Use of selective serotonin reuptake inhibitors or venlafaxine in early pregnancy

A Scandinavian cohort study found that taking specific selective serotonin reuptake inhibitors or venlafaxine in early pregnancy was associated with an increased risk of birth defects. However, the risk was not significant when infants exposed to these antidepressants were compared with brothers or sisters who had not been exposed.

Overview: Deciding whether to use medication to treat mental health problems in women who are pregnant can be difficult. If a woman with a severe mental health problem stops taking her medication when she becomes pregnant, she may adversely affect her own mental health and her ability to care for her unborn child (Kalifeh et al. 2015). However, as with most evidence generated in this field, there are no randomised controlled trials on the efficacy of antidepressants in pregnancy, and safety data for this group come from observational studies.

Studies of selective serotonin reuptake inhibitors (SSRIs), the most commonly prescribed antidepressants during pregnancy, are conflicting. The most consistent birth defects reported are cardiovascular defects, while other birth defects – such as anal and urethral defects, clubfoot and abnormally shaped skull – have also been reported in early pregnancy, but less consistently. Taking the noradrenaline reuptake inhibitor [(S)NRI] venlafaxine in early pregnancy has been associated with several types of birth defect (Polen et al. 2013).

Current advice: The NICE guideline on antenatal and postnatal mental health gives specific advice on managing depression in women during pregnancy and the postnatal period. Non-pharmacological treatments are recommended for persistent subthreshold depressive symptoms, or mild to moderate depression, unless there is a history of severe depression. The following options may be considered for women who currently have moderate or severe depression:

- a high-intensity psychological intervention (for example, cognitive behavioural therapy)
- a tricyclic antidepressant, SSRI or (S)NRI if she understands the risks associated with the medication and the mental health problem in pregnancy and the postnatal period and:
  - she has expressed a preference for medication or
  - she declines psychological interventions or
• her symptoms have not responded to psychological interventions

MHRA guidance on SSRIs and (S)NRIs highlights a small increase in the risk of cardiovascular defects from about 1 in 1000 to less than 2 in 1000 when paroxetine and fluoxetine are taken during the first trimester. It also discusses risks for the newborn when antidepressants are taken later in pregnancy. The UK Teratology Information Service provides advice to NHS professionals on medicine use in pregnancy.

The NICE pathway on antenatal and postnatal mental health brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.

New evidence: A population-based cohort study (Furu et al. 2015) looked at whether taking specific SSRIs (fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine and escitalopram) or venlafaxine in early pregnancy was associated with an increased risk of birth defects, particularly cardiovascular defects.

National health registers for Denmark, Finland, Iceland, Norway and Sweden were used to identify 2.3 million women who had single births between 1996 and 2010. Filled prescriptions for an SSRI or venlafaxine from 30 days before the first day of the last menstrual period until the end of the first trimester were considered, and outcomes of the infant up to a year after birth were studied.

Diagnosis of major birth defects was 13% higher among the 36,772 infants exposed to SSRIs or venlafaxine during the first trimester than in the 2,266,875 unexposed infants (adjusted odds ratio [OR]=1.13, 95% confidence interval [CI] 1.06 to 1.20; absolute risk=3.7% versus 3.2%).

Infants exposed to SSRIs or venlafaxine had a 15% relative increase in cardiac birth defects overall (adjusted OR=1.15, 95% CI 1.05 to 1.26; absolute risk=1.5% versus 1.2%). When specific cardiac defects were considered, infants exposed to SSRIs or venlafaxine had a higher level of right ventricular outflow tract obstruction defects (adjusted OR=1.48, 95% CI 1.15 to 1.89) and atrial and ventricular septal defects (OR=1.17, 95% CI 1.05 to 1.31).

Fluoxetine, paroxetine and citalopram were all associated with cardiac defects, whereas a significant effect was not reported with other specific SSRIs and venlafaxine. Clubfoot, abdominal wall defects (omphalocele) and anal defects were also reported.

The authors then did a sibling analysis that compared 980 infants who had been exposed to SSRIs or venlafaxine with 1308 brothers or sisters who had not been exposed. The associations between SSRIs or venlafaxine and birth defects were no longer statistically significant in this analysis (major birth defects adjusted OR=1.06, 95% CI 0.91 to 1.24; cardiac birth defects adjusted OR=0.92, 95% CI 0.72 to 1.12; right ventricular outflow tract obstruction defects adjusted OR=0.56, 95% CI 0.21 to 1.49).

A strength of this study is the large number of women in the cohort. Limitations include the smaller numbers in the sibling analysis and, therefore, lower statistical power. In addition, non-adherence to dispensed antidepressants may have caused misclassification of exposure, and the analysis did not adjust for all confounding factors, such as lifestyle, alcohol consumption and depression severity.

Commentary by Louise Jackson, Chief Pharmacist, North Staffordshire Combined Healthcare NHS Trust:

“The initial analyses in this study found an increased risk of any birth defect and overall cardiac birth defects in women exposed to SSRIs or venlafaxine in pregnancy. In particular, the prevalence of septal defects and right ventricular outflow tract defects was higher in exposed infants. However, Furu et al. (2015) concluded that exposure to these medicines during pregnancy was not associated with a
substantial increase in birth defects, with the lack of an association in the sibling controlled analyses pointing against a teratogenic effect of SSRIs or venlafaxine.

“This population-based cohort study is extensive including 2.3 million infants, of which 1.6% were assumed to have exposure to SSRIs or venlafaxine during the first trimester. However, fewer than 1000 exposed infants were assessed in the sibling comparison. This small number of cases made it difficult to detect statistically significant differences given that these birth defects are known to occur in around 1 per 1000 live births in non-exposed infants.

“An additional study by Reefhuis et al. (2015) found that only paroxetine and fluoxetine were associated with birth defects, similar to Furu et al. (2015). The strongest effect sizes seemed to be for paroxetine on neural tube and abdominal wall defects (anecephaly and omphalocele). The effects of paroxetine and fluoxetine on cardiac defects were a little greater than those reported by Furu et al. (2015). As in the Furu study, despite the large number of live births reviewed, only small numbers of infants exposed to SSRIs were included in fully adjusted analyses (n=957).

“Both studies provide further evidence to inform discussions with women considering taking SSRIs during pregnancy. However, these studies focused on live births, so do not have any information on whether SSRIs affected stillbirth or defects identified in pregnancy, and had low numbers of infants exposed to individual medicines. The results do not lead to any new conclusions, and add to the previous studies that have shown inconsistent results.

“Overall, the results from Furu et al. (2015) support current NICE recommendations. In particular, these findings emphasise the importance of reviewing each case individually to ensure optimum treatment. Where use of an antidepressant is considered appropriate, women should be made aware of both the risk of harm from medication and the risk of ineffective treatment – and this new evidence helps to clarify that.”

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