EDITORIAL

Shedding Light on the Risks of Methylphenidate and Amphetamine in Pregnancy

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As use of the stimulant medications methylphenidate and amphetamines to treat attention-deficit/hyperactivity disorder has increased in the general population,[1,2] exposure to these medications during pregnancy has also increased in recent years.[3,4]

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Like many prescription medications, little is known about the effects of stimulant medications on pregnancy outcomes and fetal outcomes.[5] Studying prescription medications in pregnancy can be challenging, both because the exposures in a single population may be relatively uncommon and many of the fetal outcomes, particularly specific congenital malformations, rarely happen. Thus, innovative approaches to assessing the risks of prescription medications during pregnancy are necessary to provide information to clinicians who prescribe and women who might take these medications.

In this issue of *JAMA Psychiatry*, Huybrechts et al[6] used an innovative approach in a study that included data from 6 countries to assess specific risks of cardiac malformations in infants born to women who used methylphenidate or amphetamines in the United States and 5 Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden).[6] For the primary analysis, which only included women in the United States, the authors used linked Medicaid Analytic eXtract data to identify pregnancies with exposures to the medications and outcomes of interest. For the validation study, findings from the primary analysis were replicated using pregnancy registry data from 5 Nordic countries using the same protocol as the primary analysis. In the pooled analysis, the study found a 28% increase in cardiac malformations for infants born to mothers who had filled prescriptions for methylphenidate during pregnancy; no increase was seen for cardiac malformations related to amphetamine exposures, and no increase was seen for overall congenital malformations for either medication.

Like all studies, the study by Huybrechts et al[6] has limitations, including the possibility for misclassification of exposures and unmeasured confounding, which might bias the findings. However, the authors performed several sensitivity analyses, which demonstrated similar findings to the primary analysis, suggesting the magnitude of bias for any of the limitations is likely to be low.

Why are the findings of this study important? Medications used to treat attention-deficit/hyperactivity disorder are increasingly used by women of childbearing age as well as by pregnant women.[3,4] Because nearly half of pregnancies are unplanned, women could be taking a prescription medication and become pregnant without being aware of the concomitant risks. Thus, it is important to provide information to women who use any medication and who are pregnant or likely to become pregnant. In the clinical setting, where a pregnant woman can be prescribed a different medication or medication can be temporarily avoided, information on risks can be particularly important to guide decision making. The approach used by Huybrechts et al,[6] in which a finding seen in 1 population was replicated in a second population within the same study design, avoids the potential for undue concern that results when studies are performed sequentially with conflicting results.

This study[6] occurs in the context of growing interest in the use of big data to assess the safety of prescription medications. Drug regulatory agencies in the European Union and the United States have explored the unique opportunities and challenges that studies using big data present.[7,8] For uncommon exposures and rare outcomes, statistical power is often lacking in study outcomes, even using data from large, population-based sources (eg, data collected by large health plans). Some approaches, like the Sentinel program, combine data from multiple health care databases using a common data model and a common analytic program distributed to each entity.[9] Other approaches include creating a common protocol and distributing the protocol to the various data holders for implementation locally. The study by Huybrechts et al[6] is the first publication of the International Pregnancy Safety Study consortium, a collaboration among research groups in multiple countries with access to health care databases. In this study, the authors allowed the data users to make decisions about implementation of the protocol based on their data source and its characteristics. For example, definitions of the first trimester varied slightly across the data sources (ie, 90 days in the US study vs 97 days in the 5-country Nordic study). The International Pregnancy Safety Study team intentionally planned the study with these features after weighing the potential advantage of tailoring the approach to the specific data set (and therefore using all the information included in each data set) vs the potential for bias resulting from differences in implementation of the study design.

Regardless of the approach, any study that sheds light on the many unknowns related to prescription medication use during pregnancy is a welcome addition to the literature, particularly when researchers apply appropriately rigorous methods, as Huybrechts et al[6] have done. While the absolute increase in cardiac malformation risk associated with meth-

ylphenidate in the study was small, these results make an important contribution to the question of the safety of methylphenidate and amphetamine use during pregnancy. The innovative approaches used by the authors add additional contributions to future questions of pregnancy-related medication safety.

ARTICLE INFORMATION

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