# Selective Serotonin Reuptake Inhibitor Exposure During Early Pregnancy and the Risk of Fetal Major Malformations: Focus on Paroxetine

Salvatore Gentile, M.D., and Cesario Bellantuono, M.D.

***Objective:*** To analyze all studies reporting primary data on the rate of fetal malformations after early in utero exposure to paroxetine, investigated either specifically or jointly with other antidepressant medications.

***Data Sources:*** Medical literature was identified through searches of MEDLINE/PubMed, TOXNET, EMBASE, and The Cochrane Library (1980 through September 2008). Search terms were *pregnancy*, *antidepressants*, *SSRIs*, *paroxetine*, and *fetal malformations.* Additional studies were identified from the reference lists of published articles.

***Data Selection:*** Twenty-five articles reporting primary data on the rate of fetal structural malformations following exposure to paroxetine or selective serotonin reuptake inhibitors as a group during the first trimester of pregnancy were electronically or manually selected.

***Data Synthesis:*** Studies on the teratogenic risk of paroxetine show a high degree of heterogeneity. Moreover, research studies performed with the same methodology and thus showing the same level of evidence report conflicting results.

***Conclusions:*** Given the inconsistency of the findings and limitations of the methodology of the published studies, the teratogenic potential of paroxetine that has been reported in some studies remains unproven. This relevant safety question is likely to remain unanswered until large, prospective studies are conducted. Such studies should be designed to include a control group of untreated mothers with similar psychiatric diagnosis so as to differentiate effects of drug exposure from impact of underlying mental disorder on the fetus. Moreover, further experimental studies are warranted to definitively assess clinical consequences of the impact on fetal development related to physiologic effects of prenatal paroxetine exposure on different maternal and fetal parameters.

*J Clin Psychiatry 2009;70(3):414–422*



*Received June 15, 2008; accepted Sept. 29, 2008. From the Department of Mental Health, Azienda Sanitaria Locale Salerno 1, Mental Health Center n. 4, Salerno (Dr. Gentile); and the Psychiatric Unit, Department of Neuroscience, Polytechnic University of Marche, United Hospitals, Ancona (Dr. Bellantuono), Italy.*

*No direct support was received for this review article.*

*Dr. Gentile has received honoraria from Eli Lilly and Boehringer Ingelheim; has been a member of the speakers or advisory board for Eli Lilly; and has received other financial or material support from AstraZeneca, GlaxoSmithKline, Lundbeck, Janssen-Cilag, Recordati, and Bristol-Myers Squibb. Dr. Bellantuono has received honoraria from and has been a member of the speakers or advisory boards for Eli Lilly, Bristol-Myers Squibb, and InnovaPharm.*

*Corresponding author and reprints: Salvatore Gentile, M.D., Department of Mental Health, ASL Salerno 1, Mental Health Center n. 4, Piazza Galdi, 841013 Cava de' Tirreni, Salerno, Italy (e-mail: salvatore_gentile@alice.it).*

A World Health Organization report has named depression as the greatest disease burden for women worldwide.[1] In particular, the childbearing years are a time of increased vulnerability to the onset of major depression for women; unfortunately, even during pregnancy, this vulnerability does not diminish. Indeed, a recent epidemiologic study demonstrated that the percentage of pregnant women experiencing affective disorders may be as high as 14%: specifically, major and minor depression were prevalent in 3.3% and 6.9% of women, respectively.[2] In specific populations, such as poorer minority groups and unmarried teenagers, the rate of clinically relevant mood symptoms in pregnancy may be as high as 51%.[3] Moreover, mood disorders at pregnancy onset are known as strong predictors of postpartum depression.[4]

Maternal depression induces significant effects on neonatal physiology: elevated cortisol and norepinephrine levels, lower dopamine levels, and greater relative right-frontal electroencephalographic asymmetry have been described in newborns of mothers with depression during pregnancy.[5] The detrimental impact of untreated maternal depression on delivery outcomes and infants' neurocognitive and psychological development is also well known.[6–8] Neonates born to depressed mothers are at increased risk of preterm birth and low birth weight and, later in life, may show shorter stature than children of healthy mothers.[9,10] In addition, mothers with mood disorders may experience serious bonding difficulties with their newborns,[11–13] which may lead to poorer cognitive functioning during childhood and young adulthood.[14–16] Thus, seriously depressed mothers may often

need psychopharmacologic treatment in order to obtain rapid improvement in their symptoms: indeed, a full symptomatic remission is an indispensable tool for minimizing risks for the mother-infant pair.[17] Furthermore, discontinuing an effective antidepressant treatment (or even lowering the optimal dose) during pregnancy may lead to a relapse of depressive symptoms.[18]

It must also be stressed that other maternal psychiatric disorders, responsive to antidepressant medications and commonly considered as relatively moderate (such as anxiety disorders), may also have detrimental effects on the mother-infant relationship.[19,20]

However, in recent years, several concerns have been raised about safe utilization of antidepressant medications during pregnancy; for example, significant concentrations of antidepressant agents in amniotic fluid have recently been demonstrated. Although the significance of this finding is still unclear, these results suggest that maternally administered antidepressants may be accessible to the fetus in an adjunctive way.[21] In particular, in 2005, on the basis of data still unpublished at that time, the U.S. Food and Drug Administration requested that GlaxoSmithKline change the pregnancy category of one of its most-used antidepressant medications, paroxetine, from category C to category D, as the drug had been suspected of increasing risk of fetal major structural malformations and, particularly, congenital cardiac defects.[22] However, despite such concerns, paroxetine remains one of the most frequently prescribed antidepressant drugs throughout the gestational period.[23]

In the light of this background, the aim of this article is to review systematically all studies reporting the prevalence of fetal major malformations after early in utero exposure to paroxetine, investigated either specifically or jointly with other antidepressant medications. The analysis is mainly focused on balancing methodological strengths against potential weaknesses of each selected study in order to assess whether this relevant clinical concern could be deemed as definitively demonstrated and, if so, to determine its magnitude.

## METHOD

### Data Sources

Medical literature published in English since 1980 was identified through searches of MEDLINE/PubMed, TOXNET, EMBASE, and The Cochrane Library. Search terms were *pregnancy*, *antidepressants*, *SSRIs*, *paroxetine*, and *fetal malformations*. Additional studies were identified from the reference lists of published articles. Searches were last updated on September 23, 2008.

### Data Selection

Twenty-two articles reporting primary data on rate of congenital malformations following exposure to paroxetine or selective serotonin reuptake inhibitors (SSRIs) as a group during the first trimester of pregnancy were electronically identified and thus acquired for the review. The manual search performed on reference lists of these articles provided 3 additional studies, published as abstracts, investigating the teratogenic risk of paroxetine. Therefore, in total, 25 articles met the inclusion criteria.

## RESULTS

### Studies on Paroxetine

Studies specifically investigating the teratogenicity of paroxetine are shown in Table 1.

***Prospective studies.*** Preliminary data from 2 controlled studies[24,25] (including 219 women overall) failed to demonstrate an increased risk of structural teratogenicity after early in utero exposure to paroxetine. Nonetheless, the extension phase[26] of the second study suggested that paroxetine might increase the rate of fetal cardiovascular anomalies if used during the first trimester of pregnancy. The first study[24] provided a control group of unexposed infants, whereas in the second study[25] and its extension phase,[26] infants exposed to paroxetine were also matched with a control group of fluoxetine-exposed infants. All of these studies collected data from one or more teratogen information services (TISs), but they have been published only as abstracts; thus, the studies provide no information as to how length and timing of exposure were determined. However, one of these groups of researchers, Diav-Citrin et al., recently published a well-designed study[27] suggesting that the use of paroxetine during early pregnancy was not associated with increased rates of cardiovascular birth defects.

A report[28] from the Swedish Register of Congenital Malformations (Swedish National Board of Health and Welfare, Stockholm, Sweden) demonstrated an increased risk of cardiovascular malformations (especially septal or ventricular septum defects) in infants exposed early in utero to paroxetine compared with infants exposed to other SSRIs. A subsequent research study[29] performed on the same database, and thus using the same source of information, confirmed that paroxetine is the only SSRI associated with a statistically significant increase in the risk of cardiac malformations if used during the first trimester of pregnancy. This register could theoretically permit collection of crucial information on maternal use of medications through routine midwife interviews at the first antenatal care visit; however, in both studies,[28,29] the assessment of drug daily dose and of the length and timing of exposure was often incomplete.

Very recently, a relatively large controlled study analyzed the outcome of paroxetine-exposed pregnancies by using 2 sources of information: data from TISs or data incorporated in specific databases.[30] Data coming from TISs include clinical findings that are not always possible to

**Table 1. Studies Specifically Investigating the Teratogenicity of Paroxetine**

| Study | Sample Size | Study Design | Study's Level of Evidence | Dose and Timing of Exposure | Main Findings | Confounding Factors Controlled |
|---|---|---|---|---|---|---|
| Unfred et al (2001)[24] | N = 101 | Prospective, controlled | NA (abstract) | NA | Paroxetine did not increase the risk of fetal malformations | None |
| Diav-Citrin et al (2002)[25] | N = 118 | Prospective, controlled | NA (abstract) | Dose: NA<br>Timing: 89 of 118 patients during first trimester | Paroxetine did not increase the risk of fetal malformations | None |
| Diav-Citrin et al (2005)[26] | N = 330, including 118 infants previously enrolled | Prospective, controlled | NA (abstract) | Dose: NA<br>Timing: 286 of 330 patients during first trimester | Paroxetine increased the risk of cardiac anomalies (RR = 3.46, 95% CI = 1.06 to 11.24) | Genetic and cytogenetic anomalies |
| Diav-Citrin et al (2008)[27] | N = 410 | Prospective, controlled | II-1 | Dose: 20 mg (median)<br>Timing: at least during first trimester | Paroxetine did not increase the risk of cardiac anomalies | Maternal age; genetic and cytogenetic anomalies; obstetric history; smoking; dose; concomitant psychotropic medication use |
| Källén and Otterblad Olausson (2006)[28] | N = 815 | Prospective | II-3 | Dose: NA<br>Timing: first trimester | Paroxetine increased the risk of cardiac anomalies (OR = 2.29, 95% CI = 1.28 to 4.09) | Year of birth; maternal age; parity; smoking |
| Källén and Otterblad Olausson (2007)[29] | N = 943 | Prospective | II-3 | Dose: NA<br>Timing: first trimester | Paroxetine increased the risk of cardiac anomalies (OR = 1.63, 95% CI = 1.05 to 2.53) | Year of birth; maternal age; obstetric history; smoking |
| Einarson et al (2008)[30] | N = 3379, including 2205 previously published cases | Prospective | II-1 | Dose: most of the women ≤ 20 mg<br>Timing: first trimester | Paroxetine did not increase the risk of cardiac anomalies | None |
| Bèrard et al (2007)[31] | N = 542 | Case-control | II-2 | Dose: < 20 mg, > 25 mg<br>Timing: first trimester | Paroxetine increased the risk of fetal malformations as a whole (OR = 2.23, 95% CI = 1.19 to 4.17) and cardiac anomalies (OR = 3.07, 95% CI = 1.00 to 9.42) for doses > 25 mg/day | Gestational diabetes |
| GlaxoSmithKline EPIP083 (2004)[32] | N = 591 | Retrospective, cohort | II-2 | Timing: first trimester | Paroxetine increased the risk of fetal malformations as a whole (AOR = 2.01, 95% CI = 1.25 to 3.25) and cardiac anomalies (AOR = 2.00, 95% CI = 0.99 to 4.03) | None |
| GlaxoSmithKline update to EPIP083 (2004)[33] | N = 815, including 591 previously enrolled infants | Retrospective, cohort | II-2 | Timing: first trimester | Paroxetine increased the risk of fetal malformations as a whole (AOR = 1.75, 95% CI = 1.15 to 2.66) and cardiac anomalies (AOR = 1.46, 95% CI = 0.77 to 2.78) | None |
| Cole et al (2007)[34] | N = 815, the same populations investigated in the update to EPIP083 | Retrospective, cohort | II-2 | Timing: first trimester | Paroxetine increased the risk of fetal malformations as a whole (AOR = 1.89, 95% CI = 1.20 to 2.98) and cardiac anomalies (AOR = 1.46, 95% CI = 0.74 to 2.88) | Exposure to other drugs known as teratogens |

Abbreviations: AOR = adjusted odds ratio, CI = confidence interval, NA = not available, OR = odds ratio, RR = relative risk.

derive from database investigations: personal (despite telephonic) interviews with the mothers confirming drug prescription (including dose and timing of exposure) and medical confirmation of infants' birth defects. The rate of fetal cardiac malformations (1.2%)[30] was substantially similar to that shown by the control group (infants exposed to nonteratogenic agents) and the general population (0.7%[30] and 0.96%,[35] respectively). However, most of the women had received paroxetine at daily doses of 20 mg or less, and there was not enough variability to perform a dose-response analysis.[30]

***Case-control studies.*** Using different Canadian administrative databases linked together into the Medication and Pregnancy registry (Quebec, Canada), Bérard et al.[31] identified a relatively large number of women who had filled prescriptions for antidepressant monotherapy during the first trimester of pregnancy (0 to 14 weeks of gestation) and had had a live birth.[31] Two nested case-control studies were carried out within the study population: the first used all major congenital malformations combined as cases; the second used only major cardiac malformations as cases. The study's results suggested that early-pregnancy exposure to paroxetine might be associated with a 2-fold increase in the risk of major congenital malformations as a whole and a 3-fold increase in the risk of cardiac defects (bulbus cordis anomalies and anomalies of septal closure were the most frequently reported cardiac defects), but only for daily doses higher than 25 mg. However, the methodology used to categorize drug exposure was inadequate to establish clearly the length of exposure; moreover, data from this registry were unable to ensure that the prescribed medication was actually taken by the women.[31]

***Retrospective studies.*** GlaxoSmithKline supported a large study[32–34,36] consisting of 2 retrospective cohort arms and a nested case-control arm. The risk of malformations associated with all but 1 (bupropion) of the identified antidepressants, including paroxetine, was only a post hoc secondary analysis. Preliminary results on births from 1995 through 2002 suggested a statistically significant increase in rates of both congenital anomalies as a whole and cardiac defects for first-trimester paroxetine exposure.[32] Nevertheless, this risk appeared to be attenuated in an updated analysis based on additional births from January 2003 through September 2004.[33] However, neither analysis included controls of women not taking antidepressant medications, and also both were limited by the retrospective design (associated with potential recall bias) and the incomplete clinical details available in an insurance database. Moreover, the methodology used to estimate both length and timing of exposure showed further facets of inaccuracy: in fact, for each infant delivery, sequences of diagnosis and procedures in medical claims data were examined to estimate a window of time when conception "probably" occurred. The first trimester was defined as occurring from the earliest possible conception date through 12 weeks following the latest possible conception date. In light of these preliminary results, GlaxoSmithKline refined these retrospective analyses to confirm or exclude possible increased prevalence of congenital malformations among infants born to women exposed to paroxetine during early pregnancy. The results emerging from this study, labeled EPI40404,[36] were subsequently published in a peer-reviewed article.[34] The prevalence of congenital malformations as a whole was statistically higher in infants exposed in utero to paroxetine monotherapy than in infants exposed to other antidepressant monotherapies, whereas no association was found between specific cardiac defects and paroxetine exposure. However, it must be stressed that the study's design failed in overcoming methodological limitations shown by the 2 previous, unpublished analyses.

### Studies in Which Paroxetine Was Investigated Jointly With Other SSRIs

Studies investigating the teratogenicity of SSRIs as a group are shown in Table 2.

***Prospective studies.*** Using ongoing information collected prospectively from TISs,[37–39] the Swedish Medical Birth Defect Register,[40] and obstetric/pediatric records,[41] 5 studies identified a relatively large number of women who reported antidepressant use during early pregnancy. In all these studies, SSRIs showed no liability to increase the rate of fetal structural malformations. In studies that analyzed data from TISs,[37–39] the methodology most commonly used to collect relevant clinical information (such as length and timing of exposure, type of drug, and dose) was based on reports from pregnant women who were referred to TISs for assessing risk related to drugs used to treat their depression; prospective data collection occurred at the time of enquiry and at 1 month after the expected date of delivery. The study that analyzed data from the Swedish Medical Birth Defect Register[40] used the same methodology described in the preceding sentence, whereas in the study by Hendrick et al.,[41] data were drawn from a population of women who were followed up on an individual basis at a specific Pregnancy and Postpartum Mood Disorder Program.

***Case-control studies.*** The possible association of maternal use of SSRIs during early pregnancy and duration of antidepressant exposure with congenital cardiovascular defects was excluded in 3 case-control studies.[42–44] The first[42] of these studies collected data from the Swedish Medical Birth Registry (The National Board of Health and Welfare, Stockholm, Sweden), the second[43] from a national Finnish project (which linked information from 4 drug reimbursement and medical registries), and the third[44] from 3 administrative databases of the province of Quebec, Canada. Among these 3 studies, only the last one[44] attempted to differentiate effects of antidepressant

Table 2. Studies Investigating the Teratogenicity of SSRIs as a Group

| Study | Sample Size | Study Design | Study's Level of Evidence | Paroxetine Dose and Timing of Exposure | Main Findings | Confounding Factors Controlled |
|---|---|---|---|---|---|---|
| McElhatton et al (1996)[37] | Paroxetine: n = 3 of 165 | Prospective | II-3 | Dose: NA<br>Timing: first trimester | SSRIs were not associated with increased risk of teratogenicity | None |
| Kulin et al (1998)[38] | Paroxetine: n = 99 of 274 | Prospective, controlled | II-2 | Dose: 10–60 mg (range)<br>Timing: first trimester | SSRIs were not associated with increased risk of teratogenicity | SSRI dose schedule and length of therapy; maternal age; parity; tobacco and/or other substance use; medical, obstetric, and genetic history; exposure to environmental toxins |
| Maschi et al (2008)[39] | Paroxetine: n = 58 of 200 | Prospective, controlled | II-2 | NA | Antidepressants were not associated with increased risk of teratogenicity | None |
| Ericson et al (1999)[40] | Paroxetine: n = 122 of 666 | Prospective | II-3 | Dose: NA<br>Timing: first trimester | SSRIs were not associated with increased risk of teratogenicity | Maternal age; parity; smoking habits |
| Hendrick et al (2003)[41] | Paroxetine: n = 6 of 28 | Prospective | II-3 | Dose: 15–40 mg (range)<br>Timing: throughout pregnancy (3 of 6 patients) | SSRIs were not associated with increased risk of teratogenicity | None |
| Källén and Otterblad Olausson (2003)[42] | 2820 cases of exposure to SSRIs other than citalopram | Case-control | II-2 | Dose: NA<br>Timing: first trimester | SSRIs were not associated with increased risk of teratogenicity | Maternal age; parity; smoking habits; years of involuntary childlessness |
| Malm et al (2005)[43] | Paroxetine: n = 298 of 1627 | Case-control | II-2 | Dose: NA<br>Timing: first trimester or throughout pregnancy (180 of 298 patients) | SSRIs were not associated with increased risk of teratogenicity | Maternal age; smoking habits; artificial reproductive technique |
| Ramos et al (2008)[44] | Paroxetine: n = 440 of 2329 | Case-control | II-2 | Dose: NA<br>Timing: first trimester | SSRIs were not associated with increased risk of teratogenicity | Maternal age; socioeconomic status; smoking, alcohol use, and illicit drug use; healthcare use and pregnancy-related variables |
| Alwan et al (2007)[45] | Paroxetine: n = 178 of 408 | Case-control | II-2 | Dose: NA<br>Timing: first trimester | Paroxetine increased the risks of ventricular outflow tract obstruction defects (AOR = 2.5, 95% CI = 1.0 to 6.0), anencephaly (AOR = 5.1, 95% CI = 1.7 to 15.3), gastroschisis (AOR = 2.9, 95% CI = 1.0 to 8.4), and omphalocele (AOR = 8.1, 95% CI = 3.1 to 20.8) | Race; maternal age; parity; education/annual income; prepregnancy BMI, diabetes, and hypertension; folic acid use; tobacco and/or alcohol use |
| Louik et al (2007)[46] | Paroxetine: n = 113 of 476 | Case-control | II-2 | Dose: NA<br>Timing: first trimester | Paroxetine increased the risk of ventricular outflow tract obstruction defects (OR = 3.3, 95% CI = 1.3 to 8.8) | Race; maternal age; parity; education; year of the last menstrual period; infertility; prepregnancy BMI, diabetes, seizures, and hypertension; folic acid use; tobacco and/or alcohol use; history of birth defects in first-degree relative; site of the study center |
| Simon et al (2002)[47] | Paroxetine: n = 28 | Retrospective, cohort | II-2 | NA | SSRIs were not associated with increased risk of teratogenicity | Maternal age; prior psychiatric treatment history; tobacco and/or other substance use |
| Wogelius et al (2006)[48] | Paroxetine: n = NA | Retrospective, cohort | II-2 | NA | SSRIs increased the risk of fetal malformations as a whole (ARR = 1.84, 95% CI = 1.25 to 2.71) | Maternal age; birth year; country; tobacco use; teratogenic drug exposure |
| Davis et al (2007)[49] | Paroxetine: n = 182 of 1602 | Retrospective | II-3 | Dose: NA<br>Timing: first trimester | Paroxetine increased the risk of eye defects (RR = 2.36, 95% CI = 1.2 to 4.66) | None |
| Oberlander et al (2008)[50] | Paroxetine: n = 993 | Retrospective | II-3 | Dose: NA<br>Timing: first trimester | SSRIs and SNRIs increased the risk of a trial septal defects (RD = 0.21, 95% CI = 0.05 to 0.36) | Maternal illness characteristics; SSRI/SNRI dose; length of SSRI/SNRI exposure; maternal adherence; concomitant diseases; benzodiazepine and methadone use |

Abbreviations: AOR = adjusted odds ratio, ARR = adjusted relative risk, BMI = body mass index, CI = confidence interval, NA = not available, RD = risk difference, RR = relative risk, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

exposure on pregnancy outcome from the detrimental impact of the underlying psychiatric disorder.

On the other hand, a statistical association between SSRI use during early pregnancy and a number of birth defects (omphalocele, craniosynostosis, and anencephaly) that had not been previously associated with placental exposure to SSRI was found in the National Birth Defects Prevention Study (a large, ongoing, multisite study).[45] Four significant associations were specifically found for paroxetine (gastroschisis, right ventricular outflow tract obstruction defects, omphalocele, and anencephaly). In this study, information on exposure to SSRIs during pregnancy was collected by standardized telephone interviews with mothers; exposure was defined as reported use of any SSRIs from 1 month before to 3 months after conception. Although the study was of relatively large size (9622 case infants identified with major birth defects), the small number of exposed infants for each individual typology of malformation remains a relevant limitation of this study.[45] Conversely, most of these associations were not found in a contemporary study[46] (reporting 9849 case infants with major birth defects) showing not only a similar experimental design but also analogous limitations; however, the relationship between prenatal paroxetine exposure and increased rates of congenital ventricular outflow tract obstruction defects was confirmed. Incidentally, it must be highlighted that the study also suggested an association between placental exposure to sertraline and an increased risk of omphalocele.[46]

***Retrospective studies.*** A retrospective cohort study from a prepaid health plan identified a small number of SSRI prescriptions filled or refilled during the 360 days before delivery.[47] The number of pregnancies exposed to paroxetine was limited. Moreover, the study showed other limitations, such as the analysis performed on pharmacy records, which indicated drug dispensing rather than actual use, and the lack of any information on daily doses and timing of exposure (all women with antidepressant prescriptions filled or refilled during the 270 days before delivery were considered exposed). Infants exposed to these antidepressant medications through the placenta did not show increased rates of fetal malformations compared with both unexposed and tricyclic antidepressant–exposed infants.[47]

Conflicting results were obtained by Wogelius et al.,[48] who documented an increased risk of congenital anomalies as a whole in 1051 infants of women treated with SSRI medications during early pregnancy. Malformations most frequently reported were muscle and bone, cardiovascular, and digestive system anomalies (31%, 29%, and 14%, respectively). However, the exact length of antidepressant exposure was not established, since the study pooled data from women with SSRI prescriptions any time during early pregnancy (from 30 days before conception until the end of the first trimester). Moreover, because of the methodological design, the study was unable to clarify whether these effects were causal or due to other factors related to the underlying psychiatric disorder.[48]

Further, placental exposure to paroxetine has been specifically associated with an increased rate of congenital ocular anomalies.[49] The authors also reported a statistically significant increase in the rate of limb anomalies in infants exposed in utero to the drug; however, the reported statistical data (RR = 0.72, 95% CI = 0.18 to 2.83) seem not to support this last conclusion. For analysis of congenital anomalies, data were drawn from automated health system databases. Use of prescribed drugs during the first trimester was evaluated by assuming a gestational age of 270 days.[49]

A recent Canadian study,[50] conducted on administrative data reporting prenatal prescription records linked to neonatal records, suggested that prenatal exposure to SSRI and serotonin-norepinephrine reuptake inhibitor (SNRI) monotherapy may specifically increase risk of atrial septal defects; in contrast, risk of major malformations as a whole seemed to be increased only in the case of concomitant exposure to benzodiazepines.[50]

## DISCUSSION

Reviewed studies on the risk of fetal major malformations associated with early-pregnancy exposure to paroxetine show a high degree of methodological heterogeneity. Moreover, research studies performed with the same methodology and thus showing the same level of evidence[51] reported conflicting results. Indispensable cautions in preparing the studies' designs, such as the exclusion of possible confounders, were only partially provided or neglected altogether. Regrettably, such methodological bias affects both studies focused on specifically investigating teratogenicity of paroxetine and studies investigating teratogenicity of SSRIs as a class.

Regarding studies designed specifically to investigate teratogenicity of paroxetine, 3 of the 7 prospective studies have been published only as abstracts and showed contradictory findings.[24–26] In addition, such studies reported neither timing of exposure nor daily dosages; further, no analyses of potential confounding factors were provided. For these reasons, their results must be interpreted with great caution. When these factors were investigated in prospective, controlled studies, the results on the reproductive safety of paroxetine were quite reassuring.[27] Two prospective studies published as peer-reviewed articles (and suggesting an increased risk of cardiac birth defects in pregnant women who had been treated with paroxetine during early pregnancy) were based on data collected from the same medical registry and were both uncontrolled.[28,29] Conversely, the last update of the retrospective research funded by GlaxoSmithKline showed

that whereas the risk of fetal malformations as a whole may rise, no increase in the rate of specific cardiac defects seems to occur.[34] Moreover, the largest prospective, controlled study[30] so far performed has shown quite reassuring results. However, most of the women in this study had been treated with relatively low doses of paroxetine; for this reason, this study was inadequate in denying findings (until now not replicated) emerging from a case-control study[31] that found increased rates in both fetal structural malformation as a whole and cardiac defects following pregnancy exposure to daily doses of paroxetine higher than 25 mg.

Among studies investigating teratogenicity of SSRIs as a class, 5 prospective studies showed concordant reassuring results.[37–41] However, all 5 studies had relevant limitations: the number of pregnancies exposed to paroxetine and other SSRIs was relatively or absolutely too small to allow investigation of teratogenicity of specific drugs; the analysis of potential confounding factors was limited; the timing of exposure was rarely clarified; and only 2 of these studies[38,39] provided a comparison with control groups of infants exposed to nonteratogen agents and/or infants who were unexposed. Three case-control studies[42–44] also failed to demonstrate association between prenatal SSRI exposure and increased rates of birth defects; however, no post hoc secondary analyses were performed specifically on paroxetine. When this analysis was included in the methodological design,[45,46] paroxetine was alternatively associated with increased rates of right ventricular outflow tract obstruction defects plus other noncardiac anomalies (gastroschisis, anencephaly, omphalocele) and right ventricular outflow tract obstruction defects without concomitant risks of other categories of fetal malformations.[45,46] Increased rates of either fetal malformations as a whole[48] or eye defects[49] have been reported in 2 retrospective studies investigating teratogenic risk of SSRIs as a class, whereas a similarly designed study[50] recently suggested that prenatal exposure to both SSRIs and SNRIs may be considered a risk factor for birth defects in general, but only in the event of concomitant exposure to a benzodiazepine.

Given this background, although a valuable attempt has been recently performed,[52] a meta-analytic approach based on highly selective criteria (i.e., selection and inclusion of studies that enrolled women treated with the same range of daily drug dose, exposed to paroxetine during the same period of pregnancy, and showing equivalent length of exposure) remains impracticable.

## CONCLUSIONS

Several mechanisms have been proposed to explain hypothetical teratogenicity of some SSRIs, but research studies focused specifically on paroxetine are scarce. Data from animal investigations[53–55] have demonstrated that SSRIs, through increase in serotonergic neurotransmission, may interfere with a variety of physiologic systems, such as the sleep-wake cycle, circadian rhythms, and the hypothalamic-pituitary-adrenal axis[53]; each of these systems seem to play an important role in regulating fetal development.[53] Moreover, maternal treatment with SSRIs, specifically fluoxetine, may have an adverse impact on the developing fetus via interference with serotonin 5-$HT_{2B}$ receptors[54]; information from animal studies has demonstrated that this receptorial subtype is involved in controlling fetal cardiovascular system development.[55] This interference is directly correlated to the degree of placental passage of SSRIs, which is relatively high for fluoxetine.[54] However, a relatively high amount of placental passage has also been demonstrated for paroxetine.[56]

In humans, preliminary findings have already highlighted that placental exposure to such a class of antidepressants may induce relevant physiologic changes in both mother and fetus. In the mother, antidepressant therapy during pregnancy has been associated with an increase in the saliva estriol levels[57]; in the fetus, studies conducted with an elegant methodology have suggested that prenatal exposure to SSRIs may increase blood flow velocity in the middle cerebral artery.[58] Gestational exposure to SSRIs has also been associated with a substantial reduction in platelet serotonergic reuptake in the newborn.[59] Such findings seem to suggest that in utero exposure to SSRIs may have specific physiologic effects on the fetus, albeit their clinical relevance remains undetermined.

Unfortunately, reviewed data are too controversial for confirming or excluding teratogenicity of paroxetine and also suffer from several relevant methodological limitations. Hence, even now, this relevant clinical concern remains unanswered. This situation is not surprising, since it is unethical to include pregnant women in randomized controlled trials. However, in order to obtain definitive conclusions about this still-open question, future research agendas should include the following:

(1) Large, epidemiologic, prospective, controlled studies should be designed to include a control group of untreated women diagnosed with the same disorder as the mothers who accept taking paroxetine during pregnancy. This design seems to be the only way to differentiate effects of drug exposure from the well-known impact of untreated psychiatric disorder on the fetus.[6–10] Moreover, prospective studies conducted with rigorous methodologies may make possible a correct meta-analytic strategy: this strategy is completely warranted for investigating rare events (such as congenital anomalies), which are likely to remain unclear even after single, large cohort studies.

(2) Further experimental studies are warranted to definitively assess clinical consequences of the impact on fetal development induced by the physiologic effects of prenatal paroxetine exposure on different maternal and fetal parameters.

***Drug names:*** bupropion (Aplenzin, Wellbutrin, and others), fluoxetine (Prozac and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others).

## REFERENCES


1. Murray CJL, Lopez AD, eds. The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability From Diseases, Injuries, and Risk Factors in 1990 and Projected to 2020. Cambridge, Mass: Harvard University Press; 1996
2. Sundstrom IM, Bixio M, Bjorn I, et al. Prevalence of psychiatric disorders in gynaecologic outpatients. Am J Obstet Gynecol 2001;184:8–13
3. Hallbreich U. Prevalence of mood symptoms and depression during pregnancy: implications for clinical practice and research. CNS Spectr 2004;9:177–184
4. Einarson A, Koren G. Counseling pregnant women treated with paroxetine: concern about cardiac malformations. Can Fam Physician 2006;52: 593–594
5. Diego MA, Field T, Hernandez-Reif M, et al. Prepartum, postpartum, and chronic depression effects on newborns. Psychiatry 2004;67:63–80
6. Dayan J, Creveuil C, Marks MN, et al. Prenatal depression, prenatal anxiety, and spontaneous preterm birth: a prospective cohort study among women with early and regular care. Psychosom Med 2006;68: 938–946
7. Andersson L, Sundstrom-Poroma I, Wulff M, et al. Implication of antenatal depression and anxiety for obstetric outcome. Obstet Gynecol 2004;104:467–476
8. Bonari L, Pinto N, Ahn E, et al. Perinatal risks of untreated depression during pregnancy. Can J Psychiatry 2004;49:726–735
9. Hollins K. Consequences of antenatal mental health problems for child health and development. Curr Opin Obstet Gynecol 2007;19:568–572
10. Surkarn PJ, Kawachi I, Ryan LM, et al. Maternal depressive symptoms, parenting self-efficacy, and child growth. Am J Public Health 2008;98: 125–132
11. Figueiredo B, Costa R, Pacheco A, et al. Mother-to-infant emotional involvement at birth [published online ahead of print March 4, 2008]. Matern Child Health J
12. Cohn JF, Tronick E. Specificity of infants' response to mothers' affective behavior. J Am Acad Child Adolesc Psychiatry 1989;28:242–248
13. Hart S, Field T, del Valle C, et al. Depressed mothers' interactions with their one-year-old infants. Infant Behav Dev 1998;21:519–525
14. Murray L, Fiori-Cowley A, Hooper R, et al. The impact of postnatal depression and associated adversity on early mother-infant interactions and later infant outcome. Child Dev 1996;67:2512–2526
15. Dunham P, Dunham F, Hurshman A, et al. Social contingency effects on subsequent perceptual-cognitive tasks in young infants. Child Dev 1989; 60:1486–1496
16. Murray L, Hipwell A, Hooper R, et al. The cognitive development of 5-year-old children of postnatally depressed mothers. J Child Psychol Psychiatry 1996;37:927–935
17. Marcus SM, Flynn HA, Blow F, et al. A screening study of antidepressant treatment rates and mood symptoms in pregnancy. Arch Women Ment Health 2005;8:25–27
18. Cohen LS, Altshuler LL, Harlow BL, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. JAMA 2006;295:499–507
19. Sutter-Dallay AL, Giaconne-Marcesche V, Glatigny-Dallay E, et al. Women with anxiety disorders during pregnancy are at increased risk of intense postnatal depressive symptoms: a prospective survey of the MATQUID cohort. Eur Psychiatry 2004;19:459–463
20. O'Connor TG, Heron J, Glover V, and the Alspac Study Team. Antenatal anxiety predicts child behavioral/emotional problems independently of postnatal depression. J Am Acad Child Adolesc Psychiatry 2002;41: 1470–1477
21. Loughhead AM, Fisher AD, Newport DJ, et al. Antidepressants in amniotic fluid: another route of fetal exposure. Am J Psychiatry 2006;163: 145–147
22. FDA Public Health Advisory. Paroxetine. Available at: http://69.20.19.211/cder/drug/advisory/paroxetine200512.htm. Accessed May 10, 2008
23. Velves, T, Kaasenbrood, H, Visser G, et al. Prevalence and patterns of antidepressant drug use during pregnancy. Eur J Clin Pharmacol 2006;62:863–870
24. Unfred CL, Chambers CD, Felix R, et al. Birth outcomes among pregnant women taking paroxetine (Paxil) [abstract]. Update presented at the Organization of Teratology Service 14th Annual Conference; June 23–28, 2001; Montreal, Quebec, Canada. Teratology 2001;63(6):321–324
25. Diav-Citrin O, Shechtman S, Weinbaum D, et al. Pregnancy outcome after gestational exposure to paroxetine: a prospective controlled cohort study [abstract]. Teratology 2002;65(6):298
26. Diav-Citrin O, Shechtman S, Weinbaum D, et al. Paroxetine and fluoxetine in pregnancy: a multicenter, prospective controlled study [abstract]. Reprod Toxicol 2005;20:459
27. Diav-Citrin O, Shechtman S, Weinbaum D, et al. Paroxetine and fluoxetine in pregnancy: a prospective, multicentre, controlled, observational study [published online ahead of print July 11, 2008]. Br J Clin Pharmacol 2008;66(5):695–705
28. Källén B, Otterblad Olausson P. Antidepressant drugs during pregnancy and infant congenital heart defect [letter]. Reprod Toxicol 2006;21(3): 221–222
29. Källén BA, Otterblad Olausson P. Maternal use of selective serotonin re-uptake inhibitors in early pregnancy and infant congenital malformations. Birth Defects Res A Clin Mol Teratol 2007:79(4):301–308
30. Einarson A, Pistelli A, DeSantis M, et al. Evaluation of the risk of congenital cardiovascular defects associated with use of paroxetine during pregnancy [published online ahead of print April 1, 2008]. Am J Psychiatry 2008;165(6):749–752. doi:10.1176/appi.ajp.2007.07060870
31. Bérard A, Ramos E, Rey E, et al. First trimester exposure to paroxetine and risk of cardiac malformations in the infants: the importance of dosage. Birth Defects Res B Dev Reprod Toxicol 2007;80(1):18–27
32. GlaxoSmithKline. Epidemiology Study EPIP083: Preliminary Report on Bupropion in Pregnancy and the Occurrence of Cardiovascular and Major Congenital Malformations. Available at: http://www.gsk-clinicalstudyregister.com/result_detail.jsp?protocolId=EPIP083&studyId=2887&compound=Bupropion. Accessed August 15, 2008
33. GlaxoSmithKline. Epidemiology Study EPIP083_2: Updated Preliminary Report on Bupropion and Other Antidepressants, including Paroxetine, in Pregnancy and the Occurrence of Cardiovascular and Major Congenital Malformation. Available at: http://www.gsk-clinicalstudyregister.com/result_detail.jsp?protocolId=EPIP083_2&studyId=3034&compound=Paroxetine. Accessed August 15, 2008
34. Cole JA, Ephross SA, Cosmatos IS, et al. Paroxetine in the first trimester and the prevalence of congenital malformations. Pharmacoepidemiol Drug Saf 2007;16:1075–1085
35. Hoffman JI, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol 2002;39:1890–1900
36. GlaxoSmithKline. Epidemiology Study EPI40404 (follow-up to EPIPO83): Paroxetine in the First Trimester and the Prevalence of Congenital Malformations. Available at: http://www.gsk-clinicalstudyregister.com/result_detail.jsp?protocolId=EPI40404&studyId=3493&compound=Paroxetine. Accessed August 15, 2008
37. McElhatton PR, Garbis HM, Eléfant E, et al. The outcome of pregnancy in 689 women exposed to therapeutic doses of antidepressants: a collaborative study of the European Network of Teratology Information Services (ENTIS). Reprod Toxicol 1996;10:285–294
38. Kulin A, Pastuszac A, Sage SR, et al. Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors. JAMA 1998;279:609–610
39. Maschi S, Clavenna A, Campi R, et al. Neonatal outcome following pregnancy exposure to antidepressants: a prospective controlled cohort study. BJOG 2008;115(2):283–289
40. Ericson A, Källén B, Wilholm BE. Delivery outcome after the use of antidepressants in early pregnancy. Eur J Clin Pharmacol 1999;55: 503–508
41. Hendrick V, Smith LM, Suri R, et al. Birth outcomes after prenatal exposure to antidepressant medications. Am J Obstet Gynecol 2003; 188:812–815

42. Källén BA, Otterblad Olausson P. Maternal drug use in early pregnancy and infant cardiovascular defect. Reprod Toxicol 2003;17:255–261
43. Malm H, Klaukka T, Neuvonen PJ. Risks associated with selective serotonin reuptake inhibitors in pregnancy. Obstet Gynecol 2005; 106:1289–1296
44. Ramos E, St-André M, Rey E, et al. Duration of antidepressant use during pregnancy and the risk of major congenital malformations. Br J Psychiatry 2008;192:344–350
45. Alwan S, Reefhuis J, Rasmussen SA, et al., for the National Birth Defects Prevention Study. Use of selective serotonin reuptake inhibitors and risk of birth defects. New Engl J Med 2007;356:2684–2692
46. Louik C, Lin AE, Werler MM, et al. First-trimester use of selective serotonin reuptake inhibitors and risk of birth defects. New Engl J Med 2007;356:2675–2683
47. Simon GE, Cunningham ML, Davis RL. Outcomes of prenatal antidepressant exposure. Am J Psychiatry 2002;159:2055–2061
48. Wogelius P, Nørgaard M, Gislum M, et al. Maternal use of selective serotonin reuptake inhibitors and risk of congenital malformations. Epidemiology 2006;17:701–704
49. Davis RL, Rubanowice D, McPhillips H, et al. Risk of congenital malformations and perinatal events among infants exposed to antidepressant medications during pregnancy. Pharmacoepidemiol Drug Saf 2007;16: 1086–1094
50. Oberlander TF, Warburton W, Misri S, et al. Major congenital malformations following prenatal exposure to serotonin reuptake inhibitors and benzodiazepines using population-based health data. Birth Defects Res B 2008;83:68–76
51. Centre for Evidence-Based Medicine. EBM Tools: Levels of Evidence. Available at: http://www.cebm.net/index.aspx?o=1025. Accessed January 28, 2008
52. O'Brien L, Einarson TR, Sarkar M, et al. Does paroxetine cause cardiac malformations? J Obstet Gynaecol Can 2008;30:696–701
53. Morrison JL, Riggs KW, Rurak DW. Fluoxetine during pregnancy: impact on fetal development. Reprod Fertil Dev 2005;17:641–650
54. Noorlander CW, Ververs FFT, Nikkels PGJ, et al. Modulation of serotonin transporter function during fetal development causes dilated heart cardiomyopathy and lifelong behavioral abnormalities. PLoS ONE 2008;3(7):e2782. doi:10.1371/journal.pone.0002782
55. Negibil CG, Hickel P, Messaddeq N, et al. Ablation of serotonin 5-HT(2B) receptors in mice leads to abnormal cardiac structure and function. Circulation 2001;103:2973–2979
56. Hendrick V, Stowe ZN, Altshuler LL, et al. Placental passage of antidepressant medications. Am J Psychiatry 2003;160(5):993–996
57. Suri R, Hellemann G, Cohen L, et al. Saliva estriol levels in women with and without prenatal antidepressant treatment [published online ahead of print May 21, 2008]. Biol Psychiatry 2008;64(6):533–537
58. Emory EK, Dieter JNI. Maternal depression and psychotropic medication effects on human fetus. Ann NY Acad Sci 2006;1094:287–291
59. Anderson GM, Czarkowski K, Ravski N, et al. Platelet serotonin in newborns and infants: ontogeny, heritability, and effect of in utero exposure to selective serotonin reuptake inhibitors. Pediatr Res 2004;56:418–422

*Editor's Note:* We encourage authors to submit papers for consideration as a part of our Focus on Women's Mental Health section. Please contact Marlene Freeman, M.D., at mfreeman@psychiatrist.com.