Summer 8-13-2016

Use of Selective Serotonin Reuptake Inhibitors During Pregnancy and Risk of Congenital Cardiac Malformations

David E. Bull
Pacific University

Follow this and additional works at: http://commons.pacificu.edu/pa
Part of the Medicine and Health Sciences Commons

Recommended Citation
Use of Selective Serotonin Reuptake Inhibitors During Pregnancy and Risk of Congenital Cardiac Malformations

Abstract

Background

Untreated maternal depression has been shown to have adverse effects in many children, yet how the mother should be treated is not clear and can vary with the situation. The use of selective serotonin reuptake inhibitors (SSRIs) during the first trimester of pregnancy carries with it potential risk of congenital cardiac malformation, but individual studies and systematic analyses vary in their results.

Methods

A literature search was performed using MEDLINE-Ovid, Web of Science, Cochrane, and Google Scholar using the terms “SSRI,” “pregnancy,” and “birth defect.” The term “birth defect” was used rather than a term more specific to the heart (e.g. “cardiac malformation”) in order to keep the search sufficiently broad. The search was further restricted to studies published in the English language between 2010 and 2015. The MEDLINE search also included the terms “serotonin uptake inhibitors,” “pregnancy outcomes,” and “congenital abnormalities.” In addition to database searches, bibliographies from select journal articles were reviewed for potential sources of relevant articles. Articles were assessed using GRADE criteria (www.gradeworkinggroup.org).

Results

Two studies were found which met the inclusion and exclusion criteria, one from the US and the other from the UK, both of which were cohort studies. There was no significant increase of risk regarding exposure to SSRIs as a class of medication in either study. The RR for general SSRI exposure in the US study was 1.02 (95% CI, 0.90–1.15). The aOR for overall SSRI exposure in the UK study ranged from 1.03 to 1.14. There was a significant increase of risk with paroxetine exposure in the UK study, evidenced by an aOR of 1.78 (95% CI, 1.09–2.88).

Conclusion

The studies demonstrated low risk of congenital cardiac malformation with exposure to SSRIs as a general class. However, paroxetine and sertraline exposure showed elevated risk that was sometimes considered significant. The decision to treat maternal depression with SSRIs should involve recent and reliable literature, as well as involve the patient.

Degree Type
Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

First Advisor
Elizabeth Crawford, MS, PA-C

This capstone project is available at CommonKnowledge: http://commons.pacificu.edu/pa/560
Second Advisor
Annjanette Sommers, MS, PA-

Keywords
SSRI, birth defect, pregnancy, selective serotonin reuptake inhibitor

Subject Categories
Medicine and Health Sciences

Rights
Terms of use for work posted in CommonKnowledge.
Copyright and terms of use

If you have downloaded this document directly from the web or from CommonKnowledge, see the “Rights” section on the previous page for the terms of use.

If you have received this document through an interlibrary loan/document delivery service, the following terms of use apply:

Copyright in this work is held by the author(s). You may download or print any portion of this document for personal use only, or for any use that is allowed by fair use (Title 17, §107 U.S.C.). Except for personal or fair use, you or your borrowing library may not reproduce, remix, republish, post, transmit, or distribute this document, or any portion thereof, without the permission of the copyright owner. [Note: If this document is licensed under a Creative Commons license (see “Rights” on the previous page) which allows broader usage rights, your use is governed by the terms of that license.]

Inquiries regarding further use of these materials should be addressed to: CommonKnowledge Rights, Pacific University Library, 2043 College Way, Forest Grove, OR 97116, (503) 352-7209. Email inquiries may be directed to: copyright@pacificu.edu

This capstone project is available at CommonKnowledge: http://commons.pacificu.edu/pa/560
NOTICE TO READERS

This work is not a peer-reviewed publication. The Master’s Candidate author of this work has made every effort to provide accurate information and to rely on authoritative sources in the completion of this work. However, neither the author nor the faculty advisor(s) warrants the completeness, accuracy or usefulness of the information provided in this work. This work should not be considered authoritative or comprehensive in and of itself and the author and advisor(s) disclaim all responsibility for the results obtained from use of the information contained in this work. Knowledge and practice change constantly, and readers are advised to confirm the information found in this work with other more current and/or comprehensive sources.

The student author attests that this work is completely his/her original authorship and that no material in this work has been plagiarized, fabricated or incorrectly attributed.
Use of Selective Serotonin Reuptake Inhibitors During Pregnancy and Risk of Congenital Cardiac Malformations

David Bull

A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies

Pacific University
Hillsboro, OR

For the Masters of Science Degree, August 13, 2016

Faculty Advisor: Elizabeth Crawford, MS, PA-C
Clinical Graduate Project Coordinator: Annjanette Sommers, MS, PA-C
Abstract

Background
Untreated maternal depression has been shown to have adverse effects in many children, yet how the mother should be treated is not clear and can vary with the situation. The use of selective serotonin reuptake inhibitors (SSRIs) during the first trimester of pregnancy carries with it potential risk of congenital cardiac malformation, but individual studies and systematic analyses vary in their results.

Methods
A literature search was performed using MEDLINE-Ovid, Web of Science, Cochrane, and Google Scholar using the terms “SSRI,” “pregnancy,” and “birth defect.” The term “birth defect” was used rather than a term more specific to the heart (e.g. “cardiac malformation”) in order to keep the search sufficiently broad. The search was further restricted to studies published in the English language between 2010 and 2015. The MEDLINE search also included the terms “serotonin uptake inhibitors,” “pregnancy outcomes,” and “congenital abnormalities.” In addition to database searches, bibliographies from select journal articles were reviewed for potential sources of relevant articles. Articles were assessed using GRADE criteria (www.gradeworkinggroup.org).

Results
Two studies were found which met the inclusion and exclusion criteria, one from the US and the other from the UK, both of which were cohort studies. There was no significant increase of risk regarding exposure to SSRIs as a class of medication in either study. The RR for general SSRI exposure in the US study was 1.02 (95% CI, 0.90–1.15). The aOR for overall SSRI exposure in the UK study ranged from 1.03 to 1.14. There was a significant increase of risk with paroxetine exposure in the UK study, evidenced by an aOR of 1.78 (95% CI, 1.09–2.88).

Conclusion
The studies demonstrated low risk of congenital cardiac malformation with exposure to SSRIs as a general class. However, paroxetine and sertraline exposure showed elevated risk that was sometimes considered significant. The decision to treat maternal depression with SSRIs should involve recent and reliable literature, as well as involve the patient.

Keywords
Depression, maternal depression, pregnancy, SSRI, selective serotonin reuptake inhibitor, antidepressant, birth defect, congenital defect, congenital malformation, heart defect, cardiac defect.
Acknowledgements

[Redacted for privacy]
# Table of Contents

Abstract ..................................................................................................................................................................... 1  
Acknowledgements .............................................................................................................................................. 2  
List of Tables ........................................................................................................................................................... 4  
List of Abbreviations ............................................................................................................................................ 4  
Background ............................................................................................................................................................. 5  
Methods .................................................................................................................................................................... 7  
Results ....................................................................................................................................................................... 7  
Discussion ..............................................................................................................................................................14  
Conclusion ..............................................................................................................................................................17  
References .............................................................................................................................................................19  
Tables .......................................................................................................................................................................21  
  
Table 1 – Characteristics of Reviewed Studies .................................................................................21  
Table 2 – Exposure Categories (Huybrechts et al) ........................................................................21  
Table 3 – Categories of Cardiac Malformations (Huybrechts et al) ........................................21  
Table 4 – Categories of Congenital Cardiac Malformations (Ban et al) ..................................21  
Table 5 – SSRIs During the First Trimester of Pregnancy (Ban et al) .....................................21  
Table 6 – Summary of Findings ..............................................................................................................22
List of Tables

Table 1 – Characteristics of Reviewed Studies
Table 2 – Exposure Categories (Huybrechts et al)
Table 3 – Categories of Cardiac Malformations (Huybrechts et al)
Table 4 – Categories of Congenital Cardiac Malformations (Ban et al)
Table 5 – SSRIs During the First Trimester of Pregnancy (Ban et al)
Table 6 – Summary of Findings

List of Abbreviations

aOR .................................................................................................................................................... Adjusted Odds Ratio
CI ......................................................................................................................................................... Confidence Interval
ICD-9 ................................................................................................................................. International Classification of Diseases, Ninth Edition
ICD-10 .......................................................................................................................... International Classification of Diseases, Tenth Edition
MCA .............................................................................................................................................. Major Congenital Anomaly
RR .................................................................................................................................................... Relative Risk
SNRI ............................................................................................................................................ Serotonin-Norepinephrine Reuptake Inhibitor
SSRI ............................................................................................................................................. Selective Serotonin Reuptake Inhibitor
TCA ................................................................................................................................................. Tricyclic Antidepressant
Use of Selective Serotonin Reuptake Inhibitors During Pregnancy and Risk of Congenital Cardiac Malformations

BACKGROUND

The prevalence of maternal depression during pregnancy is noteworthy. The literature does not agree on the prevalence, with one study stating it ranges anywhere from 10% to 30%, while another places it at 18.4%. Regardless of the number of women with depression during pregnancy, treating the depression—by some method—has been shown to be very consequential because untreated depression during pregnancy can adversely affect the mother and fetus. Depression during pregnancy is associated with preeclampsia, premature birth, low weight birth, and elective abortion. Postpartum depression has been shown to contribute to developmental problems such as temperament, attachment insecurity, missed pediatric appointments, increased utilization of emergency services, and impaired language development.

There are multiple treatment modalities for maternal depression, including pharmacological, non-pharmacological, or a combination of the two. The majority of pharmacological treatment (75%) is with a class of antidepressants called selective serotonin reuptake inhibitors (SSRIs). It is incumbent, therefore, to understand the risks to the developing child that are posed with the use of SSRIs during pregnancy.

Seroetonin is a naturally occurring neurotransmitter secreted within the human body. Most commonly it is thought to function in the central nervous system for the regulation of mood. Aside from this well-known area of involvement, serotonin is also critical for the development of the heart during embryogenesis. Selective serotonin reuptake inhibitors (SSRIs) are a type of antidepressant which alter the levels of serotonin
in the circulation and are believed to have a potential impact on cardiac development
during the first trimester of pregnancy, when organogenesis is occurring (3–8 weeks post
conception).

There are manifold studies on SSRIs and how they affect overall perinatal and
antenatal development of the child, but no individual study, meta-analysis, or systematic
review of studies has been definitive. One review demonstrated a more than twofold
difference in the number of studies that show no malformation risks (negative studies) and
studies that show malformation risk (positive studies), the former being greater in
prevalence.6 Of the various problems that are believed to occur during the first trimester,
increased risk of cardiac malformation is frequently higher in many studies.7–9 In many
cases the increased risk is considered not significant, but the fact that it is a regular
occurrence in some studies has brought increased scrutiny to that particular issue. Until
2005, all SSRIs were labeled by the FDA as pregnancy category C drugs. However, in
December of that year paroxetine was reclassified as pregnancy category D after early
testing by the manufacturer GSK (GlaxoSmithKline) showed a significant increase in heart
defects—up to twice the rate compared to women on another antidepressant or no
antidepressant.10 It is important to note that these results were from early testing, were not
peer-reviewed, and that such results have not occurred since.

What follows is a review of two of the many articles that comprise the significant
collection of study on the subject. This review reflects the outcomes and conclusions of the
majority of that body of literature.
METHODS

An exhaustive literature search was performed using MEDLINE-Ovid, Web of Science, Cochrane, and Google Scholar using the terms “SSRI,” “pregnancy,” and “birth defect.” The term “birth defect” was used rather than a term more specific to the heart (e.g. “cardiac malformation”) in order to keep the search sufficiently broad. The search was further restricted to studies published in the English language between 2010 and 2015. Using advanced search features in Ovid, the MEDLINE search also included the search terms “serotonin uptake inhibitors,” “pregnancy outcomes,” and “congenital abnormalities.” In addition to database searches, bibliographies from select journal articles were reviewed for potential sources of relevant articles. The selected studies were assessed using criteria GRADE criteria, a method designed to evaluate quality of evidence and strength of recommendations (www.gradeworkinggroup.org).

RESULTS

The searches within MEDLINE-Ovid, Web of Science, and Cochrane returned 122 articles. Each of these articles was examined for relevance. Google Scholar returned 483 articles but the relevancy of the articles was low, thus only 30 articles from Google Scholar were reviewed closely. Screening for duplicates and selecting the most relevant articles yielded two cohort studies.11,12 (See Table 1.)

Huybrechts et al

Study Description—This observational study,11 published in 2014 in the New England Journal of Medicine, examined a cohort of 949,504 pregnant women in the United States enrolled in Medicaid during the years 2000 through 2007, and within a minimum time frame of 3 months prior to their last menstrual cycle through 1 month after delivery.
The data were drawn from the Medicaid Analytic eXtract for 46 states and Washington D.C., and included females ages 12 to 55 with completed, liveborn pregnancies. Criteria excluded subjects who had restricted benefits, supplementary insurance, or private insurance. Also excluded were subjects who had been receiving treatment with known teratogenic agents during the first trimester, as well as those whose infants were diagnosed with chromosomal abnormalities.

Maternal use of antidepressants was established by examining pharmacy dispensing records. The study authors defined 8 exposure categories (see Table 2): any SSRI, paroxetine, sertraline, fluoxetine, tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), bupropion, and other antidepressants. Females with no known exposure to antidepressants during their first trimester comprised the reference group. A diagnosis of depression was not required.

The presence of congenital cardiac malformations was determined by reviewing ICD-9 codes in maternal and infant medical records during the first 90 days following delivery. Using prior studies as a guideline, the outcomes were placed into 4 categories (see Table 3): any cardiac malformation, right ventricular outflow tract obstruction, ventricular septal defect, and other cardiac malformation. In order for an anomaly to be considered present, 1 of 2 criteria had to be met: a single instance of a diagnostic code accompanied by a code for a cardiac surgery or procedure, or a diagnostic code that was associated with more than one date. Malformations associated with prematurity were excluded (patent ductus arteriosus, pulmonary valve stenosis, and pulmonary artery anomalies).

In an attempt to mitigate the effects of confounders, risk factors and proxies that are both known and suspected were considered: multiple gestation, use of teratogenic
substances, use of other psychotropic medications (those not included in Table 1), and chronic maternal illness (e.g. hypertension, diabetes, renal disease, and epilepsy). Coexisting conditions were estimated by considering the number of distinct prescription drugs used by the mothers. Indications for antidepressant use other than for depression—such as sleep disorders, chronic fatigue syndrome, premenstrual dysphoric disorder, pain-related diagnoses, and other mental health disorders—were also accounted for. In addition to the many covariates considered above, sociodemographic information was evaluated: the mother’s age, race, state of residence, year of delivery, and parity.11

**Study Results**—The outcomes underwent three levels of adjustment. In the first level of adjustment the results were simply left unadjusted. The second level, in an attempt to control for underlying illness or its related factors, was restricted to women with a documented diagnosis of depression. The third level sought to further control for depression severity proxies by restricting the results to females with depression and implementing the use of propensity-score stratification.11

In confirming the analyses, the authors used a “high-dimensional propensity-score algorithm, which evaluates thousands of diagnoses, procedures, and pharmacy-claim codes to identify and prioritize covariates that serve as proxies for unmeasured confounders.”11 Because the subjects in the study represented a broader population than previous studies, effect modification was tested according to age and race. Dose–response was also analyzed for low, medium, and high doses of antidepressants.11

Within the 949 504 eligible pregnancies that were identified, 64 389 used an antidepressant during the first trimester. Of those, 46 144 were exposed to an SSRI. The most frequently used SSRIs were sertraline (14 040 women), paroxetine (11 126), and
fluoxetine (11 048). Women who filled a prescription for an antidepressant were more likely than those with no antidepressant exposure to be white, have a chronic illness (primarily diabetes or hypertension), use other psychotropic medications, and suspected of using teratogenic medications. (Unlike the subjects with known exposure to teratogenic medications who were excluded from the study at its outset, those who were merely suspected of exposure remained in the study.)¹¹

Overall, the unadjusted rate of cardiac malformations in infants was greater in those with antidepressant exposure (90.1 malformations per 10 000) than those who were not exposed (72.3 per 10 000). Each of the specific types of malformations considered (Table 3) demonstrated a higher unadjusted risk.¹¹

In the first adjustment level (no adjustment) the RR of any cardiac malformation with SSRI exposure was 1.25 (95% CI, 1.13–1.38). The second adjustment level (subjects with diagnosed depression) yielded a relative risk of 1.12 (95% CI, 1.01–1.25). The third level of adjustment (depression and propensity-score stratification) showed a relative risk of 1.02 (95% CI, 0.90–1.15).¹¹

Modification of effect was not seen according to age or race, nor was a dose–response relationship observed. Overall, SSRI exposure demonstrated a similar risk of cardiac malformation among patients of antidepressant monotherapy and polytherapy.¹¹

Significant to note in contrast to previous studies, is the absence of association between paroxetine and right ventricular outflow tract obstruction (RR 1.07; 95% CI, 0.59–1.93) or sertraline and ventricular septal defect (RR 1.04; 95% CI, 0.76–1.41).¹¹
Ban et al

**Study Description**—This cohort study\textsuperscript{12} was published in BJOG (BJOG: An International Journal of Obstetrics & Gynaecology; formerly British Journal of Obstetrics and Gynaecology) in 2014. The stated objective was to estimate the risks of major congenital anomaly among 3 groups of children: those whose mothers were diagnosed with depression and treated with antidepressants during the first trimester, those whose mothers were diagnosed with depression but not treated, and those whose mothers did not have a diagnosis of depression. They examined UK maternal–child primary care records from 1990 through 2009 for all single births to women aged 15–45 years, resulting in a study encompassing 349 127 liveborn children. They excluded those children whose mothers who were diagnosed with bipolar disorder, schizophrenia, and other significant psychotic disorders, as well as those who had prescriptions for antipsychotic or antimanic medications before childbirth.\textsuperscript{12}

Major congenital anomalies (MCAs) were identified in the children’s records using Read codes and were classified into 1 of 14 system-specific categories (heart, limb, digestive, respiratory, etc.) that are based on ICD-10. Children with genetic anomalies or teratogenic-associated anomalies were excluded from the study. In addition to the 14 categories, specific types of cardiac malformations were assessed with the goal of comparing results among other studies. Those cardiac anomaly subgroups were: septal defects, right ventricular outflow tract defects, left ventricular outflow tract defects, and other (Table 4).\textsuperscript{12}

For purposes of statistical analysis, the outcome group wherein the mother was diagnosed with depression and treated with antidepressants during the first trimester was
divided into three distinct groups: those treated with SSRIs, those treated with TCAs, and those treated with both SSRIs and TCAs. Absolute risks were calculated to determine the disease burden of the MCAs for the entire study population as well as for the five defined exposure groups. SSRIs were the most prescribed class of antidepressant, leading to the ability to estimate risk for individual drugs within that class (fluoxetine, citalopram, paroxetine, sertraline, and escitalopram). Women who were exposed to more than a single SSRI were excluded from the analysis of the individual SSRIs, but were included in the more general analyses. Odds ratios with 95% confidence intervals were calculated for overall MCA results, as well as for each of the 14 system-specific categories—all for each class of antidepressant and specific SSRIs.\textsuperscript{12}

In order for the study results to be comparable with other literature, the baseline group for all comparisons within the study was children whose mothers did not have a diagnosis of depression. To determine if pharmacologically-treated depression (a.k.a. medicated depression) was associated with a greater risk of MCAs than unmedicated depression, an analysis was performed using mothers with unmedicated depression as the baseline group. Multivariable analyses were performed to account for various maternal characteristics: age, smoking history, BMI, and socioeconomic deprivation. They also adjusted for the congenital impact certain chronic illnesses can have (diabetes, hypertension, epilepsy, and asthma).\textsuperscript{12}

**Study Results**—Within the entire study population of 349,127 single live births, 2.7% had some type of MCA (95% CI, 2.6%–2.8%). Mothers of those with MCA had similar sociodemographic profiles as those without MCA. However, sociodemographic differences
were evident when comparing mothers with depression and those without, the former having higher levels of socioeconomic deprivation, tobacco use, obesity, and asthma.\textsuperscript{12}

Overall results showed there is an increased absolute risk of MCAs among children of mothers with unmedicated perinatal depression than those with without depression, though the relative risk is not significant (1.07; 95% CI, 0.96–1.18). Similarly, antidepressant exposure did not show an increased risk of MCA overall. For cardiac malformations related to all SSRI use, absolute risks were higher in children whose mothers had either unmedicated depression or medicated depression than those without depression. However, the adjusted odds ratios show no statistically significant increase (aOR ranges: 1.03–1.14).\textsuperscript{12}

When further broken down into specific drugs within the SSRI class, fluoxetine exposure had a lower absolute risk (66/10 000) than those with no maternal depression (75/10 000) or unmedicated depression (83/10 000). The other SSRIs had a higher absolute risk: paroxetine (142/10 000), sertraline (119/10 000), escitalopram (90/10 000), and citalopram (87/10 000). The high absolute risk of paroxetine (142/10 000) represents a 78% increase in cardiac malformations (aOR 1.78; 95% CI, 1.09–2.88). An increase in congenital cardiac defects with sertraline exposure was also present (aOR 1.52; 95% CI, 0.78–2.96).\textsuperscript{12}

When the baseline group was redefined as those with unmedicated maternal depression, most of the point estimates of the adjusted odds ratios decreased slightly for SSRIs, individual SSRIs, and TCAs. No statistically significant associations were found, but paroxetine and sertraline exposure had elevated risk when compared to other SSRIs, just as they did when the baseline group was women without a diagnosis of depression. The
adjusted odds ratios for paroxetine and sertraline were 1.67 (95% CI, 1.00–2.80; \( P=0.051 \)) and 1.39 (95% CI, 0.70–2.74, \( P=0.345 \)), respectively.\(^{12}\)

Ban et al\(^{12}\) conclude that “MCA and system-specific anomaly risks were similar in children of mothers with and without antidepressants (SSRIs or TCAs) in early pregnancy.”\(^{12}\) The only evidence of increased risk of congenital cardiac malformations associated with SSRI exposure were with paroxetine and (though not statistically significant) sertraline. In addition, most of the heart anomalies associated with paroxetine exposure were relatively mild conditions and were not related to a specific type of heart anomaly.\(^{12}\)

**DISCUSSION**

The importance of treating depression in pregnant women cannot be overstated, but difficulties quickly arise when determining the treatment plan. Will the patient benefit sufficiently from non-pharmacological treatments only? Considering that untreated depression can adversely affect pregnancy outcomes, is the risk of withholding pharmacotherapy greater than prescribing antidepressants? Which antidepressant is the safest? Why is there so much variation in the literature? These and other questions are not easily answered and should be addressed using as much reliable and up-to-date research as possible, in concert with patient preferences.

Understandably, the issues surrounding pregnancy are charged with emotion. Patients who might otherwise be ambivalent about their own health and healthcare often become very protective and concerned about their unborn children. The proliferation of discrepant information available to patients regarding SSRI safety can be very confusing. Earlier this year when reporting about a just-published BMJ article on SSRI risk,\(^{13}\) the
headlines from two trusted sources were quite different. A Reuters article started with “Study links Prozac, Paxil use with birth defects”14 while The Wall Street Journal’s headline read “Birth-defect risk from antidepressants is seen as small.”15 Pfizer’s recent successes in court defending themselves against lawsuits alleging a connection between Zoloft (sertraline) and birth defects16 are also bound to add to the doubt and frustration experienced by patients. It is important that the clinician be able to explain the issues and reassure their patients as they come to a decision on treatment options. It is also important for the clinician to understand that women who are depressed may have a higher perception of teratogenic risk of a given medication—often unrealistically so—and take it into account when counseling them about the potential risks of SSRIs.17

Both studies11,12 agree that there is no significant risk for congenital cardiac malformation in children whose mothers were exposed to SSRIs during their first trimester of pregnancy. The relative risk (Huybrechts et al11) and adjusted odds ratios (Ban et al12) were not significant. They also agree that when looking at individual drugs within the SSRI class both paroxetine and sertraline have increased risk, though the outcomes differ between studies. (See Table 6.) Elevated risk with exposure to paroxetine and sertraline are consistent with other studies, though not all of them.3 Paroxetine was reclassified in 2005 to a pregnancy class D drug4 and sertraline exposure has been associated with an increase in septal defects and craniosynostosis.18

Both studies11,12 were crafted with consideration of similar, related literature in order to contribute to and be used by those in the medical research community who are attempting to determine the safety of using SSRIs during pregnancy. The authors utilized comprehensive approaches to correct and adjust for confounders, and performed a variety
of extensive analyses, all of which contribute to the overall validity of the studies. They also attempted to draw from a representative pool. Huybrechts et al\textsuperscript{11} used data from US Medicaid records. Medicaid beneficiaries have a poorer health profile when compared with those who are privately insured or have no insurance\textsuperscript{19} and Medicaid provides coverage for medical expenses for over 40\% of births in the United States.\textsuperscript{20} This difference could lead to study results that are not representative of the general US population. However, Huybrechts et al\textsuperscript{11} state that they did not find any impact due to sociodemographic characteristics during their analysis and conclude that their study should be generalizable to other populations. Ban et al\textsuperscript{12} used primary care records in the UK, ensuring a strong link to the population in general.

This paper only addressed congenital cardiac malformations, but other areas of risk have been found and studied. One phenomenon, postnatal adaptation syndrome (PNAS), has been consistently noted in several studies\textsuperscript{3,7,8} occurring in 5\%–30\% of neonates who were exposed to SSRIs.\textsuperscript{7} PNAS, which is also referred to as poor neonatal adaptation syndrome and neonatal behavior syndrome, presents with a variety of symptoms, including irritability, tachypnea, hypothermia, hypoglycemia, and (occasionally) respiratory distress.\textsuperscript{3,7} Though PNAS consistently appears to be a somewhat frequent occurrence, this condition is usually not serious and resolves within days or weeks of delivery.

To better understand the results of the GRADE evaluation, it is helpful to note that by definition cohort studies begin with a “low” rating. There were no significant limitations or flaws in either study\textsuperscript{11,12} that led to downgrading them. And while it is possible to upgrade observational studies, it very difficult to do when dealing with the question of harm. These studies then, retained their “low” rating.
In an article examining the risks and benefits of antidepressant use during pregnancy, the authors note that study outcomes can be adversely affected by significant limitations inherent in study design. They state that retrospective studies (those which use registries like the Medicaid Analytic eXtract) are not designed to study drug safety, a fact that should be taken into account when interpreting outcomes. Another potential problem with retrospective studies is that although prescription records may imply that a woman is taking her medication as prescribed, that is not necessarily the case. In general, drug adherence for mental illness has been shown to be less than 50%.

Ascertainment bias can also occur in studies which examine the use of SSRIs during pregnancy and falsely imply a relationship between usage of the drug and congenital malformations. This can occur because women with depression have higher likelihood of undergoing ultrasound scans and echocardiograms than healthy women, increasing the chances of discovering a problem. Additionally, women with depression are more likely to utilize emergency services with their infants, again increasing the chances that a defect is found that, although present, might not be found in the child of someone who doesn't go to the emergency department as often.

CONCLUSION

While the two studies suggest a low relative risk of congenital cardiac malformation in children whose mothers used SSRIs during pregnancy, it seems prudent based on the evidence to avoid the use of paroxetine and sertraline if possible. Other SSRIs have been shown herein to have risks that are considered not significant and should probably be given preference. Because there are SSRIs that present minimal risk to the
fetus, pharmacological treatment for maternal depression does not need to be eschewed
when determining a treatment plan.

It is a truism in research that more research is beneficial and preferred to less. And
in this case, one place to start may be to determine why some studies demonstrate risk
with paroxetine and sertraline exposure while others do not. Attempting to compare and
harmonize the many studies should lead to an increased safety profile for SSRI use during
pregnancy.
References


Tables

Table 1 – Characteristics of Reviewed Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Publication Bias</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huybrechts et al\textsuperscript{11}</td>
<td>cohort</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>low</td>
</tr>
<tr>
<td>Ban et al\textsuperscript{12}</td>
<td>cohort</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>low</td>
</tr>
</tbody>
</table>

Table 2 – Exposure Categories (Huybrechts et al)\textsuperscript{11}

- any SSRI
- paroxetine
- sertraline
- fluoxetine
- tricyclic antidepressants
- serotonin–norepinephrine reuptake inhibitors
- bupropion
- other antidepressants

Table 3 – Categories of Congenital Cardiac Malformations (Huybrechts et al)\textsuperscript{11}

- any cardiac malformation
- right ventricular outflow tract obstruction
- ventricular septal defect
- other cardiac malformation

Table 4 – Categories of Congenital Cardiac Malformations (Ban et al)\textsuperscript{12}

- septal defects [including atrial septal defect, ventricular septal defect, and atrioventricular septal defect]
- right ventricular outflow tract defects
- left ventricular outflow tract defects
- other cardiac malformation [including transposition of great vessels, total anomalous pulmonary venous connection, coarctation of the aorta, Ebstein’s anomaly, tricuspid atresia and stenosis, patent ductus arteriosus, single ventricle, tetralogy of Fallot, and truncus arteriosus]

Table 5 – SSRIs During the First Trimester of Pregnancy (Ban et al)\textsuperscript{12}

<table>
<thead>
<tr>
<th>MCAs</th>
<th>Fluoxetine n=3189</th>
<th>Citalopram n=1946</th>
<th>Paroxetine n=1200</th>
<th>Sertraline n=757</th>
<th>Escitalopram n=333</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>aOR (95% CI)</td>
<td>aOR (95% CI)</td>
<td>aOR (95% CI)</td>
<td>aOR (95% CI)</td>
<td>aOR (95% CI)</td>
</tr>
<tr>
<td>n/10000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All combined</td>
<td>0.91 (0.73–1.15)</td>
<td>1.06 (0.80–1.40)</td>
<td>1.08 (0.77–1.50)</td>
<td>1.27 (0.85–1.89)</td>
<td>0.85 (0.40–1.81)</td>
</tr>
<tr>
<td>Heart</td>
<td>0.84 (0.55–1.30)</td>
<td>1.13 (0.70–1.82)</td>
<td>1.78 (1.09–2.88)</td>
<td>1.52 (0.78–2.96)</td>
<td>1.15 (0.36–3.65)</td>
</tr>
</tbody>
</table>
### Table 6 – Summary of Findings

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk of Cardiac Malformation</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All SSRIs</td>
<td>Paroxetine</td>
<td>Sertraline</td>
</tr>
<tr>
<td>Huybrechts et al^{11}</td>
<td>RR 1.02 (95% CI, 0.90–1.15)(^a)</td>
<td>RR 1.07 (95% CI, 0.59–1.93)(^b)</td>
<td>RR 1.04 (95% CI, 0.76–1.41)(^c)</td>
</tr>
<tr>
<td>Ban et al^{12}</td>
<td>aOR ranges: 1.03–1.14(^d)</td>
<td>aOR 1.78 (95% CI, 1.09–2.88)(^e)</td>
<td>aOR 1.52 (95% CI, 0.78–2.96)(^f)</td>
</tr>
</tbody>
</table>

\(^a\) - Third level of adjustment (depression of diagnosis and propensity-score stratification); considered not significant

\(^b\) - Right ventricular outflow tract obstruction; considered not significant

\(^c\) - Ventricular septal defect; considered not significant

\(^d\) - Includes 4 categories: unmedicated depression, SSRIs alone, TCAs alone, SSRIs and TCAs; considered not significant

\(^e\) - Various defects; only outcome considered significant

\(^f\) - Considered not significant