Developmental risks associated with use of psychoactive drugs during pregnancy are largely unknown

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Cantilino et al.[1] reported that, unlike obstetricians, neurologists, cardiologists, gastroenterologists, and general practitioners, only a minority of psychiatrists perceived psychoactive medications as potentially teratogenic agents. According to the authors, psychiatrists apparently consult the scientific literature on the association of psychoactive drugs with birth defects more frequently, and their perception of risk is thus influenced by evidence-based information. To emphasize that teratogenic risks are overestimated by non-psychiatrists, Cantilino et al.[1] argue that updated meta-analyses have demonstrated that, except for antiepileptic drugs, use of central nervous system (CNS)-active medicines in pregnancy does not pose a> 5% risk of birth defects.

Accumulating evidence suggests associations of valproic acid with neural tube defects and of topiramate (an anticonvulsant also used as an anti-obesity drug) with oral clefts. Associations of neuroleptics, antidepressants, anxiolytics, and other psychoactive drugs with specific birth defects have been reported in the literature, but in most cases conclusions remain elusive due to methodological weaknesses of retrospective studies with high non-response rates. At any rate, a distinction must be made between absence of evidence of risks (i.e., systematic reviews with or without meta-analyses did not find an association with birth defects) and the overall strength of the evidence supporting that use in pregnancy is safe. It is noteworthy that, due to ethical issues, most randomized controlled trials do not enroll pregnant women. Therefore, evidence that a psychoactive drug is safe in pregnancy is generally limited and stands on preclinical data, case reports, case series, and observational epidemiology studies.

Health risks associated with prenatal exposure to CNS-active drugs, however, are not limited to those related to the occurrence of congenital anomalies diagnosed at term or shortly thereafter. Population-based cohort studies and systematic reviews with meta-analyses indicated an increased risk of persistent pulmonary hypertension in newborns exposed to selective serotonin reuptake inhibitors (SSRIs) during late gestation.[2] A report by Källén & Reis[3] also suggested that polypharmacy with CNS-active drugs (SSRIs and others) in late pregnancy increases the risk of neonatal morbidity. Moreover, as highlighted by Källén et al.,[4] it is possible that prenatal and early postnatal exposures – covering key periods of brain circuitry development – to CNS-active drugs increase the risk of cognitive dysfunctions and neuropsychiatric disorders.

Recent advancements shed light on how environmental exposures acting through epigenetic mechanisms (e.g., DNA methylation, histone acetylation, micro-RNAs) program CNS development.[5] Experimental data suggesting that drugs (e.g., alcohol, valproate, and lithium) interfere with epigenetic programming add to the plausibility of this hypothesis. However, high-quality epidemiologic studies are needed to evaluate the potential long-term risks of cognitive impairments and psychiatric disorders arising from prenatal exposure to CNS-active drugs.

To translate current research data into clinical practice, physicians must be aware of both the known risks (evidence-based information) and the limitations of the existing scientific evidence base, including the uncertainty surrounding the long-term consequences of prenatal exposure to psychoactive drugs. Major depression and other psychiatric conditions entail maternal suffering and risks for the developing infant, and should thus be treated. Nonetheless, if a pregnant woman requires treatment, psychiatrists should try to keep the exposure of the unborn child to CNS-active agents as low as possible.

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Disclosure

The author reports no conflicts of interest.

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Authors' reply

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We would like to thank Dr. Paumgartten for his interest in our survey and agree that the developmental risks associated with the use of psychoactive drugs are largely

unknown, as there are far fewer studies reporting on these risks.

However, we believe that Dr. Paumgartten missed the important data that we reported and instead focused on the safety of psychotropic drug use in pregnancy. The objective of our study was to evaluate the risk perception of psychotropic drug use in pregnancy among physicians in different medical specialties, as clearly stated in both the abstract and main text.

We would like to reiterate that, based on scientific evidence, psychotropic drugs in general do not pose a significant teratogenic risk.[1,2] Even paroxetine, which women are advised to avoid in pregnancy, is associated with an only marginal increase in risk (odds ratio [OR] 1.29, 95% confidence interval [95%CI] 1 : 11 to 1 : 49), not exceeding the percentage researched in our article as being "perceived high risk" ($>$ 5%).[1,2] A recent review discussed studies that reported teratogenic potential and negative outcomes and noted that, when evaluating the benefit/risk ratio of SSRI treatment during pregnancy, the risks associated with discontinuation of treatment – e.g., higher frequency of relapse, increased risk of obstetric complications and postpartum depression – appeared to outweigh the teratogenic potential.[3] Even if we consider that the risks of antidepressants are still unknown, despite thousands of reported pregnancy outcomes in the literature, untreated perinatal depression can cause significant distress and is associated with known risks to the mother-infant relationship and to child development.

The take-home message of this survey was that most physicians, even those with informed experience in the treatment of psychiatric disorders during pregnancy, are reluctant to prescribe psychotropics in this setting. Challenges that surround drug treatment in the perinatal period are not just related to the safety/risk of medications, but also include the continuing stigma of mental illness, as well as fear of possible legal ramifications.[4] When this is factored in with an unrealistically high perception of treatment risk, it is understandable that physicians may be hesitant to treat a pregnant woman, even if armed with evidence-based information that suggests relative safety.

Deciding whether to continue to take a psychotropic medication during pregnancy is a complex decision for both women and their physicians. Information from friends, family, the media, and physicians can also have an important impact on decision-making regarding pharmacotherapy for psychiatric disorders during pregnancy. Empathy towards these women, combined with available evidence-based information, can guide physicians in advising their patients to make an informed decision, despite the absence of definitive clinical guidelines, to ensure the best possible outcome for both mother and child.

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Still on religiosity and alcohol use

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Lucchetti et al.[1] provided relatively good evidence of the consistent pattern of association found between some elements of religiosity and alcohol use. The large sample size and population-based design count as strengths of the study.

Understanding the negative relationship between religiosity and alcohol consumption sometimes highlights the need for more information, e.g., the proscriptive nature of respondents' religious affiliation. In certain non-Western countries, where some religious activities include heavy episodic drinking and ceremonial drinking bouts, it becomes more difficult to explain why regular attendance is associated with reduced alcohol consumption in those circumstances. This suggests there are possible confounders, e.g., cultural values, personality, and stressful life events, that interplay with religiosity to influence its impact on alcohol use.[2] It would be appreciated if the authors could provide more background information on the relationship between culture and religion in the study setting. This is because certain religious beliefs and practices, e.g., existence of God, are culturally sanctioned, as some societies – particularly in non-Western regions of the world – strongly discourage atheistic views. This could potentially affect the validity of the questions used to assess religiousness in this study.

One could also argue based on the "moral community hypothesis" that when religion is a clear characteristic of