Clinical reviews

Our panel of GPs review recent research papers in their specialist areas that may influence the way you practise

Reviewers

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Mental health

Should SSRIs be discontinued in pregnancy?

Exposure to selective serotonin reuptake inhibitors (SSRIs) or venlafaxine in early pregnancy is associated with a small increase in the risk of birth defects but this does not appear to be due to a teratogenic effect of the drugs, a large multinational cohort study has found.

The cohort consisted of 2.3 million liveborn singleton children from five Nordic countries (Denmark, Finland, Iceland, Norway and Sweden). Data were obtained from national birth, death and prescription registers. Antidepressant exposure was defined as a redeemed prescription from 30 days before the last menstrual period until the end of the first trimester.

A total of 36,722 (1.6%) infants were exposed to an SSRI or venlafaxine in the first trimester. Of those exposed, 3.7% had a major birth defect compared with 3.1% of those who were not exposed:

- Adjusted odds ratio (OR) for a major birth defect 1.13 (95% CI: 1.06-1.20)

There were also small significant increased risks of:

- Any cardiac birth defect OR 1.15 (95% CI: 1.05-1.26)
- Septal defects OR 1.17 (95% CI: 1.05-1.31)
- Right ventricular outflow tract obstruction defects OR 1.48 (95% CI: 1.15-1.89)

Confounding by indication is a serious problem in studies of this type i.e. it may be depression itself which is causing the increased risk of birth defects. Data were not available to allow adjustment for depression or its severity. Depression may be associated with poor health behaviours: the study did adjust for smoking but not for other lifestyle factors e.g. diet, alcohol and substance use.

Sibling controlled analysis was used to try to eliminate confounding by residual lifestyle factors; however, this will only control for poor health behaviour which was common to both pregnancies. There were 2,288 siblings identified who differed from one another both in their exposure or nonexposure to antidepressants and in the presence or absence of birth defects.

In the sibling analyses, the risk of birth defects was no longer significantly increased adjusted OR 1.06 (95% CI: 0.91-1.24) and the risk of any cardiac birth defect was reduced OR 0.92 (95% CI: 0.72-1.17) as was the risk of right ventricular outflow tract obstruction defects OR 0.56 (95% CI: 0.21-1.49).

This suggests that the association was due to lifestyle factors. However:

- The sibling cohort was only one-thousandth the size of the total cohort
- There is a plausible teratogenic mechanism i.e. disruption of serotonin signalling during embryogenesis
- The variation in risk between antidepressants (e.g. 45% increased risk of septal defects with fluoxetine, 18% reduced risk with escitalopram) suggests a causal link, although the confidence intervals overlap.

There are two reasons why the study may have underestimated the size of the association between SSRI/venlafaxine exposure and birth defects. First, the definition of antidepressant exposure was less stringent than that adopted by a previous study (two or more prescription redemptions) which used some of the same data and reported a higher risk of septal heart defects OR 1.99.[1]

Second, there were no data regarding termination of pregnancy for fetal abnormalities, miscarriages and stillbirths due to birth defects. A large Danish national cohort study found that women who took an SSRI in early pregnancy had a 27% increased risk of miscarriage.

However, the rate of miscarriage was also increased by 24% among women who stopped their SSRI treatment 3-12 months before pregnancy.[2]

In my opinion, the teratogenic potential of SSRIs/venlafaxine remains neither proven nor disproven.

The decision whether or not to stop antidepressant treatment in women who are planning pregnancy or have an unplanned pregnancy is not easy. However, the evidence suggests:

- If SSRIs are teratogenic, the absolute risk is very low (previous estimate of NNH = 246)[1]
- Stopping treatment does not reduce the risk of miscarriage[2]
- The risk of depression relapse during pregnancy is substantially greater if treatment is stopped.[3]

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- **Furu K, Keiler H, Haglund B et al. Selective serotonin reuptake inhibitors and venlafaxine in early pregnancy and risk of birth defects: population based cohort study and sibling design. *BMJ* 2015;350:h1798**

REFERENCES

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3 Cohen LS, Altshuler LL, Harlow BL et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. *JAMA* 2006;295:499-508

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