?

RÉPONSE Selon les données scientifiques actuelles, le recours aux amphétamines à doses thérapeutiques ne comporte pas de risque accru de malformations et l'exposition par inadvertance durant la grossesse ne devrait probablement pas être dommageable. Les données sur les sujets humains concernant le traitement au méthylphénidate et à l'atomoxétine durant la grossesse sont très limitées. Les cas documentés ne révèlent pas qu'ils sont tératogènes, mais nous ne pouvons pas écarter cette possibilité compte tenu des renseignements à notre disposition.

Attention deficit hyperactivity disorder (ADHD) is a common neuropsychological disorder characterized by symptoms of inattention, distractibility, and impulsivity.¹ Although previously considering it to be a childhood condition, experts now recognize that up to 70% of children with ADHD will continue to have symptoms as adults and that approximately 4% of the adult population might suffer from this disorder.²

Stimulant medications, such as dextroamphetamine and methylphenidate (MPH), are considered first-line therapy for ADHD in adults and are generally effective and well tolerated.³⁻⁵ The non-stimulant medication atomoxetine is also approved for adult ADHD and could be used as first-line therapy for certain patients.³⁻⁵

The safety of prenatal exposure to ADHD medications has not been well established; however, many women with this disorder might require treatment during pregnancy to maintain their level of function. Also, considering the high rate of unplanned pregnancies in this group, there is much potential for inadvertent exposure to these drugs. Therefore, it is important to review the available data for the use of these medications during gestation.^{6,7}

Dextroamphetamine

Most data on prenatal amphetamine exposure among human beings come from studies of illicit rather than

therapeutic use. Abuse of amphetamines in pregnancy has been associated with low birth weight, prematurity, and increased maternal and fetal morbidity. These adverse outcomes were also observed with cocaine use, and are likely related to placental vasoconstriction.⁸ However, factors such as independence from alcohol, polydrug use, and lifestyle choices have not been established.

Decreased birth weight has also been observed in infants born to women prescribed dextroamphetamine for weight control, when compared with matched controls. A mean 4% weight decrease was seen when the drug was continued beyond the 28th week, but only in women with specific prepregnancy and pregnancy weight characteristics.⁹ The absolute weight reduction ranged from 100 g to 400 g, and no difference in birth length or head circumference was noted.^{9,10} The clinical relevance of the small observed weight reduction is unclear.

The available literature on the therapeutic use of amphetamines in pregnancy suggests no increased risk of malformations. A prospective study evaluated the rate of congenital anomalies in children born to 1694 women using amphetamines as anorectics in pregnancy. When compared with a control group of 8989 women, the incidence of malformations was not increased. Anomalies were present in 3.4% of each group (relative risk [RR] 1.01, 95% confidence interval [CI] 0.76-1.32).¹¹

A large cohort study that monitored 50282 women with medication exposures during pregnancy reported on 367 women taking dextroamphetamine and 215 women taking unspecified amphetamines during the first trimester. There were 29 malformations in the dextroamphetamine group (RR 1.23, 95% CI 0.82-1.82) and 17 malformations in the general amphetamine group (RR 1.23, 95% CI 0.72-2.05). Using corrected data, the standardized risk was 1.08 (95% CI 0.65-1.68), indicating no increased risk of malformations. When all exposures were considered (1069 for dextroamphetamine, 509 for amphetamine), the relative risk remained unchanged.^{10,12}

Methylphenidate

There are very few data on the teratogenicity of MPH in humans. In total, 63 cases of MPH exposure are reported in the literature to date. Heinonen et al¹² monitored 11 mother-child pairs with first-trimester MPH exposure as part of a larger study, including 50282 women. The MPH exposures were analyzed as part of 96 pregnancies exposed to sympathomimetics, and no significant increase in malformations was observed.^{12,13} A second group of 13 newborns with early-pregnancy MPH exposure was examined as part of a surveillance study of Michigan Medicaid recipients. One major malformation and 1 cardiac defect were found among this group.¹⁴

A retrospective chart review by Debooy et al¹⁵ examined the effects of intravenous MPH and pentazocine abuse among 38 pregnant women. There were 39 exposed infants (1 set of twins), of which 21% were born prematurely, 31% had growth retardation, and 28% had symptoms of withdrawal. The set of twins had malformations compatible with fetal alcohol syndrome, and major malformations were recorded in 2 other babies. Low-normal intelligence was also seen in 4 of 21 infants that had developmental follow-up. Unfortunately, this study had no control group and was confounded by the concurrent abuse of cigarettes, alcohol, and other drugs during the pregnancies.

Atomoxetine

There are no human studies to establish the safety of atomoxetine in pregnancy. Three pregnancies have been documented in adult clinical trials, the details of which have not been published. Of these pregnancies, 2 resulted in healthy newborns and 1 was lost to follow-up.¹⁶

Animal studies have shown adverse fetal effects with atomoxetine at high doses. Pregnant rats treated with 25 mg/kg or more daily displayed decreased pup survival, and at 40 mg/kg daily, decreased fetal weight and delayed ossification were observed. In rabbits, maternal doses of 100 mg/kg daily produced offspring with reduced viability and with blood vessel abnormalities. This dose also produced slight maternal toxicity and resulted in plasma levels 3.3 times the usual human

exposure.^{14,17} Atomoxetine metabolism (metabolized by CYP 2D6) is polymorphic; therefore, a minority of women in the population would be poor metabolizers of atomoxetine, and might have plasma concentrations of this drug above the teratogenic level observed in animals.¹⁴ However, adverse effects at these high plasma levels would be likely to lead to consequent dose tapering or discontinuation. Therefore, the clinical significance of this is not clear.

Conclusion

There are not enough data on the use of ADHD medications in pregnancy to make a clear statement about their safety. Available evidence for amphetamines suggests no increased risk of malformations with use of therapeutic doses, and inadvertent exposure during pregnancy is unlikely to be harmful. Exposed infants might have slightly lower birth weights, but the clinical relevance of this is unclear.

Human data for MPH and atomoxetine treatment in pregnancy are very limited. The available cases do not suggest teratogenicity, but we cannot rule out this risk with the information available.

Alternative treatment options for ADHD, including bupropion and clonidine, have more evidence for safety in pregnancy; however, there is less evidence for the efficacy of these drugs in adult ADHD, and responses might vary. Risks and benefits need to be weighed for each patient when making treatment decisions. Careful consideration should also be given to the possibility of a withdrawal reaction if ADHD medications are abruptly discontinued. If a woman chooses to stop treatment during pregnancy, this should be done under medical supervision. ✿

MOTHE RISK

Motherisk questions are prepared by the **Motherisk Team** at the Hospital for Sick Children in Toronto, Ont. **Dr Humphreys** works at the University of British Columbia in Vancouver. **Dr Garcia-Bournissen** and **Dr Ito** are members and **Dr Koren** is Director of the Motherisk Program. **Dr Garcia-Bournissen** is supported by the Clinician Scientist Training Program, which is funded by the Ontario Student Opportunity Trust Fund, part of the Hospital for Sick Children Foundation's Student Scholarship Program. **Dr Koren** is supported by the Research Leadership for Better Pharmacotherapy during Pregnancy and Lactation and, in part, by a grant from the Canadian Institutes of Health Research. He holds the Ivey Chair in Molecular Toxicology at the University of Western Ontario in London.

Do you have questions about the effects of drugs, chemicals, radiation, or infections in women who are pregnant or breastfeeding? We invite you to submit them to the **Motherisk Program** 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) and also on the Motherisk website (www.motherisk.org).

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