**Aetiology**

**Review: fluoxetine use during the first trimester of pregnancy is not associated with an increased risk of major malformations**


**QUESTION:** Is there an increased risk of major malformations with the use of fluoxetine during the first trimester of pregnancy?

**Data sources**

Studies were identified by searching Medline and EMBASE/Excerpta Medica (up to August 1996), PSYCHOINFO and Current Contents (up to November 1996), by scanning the reference lists of all identified articles, and by contacting editors, agencies, foundations, and content experts.

**Study selection**

Studies were selected if they were prospective reports of pregnancy outcomes in women who were exposed to any dose of fluoxetine during the first trimester of pregnancy.

**Data extraction**

Data were extracted on study design, number of women exposed, and number and type of major malformation. Data were pooled to calculate a weighted average of fetal risk of major malformation.

**Main results**

31 articles were identified of which 4 met the selection criteria. These 4 studies (2 with a control group) included 367 women. 10 major malformations were reported. The weighted average of fetal risk of major malformations was 2.6% (95% CI 1.0% to 4.2%). A test of homogeneity showed that all studies detected an effect size of similar magnitude and direction. The summary odds ratio from the 2 controlled studies was not statistically significant, although it lacked precision and had a wide confidence interval (odds ratio 1.3, CI 0.5 to 3.6). With 367 women included in this analysis between 4 and 11 major malformations would be expected; 10 were observed. A review of the 10 malformations that occurred revealed no clear pattern.

**Conclusion**

The use of fluoxetine during the first trimester of pregnancy is not associated with an increased fetal risk of major malformations.

**COMMENTARY**

Addis and Koren conclude that fluoxetine is not a major teratogen and that it probably does not increase the baseline teratogenic risk in a clinically important manner. Added to their recent research, they contend that in utero exposure to fluoxetine also does not lead to neurodevelopmental problems. Altogether, this might be interpreted that fluoxetine is safe to use during pregnancy.

The results, however, should probably be considered inconclusive by clinicians because of the lack of precision shown by the wide confidence interval of the combined result of the 2 controlled studies. The confidence interval indicates that the odds ratio could be as high as 3.6 (which would be a clinically significant increase in risk)—although it is more likely to be closer to the observed pooled estimate of 1.3. What clinicians need is a point estimate with a confidence interval that excludes clinically significant risk. Larger, well controlled studies are therefore needed. In the meantime, the absence of clear evidence of an association does not prove the absence of an association.

Even if first trimester exposure did not lead to major malformations, prenatal exposure to fluoxetine could potentially lead to emotional disorders later in life. In animals, prenatal exposure to fluoxetine affects the density of serotonin transporters on serotonergic neurons in the hippocampus, amygdala, and hypothalamus, all areas that mediate emotional responses. Assessing this risk in humans will require large cohort studies with long follow up because the onset of disorders of mood or anxiety is usually in adolescence or later.

From a clinical point of view it is important to stress that the contraindications of taking drugs during pregnancy, including fluoxetine, are almost never absolute, but that a patient and her doctor need to weigh all possible risks and benefits. This concerns patients who either wish to conceive or are pregnant already, and pregnant women who develop psychiatric illness. The findings from this useful review by Addis and Koren will allow clinicians and their patients to use the best available information to make these difficult decisions.

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