

Antidepressant exposure during the first trimester does not increase the risk of cardiac malformations in infants

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COMMENTARY ON: Huybrechts KF, Palmsten K, Avorn J, *et al.* Antidepressant use in pregnancy and the risk of cardiac defects. *N Engl J Med* 2014;370:2397–407.

WHAT IS ALREADY KNOWN ON THIS TOPIC?

Previous studies have had conflicting and inconsistent findings regarding the rates of cardiac malformations in infants exposed to antidepressant medications during the first trimester. Concerns remain, particularly with regard to paroxetine, which has been associated with ventricular outflow tract obstruction,¹ and sertraline, which has been associated with ventral septal defects.^{1 2} It has remained unclear if these associations are causal or if risk factors having to do with the underlying illness, depression, play a role. The goal of this study was to conduct a large cohort study examining the risk of cardiac malformations in infants exposed to antidepressant medications in utero while controlling for the illness, depression.

WHAT DOES THIS PAPER ADD?

- ▶ The unadjusted OR for cardiac malformations for infants exposed to any antidepressant was 1.25 (95% CI 1.15 to 1.36) but declined to 1.12 (95% CI 1.01 to 1.25) when the analysis was restricted to women diagnosed with depression, and to 1.02 (95% CI 0.90 to 1.15) with propensity-score stratification, which controlled for proxies of depression severity.
- ▶ The results demonstrate no substantial increase in the risk of cardiac malformations in infants exposed to antidepressants during the first trimester when the analysis was restricted to women with depression.
- ▶ Owing to the large sample size (949 504 women), the authors were able to compare the outcomes of women with depression who took antidepressants with the outcomes of women who did not take antidepressants in the first trimester, thus controlling for the illness itself. This is important because other factors that are more common in the population of women with depression, such as smoking, concomitant medication use, obesity or diabetes, might underlie an association between antidepressants and cardiac malformations.³

LIMITATIONS

- ▶ The cohort included only live births, thus missing cardiac malformations that resulted in death or termination, which could potentially underestimate the total risk.
- ▶ Prescription records were used to determine exposure, which may overestimate the number of women who took medication, since filling a prescription does not mean that the woman took the medication.
- ▶ Incomplete information existed for lifestyle factors, such as smoking, obesity and substance use, which may have influenced the risks.

- ▶ The authors used proxies for depression severity and did not control for severity via direct measurement or determine whether women were actively depressed during pregnancy. Severity of depression and depressive symptoms during pregnancy might conceivably increase the risk for cardiac malformations via depression-associated behaviours such as smoking, substance use or concomitant medication use.³

WHAT NEXT IN RESEARCH

These results should be replicated in another sample that will allow identification of what risk factors and behaviours found more commonly in women with depression might underlie the association with cardiac defects seen in previous studies and in the unadjusted analysis in this study. Future research should also control for severity of depressive illness during pregnancy using prospectively collected direct measurements with mood rating scales such as the Hamilton Depression Scale or the Edinburgh Postnatal Depression Scale, rather than proxies.

COULD THESE RESULTS CHANGE YOUR PRACTICES AND WHY?

These results from a study conducted in such a large sample are reassuring and will help inform the discussion of the risks and benefits of antidepressant use during pregnancy with patients. My clinical practice will change in that I can now offer my patients a large definitive study that addresses this question rather than discuss multiple, inconsistent and smaller studies.

Competing interests JLP has received legal consulting fees from law firms representing Astra Zeneca, Eli Lilly, Pfizer and Johnson & Johnson.

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