MOTHERISK ROUNDS

Does Paroxetine Cause Cardiac Malformations?

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Abstract

Background: Debate has recently arisen about the safety of paroxetine use in pregnancy, prompted by reports of increased risks for cardiac defects following first trimester exposure.

Methods: We conducted a meta-analysis of nine studies.

Results: Three case-control studies (N = 30 247) found no increased risk of congenital malformations associated with paroxetine (OR = 1.18; 95% CI 0.88–1.59). Cardiac malformation rates were similar (1.1% each) and within population norms (0.7–1.2%). Six cohort studies (N = 66 409) found a non-significant weighted average difference of 0.3% (95% CI -0.1–0.7%; *P* = 0.19).

Conclusion: First-trimester exposure to paroxetine does not appear to be associated with increased rates of cardiac malformations. This information should be reassuring to prescribing physicians and women who require treatment with paroxetine in pregnancy.

Résumé

Contexte : L'innocuité de la paroxétine pendant la grossesse a récemment fait l'objet de débats provoqués par des signalements d'une hausse des risques d'anomalies cardiaques à la suite d'une exposition au cours du premier trimestre.

Méthodes : Nous avons mené une méta-analyse de neuf études.

Résultats : Trois études cas-témoins (N = 30 247) ont constaté qu'aucune hausse du risque de malformations congénitales n'était associée à la paroxétine (RC = 1,18; IC à 95 % = 0,88–1,59). Les taux de malformation cardiaque étaient semblables (1,1 % chacun) et se situaient dans les limites des normes de la population (0,7 %–1,2 %). Six études de cohorte (N = 66 409) ont constaté une différence moyenne pondérée non significative de 0,3 % (IC à 95 % - 0,1–0,7 %; P = 0,19).

Conclusion : L'exposition à la paroxétine au cours du premier trimestre ne semble pas être associée à une hausse des taux de malformation cardiaque. Cette information devrait rassurer les médecins qui prescrivent de la paroxétine et les femmes qui doivent en prendre au cours de la grossesse.

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INTRODUCTION

Mood disorders, including depression and anxiety, are commonly treated with selective serotonin reuptake inhibitor antidepressants (SSRIs). These disorders often begin during the childbearing years, and it is therefore not uncommon for women to be receiving pharmacotherapy for these conditions when they become pregnant.[1] Drug utilization surveys in Europe found that between 0.2% and 2.8% of pregnant women received a prescription for an antidepressant during early pregnancy[2–4]; in a recent study from the United States, approximately 8% of pregnant women were dispensed antidepressants during pregnancy.[5] Consequently, fetal exposure to these medications occurs frequently in the course of treating antenatal mood disorders.

Early studies examining the use of SSRIs in pregnancy did not find an increase above the baseline risk for major malformations of 1% to 3% in the general population.[6–9] More recently, however, several studies have identified an association between SSRIs and an increased risk for major malformations. Paroxetine in particular was singled out as a medication of concern.[10–13] In late 2005, GlaxoSmithKline (the manufacturer of paroxetine), the US Food and Drug Administration, and Health Canada issued warnings regarding a possible increased risk of cardiac malformations in infants exposed to this medication during the first trimester. These warnings were based on findings that were unpublished at the time.[11] Subsequently, a debate has arisen about the safety of paroxetine in the first trimester of pregnancy.

In a meta-analysis of the first few studies, we found an apparent increased risk of cardiac malformations associated with paroxetine.[14] It has long been acknowledged that bias against the null hypothesis may lead to early publication of

"positive" studies and a delayed and partial publication of "negative" studies. Since our original study, a number of additional studies have been published, increasing the overall sample size and enabling more accurate estimation of potential fetal risk.

The objectives of this report were to carry out a systematic review of the current literature and to summarize the existing data to ascertain whether first trimester exposure to paroxetine is in fact associated with an increased rate of cardiac defects. Such analysis is of utmost importance in counselling and managing women who need to use SSRIs during pregnancy.

METHODS

Data Sources

A search of the relevant literature between January 1985 and November 2007 was conducted using the Medline, EMBASE, REPROTOX, Scopus, and Biological Abstracts databases. The following terms were used in the search strategy: pregnancy outcome, congenital or fetal *and* anomalies, malformations, cardiac/heart defects *and* selective serotonin reuptake inhibitors, paroxetine, and Paxil. Additional articles and abstracts were identified by examining the references of retrieved articles, proceedings from meetings of professional societies (e.g., in the fields of teratology, obstetrics, psychiatry, pediatrics), and Internet websites.

Study Selection

We sought to retrieve all studies reporting the risk of cardiac malformations after in utero exposure to paroxetine. Studies in any language that reported first trimester (0–14 weeks' gestation) exposure to paroxetine and included a comparison group of pregnant women unexposed to paroxetine were included in the analysis. Case-control studies and cohort studies were both accepted for analysis provided that the populations from which study and control groups were drawn were similar. Review articles, case reports, editorials, studies without a comparison group, and studies that did not specifically report cardiac defects were excluded from the analysis. The inclusion and exclusion process was carried out by two reviewers, each of whom independently evaluated the articles for acceptance into the study. A third reviewer acted as an adjudicator for any unresolved disputes.

Data Extraction

The reviewers extracted the following data from the included studies into 2 × 2 tables: the number of infants born with cardiac malformations (exposed and not exposed to paroxetine in the first trimester) and the number of infants without cardiac malformations (exposed and not exposed to paroxetine in the first trimester). Again, a third reviewer was used to resolve disagreements. The 27-item checklist developed by Downs and Black[15] was used to assess the quality of the included articles and abstracts. The quality score was expressed as a percentage of the applicable items presented in the article. Again, two reviewers assessed quality; discrepancies were settled first through consensus and then through adjudication by a third reviewer if needed.

Statistical Analysis

Case-control and cohort studies were analyzed separately because of their inherent methodological differences. Data from case-control studies were combined into a summary odds ratio using a random-effects meta-analysis, which provides weights by use of both within study variance and between study variance.

For cohort studies, we calculated rates of cardiac malformations for infants exposed and not exposed to paroxetine. The effect size of interest was the difference between these rates in exposed and non-exposed infants. Rate differences were combined across cohort studies to yield a weighted average rate difference with standard error. For all analyses, we considered outcomes for live births only.

As quality assurance measures, we first assessed for the presence of heterogeneity of effects using chi-square tests. Since those tests are weak, we used a liberal cut-off for significance ($P < 0.10$). We also calculated the I^2 value, which is the proportion of between-study variance arising from study differences rather than random error.[16] Publication bias was assessed using a funnel plot and by calculating tau values according to the Begg-Mazumdar test.[17]

RESULTS

Overall, we identified 21 relevant studies in the literature search. Of these 21,12 studies were rejected either because they were review articles[7,18–20] or editorials,[21] or because they did not provide specific information regarding cardiac defects in the exposed and non-exposed groups.[22–28] Therefore, nine studies were included in the analysis: six cohort studies and three case-control studies (Table 1). Six studies[9,29–33] had comparison groups consisting of women exposed to antidepressants other than paroxetine, and three studies[34–36] used women exposed to known non-teratogenic medications as a control group.

When we examined the case-control studies for evidence of heterogeneity of effects, the chi-square value was not significant ($\chi^2 = 0.91$, df = 2, $P = 0.64$) and the I^2 value was zero, suggesting that results could reasonably be combined. There were too few studies for a funnel plot; however, the Begg-Mazumdar test found a small non-significant coefficient (tau = -0.33, $P = 0.60$).