The risk of major cardiac malformations associated with paroxetine use during the first trimester of pregnancy.

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Depressive and anxiety disorders are common in the perinatal period, with at least one in ten pregnant women in Australia suffering from depression and/or anxiety. There are well established impacts of perinatal anxiety and depression on not only the woman and her family’s well-being, but also on the emotional and cognitive development of the child, as well as an increased risk of pregnancy and birth complications. Given parental preferences and potential concern about health impacts on fetal and infant health outcomes, non-pharmacological treatment options, particularly social and psychological interventions, are particularly important in the perinatal period. Nevertheless, for some women with perinatal mental health difficulties treatment with medication will be an important therapeutic option.

In 2005, on the basis of early results of two studies which suggested an increased risk of cardiac malformations associated with in utero exposure to paroxetine, the FDA changed its classification of paroxetine from pregnancy category C to D. Subsequently a number of studies employing various research methods (with various associated methodological shortcomings) have looked at the relationship between in-utero paroxetine exposure and cardiac malformations, with sometimes conflicting results. This is in the context of a broader literature looking at the risk of cardiac and other birth defects associated with SSRIs and venlafaxine, which has similarly yielded diverse findings. As noted by Huybrechts et al the controversy remains as to whether this is a “serious concern or much ado about little.”

The implications of the concerns expressed and the lack of consensus in the literature include increased anxiety in women who are prescribed antidepressants (particularly paroxetine) during pregnancy, risks of treatment discontinuation and a lack of consistent information on which to base treatment recommendations for prescribing physicians.

Berard et al have added to the picture with their recent meta-analysis examining the risk of cardiac malformations associated with first trimester exposure to paroxetine. Notably their systematic review and meta-analysis revealed a 23% increased risk of any major congenital malformation and a 28% increased risk of major cardiac malformations associated with paroxetine. Although this paper has the methodological strengths of including more recent studies and studies with comparison groups, it is important to note that it reports associations rather than causality and that although the relative risks of exposure are increased, the absolute risks remain small and are still subject to confounding factors (the severity of depressive disorder being a significant one).

It is noteworthy that Berard has acted as a consultant for plaintiffs in litigation over antidepressants and birth defects. The comment “However, given that the benefit of using these medications during pregnancy is debatable, any increase in risk is significant” (p14), is concerning as it suggests author bias against the use of antidepressants in pregnancy - there is significant support...
for the contention that antidepressants are an effective treatment for depression, particularly severe cases, albeit the research evidence in pregnant women is not comprehensive\(^7\).

It is unlikely that this article will have a significant impact on current prescribing practices during the perinatal period. No psychotropic medication in Australia is marketed as safe for women who are pregnant and breastfeeding. As is customary practice, it remains important for the prescribing clinician, with careful consideration of the key principles of assessment and facilitation of informed consent, to provide the woman with information and assistance in weighing up the known risk and benefits of taking medication with the risks of not treating with medication, both for the woman and the fetus. Since the FDA publicity in 2005 there has been an understandable reluctance to prescribe paroxetine de novo in pregnancy, however the decision making process remains more difficult in the context of advising a pregnant woman in her first trimester who is already on paroxetine. In this case the risk benefit equation would need to consider the risks of (a) withdrawal of paroxetine and exposure of the woman/fetus to a potential withdrawal syndrome (b) relapse of anxiety/depression and its effects on mother/fetus and (c) potential impacts of a second antidepressant being prescribed during the first trimester of pregnancy (thereby exposing the fetus to the combined risks of two rather than one antidepressant).

References