

MOTHERISK ROUNDS

Does Paroxetine Cause Cardiac Malformations?

Lisa O'Brien, MSc,^{1,2} Thomas R. Einarson, PhD,^{1,3,4} Moumita Sarkar, MSc,^{1,2} Adrienne Einarson, RN,¹ Gideon Koren, MD^{1,2,3}

¹The Motherisk Program, The Hospital for Sick Children, Toronto, Toronto ON

²Institute of Medical Science, University of Toronto, Toronto ON

³Department of Pediatrics, The Hospital for Sick Children, Toronto, Toronto ON

⁴Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto ON

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

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“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 Black¹⁵ 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, $P = 0.60$).

Summary of studies included in the meta-analysis

Study	Publication year	Type of publication	Study design	Control group	Quality score (%)	Country
Cole et al. ³⁰	2007	Journal article	Retrospective cohort	Other SSRI or other antidepressant*	93	USA
Davis et al. ³¹	2007	Journal article	Population-based retrospective cohort	No antidepressant exposure	73	USA
Einarson et al. ³³	2007	Abstract	Cohort study	No antidepressant exposure	73	Australia, Canada, Germany, Israel, Italy, Switzerland, USA
Kallén et al. ²⁹	2007	Journal article	Prospective, recording-registry	Other SSRIs or other antidepressants*	73	Sweden
Malm et al. ⁹	2005	Journal article	Population-based cohort	No drug purchased	93	Finland
Wichman et al. ³²	2007	Abstract	Retrospective chart review	Other SSRIs or other antidepressants*	70	USA
Alwan et al. ³⁴	2007	Journal article	Case-control	Other SSRIs or other antidepressants*	93	Canada, USA
Berard et al. ³⁶	2007	Journal article	Case-control	Other SSRIs or other antidepressants*	93	Canada
Louik et al. ³⁵	2007	Journal article	Case-control	Other SSRIs or other antidepressants*	87	Canada, USA

*Other than paroxetine

The three case-control studies examined the records of more than 30 000 women and produced a non-significant summary OR of 1.18 (95% CI 0.88–1.59) (Figure 1). With this OR, an additional 170 351 patients would be required to achieve statistical significance.

No heterogeneity of effects was detected among the six cohort studies ($\chi^2 = 4.97$, $df = 5$, $P = 0.419$; $I^2 = 0$); therefore, these results were deemed suitable for combining. The funnel plot was symmetrical, with no evidence of publication bias; the Begg-Mazumdar test similarly found a small and non-significant coefficient ($\tau = 0.33$, $P = 0.60$), suggesting a lack of publication bias.

When the cohort studies were analyzed, the rates of cardiac malformations were 1.14% in the 3 428 infants exposed to paroxetine and 1.09% in the 62 981 controls. These two rates both fall within the 95% confidence interval (0.7–1.2%) for the population at large, as reported by Hoffman and Kaplan.³⁷ The weighted average difference in cardiac malformation rates between the paroxetine-exposed and non-exposed groups was very small (0.3%) and non-significant (-0.1 to 0.7%; $P = 0.19$). The results are shown in Figure 2. We had sufficient statistical power to detect significance at a rate as low as 1.26% (note that the upper 95% confidence interval in the population is 1.19%).

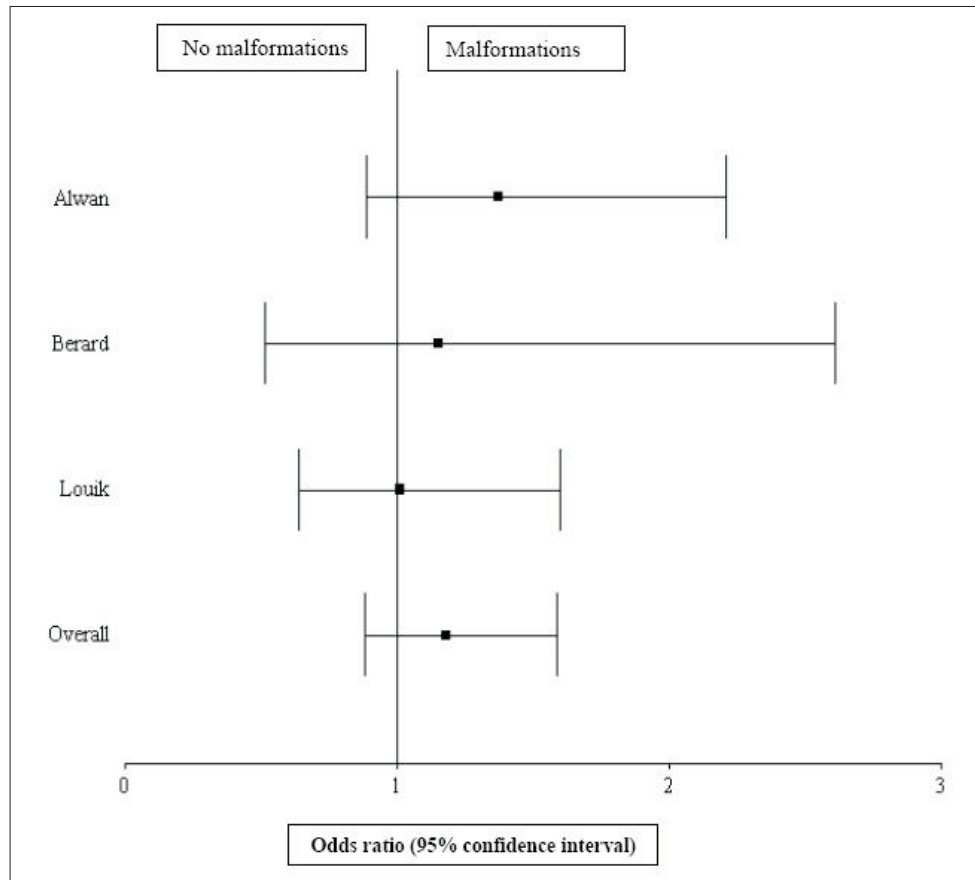
DISCUSSION

The results of the present meta-analysis, incorporating the results from nine studies,^{9,29–36} show no increased risk for congenital cardiac defects associated with paroxetine use in early pregnancy. The rates of congenital heart defects found in cohort studies (1.14% in exposed infants and 1.09% in controls) closely approximate rates found in the general population (0.7–1.2%).³⁷

In 2002, Hoffman and Kaplan³⁷ summarized all the incidence rates of malformations that had been reported in the literature. They aggregated data from thousands of births and all types of malformations. There were 43 studies that reported on cardiac outcomes. Across those studies, the rate of cardiac malformations was 0.96% (95% CI 0.73–1.19). These values therefore represent what would be expected in the general population. It is interesting that our estimates of cardiac defects fell within this range for both the exposed and comparison groups. The two distributions overlapped almost entirely.

A previous meta-analysis conducted by our group¹⁴ appeared to show an association between first trimester exposure to paroxetine and congenital heart defects. However, that apparent association disappeared in the current study when a larger sample size was available. The rates of

Figure 1. Case-control studies: odds ratio meta-analysis plot (random effects)



malformations are almost identical between groups, and both fall within what would be expected in the (non-exposed) general population. It must be acknowledged that results suggesting possible teratogenicity published relatively soon after the introduction of a therapeutic agent may merely be false positives due to random sampling. This bias against the null hypothesis stems from the early publication of “positive” results and the delayed (or absent) publication of “negative” results due to the “file drawer syndrome.”^{38,39}

It is very important that the debate surrounding the potential teratogenicity of paroxetine be resolved, because uncertainty about its safety can have adverse effects on women who require treatment for mood disorders during pregnancy. Paroxetine is one of the most commonly prescribed medications in North America; in Canada, it is the most frequently prescribed antidepressant, and in the United States, it is the third most frequently prescribed antidepressant.^{19,40} After US and Canadian regulatory agencies issued warnings regarding the potential risk of an increased rate of birth defects associated with the use of paroxetine in early pregnancy, some women who were taking paroxetine before these warnings discontinued their medication, as had

occurred when similar warnings had been issued about other drugs.⁴¹ It has been well established that discontinuation, especially abrupt discontinuation, of antidepressants in pregnancy may lead to relapse of the initial psychiatric condition, suicidal ideation, and other potentially seriously side effects, including postpartum depression.^{42,43}

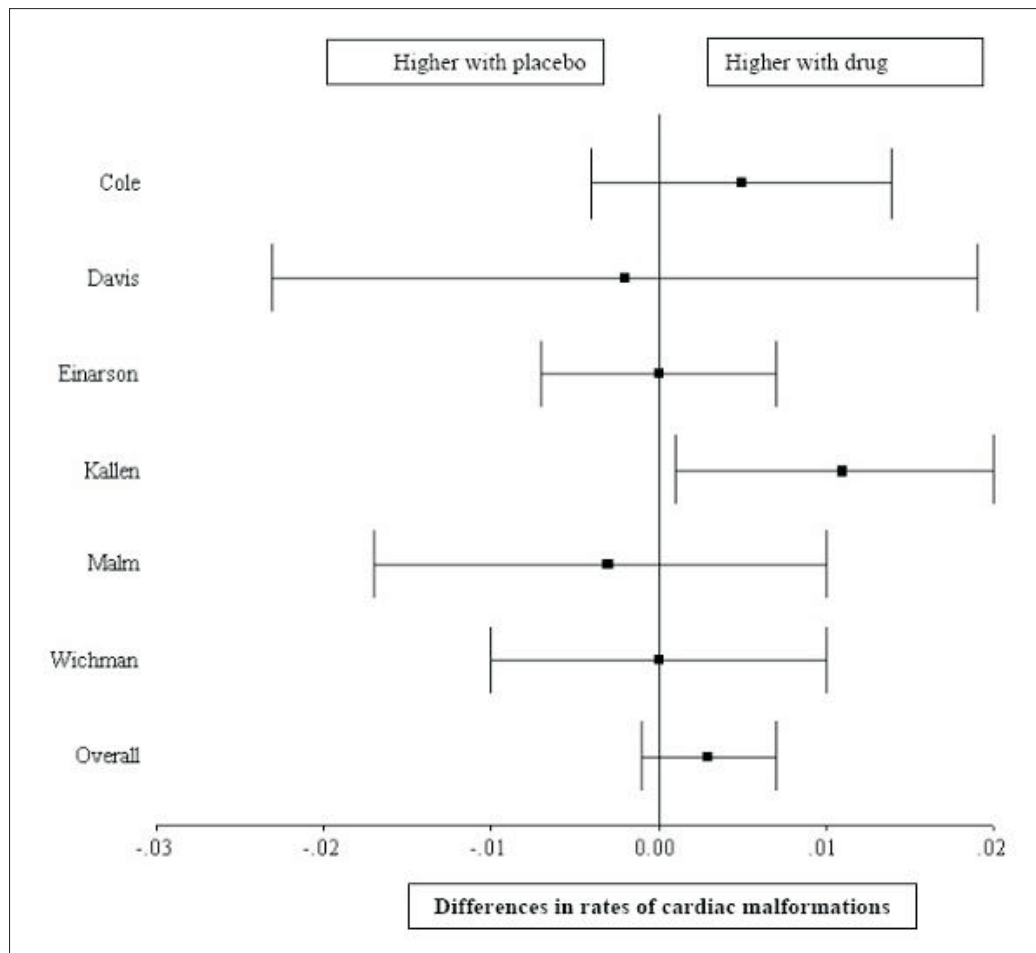
CONCLUSION

On the basis of the results of this meta-analysis, we conclude that first-trimester exposure to paroxetine appears not to be associated with an increased risk of cardiac malformations. This evidence-based information will assist women, together with their physicians and other health care providers, to make an informed decision with respect to the use of paroxetine during pregnancy. The risks and benefits associated with antidepressant therapy during pregnancy should always be assessed on a case-by-case basis.

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Figure 2. Cohort studies: meta-analysis plot (per 100 births)



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