Antiseizure medication and early pregnancy loss: should we be worried?

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Each year, a large number of pregnancies are exposed to antiseizure medication (ASM) worldwide, when women treated with ASMs for conditions such as epilepsy, bipolar disorder, anxiety, depression, migraine or neuropathic pain become pregnant, and the use is rising.[1] The impact that ASMs may have on maternal, pregnancy and child outcomes has been widely debated for decades, yet knowledge about the risk posed by ASMs on fundamental outcomes, such as early pregnancy loss, remains limited. Forbes and colleagues report findings from a cohort study based on data on more than 1 million pregnancies in the UK from 1995 to 2018, suggesting that first-trimester ASM use does not increase the risk of miscarriage.[2]

To understand how they reach their conclusion, one must be familiar with a common type of bias in pharmacoepidemiological studies, known as confounding by indication—a bias that arises when the indication for using a particular drug is independently associated with the outcome of interest. Forbes and colleagues initially demonstrate that the three main indications for ASM use in their pregnant population are all associated with an increased risk of miscarriage (regardless of ASM use), thereby emphasising the need to account for this type of bias. The key to overcoming confounding by indication is to select a reference group that shares the indication with the exposed group but without sharing the exposure, thereby ideally cancelling out the effect of the underlying indication for treatment and leaving any remaining risk difference due to the drug exposure itself (once adjusted for other confounders). Using this rationale, Forbes and colleagues defined several different reference groups (eg, ASM-unexposed pregnancies of mothers with conditions treatable with ASMs; pregnancies of ASM discontinuers; and pregnancies with first-trimester exposure to lamotrigine, the ASM with the safest known risk profile), and showed that once the indication was accounted for, the miscarriage rates in pregnancies with first-trimester ASM exposure were generally not elevated beyond that of the reference groups. Careful consideration must, however, be given to the choice of these reference groups, because they may differ in other aspects than ASM treatment, for example, women who are able to discontinue treatment prior to pregnancy likely differ from women in need of continuous ASM treatment in pregnancy, and this may potentially be related to the risk of pregnancy loss.

So, do the study findings mean that there is no longer reason for worry with regard to ASM use and early pregnancy loss? Not just yet. Studying early pregnancy losses is inherently difficult since as many as 60% of all conceptions are lost before the pregnancy is clinically recognised.[3] These unrecognised early pregnancy losses were not captured in the study by Forbes and colleagues, and as such, the study was not able to rule out that ASMs may influence the risk of loss in the earliest parts of pregnancy. Furthermore, 13.4% of eligible pregnancies (15 976 of 1 190 343) were excluded in the study by Forbes and colleagues since the pregnancy outcome was unknown. While these pregnancies were broadly similar to those with known outcomes, a slightly elevated proportion of ASM exposure was observed among the excluded pregnancies (0.93%) compared with the included ones (0.77%). This discrepancy could potentially lead to an underestimation of the association between ASM usage and miscarriage within the study sample, if miscarriages were also more prevalent among pregnancies with unknown outcome. Finally, in pregnancies of people with epilepsy, Forbes and colleagues found indications of a dose-dependent risk of miscarriage, particularly for valproate, and although this was not observed in pregnancies with indications other than epilepsy, it underscores that additional research into this area is still needed. Moreover, considering the recent concerns regarding the reproductive toxicity of paternal valproate exposure as well,[4] such investigations may be warranted for both maternal and paternal ASM use.

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