Original Article

First Trimester Exposure to Paroxetine and Risk of Cardiac Malformations in Infants: The Importance of Dosage

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BACKGROUND: Conflicting findings with regard to the teratogenic risks of first trimester use of paroxetine have prompted the FDA, Health Canada, and the manufacturer of the drug to issue warnings against its use during pregnancy. Given that untreated depression during pregnancy can lead to deleterious effect on the mother and her unborn fetus, data on the relationship between the dose and the range of malformations is warranted. This study attempts to quantify the association between first trimester exposure to paroxetine and congenital cardiac malformations, adjusting for possible confounders, and to quantify the dose–response relationship between paroxetine use and cardiac defects. **METHODS:** The Medication and Pregnancy registry was used. This population-based registry was built by linking three administrative databases (RAMQ, Med-Écho, and ISQ), and includes all pregnancies in Quebec between 01/01/1997 and 06/30/2003. Date of entry in the registry is the date of the first day of the last menstrual period. To be eligible for this study, women had to: 1) be 15–45 years of age at entry; 2) be covered by the RAMQ drug plan $\geq$12 months before and during pregnancy; 3) be using only one type of antidepressant during the first trimester; and 4) have a live birth. Two nested case-control studies were carried out comparing the prevalence of paroxetine use in the first trimester of pregnancy to the prevalence of other antidepressant exposures during the same time period. Cases were defined as: 1) any major malformations; or 2) any cardiac malformations diagnosed in the first year of life; controls were defined as no major or minor malformations. Multivariate logistic regression techniques were used to analyze data. **RESULTS:** Among the 1,403 women meeting inclusion criteria, 101 infants with major congenital malformations were identified; 24 had cardiac malformations. Adjusting for possible confounders, the use of paroxetine (odds ratio [OR] = 1.38, 95% confidence interval [CI] = 0.49–3.92), and the use of other SSRIs (OR = 0.89, 95% CI = 0.28–2.84) during the first trimester of pregnancy did not increase the risk of congenital cardiac malformations compared with the use of non-SSRI antidepressants. When considering the dose, however, a dose–response relationship was observed, thus women exposed to >25 mg/day of paroxetine during the first trimester of pregnancy were at increased risk of having an infant with major congenital malformations (adjusted [adj] OR = 2.23, 95% CI = 1.19, 4.17), or major cardiac malformations (adj OR = 3.07, 95% CI = 1.00, 9.42). **CONCLUSIONS:** Gestational exposure to paroxetine is associated with major congenital malformations and major cardiac malformations for only first trimester exposure above 25 mg/day. *Birth Defects Res (Part B)* 80:18–27, 2007. © 2006 Wiley-Liss, Inc.

Key words: ***paroxetine; pregnancy; major congenital malformations; major cardiac malformations; dosage; pregnancy registry***

INTRODUCTION

Perinatal psychiatric disorders account for a significant proportion of complications in obstetrical populations, with estimates as high as 14% in a recent study (Hallbreich, 2004). This high prevalence emphasizes the importance of appropriate treatment strategies in this group of women. Recently, the FDA and Health Canada, in agreement with the manufacturer of the drug, issued two warnings in September and December 2005 regarding first trimester exposure to paroxetine and risk of cardiac malformations in newborns. Paroxetine is the third most frequently prescribed antidepressant in the United States (Gentile, 2005), and is the most prescribed in Canada (Ramos et al., 2005). Regardless of the quality of the data provided in the warnings, this had an

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immediate impact on the concerns expressed by pregnant women and health care providers regarding gestational use of antidepressants. Indeed, in the week after both warnings, a 43% increase in the number of calls regarding antidepressant use during pregnancy was observed at IMAGe, a teratology information service serving the province of Quebec, based at the CHU Sainte-Justine in Montreal (Bérard and Oraichi, 2006); concerns were regarding the potential risks of exposure with diminished attention on potential benefits of treatment or prophylaxis in high risk populations.

Controversy regarding the risk of cardiac malformations associated with the use of paroxetine in the first trimester of pregnancy relies primarily on two unpublished reports (GlaxoSmithKline, 2005a,b), and another study published recently (Kallen and Otterblad Olausson, 2006). The first report giving rise to the September 2005 warning was a company-sponsored study that was designed primarily to look at the association between gestational exposure to bupropion and the risk of combined minor and major congenital malformations, using a large United States managed care administrative database (GlaxoSmithKline, 2005a). Bupropion was not statistically significantly associated with congenital malformations but it seemed that paroxetine was associated with a two-fold increase in the risk of birth defects (rate of congenital malformations in the paroxetine group: 23 cases/527 exposures = 4%; odds ratio [OR] = 2.20; 95% confidence interval [CI] = 1.34, 3.63), and more specifically cardiac defects, when compared with a group of pregnant women exposed to other antidepressants (rate of cardiac malformations in the paroxetine group: 11 cases/589 exposures = 2%; OR = 2.08; 95% CI = 1.03, 4.23) (GlaxoSmithKline, 2005a). Using the Swedish Birth Registry, Kallen and Otterblad Olausson (2006) showed similar results. Indeed, using self-reported exposure to medications at one point in time during the first trimester of pregnancy, and comparing pregnant users of paroxetine to the overall group of pregnant women in the Swedish Birth Registry irrespective of whether they were exposed or not to other medications, a two-fold increase in the risk of cardiac malformations was found (rate of cardiac malformations in the paroxetine group: 17 cases/815 exposures = 2%; OR = 2.22; 95% CI = 1.39, 3.55) (Kallen and Otterblad Olausson, 2006).The same was found when using a group of other antidepressant users as the comparator. Similarly, a smaller European study also showed an association between paroxetine use during pregnancy and incidence of cardiac malformations in infants using a control group of pregnant women not using medications (RR = 1.92; 95% CI = 1.01, 3.65) (Diav-Citrin et al., 2005).

In December 2005, new information were issued by the FDA and Health Canada in the light of new findings from the United States managed care study (GlaxoSmithKline, 2005b). Updates were made to the original cohort of pregnant antidepressant users, including pregnancies leading to live births that had occurred between 2002–2004. Although paroxetine was associated with an 82% increase in the risk of any congenital malformations in newborns (rate of congenital malformations in the paroxetine group: 27 cases/717 exposures = 4%; OR = 1.82; 95% CI = 1.17, 2.82), no statistically significant increase in the risk of cardiac malformations (rate of cardiac malformations in the paroxetine group: 12 cases/814 exposures = 4%; OR = 1.54; 95% CI = 0.81, 2.92) was observed, comparing pregnant users of paroxetine to pregnant users of other antidepressants (GlaxoSmithKline, 2005b).

Given the uncertainty of the teratogenic effect of paroxetine, and considering that untreated depression during pregnancy can result in significant morbidity such as loss of appetite, low calorie intake, unhealthy behaviors such as smoking, alcohol, and substance abuse, and overall lower quality of life for the mother, as well as higher rates of therapeutic abortions, relapse of depressive symptoms, pre-term births, low birth weight, small for gestational age babies, and overall perinatal and psychosocial complications for the baby (Einarson et al., 2001; Koren, 2004; Cohen et al., 2006), more data are needed to fully appreciate the risk/benefit ratio of this psychopharmacologic treatment. Furthermore, given that thus far cognitive-behavioral therapy does not seem to have a significant effect on the remission of depressive symptoms during pregnancy (Misri et al., 2004), and that women suffering from depression during pregnancy are at higher risk of postpartum depression (Heron et al., 2004), additional data on the risk of gestational exposure to paroxetine, more specifically in relation to dosage, are warranted. No one thus far has looked at the extent of paroxetine utilization in terms of dosage. Better ascertainment of malformations is essential given that some of the malformations are asymptomatic and may resolve spontaneously.

The objectives of our study were to quantify the association between exclusive first trimester exposure to paroxetine and occurrence of any major congenital malformations, and more specifically, major cardiac malformations, as compared with exclusive first trimester exposure to other selective serotonin reuptake inhibitors (SSRIs) or other antidepressants, in a population-based pregnancy registry. The dose–response relationship was also studied using the average daily dose of paroxetine use during the first trimester of pregnancy (mg/day) in relation to the study outcomes.

MATERIALS AND METHODS

Data Sources

We used three administrative databases of the Province of Québec; La Régie de l'Assurance Maladie du Québec (RAMQ), Med-Écho, and Le fichier des événements démographiques du Québec (birth and death registries) of l'Institut de la Statistique du Québec (ISQ). The RAMQ database contains information on medical services (diagnoses and procedures) received by all Quebec residents. All diagnoses are classified according to the International Classification of Diseases, Ninth revision, (ICD-9). Although RAMQ covers all Quebec residents for the cost of physician visits, hospitalizations, and procedures, it only covers a portion of residents for the cost of prescribed medications. The RAMQ drug plan covers individuals 65 years and older, recipients of social assistance (welfare beneficiaries), and workers and their families (adherents) who do not have access to a private insurance program, accounting for approximately 43% of the overall Quebec population (Régie de l'assurance maladie du Québec, 1997). It is also estimated that 30% of women between 15–45 years of age

in Quebec are covered by the RAMQ drug plan for their medication (Lacasse et al., 2005). The Med-Écho database is a provincial database that records acute care hospitalization data for all Quebec residents; it also records gestational age (from the first day of the last menstrual period until end of pregnancy) for planned abortions, miscarriages, and deliveries. Le fichier des événements démographiques du Québec (ISQ) provides demographic variables on the mother, father, and baby as well as birth weight and gestational age for live births and stillbirths. Linkage between RAMQ and Med-Écho data was done using patients' 'Numéro d'assurance maladie (NAM)' that is a unique personal identifier for each person living in Quebec. Linkage between RAMQ and ISQ data was done using the mothers' and babies' names, family names, and dates of birth.

The RAMQ and Med-Écho databases have often been used in the past for epidemiological research (Garbe et al., 1997; Avorn et al., 1998; Blais et al., 2000). The ISQ database has also been used in epidemiological studies (Roy et al., 2004). Data recorded in the medication database of the RAMQ have been evaluated suitably and found to be comprehensive and valid (Tamblyn et al., 1995). The same has been found for medical diagnoses recorded in the Med-Écho database (Levy et al., 1995).

Population

The RAMQ, Med-Écho, and ISQ databases were linked together to create the 'Medication and Pregnancy' registry that contains data on all pregnancies that occurred in Quebec between 01/01/1997 and 06/30/2003. This population-based pregnancy registry is composed of women with a diagnosis or procedure code related to pregnancy.

Within the 'Medication and Pregnancy' registry, women meeting the following eligibility criteria were included in this present study. Women had to: 1) be between 15–45 years of age at the date of entry in the registry defined as the first day of gestation (first day of the last menstrual period provided in the Med-Écho and ISQ databases); 2) be continuously insured by the RAMQ drug plan for at least 12 months before the first day of gestation, and during pregnancy; 3) have filled only one type of antidepressant during the first trimester of pregnancy (0–14 weeks of gestation); and 4) have a live birth. Women also exposed to known teratogens during pregnancy such as carbamazepine, phenytoin, valproic acid, lithium, acitretin, isotretinoin, HMG CoA reductase inhibitors, antineoplastic agents (American Hospital Formulary System [AHFS] Class 10:00), leflunomide, and the androgens (including danazol, testosterone, and methyltestosterone) (Briggs et al., 2002) were excluded. All pregnancies meeting eligibility criteria were analyzed. If a woman had more than one pregnancy during the study period, only the first pregnancy meeting eligibility criteria was analyzed.

Design

Within the study population, two-nested case-control studies were carried out (first, using all major congenital malformations combined as cases; second, using only major cardiac malformations as cases).

Case Selection

Within our study population, we identified all cases of major congenital malformations by searching the RAMQ and Med-Écho databases for ICD-9 codes 740.0-759.9, recorded within the first 12 months of each infant's life, to allow for delayed detections or registrations (excluding codes for minor malformations: 743.6, 744.1, 744.2-744.4, 744.8, 744.9, 747.0, 747.5, 750.0, 752.4, 752.5, 754.6, 755.0, 755.1, 757.2-757.6, 757.8, 757.9, 758.4). Major cardiac malformations were identified with the following codes: 745.0–745.9 (bulbus cordis anomalies and anomalies of cardiac septal closure including transposition of great vessels and endocardial cushion defects), 746.0–746.9 (congenital anomalies of the heart), and 747.0–747.4 and 747.8 (malformations of the central cardiovascular system including; patent ductus arteriosus, co-arctation of the aorta, anomalies of the pulmonary artery, anomalies of the great veins and primary pulmonary hypertension of the newborn). Because we were able to assess congenital malformations within the first year of life and that all children in Quebec with a diagnosis of malformations have a systematic recall visit at 12 months, we were able to see whether the diagnosis of malformations remained at 1 year of age, giving us evidence that the malformations did not resolve spontaneously. Index date was the time of the delivery.

Control Selection

For analyses on all major congenital malformations combined, as well as for analyses on major cardiac malformations, all infants without any minor or major malformations diagnosed in the first 12 months of life were selected as controls.

Exposure to Antidepressants

All types of antidepressants were considered and grouped in three categories of use during the first trimester of pregnancy (0–14 weeks of gestational age): paroxetine group; other SSRIs group (excluding paroxetine); and other antidepressants group (other than SSRIs). The reference category was women using other antidepressants (other than SSRIs), and adjustment on antidepressant exposure during the second and third trimesters of pregnancy was done dichotomously regardless of class. Antidepressants considered were paroxetine, other SSRIs such as fluoxetine, citalopram, fluvoxamine, sertraline, and other antidepressants such as amitriptyline, amoxapine, bupropion, clomipramine, desipramine, doxepin, imipramine, maprotiline, mirtazapine, moclobemide, nefazodone, nortriptyline, phenelzine, tranylcypromine, trazodone, trimipramine, and venlafaxine. We considered women who filled at least one prescription for an antidepressant during the first trimester or those who filled prescriptions for an antidepressant before the first day of gestation but where the duration of treatment lasted into the first trimester period as exposed. Duration of exposure during the first trimester (0–14 weeks of gestational age) in the three study groups was calculated by adding all antidepressant prescription durations over the length of the first trimester. Average daily dose (mg/day) of paroxetine use during the first trimester was calculated by dividing the cumulative daily dose of paroxetine exposure (mg)

by the total duration of paroxetine use during the first trimester of pregnancy (day).

Covariates

Healthcare utilization variables (RAMQ/Med-Écho databases) such as hospitalizations and emergency department (ED) visits, medical visits, visits to a psychiatrist, and number of prescribers were selected as markers of health status; these were measured in the 12 months before and during pregnancy. We determined the presence of the following chronic co-morbidities (using the RAMQ/Med-Écho databases), and the use of specific medications: the diagnosis of chronic hypertension in the year before and during pregnancy (ICD-9 codes 401.0–405.9, 362.1, 416.0, 437.2, 796.2) or of gestational hypertension (defined as a diagnosis made at $\geq$20 weeks of pregnancy with ICD-9 codes 642.0–642.9) or use of antihypertensive drugs (AHFS; 24:08); the diagnosis of diabetes in the year before or during pregnancy (ICD-9; 250.0–250.9, 271.4, 790.2) or gestational diabetes diagnosed at $\geq$26 weeks of pregnancy (ICD-9; 648.0, 648.8), or the dispensing of medications for diabetes in the 12 months before and during pregnancy, including insulin and oral hypoglycemic agents (AHFS; 68:20.08, 68:20.20, 68:20.92); the diagnosis of depression in the year before or during pregnancy (ICD-9; 296.x, 300.4, 309, 311), or the use of antidepressants in the year before pregnancy. Pregnancy related variables considered were the number of prenatal visits, visits to obstetricians, and dispensed co-medications during pregnancy; a pregnancy or abortion or miscarriage in the year before pregnancy as well as gestational age, birth weight, multiplicity, newborn gender, and calendar year of delivery were also considered. Where prescribed medications were considered, we accounted for items dispensed outside the period of interest (12 months before or during pregnancy) but whose duration overlapped into that period. We also determined the following socio-economic variables on index date from the RAMQ/ISQ databases: maternal age, region of residence (urban vs. rural dwellers), maternal marital status (living alone vs. cohabiting), and RAMQ insurance status (welfare beneficiary vs. adherent).

Statistical Analysis

Descriptive statistics were used to compare women from the three study groups using first trimester exposure to non-SSRI antidepressants as the reference category. Major congenital malformations were also listed. Two case-control analyses were carried out: first, using all major congenital malformations combined as cases, and second using only major cardiac malformations as cases. A paroxetine dose–response analysis was also done using 0 mg/day as the reference category, and using the clinically relevant distribution quartiles as cut-off points ($>$0–20 mg/day, $>$20–25 mg/day, $>$25 mg/day). In addition, paroxetine users were compared with other SSRI users in terms of major congenital malformations, more specifically major cardiac malformations. Finally, sensitivity analyses were carried out excluding women with pre-existing diabetes or gestational diabetes (given that diabetes is a significant risk factor associated with birth defects), or women with second or third trimester exposure to paroxetine. Univariate and multivariate unconditional logistic regression models were built, adjusting for important confounders and socioeconomic variables. A variable that modified the point estimate of the relationship between paroxetine use and malformations by $>$20% was considered a confounder and was included in the multivariate model. All analyses were conducted in SAS system for windows version 8.02. This study has received ethics approval from the Research and Ethics Committee of CHU Sainte-Justine, and from the Commission d'accès à l'information du Quebec.

RESULTS

Within the Medication and Pregnancy registry, 1403 women met inclusion criteria, and were thus included in this study; 542 (39%) were exposed to paroxetine during the first trimester of pregnancy, 443 (31%) to other SSRIs, and 418 (30%) to other antidepressants. Other SSRIs used during the first trimester were sertraline (186 [42%]), citalopram (113 [26%]), fluoxetine (101 [23%]), and fluvoxamine (43 [9%]); non-SSRI antidepressants used during the first trimester were for the majority venlafaxine (153 [37%]), and amitriptyline (140 [33%]). Paroxetine users were exposed to 22.4 mg/day on average (standard deviation [SD] = 9.0) for a mean duration of 64 days (SD = 2.3) during the first trimester of pregnancy; similar pattern of duration and timing of exposure was seen in women exposed to other SSRIs or to non-SSRI antidepressants. Twenty-seven percent of paroxetine users, 2% of other SSRI users, and 1% of other antidepressant users decreased their dosage on recognition of the pregnancy; the remaining stayed on the same daily dosage until discontinuation or end of pregnancy, whichever occurred first, and no increase in dose was noted.

We identified 101 cases of major congenital malformations (7.2%; 95% CI = 5.9%, 8.5%), of which 24 were of cardiac origin (1.8%; 95% CI = 0.8%, 2.8%). The rate of major congenital malformations was 8% in the paroxetine group, 6% in the other SSRI group, and 6% in the other antidepressant group; the rate of major cardiac malformations was 2%, 1%, and 1%, in the paroxetine, other SSRIs, and other antidepressants groups, respectively. Table 1 lists all major congenital malformations identified in the three study groups. The malformations observed most frequently were for bulbus cordis anomalies and anomalies of cardiac septal closure (ICD-9; 745), and for musculoskeletal anomalies (ICD-9; 754); no cases of primary pulmonary hypertension of the newborn was found, and one case of patent ductus arteriosus in the paroxetine group (exposed during 0–3 weeks of gestational age) was found. All cardiac malformations were isolated.

For baseline characteristics, cases of major congenital malformations were comparable to controls regarding maternal age and gestational age at delivery, but were more likely to be on welfare, rural dwellers, and have a lower education level (Table 2). Cases and controls were also similar regarding their maternal use of health care services before and during pregnancy, including visits to psychiatrists (Table 2). Cases were less likely to have twins as compared with controls, and were more likely to have been diagnosed with hypertension or diabetes before or during pregnancy; the prevalence of depression

Table 1
Major Congenital Malformations Observed*

Congenital Malformations (ICD-9 code)	Paroxetine (n = 60)	Other SSRIs[a] (n = 38)	Other Antidepressants[b] (n = 43)
Anencephalus (ICD-9; 740)	0 (0.00)	0 (0.00)	0 (0.00)
Anomaly of ear, face, neck (ICD-9; 744)	0 (0.00)	0 (0.00)	0 (0.00)
Anomaly of eye (ICD-9; 743)	3 (5.00)	1 (2.63)	7 (16.28)
Anomaly of genital organs (ICD-9; 752)	3 (5.00)	3 (7.89)	2 (4.65)
Anomaly of respiratory system (ICD-9; 748)	1 (1.67)	0 (0.00)	2 (4.65)
Anomaly of urinary system (ICD-9; 753)	1 (1.67)	0 (0.00)	0 (0.00)
Anomaly of the integument (ICD-9; 757)	0 (0.00)	0 (0.00)	0 (0.00)
Bulbus cordis anomalies and anomalies of cardiac septal closure (ICD-9; 745)	9 (15.00)	6 (15.79)	8 (18.60)
Chromosomal anomalies (ICD-9; 758)	2 (3.33)	0 (0.00)	2 (4.65)
Cleft palate and lip (ICD-9; 749)	3 (5.00)	0 (0.00)	3 (6.98)
Musculoskeletal deformity (ICD-9; 754)	7 (11.67)	4 (10.53)	1 (2.33)
Spina bifida (ICD-9; 741)	1 (1.67)	0 (0.00)	0 (0.00)
Other anomaly of circulatory system (ICD-9; 747)	1 (1.67)	1 (2.63)	1 (2.33)
Other anomaly of heart (ICD-9; 746)	3 (5.00)	2 (5.26)	1 (2.33)
Other anomaly of nervous system (ICD-9; 742)	3 (5.00)	8 (21.05)	2 (4.65)
Other anomaly of digestive system (ICD-9; 751)	2 (3.33)	2 (5.26)	1 (2.33)
Other anomalies of limbs (ICD-9; 755)	0 (0.00)	0 (0.00)	2 (4.65)
Other anomaly of upper alimentary tract (ICD-9; 750)	4 (6.67)	0 (0.00)	1 (2.33)
Other musculoskeletal anomalies (ICD-9; 756)	10 (16.67)	9 (23.68)	5 (11.63)
Other and unspecified anomalies (ICD-9; 759)	7 (11.67)	2 (5.26)	5 (11.63)

*Because an infant may be diagnosed with multiple malformations, the total number of malformations does not equal the number of infants with malformations.
[a]Excluding paroxetine.
[b]Excluding SSRIs.

before or during pregnancy was similar in cases and controls (Table 2).

Cases of major congenital cardiac malformations and their controls had similar characteristics to cases of major congenital malformations and their controls (Table 3).

Adjusting for all potential confounding variables, as well as for second and third trimester exposure to antidepressants, paroxetine exposure during the first trimester of pregnancy did not significantly increase the risk of major congenital malformations (OR = 1.32; 95% CI = 0.79, 2.20) compared with the use of non-SSRI antidepressants (Table 4). Similarly, the use of other SSRIs (other than paroxetine) during the first trimester of pregnancy did not significantly increase the risk of major congenital malformations (OR = 0.93; 95% CI = 0.53, 1.62) as compared with the use of non-SSRI antidepressants (Table 4). The same was found for the risk of major cardiac malformations associated with first trimester exposure to paroxetine (OR = 1.38; 95% CI = 0.49, 3.92), or to other SSRIs (OR = 0.89; 95% CI = 0.28, 2.84) as compared with the use of non-SSRI antidepressants (Table 4).

When women were classified according to their dosage of paroxetine use during the first trimester of pregnancy, however, a dose–response relationship was observed (Table 5). Hence, women exposed to more than 25 mg/day of paroxetine on average during the first trimester of pregnancy were at increased risk of having an infant with major congenital malformations (OR = 2.23; 95% CI = 1.19, 4.17) (Table 5). The same was found for the risk of major congenital cardiac malformations for exposure above 25 mg/day (OR = 3.07; 95% CI = 1.00, 9.42) (Table 5).

Given that diabetes is an important risk factor for congenital malformations, sensitivity analyses were carried out excluding women with diabetes either before or during pregnancy. Given the small prevalence of women with diabetes in our study populations, this exclusion resulted in similar findings. In addition, restricting analyses to women who used only paroxetine during the first trimester of pregnancy did not again change the findings because the majority of them used the drug at the very beginning of pregnancy. In all analyses, other SSRIs behaved similarly to non-SSRI antidepressants with regard to their effect on the study outcomes.

DISCUSSION

This study showed that without considering dose intake, within a population-based cohort of pregnant users of antidepressants, first trimester exposure to paroxetine did not significantly increase the risk of major congenital malformations, and more specifically major cardiac malformations. However, when considering the average daily dosage of paroxetine use during the first trimester of pregnancy, paroxetine was significantly associated with a two-fold increase in the risk of major congenital anomalies, and more specifically with a three-fold increase in the risk of major cardiac anomalies, for average daily intake of >25 mg. The main cardiac malformations found were bulbus cordis anomalies and anomalies of cardiac septal closure. This study is the first showing a dose–response relationship between gestational exposure to paroxetine in the first trimester of pregnancy and risk of major cardiac malformations. Excluding women with a history of diabetes or

Table 2
Characteristics of Infants With Major Congenital Malformations and Their Controls[a]

Variables	Cases (n = 101)	Controls (n = 1302)
1st trimester exposure to antidepressants:		
Paroxetine	43 (42.6)	499 (38.3)
Other SSRIs[b]	28 (27.7)	415 (31.9)
Other antidepressants[c]	30 (29.7)	388 (29.8)
2nd trimester exposure to any antidepressants	33 (32.7)	469 (36.0)
3rd trimester exposure to any antidepressants	24 (23.8)	406 (31.2)
Pregnancy-related:		
Gestational age (weeks), mean (±SD)	38.64 (1.91)	38.64 (2.05)
Multiple pregnancy	3 (0.21)	31 (2.38)
Birth weight (g) mean (±SD)	3186.05 (612.40)	3225.10 (615.69)
Newborn gender (male)	58 (57.43)	679 (52.15)
Prenatal visits, mean (±SD)	9.36 (3.0)	8.97 (3.6)
Visit to an obstetrician	85 (84.2)	1039 (79.8)
Pregnancy in year before this pregnancy	8 (7.92)	141 (10.83)
Maternal co-morbidities in the year before or during pregnancy:		
Diabetes mellitus	15 (14.9)	116 (8.9)
Hypertension	16 (15.8)	123 (9.5)
Depression	46 (45.5)	684 (52.5)
At the time of delivery:		
Maternal age (years), mean (±SD)	29.65 (6.23)	29.26 (6.06)
Urban dwellers	16 (15.8)	321 (24.7)
Welfare beneficiaries	50 (49.5)	638 (45.5)
Living alone	69 (68.3)	903 (69.4)
Calendar year:		
Jan 1–Dec 31, 1998	13 (12.9)	246 (18.9)
Jan 1–Dec 31, 1999	17 (16.8)	298 (22.9)
Jan 1–Dec 31, 2000	26 (25.7)	274 (21.0)
Jan 1–Dec 31, 2001	30 (29.7)	275 (21.1)
Jan 1–Dec 31, 2002	15 (14.9)	209 (16.1)
Health services utilization in the year before pregnancy:		
Visits to a physician, mean (±SD)	11.13 (9.1)	11.46 (8.9)
Visit to a psychiatrist	23 (22.77)	305 (23.43)
Emergency department visit or hospitalization	19 (18.8)	216 (16.6)
No. of different medications used other than antidepressants		
0	6 (5.9)	80 (6.1)
1–2	24 (23.8)	343 (26.4)
3–5	35 (34.7)	491 (37.7)
≥6	36 (35.6)	388 (29.8)
No. of different prescribers		
1–2	15 (14.8)	221 (17.0)
≥2	86 (85.2)	1081 (83.0)
Health services utilization during pregnancy:		
Visit to a psychiatrist	14 (13.86)	233 (17.90)
Emergency department visit or hospitalization	88 (87.1)	1176 (90.3)
No. of different medications used other than antidepressants		
0	7 (6.9)	148 (11.4)
1–2	43 (42.6)	473 (36.3)
3–5	32 (31.7)	439 (33.7)
≥6	19 (18.8)	242 (18.6)
No. of different prescribers		
1–2	16 (15.8)	253 (19.4)
≥2	85 (84.2)	1049 (80.6)

Abbreviation: SD, standard deviation.
[a]Values are numbers (percentages) unless stated otherwise.
[b]Excluding paroxetine.
[c]Excluding SSRIs.

gestational diabetes, or women with second or third trimester exposure to paroxetine did not change the findings.

The methodology of our study is similar to others published thus far on the same research question as to the population-based origin of the sample, study design, and sample size, or statistical power. Indeed, the United States managed care study (GlaxoSmithKline, 2005a,b), and the Kallen and Otterblad Olausson (2006) study also used a nested case-control design approach and large sample sizes, increasing the power to detect an association. Furthermore, we excluded all women that were

Table 3
Characteristics of Infants With Major Cardiac Malformations and Their Controls[a]

Variables	Cases (n = 24)	Controls (n = 1302)
1st trimester exposure to antidepressants:		
Paroxetine	10 (41.7)	499 (38.3)
Other SSRIs[b]	6 (25.0)	415 (31.9)
Other antidepressants[c]	8 (33.3)	388 (29.8)
2nd trimester exposure to any antidepressants	6 (25.0)	469 (36.0)
3rd trimester exposure to any antidepressants	4 (16.7)	406 (31.2)
Pregnancy-related:		
Gestational age (weeks), mean (±SD)	38.5 (2.0)	38.6 (2.0)
Multiple pregnancy	1 (4.17)	31 (2.38)
Birth weight (g) mean (±SD)	2966.3 (696.2)	3225.1 (615.7)
Newborn gender (male)	9 (37.5)	679 (52.2)
Prenatal visits, mean (±SD)	9.5 (3.4)	9.0 (3.6)
Visit to an obstetrician	17 (70.8)	1039 (79.8)
Pregnancy in year before this pregnancy	0 (0.0)	141 (10.8)
Maternal co-morbidities in the year before or during pregnancy:		
Diabetes mellitus	4 (16.7)	116 (8.9)
Hypertension	5 (20.8)	123 (9.5)
Depression	10 (41.7)	684 (52.5)
At the time of delivery:		
Maternal age (years), mean (±SD)	29.7 (6.2)	29.3 (6.1)
Urban dwellers	15 (62.5)	981 (75.4)
Welfare beneficiaries	12 (50.0)	638 (49.0)
Living alone	20 (83.3)	903 (69.4)
Calendar year:		
Jan 1–Dec 31, 1998	4 (16.7)	246 (18.9)
Jan 1–Dec 31, 1999	4 (16.7)	298 (22.9)
Jan 1–Dec 31, 2000	8 (33.3)	274 (21.0)
Jan 1–Dec 31, 2001	6 (25.0)	275 (21.1)
Jan 1–Dec 31, 2002	2 (8.3)	209 (16.1)
Health services utilization in the year before pregnancy:		
Visits to a physician, mean (±SD)	11.5 (3.4)	11.5 (8.9)
Visit to a psychiatrist	3 (12.5)	305 (23.4)
Emergency department visit or hospitalization	6 (25.0)	216 (16.6)
Number of different medications used other than antidepressants		
0	1 (4.2)	80 (6.1)
1–2	7 (29.2)	343 (26.4)
3–5	8 (33.3)	491 (37.7)
≥6	8 (33.3)	388 (29.8)
Number of different prescribers		
1–2	3 (12.5)	221 (17.0)
≥2	21 (87.5)	1081 (83.0)
Health services utilization during pregnancy:		
Visit to a psychiatrist	3 (12.5)	233 (17.9)
Emergency department visit or hospitalization	19 (79.2)	1176 (90.3)
Number of different medications used other than antidepressants		
0	2 (8.3)	148 (11.4)
1–2	7 (29.2)	473 (36.3)
3–5	9 (37.5)	439 (33.7)
≥6	6 (25.0)	242 (18.6)
Number of different prescribers		
1–2	2 (8.3)	253 (19.4)
≥2	22 (91.7)	1049 (80.6)

Abbreviation: SD, standard deviation.
[a]Values are numbers (percentages) unless stated otherwise.
[b]Excluding paroxetine.
[c]Excluding SSRIs.

exposed to multiple antidepressants during the first trimester of pregnancy per design, as was done in the United States managed care study (GlaxoSmithKline, 2005a,b). This was done to better assess the risk of the drug exposure without considering interactions or synergy between different types of antidepressants. Our non-paroxetine user groups were similar to the United States managed care study but different from Kallen and Otterblad Olausson's (2006). We used as the reference category women who were exposed to non-SSRI antidepressants during pregnancy; paroxetine users and other SSRI users were compared with the reference

Table 4
Multivariate Analyses for First Trimester Exposure to Paroxetine (Dichotomous) and Risk of Major Congenital Malformations or Major Cardiac Malformations

	Major Congenital Malformations		Major Cardiac Malformations	
Variables	Crude OR (95% CI)	Adj OR (95% CI)[a]	Crude OR (95% CI)	Adj OR (95% CI)[a]
1st trimester exposure to antidepressants:				
Other antidepressants[b]	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Paroxetine	1.12 (0.69–1.81)	1.32 (0.79–2.20)	0.97 (0.38–2.49)	1.38 (0.49–3.92)
Other SSRIs[c]	0.87 (0.51–1.49)	0.93 (0.53–1.62)	0.70 (0.24–2.04)	0.89 (0.28–2.84)
2nd trimester exposure to any antidepressants (y/n)	0.86 (0.56–1.33)	1.23 (0.62–2.43)	0.59 (0.23–1.50)	0.72 (0.17–3.01)
3rd trimester exposure to any antidepressants (y/n)	0.69 (0.43–1.10)	0.53 (0.25–1.11)	0.44 (0.15–1.30)	0.46 (0.09–2.30)

Abbreviations: Adj, adjusted; CI, confidence interval; OR, odds ratio.
[a]Adjusted for gestational and maternal age at the time of delivery, mean number of prenatal visits, visits to an obstetrician during pregnancy, pregnancy in the year before this pregnancy, diagnosis of diabetes, hypertension, and depression in the year before or during the pregnancy, place of residence, living alone, welfare status, calendar year, mean number of physician visits in the year before pregnancy, visits to a psychiatrists before or during pregnancy, emergency department visits or hospitalization in the year before or during pregnancy, number of different medications taken (excluding antidepressants) in the year before or during pregnancy, number of different prescribers in the year before and during pregnancy.
[b]Excluding SSRIs.
[c]Excluding paroxetine.

Table 5
Multivariate Analyses for Dose of Paroxetine Use During the First Trimester of Pregnancy and Risk of Major Congenital Malformations or Major Cardiac Malformations

Daily Dosage of Paroxetine (mg/day) Use During 1st Trimester of Pregnancy	Major Congenital Malformations				Major Cardiac Malformations			
	n = 1403	No. of Cases (n = 101)	Crude OR (95% CI)	Adj OR (95% CI)[a]	n = 1326	No. of Cases (n = 24)	Crude OR (95% CI)	Adj OR (95% CI)[a]
0	851	58 (6%)	1.00 (Reference)	1.00 (Reference)	817	14 (1%)	1.00 (Reference)	1.00 (Reference)
>0–20	135	6 (4%)	0.64 (0.27–1.50)	0.71 (0.29–1.71)	121	3 (2%)	1.32 (0.37–4.65)	1.76 (0.45–6.82)
>20–25	274	21 (8%)	1.14 (0.68–1.91)	1.30 (0.76–2.25)	250	2 (1%)	0.49 (0.10–1.98)	0.61 (0.13–2.88)
>25	143	16 (11%)	1.72 (0.96–3.09)	2.23 (1.19–4.17)	138	5 (4%)	2.23 (0.79–6.30)	3.07 (1.00–9.42)

Abbreviations: Adj, adjusted; CI, confidence interval; OR, odds ratio.
[a]Adjusted for second and third trimester exposure to antidepressants, gestational and maternal age at the time of delivery, mean number of prenatal visits, visits to an obstetrician during pregnancy, pregnancy in the year before this pregnancy, diagnosis of diabetes, hypertension, and depression in the year before or during the pregnancy, place of residence, living alone, welfare status, calendar year, mean number of physician visits in the year before pregnancy, visits to a psychiatrists before or during pregnancy, emergency department visits or hospitalization in the year before or during pregnancy, number of different medications taken (excluding antidepressants) in the year before or during pregnancy, number of different prescribers in the year before and during pregnancy.

group. Further comparison was done between paroxetine and other SSRI users in our study only. This was done to determine whether paroxetine was different from other SSRIs with respect to its effect on the development of the cardiac system of the fetus. Given that antidepressant users have very different characteristics than non-users with regard to lifestyle, history of co-morbidity including mood and anxiety disorders, and socio-economic status all of which can be difficult to measure with precision (Ramos et al., 2005), we do not believe that having a population-based comparator as was done by Kallen and Otterblad Olausson (2006) is optimal. Similar to the United States managed care study (GlaxoSmithKline, 2005a,b) but unlike Kallen and Otterblad Olausson (2006), our categorization of exposure was done on the basis of filled prescriptions. Although it is true that this does not necessarily mean that women actually took their medications, De Jong van den Berg et al. (1999) found that the majority of filled prescriptions by pregnant women are taken. In addition, given that antidepressants

should be taken on a continuous basis and over extended periods of time, that medications in our pregnancy registry are prescribed for 30-day durations in general, and that women in our study took their antidepressants for >60 days on average during the first trimester of pregnancy and needed to return to the pharmacy for refills, we feel confident that they truly took their medications and were thus exposed. Furthermore, we believe that prescription fillings are a better way to assess medication exposure than using women's self-report at only one point in time during pregnancy. Indeed, self-report is prone to recall bias but more specifically having information on prescription fillings over a 9-month period (a pregnancy) gives a much better picture of exposure status than asking medication use at only one point in time, usually in the first trimester of pregnancy. Contrary to other studies published thus far, we only considered major congenital malformations that did not resolve spontaneously, and that were diagnosed within the infant's first 12 months of life. Therefore, we feel confident that what we observed were truly malformations as defined by the World Health Organization (2006).

The findings of our study are similar to other studies with similar control groups (non-significant 38% increase in cardiac malformations in our study vs. 54% in the United Stated managed care study (GlaxoSmithKline, 2005b) for first trimester users of paroxetine). Furthermore, we found a 1.8% risk of cardiac malformations in paroxetine users, which is similar to what was found in the United States managed care study (GlaxoSmithKline, 2005a,b) and Kallen and Otterblad Olausson (2006). The smaller risk estimate in our study can be partly explained by the fact that we also adjusted for second and third trimester exposure to antidepressants, and that we separated our non-paroxetine exposed group (other SSRIs and non-SSRI antidepressants). In our study, no increased risk in major congenital malformations or major cardiac malformations was found for first trimester exposure to other SSRIs. When looking at average daily dose of paroxetine exposure during the first trimester of pregnancy, women that were exposed to doses >25 mg/day on average were at a two-fold increase for any major congenital malformations, and a three-fold increase for major cardiac malformations compared with non-SSRI users. Comparison between paroxetine and other SSRI users gave similar results. This finding suggests that pregnant women that are using high doses of paroxetine are the ones for which there is a risk of major cardiac malformations. Dosage in this regard could be viewed as a proxy for severity of mood and anxiety symptoms. Given that depression per se, to the best of our knowledge, is not associated with congenital malformations, it is unlikely that it would confound the association between dosage of paroxetine exposure during the first trimester of pregnancy and major congenital malformations. It remains however that our finding is based on few cases of major cardiac malformations in our dose–response analysis, and that our estimate (OR = 3.07) is not robust. This finding needs to be replicated in other study populations.

Within the context of our pregnancy registry, we were not able to measure smoking status, folic acid intake, alcohol use, pregnancy weight gain, and over-the-counter (OTC) medication use. However, we indirectly adjusted for lifestyles such as smoking and alcohol intake by design given that we restricted our study population to antidepressant users. Thus far, smoking has not been associated with congenital malformations other than clef lip/palate (Little et al., 2004), and digital anomalies (Man and Chang, 2006). In our study, the prevalence of clef lip/palate among malformed was 5%, 0%, and 7% for paroxetine users, other SSRI users, and non-SSRI antidepressant users, respectively. It is unlikely that smoking could fully account for the different rates in cardiac malformations between paroxetine and non-SSRI antidepressant users. As for folic acid intake, it has been associated with a wide variety of malformations including spina bifida and cardiac malformations (Czeizel and Dudas, 1992). One case of spina bifida has been identified in our study, and it was amongst paroxetine users, and the majority of cardiac malformations have been detected in the paroxetine group. Given the design of the study, there is no reason to believe that paroxetine users took folic acid differently than other antidepressant users, leading to non-differential misclassifications. In addition, because 101 cases of major congenital malformations have been found in our study, and that the majority of them have been in the paroxetine group, it is improbable that lack of data on folic acid intake could account for the totality of the added risk associated with paroxetine use in the dose–response analyses. Other than non-steroidal anti-inflammatory drugs (NSAIDs) (Ofori et al., 2006), we are not aware of any other OTC medications that have been associated with congenital malformations. Given that our study population was composed of women insured by the RAMQ for their medications, it is unlikely that they would get OTC drugs without a prescription. Nevertheless, we cannot rule out the fact that some of them did get OTC medications without a prescription but it is doubtful that this would be differential between the three study groups, leading to the underestimation of our estimates of risk. Finally, women had to be covered by the RAMQ medication plan to enter the study. We do not believe that this leads to bias by confounding. However, insurance status could be an effect modifier, thus limiting the external validity of our findings. Our study covers all pregnant women from Quebec insured for their medications by the RAMQ, thus it is population-based for a stratum of the Quebec population.

Using a population-based pregnancy registry, our study showed no increased risk of major congenital malformations, specifically major cardiac malformations, associated with first trimester exposure to paroxetine when exposure was dichotomized. For the first time, however, a dose–response relationship between average daily dose of paroxetine utilization during the first trimester of pregnancy and occurrence of major congenital malformations, and major cardiac malformations, was found. Pregnant users of more than 25 mg/day of paroxetine were at a two-fold increased risk of having an infant with a major malformation, and at a three-fold increased risk of having an infant with a major cardiac malformation. Given that cardiac malformations are the most common types of congenital anomalies in the general population, the risks and benefits of paroxetine use during pregnancy should be carefully assessed. Switches to other types of antidepressants, more specifically other SSRIs or venlafaxine, should be considered in the light of

women's history of average daily dose intake (mg/day), tolerance, and severity of underlying disease. In cases where paroxetine use is indicated, strategies to reduce paroxetine dosage such as adjuvant psychopharmacologic treatments might be considered according to specific clinical circumstances and needs.

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