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EDITORIALS

Prenatal exposure to antidepressants and increased risk of psychiatric disorders

How can we disentangle the effects of antidepressants from the underlying risks?

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"Will this drug harm my child's brain?" Pregnant women who need antidepressants to treat severe depression ask this question every day worldwide. Despite antidepressants being one of the most studied drug groups in pregnancy, conflicting research findings and a polarised debate make this question extremely challenging to answer. As pregnant women are rarely included in randomised controlled trials, we need alternative methods to establish fetal safety. Prospective, long term pharmacoepidemiological studies among pregnant women offer the only real solution.

Liu and colleagues (doi:10.1136/bmj.j3668) find an association between prenatal exposure to antidepressants and psychiatric disorders in childhood.[1] They suggest that the observed association may be due to the underlying maternal illness, antidepressants, or a combination of both. To a greater extent than previous studies, they explore a range of psychiatric outcomes including autism, mental retardation, and mood disorders. Using data from several Danish healthcare registries, the authors identified more than 900 women who continued antidepressants during pregnancy and more than 1400 women who discontinued them.

Overall, the children of women who continued using antidepressants had a 30% higher risk of psychiatric disorders than children of women who discontinued antidepressants during pregnancy (hazard ratio 1.3, 95% confidence interval 1.2 to 1.4). The largest effect estimate was found for mood disorders, for which the adjusted hazard ratio was 2.8 (1.6 to 4.8) when antidepressant continuers were compared with discontinuers. In absolute terms, 0.5% of psychiatric disorders could be prevented if the association is causal and mothers in the antidepressant continuation group stopped taking their antidepressants before pregnancy.

Several things should be considered when interpreting the results. Firstly, pregnant women do not have antidepressants prescribed at random. Among the continuers, 7.7% had an inpatient psychiatric treatment up to two years before pregnancy and 28.5% had an outpatient one, compared with 4.3% and 2.5% among the women who discontinued antidepressants during pregnancy. Only the most severely sick women have drugs prescribed in pregnancy. Consequently, confounding by indication is a major challenge in pharmacoepidemiological studies.[2] Including a disease comparison group with women discontinuing antidepressants before pregnancy, as in Liu and colleagues' study, offers an important advantage over studies using only healthy comparison groups, as it allows researchers to disentangle the effect of antidepressants from the underlying maternal psychiatric disease.

The authors also use paternal exposure to antidepressants to explore unmeasured confounding by family environment.[3 4] Such negative controls have been used in other recent studies on antidepressants,[5] as well as on other substances in pregnancy.[6-8] Liu and colleagues' study finds an association between paternal antidepressant use and any child psychiatric disorder and neurotic, stress related, and somatoform disorders, but not the other outcomes for which maternal antidepressant use was associated with increased risks. This suggests that we cannot entirely exclude unmeasured familial confounding as an alternative explanation for the findings.

Secondly, the study contributes to the emerging discussion about how we should measure long term neurodevelopmental outcomes. As new studies on the effects of drugs on human neurodevelopment are published,[5-10] we need to think critically about different outcome measures. To what extent can psychiatric diagnoses adequately capture subtle effects on the developing fetal brain? Can psychometric instruments predict cognitive, psychomotor, or behavioural disorders in children? Recent initiatives suggest that consideration of a spectrum of neurodevelopment, not just diagnostic categories, is important.[11] Further debate and the development of authoritative guidance on how to measure neurodevelopmental outcomes and how to analyse, interpret, and report study data should be a priority.

Lastly, it is important that researchers report absolute risks to facilitate communication between clinicians and pregnant women, as Liu and colleagues have done in their paper. For

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example, if prenatal exposure to antidepressants is associated with a 23% increased risk of autism in children,[1] and assuming a baseline prevalence of autism of 1%,[12] then for every 10 000 women who continue treatment during pregnancy 23 additional cases of autism would occur. This number may be alarming to some patients and reassuring to others.

Understanding the reproductive safety of drugs requires consideration of long term neurodevelopmental outcomes. Observational studies, for all their flaws, are a necessary piece of the puzzle, and healthcare databases such as the one used for this study provide a rich resource, particularly if they are augmented by additional data sources to reduce confounding.[13] However, database and registry studies have limitations and must be supplemented by genetic and epigenetic studies, pharmacokinetic data, animal studies, and in vitro research, which together can provide a more complete picture of the mechanisms by which drugs may act on the developing fetus.

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