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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