Use of *Paxil CR Tablets* or *Paxil Tablets* During Pregnancy

This response may include reference to information about Paxil CR® (paroxetine HCl) Controlled-Release Tablets; Paxil® (paroxetine HCl).

SUMMARY

- Epidemiological studies of pregnancy outcomes following maternal exposure to antidepressants have reported an increased risk of congenital malformations. There have also been some reports of premature birth in pregnant women exposed to paroxetine or other selective serotonin reuptake inhibitors (SSRIs).
- A meta-analysis looked at pregnancy outcomes following exposure to SSRIs (including paroxetine). The results showed that SSRIs increased the risk of spontaneous abortion and major malformations during pregnancy; they did not increase the risk of cardiovascular malformations and minor malformations.
- A register-based retrospective Danish cohort study analyzed the relation between SSRIs and congenital heart malformations. The risks of congenital heart malformations were similar for pregnancies exposed to an SSRI throughout the first trimester (adjusted OR 2.01) and for pregnancies with paused SSRI treatment during pregnancy (adjusted OR 1.85). The authors did not find an association with dosage; the authors did find similar increased risks of congenital malformations of the heart for the individual SSRIs.
- Other studies have found varying results as to whether there was an increased risk of overall, cardiovascular, or specific congenital malformations.
- Neonates exposed to *Paxil CR Tablets*, *Paxil Tablets*, and other SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. There have also been postmarketing reports of premature births in pregnant women exposed to paroxetine or other SSRIs.
- Two large case-control studies using separate databases, each with >9000 birth defect cases and >4000 controls, found that maternal use of paroxetine during the first trimester of pregnancy was associated with a 2- to 3-fold increased risk of right ventricular outflow tract obstructions. In one study the odds ratio (OR) was 2.5 (95% confidence interval, 1.0–6.0, 7 exposed infants) and in the other study the OR was 3.3 (95% confidence interval, 1.3–8.8, 6 exposed infants).
- Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1–2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality. Epidemiological studies have shown that the use of SSRIs (including paroxetine) in pregnancy, particularly use in late pregnancy, was associated with an increased risk of PPHN. The increased risk among infants born to women who used SSRIs late in pregnancy was reported to be 4 to 5 times higher than observed in the general population.
- One study including two-nested, case-control analyses purported to find a dose-response relationship for both major congenital malformations and major cardiac malformations. Infants born to women exposed to >25 mg/day of paroxetine during the first trimester had an increased risk of both major congenital malformations and major cardiac malformations. The authors commented that this finding was based on few cases of major cardiac malformations in the dose-response analysis and the estimate was not robust.

- The results of a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy showed that women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.
- When treating a pregnant woman with paroxetine health care professionals should carefully consider the potential risks and benefits of treatment.
- *Paxil CR Tablets* and *Paxil Tablets* are Pregnancy Category D.
- Important safety information is found in the attached Prescribing Information.
- The prescribing information for this product contains a boxed warning. Please consult the WARNING section of the attached prescribing information for further details and for important safety information.

OVERVIEW

Some epidemiological studies of pregnancy outcomes following maternal exposure to antidepressants in the first trimester have reported an increase in the risk of congenital malformations associated with the use of paroxetine.(1) Other studies have found varying results as to whether there was an increased risk of overall, cardiovascular, or specific congenital malformations. There have been reports of premature birth in pregnant women exposed to paroxetine or other SSRIs.

Neonates should be observed if maternal use of paroxetine continues into the later stages of pregnancy, because there have been reports of complications in neonates exposed to paroxetine or other SSRIs late in the third trimester of pregnancy.(1) Reported clinical findings have included: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying and somnolence. In some instances, the reported symptoms were described as neonatal withdrawal symptoms. In a majority of instances the complications were reported to have arisen either immediately or soon (<24 hours) after delivery.

The prevalence of congenital malformations in the United States (U.S.) general population is approximately 3% for any malformation and approximately 1% for cardiovascular malformations alone.(2)

Cohen et al reported in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, that women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.(3)

CONGENITAL MALFORMATIONS

Meta-Analyses

A meta-analysis of databases from 1990 to March 2012 was conducted to identify studies (n=25) investigating pregnancy outcomes following exposure to any therapeutic dosage of any SSRI (including paroxetine) during pregnancy.(4) Compared with placebo, the SSRIs were found to have an increased risk of spontaneous abortion (odds ratio (OR) 1.87 (95% CI: 1.5-2.33, $P < 0.0001$) and major malformations (OR 1.272 (95% CI: 1.098-1.474, $P = 0.0014$). Statically nonsignificant increases were observed for cardiovascular malformations (OR 1.192 (95% CI 0.39-3.644, $P = 0.7578$) and for minor malformations (OR 1.36 (95% CI: 0.61 to 3.04, $P = 0.4498$).

A meta-analysis based on original research published from 1992 to September 30, 2008 (n = 20) was conducted to provide a systematic review of epidemiological data regarding first trimester paroxetine use and the prevalence of congenital, including cardiac, malformations.(5) Data from case reports, case series, non-human data, neonatal consequences from breast-milk exposure, third trimester-only exposure,

and neonatal complications unrelated to congenital defects were excluded. The analysis suggested that first-trimester paroxetine exposure was associated with an increased risk of cardiac defects (prevalence odds ratio [POR] 1.46; 95% confidence interval [CI] 1.17-1.82) and total malformations (POR 1.24; 95% CI 1.08-1.43).

A meta-analysis of 9 studies published between 1985 and 2007 was conducted to examine the risk of cardiac defects in infants following first trimester exposure to paroxetine.[6] Three case-control studies demonstrated a non-significant increase in risk (OR 1.18; 95% CI 0.88-1.59). In the 6 remaining cohort studies, the rates of cardiac malformations were 1.14% in the paroxetine-exposed infants and 1.09% in the controls, both of which fell within the 95% confidence interval for the population at large (0.7%-1.2%). Additionally, a non-significant weighted average difference of 0.3% was noted between the paroxetine-exposed and non-exposed groups.

A meta-analysis of 7 studies conducted from 1985 to 2006 was conducted to quantify first-trimester exposure to paroxetine and birth defects.[7] Results indicated that first-trimester exposure to paroxetine was associated with a significant increase in the risk of cardiac malformations (OR 1.72; 95% 1.22-2.42). The authors discuss the potential for a detection bias to influence this finding.

Cohort, Case Control and Other Studies

A nationwide cohort study looked at the relation between SSRI use (including paroxetine) and major congenital malformations, with a focus on heart malformations.[8] Through the Danish Medical Birth Registry, all pregnancies in Denmark between 1997 and 2009 were identified. Of the 848,786 pregnancies identified, 4183 were exposed to a SSRI throughout the first trimester and 806 pregnancies had paused exposure during pregnancy. Risks of congenital heart malformations were similar for pregnancies exposed in the first trimester (adjusted OR 2.01; 95% CI 1.60-2.53) and for pregnancies with paused SSRI treatment with pregnancy (adjusted OR 1.85; 95% CI 1.07-3.20), $P = 0.94$. A subanalysis found an association between exposure to any SSRI and septal heart defects (adjusted OR 2.04; 95% CI 1.53-2.72).Ventricular septal defects and atrial septal defects were associated with an increased risk. The increased risk of congenital septal defects was also found for pregnancies with paused exposure (adjusted OR 2.56; 95% CI 1.41-4.64). Also reported was an association of craniosynostosis (n=9) and exposure to SSRI in the first trimester (adjusted OR 3.64; 95% CI 1.00-3.76). For pregnancies with paused exposure, the authors found an association with craniosynostosis (n=3) with exposure to SSRI in the first trimester (adjusted OR 3.64; CI 1.17-11.34). The authors found no association with dosage.

An observational cohort study in the United Kingdom (UK), conducted by Prescription Event Monitoring (PEM), investigated the frequency of events that were noted by practitioners following the prescribing of paroxetine.[9,10,11] PEM questionnaires, generated from prescriptions written by general practitioners during the first year that paroxetine was marketed, requested that the practitioner report all significant events recorded in the treated patients' records without regard of the event's relationship to the use of paroxetine. Between March 1991 and March 1992, data collected on 13,741 patients treated with paroxetine were analyzed. Of the sample, there were 9279 women (67.5%) with a mean age of 48.8 years. There were 138 pregnancies reported during this time period. Exposure to paroxetine during the first trimester was likely for 63 of the pregnancies. The pregnancy outcomes are summarized in Table 1. There were no congenital abnormalities in the live births. One baby of a set of twins was stillborn, 1 intrauterine death was reported at 18 weeks gestation in a mother diagnosed with idiopathic thrombocytopenic purpura and 1 baby was reported to have a 'jittery episode'. Note that the pregnancies may have involved exposure to other agents and may have included women with various medical conditions.

Table 1. Pregnancy Outcomes in Women Exposed to Paroxetine during the First Trimester[9,10,11]

Pregnancies	Live Birth	Ectopic	Spontaneous Abortion	Elective Termination	Still Birth	IUD	Not known
63*	42	0	8	11	1†	1	3

IUD = Intra-uterine death.

*Drawn from 63 pregnancies which included three sets of twins.

†One baby of a set of twins.

Kulin et al reported retrospectively collected pregnancy outcomes in 267 mothers exposed to an SSRI during the first trimester of pregnancy (n = 97 exposed to paroxetine) and compared these outcomes to those of a prospectively identified group of women who were not exposed to any known teratogens during pregnancy.[12] A statistical analysis of the outcomes showed no statistical differences between the study group outcomes and the control group outcomes. Though specific data were not provided, the investigators indicated that pregnancy outcome among women who took an SSRI throughout pregnancy (n = 49; number specifically receiving paroxetine not provided) did not differ from those who took the drug only during the first trimester.

Hendrick et al prospectively followed women who received SSRI antidepressants to determine the incidence of congenital anomalies and neonatal complications after prenatal exposure.[13] Birth outcomes were obtained from a review of obstetric and neonatal records of 138 women who were treated with fluoxetine (n = 73), sertraline (n = 36), paroxetine (n = 19), citalopram (n = 7) or fluvoxamine (n = 3). Eighty-five of these women received antidepressants during the entire pregnancy and 131 women were receiving the medication at delivery. The incidence of congenital anomalies in this study was 1.4% which is comparable to general population. Four cases (2.9%) of low birth weight were reported; all involved infants who had been exposed to fluoxetine therapy (40 to 80 mg daily) throughout pregnancy. Nine cases (6.5%) of preterm births were reported; five fluoxetine exposures (6.8%), two paroxetine exposures (including one birth of twins, 10.5%), and two sertraline exposures (5.5%).

Malm et al conducted a population based study of 1782 women exposed to SSRIs during pregnancy from three governmental organization databases in Finland during 1996–2001 and reported major malformations were not more common in infants or fetuses of women with first trimester SSRI purchases (n = 1398) when compared with matched controls with no drug purchases (n = 1398; $P = 0.4$).[14] For first trimester purchases of paroxetine (n = 152), the crude odds ratio compared to women with no drug purchases (n = 1782) was 1.0 (95% CI, 0.4-2.8). After adjustment for maternal age, smoking, low social status, nulliparity, and purchases of other reimbursed drugs than SSRIs during the corresponding period, the adjusted odds ratio was 0.4 (95% CI 0.1-3.3). In addition, a higher rate of neonatal treatment in special or intensive care unit was observed after third trimester exposure to SSRIs; however, these results were not reported by individual SSRI exposure. A separate retrospective cohort study based on some of the same Finnish population based registries but using years 1996–2006 was reported by Malm et al in 2011.[15] In offspring exposed to any SSRI (n=6,881) compared to matched controls (n=618,727), major congenital anomalies were more common (crude OR 1.24; 95% CI 1.10–1.39), but the difference did not remain statistically significant after adjusting for cofounding factors (adjusted OR 1.08; 95% CI 0.96–1.22). Of individual SSRIs, use of paroxetine (n=968) was associated with an increased risk for overall major congenital anomalies (crude OR 1.39; 95% CI 1.03–1.86), but the risk did not remain statistically significant after adjusting for confounders (adjusted OR 1.22; 95% CI 0.91–1.64). Looking at specific malformations, paroxetine use during pregnancy was associated with a statistically significant increase in right ventricular outflow tract defects, (adjusted OR 4.68; 95% CI 1.48–14.74).

Alwan et al evaluated data from the National Birth Defects Prevention Study, an ongoing case study of risk factors for birth defects, on infants delivered from 1997 to 2002 with or without selected major birth defects.[16] A total of 9622 infants with selected major birth defects (either isolated or multiple) and 4092 normal controls were identified. Adjusted analyses showed that women who took an SSRI in the period between 1 month before and 3 months after conception were more likely than those who were not exposed to have an infant with anencephaly (OR 2.4; 95% CI 1.1-5.1), craniosynostosis (OR 2.5; 95% CI 1.5-4), or

omphalocele (OR 2.8; 95% CI; 1.3-5.7). When pooling the occurrence of these three defects together, the use of paroxetine (OR 4.2; 95% CI 2.1-8.5) was reported to be associated with the strongest effect. For isolated defects, paroxetine was significantly associated with anencephaly (OR 5.1; 95% CI 1.7-15.3) and omphalocele (OR 8.1; 95% CI 3.1-20.8). A nonsignificant trend for higher risk of right ventricular outflow tract obstruction (OR 2.5; 95% CI 1.0–6.0) and gastroschisis (OR 2.9; 95% CI 1.0–8.4) was observed with paroxetine. Reefhuis et al reported preliminary results from this same study through 2007.[17] In 8115 controls, sertraline, fluoxetine, and paroxetine were used by 89 (1.1%), 62 (0.8%) and 37 (0.5%), respectively. There were no defects associated with all three SSRIs. Sertraline, fluoxetine, and paroxetine were each associated with some specific birth defects, but without any common pattern. Paroxetine was associated with anencephaly (OR 2.7; 95% CI 1-6.8), total anomalous pulmonary venous return (OR 4.2, 95% CI 1.5-11.8), omphalocele (OR 3.5, 95% CI 1.4-9.1) and gastroschisis (OR 2.1, 95% CI 1.0-4.4).

Diav-Citrin et al reported pregnancy outcomes in pregnant women exposed to paroxetine (n = 463; 410 in the first trimester) or fluoxetine (n = 346; 314 in the first trimester) who contacted teratogen information services in Israel, Italy, or Germany.[18] After exclusion of genetic and cytogenetic anomalies, there was a higher overall rate of major congenital malformations in infants exposed to paroxetine in the first trimester [18/348 (5.2%)] compared to infants in a control group with drug exposures not known to be teratogenic [34/1359 (2.5%)] [$P < 0.05$]. A higher rate of cardiovascular anomalies was also observed in the paroxetine group [7/348 (2.0%)] compared to the control group [8/1359 (0.6%)] [$P < 0.05$; adjusted odds ratio 2.66; 95% CI 0.80–8.90]. Similar trends were reported in the fluoxetine group and were statistically significantly higher than the control group. Logistic regression was conducted to evaluate the relative contribution of variables to the risk of cardiovascular anomalies. Only cigarette smoking ≥10 cigarettes a day and fluoxetine exposure were significant variables. Pregnancy outcome was a secondary objective. For paroxetine, 85.3% (395/463) of deliveries resulted in a live-born infant compared to 89.8% (1318/1467) in the control group ($P<0.05$ exposed vs. control). In those exposed to paroxetine, 9.1% (42/463) of deliveries resulted in miscarriage, 4.8% (22/463) were elective terminations of pregnancy, 0.9% (4/463) were stillbirths, and none resulted in ectopic pregnancy. For the control group, there were 6.6% (97/1467) miscarriages, 2.8% (43/1467) elective terminations of pregnancy, 0.5% (8/1467) stillbirths, and 0.1% (1/1467) ectopic pregnancies.

Maschi et al prospectively followed pregnant women (n = 200, mean age 31 years) who received SSRI antidepressants to determine the incidence of early adverse effects in newborns associated with antidepressant exposure during pregnancy.[19] A control group (n = 1200) not exposed to teratogenic medications known to cause neonatal side effects was also followed during the same time. Paroxetine was the most used antidepressant (n = 58) with the median dose of 20 mg daily. No significant adverse event differences were found between neonates exposed to antidepressants *in utero* and the control group. Adverse effects associated with paroxetine included respiratory distress (n = 2), jaundice (n = 1), and heart defect (n = 1). Differences were found in prematurity rate in exposed newborns compared with nonexposed newborns (OR 2.31; 95% CI 1.14-4.63) and in the rate of caesarean deliveries (OR 1.92; 95% CI 1.40-2.63).

A population-based cohort study of 493,113 children born in Denmark between 1996–2003 was conducted to investigate any association between SSRI use during pregnancy and major congenital malformations.[20] Outcomes analyses were adjusted for maternal age, calendar time, marital status, income, and smoking status. Of the study population, 299 children had been exposed to paroxetine. The combined prevalence of major malformations or non-cardiac malformations was not significantly higher among children exposed to any SSRI; however, SSRI use was associated with a significantly increased prevalence of septal heart defects (OR 1.99; 95% CI 1.13–3.53). There was an increased prevalence of septal heart defects for children of mothers who had used sertraline (OR 3.25; 95% CI 1.21–8.75) or citalopram (OR 2.52; 95% CI 1.04–6.10). One paroxetine-exposed child was found with a septal heart defect, yielding a crude OR of 0.76. Use of more than 1 type of SSRI was associated with a significantly increased risk of any cardiac malformation (OR 3.42; 95% CI 1.4–8.34) and septal heart defects (OR 4.70; 95% CI 1.74–12.7).

Nordeng et al conducted a review of data prospectively collected from the Norwegian Mother and Child Cohort Study between 2000-2006 to examine the occurrence of congenital malformations after first

trimester maternal exposure to antidepressants, including paroxetine.[21] A sample of 63,395 women was identified who had prospectively completed 2 questionnaires during pregnancy at weeks 17 and 30 and of those, 699 (1.1%) reported antidepressant use at any time during pregnancy, paroxetine n=76 (0.1%). After adjusting for maternal depression, maternal age at delivery, parity, and use of psychotropic drugs during pregnancy, exposure to SSRIs or paroxetine during the first trimester was not associated with increased risk of congenital malformations: SSRI adjusted OR= 1.22 (95% CI, 0.81-1.84), paroxetine adjusted OR= 0.95 (95% CI, 0.30-3.02). SSRI exposure during pregnancy was also not associated with cardiovascular malformations (adjusted OR, 1.51; 95% CI, 0.67-3.43), an increased risk of preterm birth (adjusted OR, 1.28; 95% CI, 0.90-1.84) or low birth weight (adjusted OR, 0.64; 95% CI, 0.32-1.26). Paroxetine adjusted OR for cardiovascular malformations was not calculated due to low incidence (n=1).

Stephansson et al conducted a population-based cohort study from all Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) between 1996-2007 to study the risk of stillbirth and infant mortality associated with use of SSRIs for psychiatric illness during pregnancy.[22] The study included women with singleton births and obtained information from prescription, patient, and medical birth registries. They used logistic regression to estimate relative risks of stillbirth, neonatal death, and postneonatal death associated with SSRI use during pregnancy taking into account maternal characteristics and previous psychiatric hospitalization. Among 1,633,877 births in the study, there were 6054 stillbirths, 3609 neonatal deaths, and 1578 postneonatal deaths. A total of 29,228 (1.79%) of mothers filled a prescription for an SSRI during pregnancy, including 3745 for paroxetine. Women exposed to an SSRI compared with those not exposed had higher rates of stillbirth (4.62 vs 3.69 per 1000, $P = 0.01$) and postneonatal death (1.38 vs 0.96 per 1000, $P = 0.03$) while the rate of neonatal death was similar (2.54 vs 2.21 per 1000, $P = 0.24$). However, in multivariable models, SSRI use was not associated with stillbirth (adjusted OR 1.17; 95% CI, 0.96-1.41; $P = 0.12$), neonatal death (adjusted OR, 1.23; 95% CI, 0.96-1.57; $P = 0.11$), or postneonatal death (adjusted OR 1.34; 95% CI, 0.97-1.86; $P = 0.08$). Estimates were further attenuated when stratified by previous hospitalization for psychiatric disease. The authors did not interpret results by individual SSRI. There were 21 events of stillbirth, 5 neonatal mortality, and 4 postneonatal death in women exposed to paroxetine.

A retrospective cohort study using U.S. United Healthcare data evaluated 5956 infants of mothers dispensed paroxetine or other antidepressants during the first trimester (n = 815 for paroxetine).[23,24] This study showed a nonsignificant trend towards an increased risk for cardiovascular malformations for paroxetine as monotherapy compared to other antidepressants (OR 1.46; 95% CI 0.74-2.88). The prevalence of cardiovascular malformations following first trimester dispensing was 1.5% for paroxetine vs. 1% for other antidepressants. Nine out of 12 infants with cardiovascular malformations whose mothers were dispensed paroxetine in the first trimester had ventricular septal defects (VSDs). This study also suggested an increased risk of overall major congenital malformations (inclusive of the cardiovascular defects) for paroxetine compared to other antidepressants (OR 1.89; 95% CI 1.20-2.98). The prevalence of all congenital malformations following first trimester exposure was 4% for paroxetine vs. 2% for other antidepressants.

A retrospective cohort study using administrative data from five large managed care organizations, evaluated 1047 infants of mothers who used a selective serotonin reuptake inhibitor (SSRI) during early pregnancy (n = 182 for paroxetine).[25] Paroxetine exposure was not associated with an increased risk of septal defects (relative risk [RR] 0.50; 95% CI 0.07-3.54) or other congenital anomalies of the heart (RR 1.98; 95% CI 0.64-6.15). In subanalyses, an increased risk for congenital anomalies of the eye was found with paroxetine exposure (RR 2.36; 95% CI 1.2-4.66). A chart review of these cases revealed most of the eye conditions were either not confirmed or self resolving conditions common in infancy (dacryostenosis). Overall, the risk of preterm delivery was significantly increased among infants exposed to SSRIs compared to infants unexposed to SSRIs (RR 1.45; 95% CI 1.25-1.68). Fullterm infants with first-trimester exposure to any SSRI were not at increased risk of congenital anomalies.

An analysis of the case-control surveillance data from the Slone Epidemiology Center Birth Defects Study was conducted to evaluate whether exposure to SSRIs (fluoxetine, sertraline, paroxetine) and non-SSRIs during the first trimester increases the overall risk of major structural birth defects, the overall risk of cardiac defects or risk of specific cardiac defects.[26] Cases were defined as mothers of infants with any birth

defect (n = 9849) and controls were defined as mothers of infants with no birth defects (n = 5860). Overall, use of SSRIs was not associated with significantly increased risks of craniosynostosis, omphalocele, or heart defects overall. When specific defects were analyzed, there was a statistically significant increase in the risk for right ventricular outflow tract obstruction (RVOTO) defects (OR 3.3; 95% CI 1.3-8.8), risk of neural-tube defects (OR 3.3; 95% CI 1.1-10.4) and clubfoot (OR 5.8; 95% CI 2.6-12.8) with paroxetine. The association between paroxetine and undescended testis had a lower confidence bound of 1 (OR 2.8; 95% CI 1.0-7.8). For "any SSRI", there was a significantly increased risk of clubfoot (OR 2.2; 95% CI 1.4-3.6). Yazdy et al reported preliminary results with a lower magnitude of clubfoot risk from this same study through 2011.[27] They included 578 clubfoot cases and 2032 non-malformed controls born between 2006 and 2011 in Massachusetts, New York, and North Carolina to women who reported any SSRI use in the 2nd through 4th month of pregnancy. Reported SSRI use was slightly higher in case than control mothers (4.8% vs 3%). After adjustment for maternal race and smoking, the OR for any SSRI use and clubfoot was 1.42 (95% CI: 0.9-2.3). When individual SSRIs were examined, ORs were elevated for paroxetine and escitalopram, but numbers were reportedly small and confidence intervals were wide.

Outcomes of infants exposed to paroxetine during pregnancy were collected from teratology information services and database studies to determine the rate of cardiovascular effects compared to that of an unexposed population (women from teratology services with exposures to medications considered safe).[28] Of 1174 cases of first-trimester, paroxetine exposures obtained through teratogen information services, there were 9 cardiovascular birth defects [incidence = 0.7%; 95% CI, 0.4-1.4]. In the unexposed group, the rate of cardiovascular defects was 0.7% (odds ratio = 1.1, 95% CI, 0.36-2.78, nonsignificant difference compared to exposed cases). Additionally, there were 34 cases of cardiovascular malformations based on information from 2205 published cases on paroxetine exposures during pregnancy (incidence = 1.5%; 95% CI, 1.1-2.1). When the two data sets were combined, the mean rate of cardiovascular defects was 1.2% (95% CI, 1.1-2.1).

Merlob et al conducted a prospective cohort study to compare the rate of congenital heart malformations in newborns with first trimester exposure to SSRIs (n = 235) compared to a control group of non-exposed newborns (n = 67,636).[29] Ninety-two infants had been exposed to paroxetine in utero. All infants were examined for cardiac murmur on the first day of life, and those with a persistent murmur were examined by a pediatric cardiologist and referred for electrocardiography and echocardiography. Cardiologists were not blinded to SSRI exposure. The difference in the prevalence of congenital heart malformations between the study and control group was statistically significant (8/235 [3.40%] vs. 1083/67,636 [1.60%], respectively; $P = 0.023$; RR 2.17; 95% CI 1.07–4.39). Four of the 8 SSRI-exposed infants with congenital heart malformations were exposed to paroxetine, yielding a 4.3% (4/92) incidence of cardiac anomalies. VSD was the most common cardiac malformation (6 infants, 3 of whom were exposed to paroxetine). All cases of VSD were mild.

Bakker et al conducted a case-control study using data from a population-based birth defects registry of children born between 1997 and 2006 in the Netherlands to investigate any association between first trimester paroxetine use and the occurrence of specific heart defects.[30] Children were considered exposed if the mother took paroxetine at any point in the period from 4 weeks before conception through week 12 of the pregnancy. Use of paroxetine outside the first trimester was an exclusion criteria. The following possible confounders were accounted for: year of birth, pregnancy outcome, maternal age, gravidity, mother's educational level, smoking, use of alcohol, body mass index, use of folic acid, and maternal diabetes and epilepsy. Cases (n = 678) were defined as fetuses or children with isolated heart defects, and controls (n = 615) were defined as those with a genetic disorder with no heart defect. Exposure to paroxetine during the first trimester occurred in 1.5% (n = 10) of cases compared to 1% (n = 6) of controls. The majority of mothers were taking 20 mg daily of paroxetine. There was not a significantly increased risk for overall heart defects (10 exposed cases, AOR 1.5, 95% CI 0.5–4.0). A significantly increased risk for atrium septum defects was found (3 exposed cases, AOR 5.7, 95% CI 1.4–23.7).

Berard et al conducted two nested case-control analyses to evaluate the association between exposure to paroxetine in the first trimester of pregnancy and cardiac malformations as well as a potential dose-response relationship.[31] Controls in both studies were defined as no major or minor malformations.

Data from all pregnancies occurring in Quebec from January 1, 1997 to June 30, 2003 were retrieved from the population-based Medication and Pregnancy Registry. Of these, 1403 women met the study inclusion criteria and had exposure to the following antidepressants in the first trimester of pregnancy: paroxetine (n = 542; 39%), other SSRIs (n = 443; 31%), and non-SSRI antidepressants (n = 418; 30%). Major congenital malformations were identified in 101 infants, 24 of whom had major cardiac malformations. The rate of major congenital malformations was 8%, 6%, and 6% in the paroxetine, other SSRI and non-SSRI groups, respectively. The rate of major cardiac malformations was 2% in the paroxetine group and 1% in both the other SSRI and non-SSRI groups. Paroxetine (adjusted odds ratio [AOR] 1.32; 95% CI 0.79-2.2) and other SSRIs (AOR 0.93; 95% CI 0.53-1.62) did not increase the risk of major congenital malformations compared to non-SSRI antidepressants. Neither paroxetine (AOR 1.38; 95% CI 0.49-3.92) nor other SSRIs (AOR 0.89; 95% CI 0.28-2.84) increased the risk of major cardiac malformations compared to non-SSRI antidepressants. However, classification of women by the dose of paroxetine received during the first trimester of pregnancy suggested a dose-response relationship for both major congenital malformations and major cardiac malformations. The authors note that this finding was based on few cases of major cardiac malformations in the dose-response analysis and the estimate was not robust. Infants born to women exposed to >25 mg/day of paroxetine on average during the first trimester had a significantly increased risk of major congenital malformations (AOR 2.23; 95% CI 1.19-4.17). Major cardiac malformations was non-significantly increased (AOR 3.07; 95% CI 1.00-9.42).

Berard et al reported, in an abstract, an additional evaluation of the Quebec Pregnancy Registry (1998–2004), whereby 1,612 (1.5%) pregnancies with exposure to paroxetine were identified.[32] Among those using paroxetine, 49% had a planned abortion, 7% a spontaneous abortion, and 44% a delivery. Among babies delivered, 3% had a cardiac malformation, with the most prevalent type being atrial and septal defects (74%). Berard et al estimated the prevalence of paroxetine use during pregnancy and diagnosed cardiac malformations in an ecologic study of two distinct pregnancy databases, the Quebec Pregnancy Registry and the French EFEMERIS database, after warnings about cardiac malformations in 2005.[33] In Quebec, among the 109,344 eligible pregnancies, 1,612 (1.5%) were exposed to paroxetine; paroxetine use during pregnancy increased from 0.7% to 1.2% between 1998 and 2003, simultaneously to the increase of the prevalence of cardiac malformation diagnoses. In France, among 40,317 eligible pregnancies, 173 (0.4%) were exposed to paroxetine; paroxetine use and cardiac malformation diagnoses remained constant between 2004 and 2008.

Two studies using data from the Danish Medical Birth Registry examining the association between SSRI use during pregnancy and congenital malformations have been published.[34,35] Kornum et al. examined early pregnancy (first trimester) and overall risk of congenital malformations and cardiac malformations in infants of 216,042 mothers from Northern Denmark with a live birth after 20 weeks of gestation.[34] The data were collected at different time periods for the 3 geographical areas included, but all pregnancies occurred between 1991-2007. The prevalence of malformations in infants born to women who had filled at least one SSRI prescription during early pregnancy (n = 2062) were compared to women who had not filled any prescriptions for a SSRI during pregnancy (n = 213,712). Exposed women gave birth to 105 infants (5.1%) with congenital malformations, compared to 7449 infants (3.5%) of unexposed mothers. The prevalence of cardiac malformations was 1.3% among infants born to exposed mothers and 0.7% among infants of unexposed mothers. SSRI use during early pregnancy was associated with a significantly increased risk of overall malformations (AOR 1.3; 95% CI 1.1–1.6) and cardiac malformations (AOR 1.7; 95% CI 1.1–2.5). Second or third trimester SSRI use was not associated with a significantly increased risk of overall malformations (AOR 1.0; 95% CI 0.5–1.9). The overall AOR for any malformation with any SSRI use during pregnancy was 1.3 (95% CI 1.1–1.6). Of the study population, 297 women were exposed to paroxetine monotherapy during early pregnancy. Eleven infants (3.7%) were born with any malformation, and 1 infant (0.3%) was diagnosed with a cardiac malformation (septal heart defect).

Jimenez-Solem et al included all pregnancies included in the Danish Medical Birth Registry between 1997 and 2009 in their analysis (848,786 pregnancies, 4183 were exposed to an SSRI throughout the first trimester and 806 pregnancies paused exposure during pregnancy [paroxetine n= not provided]). Some of the patient population in this study overlapped a portion of the patient population in the Komum

study.[35] The overall AOR for the occurance of any major congenital malformation after first trimester SSRI exposure was 1.33 (95% CI 1.16 to 1.53), and for congenital malformations of the heart, AOR 2.01 (95% CI 1.60 to 2.53). In this study, an increased risk of congenital malformations of the digestive system was observed among women exposed to an SSRI in the first trimester, AOR 1.80 (95% CI 1.04 to 3.12). This study also examined pregnant women who were classified as having a paused exposure if exposure to an SSRI occured 3-12 months before conception or 1-12 months after giving birth but with no exposure to an SSRI between 3 months before conception to 1 month after giving birth. Patients with a paused exposure did not have a statistically significant increase in any major malformation, but in a subanalysis of individual major congenital malformations, paused exposure was associated with congenital malformations of the heart, adjusted AOR 1.85 (95% CI 1.07 to 3.20). In a subanalysis of various major congenital malformations, paroxetine use was not associated with a statistically significant increased risk of overall or cardiac malformations in either of these 2 studies.[34,35]

Studies of delivery outcomes following maternal use of SSRI antidepressants in early pregnancy were conducted utilizing the Swedish national registry data.[36,37,38,39] An analysis included infants (n = 6555) born to 6481 women exposed to SSRIs in early pregnancy from July 1, 1995 to December 31, 2004.[37] Among them, 943 women (959 infants) reported the use of paroxetine, 35 of whom used paroxetine in combination with another antidepressant. No increase in the overall rate of congenital malformations was observed in infants exposed to SSRIs (4.1%), compared with the general population (4.7%) (adjusted OR 0.89; 95% CI 0.79-1.07). Congenital malformations were observed in 46 infants exposed to paroxetine during early pregnancy (nonsignificant adjusted OR 1.03; 95% CI 0.76-1.38). There was an increased risk for cardiac defects in infants exposed to paroxetine (OR 1.63; 95% CI 1.05-2.53), including an increased risk of ventricular septal defect (VSD) and an increased risk of atrial septal defect (ASD) (OR 1.81; 95% CI 0.96-3.09); 13 of 20 paroxetine-exposed infants with cardiac defects had a VSD or ASD. The increase was nonsignificant for both the ASD and VSD combined. An increased risk of cardiac defects was not observed in infants whose mothers received an SSRI other than paroxetine. Two separate analyses were conducted to evaluate the relative risk (RR) of cardiac defects occurring with paroxetine therapy compared to other SSRIs. The first analysis excluded non-Swedish women, subfertile women and women with high body mass index (BMI >26). In infants born to paroxetine-treated women (n = 405), the relative risk for any cardiac defect was 2.63 (95% CI, 1.4-4.5) and for VSD and/or ASD was 3.07 (95% CI, 1.32-6.04). Infants exposed to other SSRIs had an odds ratio of 0.64 (95% CI, 0.41-1.01) for any cardiac defect and 0.56 (95% CI, 0.29-1.08) for VSD/ASD. The second analysis additionally excluded women who had taken certain identified medications in combination with their SSRI (neuroleptics, sedatives, hypnotics, folic acid, nonsteroidal anti-inflammatory drugs [NSAIDs] and anticonvulsants). For infants born to paroxetine-treated women (n = 340), the relative risk for any cardiac defect was 2.93 (95% CI, 1.52-5.13) and for VSD/ASD was 3.23 (95% CI, 1.30-6.65). Infants exposed to other SSRIs had an odds ratio of 0.61 (95% CI, 0.37-1.01) for any cardiac defect and 0.38 (95% CI, 0.16-0.87) for VSD/ASD.

A more recent analysis of data from 1995–2007 from the Swedish Medical Birth Registry was conducted by Reis and Källén.[40] All women who had reported “early” (since becoming pregnant) or “later” (prescribed by antenatal care) use of antidepressants were identified and compared with women not reporting such use in the registry. Of the 14,821 exposed women, 12,914 had early exposure, 5987 had later exposure, and 4080 had both. Any SSRI exposure was reported in 14,979 women and of these 1208 and 405 were early or later paroxetine exposure, respectively. A significantly increased risk of persistent pulmonary hypertension (PPHN) was observed in infants exposed to SSRIs (RR 2.30 for early exposure [95% CI, 1.29–3.80]; RR 2.56 for later exposure [95% CI, 1.17–4.85]; RR 3.44 for both early and later exposure [95% CI, 1.49–6.79]). Rate of preterm birth was also significantly higher in infants with later SSRI exposure (OR 1.46; 95% CI 1.31–1.63). Infants with exposure to paroxetine had a higher risk of any cardiovascular defect (n = 24; OR 1.66; 95% CI 1.09–2.53). Of these 24 infants, 7 had VSDs 4 had ASDs, and 1 had both VSD and ASD. A significantly increased risk for hypospadias was also observed after paroxetine exposure (n = 9; OR 2.45; 95% CI 1.12–4.64). After removing infants with exposure to other possible teratogens from the analysis, the OR increased for risk of relatively severe malformations (OR 1.31; 95% CI 0.98–1.76), any cardiovascular defect (OR 1.81; 95% CI 1.19–2.76), and VSD or ASD (OR 1.79; 95% CI 0.99–3.22) after paroxetine exposure.

Colvin et al conducted a population-based study relating to all births in Western Australia from 2002 to 2005 and linking to a national pharmaceutical claims dataset.[41] The study included 123,405 pregnancies, with 3764 children born to 3703 women who were dispensed an SSRI during their pregnancy. During the first trimester, 97.6% of the pregnancies resulting in a birth were dispensed only one SSRI without switching: 32.4% sertraline, 27.3% citalopram, 20.4% paroxetine, 10.1% fluoxetine, 4.3% escitalopram (not available until 2004), and 3.1% fluvoxamine. Based on dispensing of SSRI at any time during pregnancy, 95% were dispensed one SSRI. Women dispensed an SSRI were more likely to give birth prematurely (adjusted OR, 1.4; 95% CI 1.2–1.7), particularly in women dispensed an SSRI in the first trimester (OR 1.5; 95% CI 1.3–1.8). In addition, children were more likely to have a birth weight <2500 g (OR 1.4; 95% CI 1.3–1.6) and a birth length of 50 cm or less (OR 1.5; 95% CI 1.4–1.6). In addition, there was an increased risk of major cardiovascular defects (OR 1.6; 95% CI 1.1–2.3). Of 572 children exposed to paroxetine in utero, 23 children had a major birth defect. With paroxetine, there were significant risks of anomalies of the pulmonary arteries (OR 19.9; 95% CI 6–66.2), other anomalies of the peripheral vascular system (OR 10.4; 95% CI 2.5–43.4) and cystic kidney disease (OR 5.4; 95% CI 1.3–22.2). Ostium secundum type atrial septal defects neared statistical significance (OR 3.7; 95% CI 0.9–15).

Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN).[42] Chambers et al enrolled 377 infants born with PPHN and 836 healthy infants in a retrospective case-control evaluation to evaluate whether PPHN is associated with exposure to SSRIs during late pregnancy. Of these infants, 14 with PPHN and 6 healthy controls were exposed to an SSRI after the 20th week of pregnancy (adjusted OR 6.1; 95% CI 2.2- 16.8). The risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. Of the 377 infants with PPHN, 4 had been exposed to paroxetine. The number of patients in each group was too small to examine the effects of dose size, specific SSRI used, or reduction of the length of exposure before delivery.

Andrade et al completed a retrospective study using the databases of four health plans to evaluate the prevalence of PPHN among infants whose mothers were exposed to antidepressants (SSRIs, TCAs, and miscellaneous antidepressants) in the third trimester of pregnancy compared to the prevalence among infants whose mothers were not exposed.[43] Women delivering an infant in a hospital from January 1, 1996, through December 31, 2000, were included. Of the 1104 infants exposed to antidepressants in the third trimester and a matched sample of 1104 unexposed infants, five infants were classified with PPHN. The prevalence of PPHN among infants exposed to any antidepressant was 1.81 per 1000 (95% CI 0.22, 6.54), while the prevalence of PPHN among nonexposed infants was 2.72 per 1000 (95% CI 0.56, 7.93). Among infants exposed to SSRIs in utero during the third trimester, the prevalence of PPHN was 2.14 per 1000 (95% CI 0.26, 7.74). The prevalence ratio for an association between PPHN and any antidepressant use was 0.67 (95% CI 0.06, 5.82) and for SSRI use was 0.79 (95% CI 0.07, 6.89). While an association between the use of SSRIs and PPHN was not found, several limitations of the study were identified, including the potential for undetected cases of PPHN, the small number of cases of PPHN identified, lack of information related to potential confounders, lack of information related to length of gestation and inclusion of mostly full-term or near-term infants.

Wichman et al conducted a retrospective cohort study at the Mayo Clinic 1993 to 2005 to determine the incidence of congenital cardiac abnormalities associated with SSRI use during pregnancy.[44] Of 25,214 total deliveries, 808 mothers (3.2%) had been prescribed SSRIs, including paroxetine (n = 134), at some point during their pregnancy. Results were categorized according to timing of first SSRI exposure (conception, discontinuation because of a positive pregnancy test result, first trimester, second trimester, and third trimester). The majority of paroxetine exposure was at conception (76.5%) or discontinued due to positive pregnancy test (10.9%). The median dose of paroxetine during all trimesters was 20 mg/d (n = 15). Cardiac abnormalities assessed consisted of CHD (congenital heart disease), VSD (ventricular septal defect), and PPHN. Of all deliveries, 208 newborns (0.8%) were diagnosed with CHD; prevalence of CHD in neonates born to SSRI-exposed mothers was similar to the unexposed group (0.4% vs 0.8%, $P = 0.23$).

The incidences of events by SSRI were not provided. No newborns with known exposure to SSRIs were diagnosed with PPHN or VSD.

GSK conducted a review of over 1100 reports of patients who were treated with paroxetine during pregnancy, most of whom received paroxetine during the first trimester.[45] At the time of review, an outcome was available for over 650 of these pregnancies, and in most of these cases the mother had been exposed to paroxetine during the first trimester. These pregnancies with a known outcome included those that had been notified to GSK prospectively the initial notification of exposure to paroxetine in pregnancy was received before the final outcome of pregnancy was known to the reporter and those received retrospectively the outcome was already known at the time of reporting. Many of the reports received stated a normal outcome, however, abnormal pregnancy outcomes, including congenital abnormalities, miscarriages, intra-uterine death, stillbirth, elective and medical terminations and ectopic pregnancy have been reported. Overall, the pattern of congenital abnormalities was similar to that reported in the general population and there was no unexpected clustering of abnormalities among the reports which might be suggestive of a teratogenic effect. Observations since the review have been consistent with the findings. Please note that these reports primarily consist of spontaneous reports and do not reflect a systematic collection of pregnancy outcomes. In addition, concomitant disease or drug therapy may confound outcome data collected.

OTHER NEONATAL OUTCOMES

Hostetter et al assessed the medication dosage requirements of SSRIs in pregnant women with a primary diagnosis of major depressive disorder in a naturalistic study.[46] These women were followed prospectively through pregnancy at monthly intervals with symptom assessment. Thirty-four women treated with SSRI monotherapy were included in the final analysis. Of these, 19 women entered the study during their first trimester and 15 entered during their second trimester. These patients received paroxetine (n = 12), sertraline (n = 13) or fluoxetine (n = 9). Twenty-two of the 34 women (65%) required an increase in dose to maintain euthymia during pregnancy; there was no difference among the 3 SSRIs with respect to dosage adjustment. While the primary purpose of this study was to assess dosage change requirements in these patients, obstetrical outcomes were reported overall. Thirty-one women had normal deliveries of healthy infants. Two women experienced pre-term delivery and 1 woman suffered a placental abruption at week 37 with fetal demise. Overall, no significant differences in neonatal outcome were found between the medications.

Simon et al compared the effects of prenatal exposure (identified by mothers having antidepressant prescription filled or refilled during the 270 days prior to delivery) to a tricyclic antidepressant (TCA; n = 209) or SSRIs (paroxetine, n = 28) on gestational age, head circumference, birth weight, Apgar scores, major malformations, minor malformations, motor delay, and speech delay with an equal number of matched infants not exposed to antidepressants.[47] Significantly more women in the exposed group (n = 8) self-reported cocaine use compared to the unexposed group (n = 0). No significant differences were observed between exposed and unexposed infants in the rates of major malformations, minor malformations, developmental delay, head circumference or other neurological disorder in either the TCA or SSRI groups. There were statistically significant differences in gestational age, birth weight, and Apgar scores at 5 minutes between infants exposed to SSRIs and those not exposed. Since differences in birth weights or Apgar scores may be due to differences in rates of prematurity, secondary analyses were done to adjust for gestational age. After this adjustment, infants exposed to SSRIs did not differ significantly in mean birth weight. Analyses of perinatal outcomes according to specific SSRI agent yielded similar results for paroxetine, fluoxetine, and sertraline. Exposure to SSRIs during the third trimester was associated with statistically significantly lower Apgar scores. The long-term clinical impact of this difference is not known.

Altamura et al studied the efficacy and safety of SSRIs during pregnancy (n= 56). Thirty women who were prescribed SSRIs for depression were included in the study (52% first trimester, 19% second trimester and 28% third trimester).[48] This group was matched in mean age, race, gravidity, substance abuse, personality disorder, partner/no partner, degree and high school attendance to a comparison group of 26 women

matched. Eight women were taking paroxetine 20-40 mg/day. No significant differences was reported for fetal weight (across all 3 trimesters), birth weight, Apgar score at first and fifth minute and no newborns were admitted to the Neonatal Intensive Care Unit between the treated group and the comparison group. Two limitations of the study were the small group of patients studied and the study did not evaluate the potential long-term effects of SSRIs on the offspring.

Preliminary data on antidepressant use during pregnancy and miscarriage risk were reported from a nested case-control study in Quebec.[49] Cases (n = 5,124) were defined as pregnant women with a diagnosis or procedure related to a miscarriage, and controls (n = 51,240) were selected from the cohort and matched to each case according to the index date (date of diagnosis or procedure). Preliminary analyses indicated that use of any antidepressant was associated with an increased risk of miscarriage (OR 1.68; 95% CI 1.38–2.06). Paroxetine (OR 1.75; 95% CI 1.31–2.34) and venlafaxine (OR 2.10; 95% CI 1.34–3.30) users had a higher risk of miscarriage than other antidepressants. This study and the study by Diav-Citrin et al, summarized earlier, [18], were among 15 studies included in a systematic review of 15 studies published 1975–2009, evaluating the risk of spontaneous abortion after gestational exposure to antidepressants.[50] In adjusted analyses, paroxetine (OR1.7; 95% CI 1.3–2.3) and venlafaxine (OR 2.1; 95% CI 1.3–3.3) were significantly associated with the risk of spontaneous abortion.

Perinatal outcomes associated with antidepressant exposure during pregnancy are described in the literature.[19,51,52,53,54,55,56,57,58]

Casper et al compared the structural growth and developmental outcome of 31 children exposed to SSRIs in utero (26% exposed to paroxetine) with 13 children not exposed.[59] There were no differences observed between groups for gestational age, premature births, birth weight and/or length; however, drug-exposed infants had lower APGAR scores at 1 (P=0.05) and 5 minutes (P=0.00). There were no significant differences in the Mental Development Index (MDI) between groups; however, exposed children were rated significantly lower in the Psychomotor Development Index (PDI) (P=0.03) and the Behavioral Rating Scale (BRS) (P=0.04). Evaluation of the BRS factor scales showed lower scores for motor quality in SSRI-exposed infants (P=0.01), with noticeable differences for tremulousness and fine motor movements.

Calderon-Margalit et al conducted a prospective cohort study of 2793 pregnant women to determine the association between psychotropic medication use during pregnancy with preterm delivery (primary outcome) and other adverse perinatal outcomes.[60] Three hundred women had used any psychotropic medication during pregnancy, and 31 women had taken paroxetine. Odds ratios were adjusted for maternal age, race/ethnicity, marital status, education, smoking during pregnancy, preeclampsia, parity, and singleton pregnancy. Maternal use of any SSRI or SNRI was associated with a nonsignificant increased risk of preterm delivery (adjusted OR, 1.34; 95% CI, 0.76–2.36); this risk was statistically significant for mothers who began taking SSRIs after the first trimester (adjusted OR, 4.79; 95% CI 1.66–13.9; P = 0.004). Maternal use of paroxetine was associated with a non-statistically significant increased risk of preterm delivery (adjusted OR, 2.30; 95% CI, 0.90–5.83; P = 0.081). Maternal use of any SSRI therapy was not associated with small-for-gestational-age infant, low Apgar score, or respiratory distress syndrome. Use of any SSRI after the first trimester was associated with low birthweight (OR, 5.01; 95% CI, 1.37–18.4; P = 0.015).

Yonkers et al conducted a prospective cohort study of 2793 pregnant women, oversampled for a recent episode of major depression or use of an SRI.[61] They found that use of an SRI, both with (odds ratio = 2.1 [95% confidence interval = 1.0 – 4.6]) and without (1.6 [1.0 –2.5]) a major depressive episode, was associated with preterm birth (defined as <37 weeks' gestation). None of these exposures were associated with early preterm birth (defined as <34 weeks' gestation). Of 2654 subjects with singleton live births, 293 were treated with a SRI. Twenty one patients were treated with paroxetine.

Kallen conducted an epidemiological study utilizing the Swedish Medical Birth Registry to examine neonatal outcome after maternal use of antidepressants in late pregnancy.[57] Infants born between July 1995 and December 2001 were selected for study and those whose mothers had been prescribed an antidepressant after the first antenatal care visit were identified. A total of 997 infants whose mothers received antidepressant therapy after the first antenatal visit were included in the study. Among the 987

mothers, 395 had used tricyclic drugs, 558 had used SSRIs (paroxetine, n = 106), and 63 had used other antidepressants. There were 31 women who had used 2 antidepressants during late pregnancy, of whom 19 had used a tricyclic and an SSRI and 8 had used an SSRI and an antidepressant other than a tricyclic or another SSRI. The pregnancy weeks when the drug was used were not stated in 387 cases, in 70 cases the drug was stopped before week 24, and in 561 cases, the drug was started or continued past week 23. Gestational duration, birth weight and fetal growth were examined in singleton births. The OR for preterm delivery (<37 weeks) for infants exposed to any antidepressant was 1.96 (95% CI, 1.60-2.41), and there was no significant difference between the ORs when the mother had used a tricyclic drug [2.50 (95% CI, 1.87-3.34)] and when she had used an SSRI [2.06 (95% CI, 1.58-2.69)]. For women using any antidepressant after pregnancy week 23, the OR for preterm delivery was 2.02 (95% CI, 1.54-2.63). The OR for low birth weight (<2500 g) was also around 2, and similar between the tricyclic and SSRI groups. There was no increase in the risk of small for gestational age (SGA), but a higher rate of large for gestational age (LGA) in the antidepressant exposed infants that did not reach statistical significance [OR 1.20 (95% CI, 0.93-1.56)]. With respect to infant diagnoses, there was a statistically significant increase in the OR for respiratory distress [2.21 (95% CI, 1.71-2.86)] among those exposed to antidepressants. This was slightly higher after the use of tricyclics [2.20 (95% CI, 1.44-3.35)] than after use of SSRIs [1.97 (95% CI, 1.38-2.83)], but the authors noted that the difference may be random. There was no significant effect on the rate of neonatal jaundice, which was non-significantly increased after the use of tricyclics but not after the use of SSRIs. For neonatal hypoglycemia, a significantly increased OR was seen, which was stronger after the use of tricyclic antidepressants than after the use of SSRIs. The OR for low Apgar score (in singletons) was increased after the use of antidepressants drugs, with a similar magnitude for tricyclic drugs [2.99 (95% CI, 1.58-5.65)] and SSRIs [2.28 (95% CI, 1.27-4.1)]. Neonatal convulsions were registered more often with than without antidepressants, and the risk ratio was higher after the use of tricyclic antidepressants [OR 6.8 (95% CI, 2.2-16)] than after the use of SSRIs, which was nonsignificantly increased [OR 3.6 (95% CI, 1-9.3)]. The frequency of a diagnosis of cerebral excitation was also higher with than without antidepressants, but the difference did not reach statistical significance [OR 1.22 (95% CI, 0.91-1.65)].

In view of the previous findings on paroxetine the author specifically compared neonatal outcome following paroxetine exposure with that for other SSRIs (as a group).[57] Only crude comparisons were made (without adjustment for year of birth, maternal age, etc.), because numbers were low and comparisons were made within SSRIs, where it was noted that confounding factors should be roughly equal. Paroxetine exposure gave higher ORs than exposure to other SSRIs for some conditions [preterm delivery (OR 1.28), low birth weight (OR 1.44), LGA (OR 1.77), respiratory distress (OR 1.23) and convulsions (OR 1.4)], but none reached statistical significance. Paroxetine was associated with lower ORs than other SSRIs for SGA, jaundice and hypoglycemia. On the basis of these data, the author concluded that outcomes after exposure to paroxetine were not worse than after exposure to other SSRIs.

Sanz et al conducted a review of spontaneously reported cases of suspected SSRI-induced neonatal withdrawal syndrome reported to the World Health Organization Collaborating Centre for International Drug Monitoring before the second quarter of 2003.[62] Of the 93 suspected cases identified, 64 were associated with paroxetine. Based on a logarithmic analysis to measure for an association of particular drugs and adverse drug reports, paroxetine, sertraline (n = 9), citalopram (n = 7), and fluoxetine (n = 14) were all demonstrated to have a statistically significant association between the drug and neonatal convulsions or neonatal withdrawal syndrome.

Levinson-Castiel et al found a 30% (18/60) rate of neonatal abstinence syndrome (NAS) [45% severe and 55% mild] in a large population-based study that included infants with a reported prolonged in-utero exposure to SSRIs.[63] Of these neonates 62% (37/60) were exposed to paroxetine at a dose range of 10-40 mg.

Dubnov-Raz et al analyzed data collected on all neonates born to mothers receiving SSRIs or venlafaxine during pregnancy in Israel between 2000 and 2005 to determine the effect of antenatal SSRI exposure on the QT interval in newborns.[64] Prolonged QTc interval was defined as >460 milliseconds (ms). Fifty-two neonates born to mothers receiving a SSRI (paroxetine, n = 25) at onset of labor (with no other concomitant

chronic medications) were compared with 52 newborns of healthy mothers taking no medications before delivery, matched according to gestational age. The mean QTc interval was significantly longer in neonates exposed to SSRIs compared with control (unexposed) neonates (409 vs 392 ms; $P = 0.02$). The mean uncorrected QT interval was 7.5% longer (280 vs. 261 ms, $P < 0.001$) and the mean JT interval was 10% longer (229 vs. 209 ms; $P < 0.001$) in exposed newborns. Mean QTc intervals were similar among the most commonly used SSRIs, suggesting a class effect on QT interval. Five SSRI-exposed neonates (10%) had a markedly prolonged QTc interval (>460 ms) compared to no unexposed infants ($P = 0.057$); 3 of these infants had been exposed to paroxetine and the remaining 2 to fluoxetine. All 5 infants had normal QTc intervals upon follow-up ECG (within 48 hours for 3 infants and at 1 year for 2 infants).

Nijenhuis et al conducted a cohort study that examined the effects on the development of the enteric nervous system in children following prenatal exposure to SSRIs, including paroxetine, and TCAs.[65] Data were obtained from the Netherlands pharmacy prescription database (IADB.nl) between 1995-2009, where 35,400 qualifying pregnancies were identified, and from which 36,323 children were born (paroxetine n=310 pregnancies resulting in n=301 children). The use of laxatives or anti-diarrheal agents recorded by the database in the exposed children and the reference group was regarded as a proxy for constipation and diarrhea. There was a statistically significant increase in laxative use in children from the paroxetine group exposed at anytime during pregnancy (incidence risk ratio [IRR] 1.35 95% CI 1.03, 1.78), exposed at least in the first trimester (IRR=1.41, 95% CI 1.06, 1.88), and at least in the second and third trimester (IRR=1.72 95% CI 1.22, 2.42). Maternal exposure to paroxetine in only the first trimester or only the second trimester was not associated with increased laxative use in the prenatally exposed children. No increase in the use of anti-diarrheal medications was seen in the group exposed to paroxetine.

Misri et al assessed the internalizing behaviors in children 4–5 years of age after previous prenatal exposure to psychotropic medications including SSRIs or SSRIs plus clonazepam (n=14 exposed to paroxetine).[66] There were no significant differences between the exposed and nonexposed groups based on parent and teacher/caregiver ratings. Based on clinician coding of the children's positivity, withdrawal, and irritability during a structured laboratory interaction, there were no significant differences observed between the two groups.

Oberlander et al compared attentional and activity behaviors in 22 four-year-olds following SSRI exposure (including paroxetine) in utero with 14 children without prenatal exposure.[67] Child externalizing behaviors (attention, aggression, attention deficit/hyperactivity, and oppositional or defiant behaviors) rated by parent or teacher were not statistically different between groups. On direct observation, persistence was significantly lower in the exposed group (P=0.03), while individual measures and composite behavioral scores of movement (activity), aggressiveness, attention, and emotion were not significantly different between the two groups.

Pedersen et al conducted a study assessing whether prenatal antidepressant exposure was associated with time needed to achieve developmental milestones early in life compared to unexposed infants.[68] The study population consisted of 81,946 women from the Danish National Birth Cohort, of which 415 used an antidepressant during pregnancy (n = 76 paroxetine alone). At 6 months of age, fewer children exposed to antidepressants during the second or third trimester achieved all milestones (adjusted OR 2.6; 95% CI 1.2–5.8) and some motor function milestones compared to children of mothers with untreated depression (adjusted OR for sits without support" 2.1; 95% CI 1.2–3.6 and adjusted OR for "all motor activity" 2.2; 95% CI 1.2–3.8). At 19 months, none of the differences between exposed children and children of women with untreated depression was statistically significant except for an association between second or third trimester exposure and the inability to occupy themselves for >15 minutes (adjusted OR 2.1; 95% CI 1.09–4.02). Children exposed to SSRIs at any point during pregnancy sat without support and walked without support 8.7 and 15.2 days later (adjusted differences), respectively, than children of mothers with untreated depression, and this difference increased to 16.6 and 28.9 days in children exposed to SSRIs during the second or third trimester. The sample size did not allow stratification according to individual SSRI.

Pedersen et al also studied the children of 127 mothers who used antidepressants during pregnancy (n= 38 on paroxetine) and compared these to 98 children of mothers with prenatal depression with no use of antidepressants during pregnancy and 723 children of mothers with no prenatal depression and no use of antidepressants during pregnancy.[69] A parent-reported SDQ was filled out at age 4 or 5 to assess behavioral problems. Untreated prenatal depression was associated with abnormal SDQ scores in the subscales of conduct (adjusted OR 2.3; CI 1.2-4.5) and prosocial problems (adjusted OR 3.0; 95% CI 1.2-7.8) compared with unexposed children. Prenatal antidepressant exposure was not associated with abnormal SDQ scores compared with prenatal exposure to untreated prenatal depression or to no exposure at 4-5 years of age. Limitations of the study include that parent-reported SDQ scores may not reflect actual child behavior and that potential changes in the fetal brain may be detected later in life.

Nulman et al looked at four groups of children born to: depressed women who took venlafaxine during pregnancy (n=62), depressed women who took SSRIs during pregnancy (n=62 total; n= 20 exposed to paroxetine), depressed women who were untreated during pregnancy (n=54) and nondepressed, health women (n=62).[70] Behavior outcomes and the children's intelligence were evaluated with standardized testing at one time point between the ages of 3 to 6 years, 11 months. The results showed that children exposed to venlafaxine, SSRIs and maternal depression during pregnancy had similar full-scale IQs (105,105 and 108 respectively). The IQs of the venlafaxine and SSRI groups were significantly lower than that of the children of nondepressed mothers (112). The groups that were exposed to maternal depression had consistently, but nonsignificantly higher rates of most problematic behaviors than the children of nondepressed mothers. No significant correlations were found between dose or duration of antidepressant treatment during pregnancy and cognitive and behavioral outcomes.

Croen et al conducted a population-based case-control study to evaluate whether prenatal exposure to antidepressant medications is associated with an increased risk of Autism Spectrum Disorders (ASD).[71] A total of 298 case children with ASD (paroxetine, n=13) and 1507 randomly selected control children were drawn from the membership of the Kaiser Permanente Medical Care Program in Northern California. Prenatal exposure to antidepressant medications was reported for 20 case children (6.7%) and 50 control children (3.3%). The study found an increased risk of ASD associated with SSRI treatment by the mother during the year before delivery (adjusted OR 2.2; 95% CI 1.2- 4.3), with strongest effect observed in the first trimester (adjusted OR 3.8; (95% CI 1.8-7.8). Analysis for specific SSRI medications was not reported. No increase in risk was found for mothers with a history of mental health treatment that were not exposed to SSRIs during pregnancy. The authors note that prenatal exposure to SSRIs during pregnancy, especially during the first trimester, may increase the risk of developing ASD, but recommend their findings should be considered preliminary treated with caution pending results from further studies.

Mulder et al conducted a prospective observational study was to investigate whether the use of SSRIs by pregnant women influence fetal neurobehavioral development.[72] The authors investigated developmental milestones of fetal behavior during the pregnancy of three groups of women; two groups with psychiatric disorders and a controlled group of healthy unexposed fetuses of women without mental disorders (n=130). The two study groups comprised of one who took SSRIs throughout gestation (medicated group; n=96, paroxetine usage in 44%), and one who had discontinued medication early in gestation or before conception (unmedicated group; n=37). Using ultrasonographic observations of fetal behavior three times during pregnancy, the study found that fetuses exposed to standard or high SSRI dosages compared with control, unmedicated, or low-medicated fetuses showed significantly increased motor activity at the beginning and increased bodily activity at the end (T2) of the second trimester ($P < 0.0001$). The fetuses exposed to standard or high dose SSRIs were also found to have more general movements reflecting a decrease of non-rapid eye movement (non-REM) sleep during the third trimester ($P < 0.02$). The effects on the fetuses attributed to maternal SSRI exposure were dose-related but independent of the type of SSRI evaluated. Alterations in fetal motor activity and non-REM sleep is an abnormal finding, but the authors state that the significance of these effects in postnatal development is unclear and suggest further investigation.

PRESCRIBING INFORMATION

In December 2005, the pregnancy warning for *Paxil CR* and *Paxil* was revised to a Pregnancy Category D.[1] These revisions are based on updated data from two epidemiological studies showing that infants born to women who had first trimester paroxetine exposure had an increased risk of cardiovascular malformations, primarily ventricular septal defects (VSDs) and atrial septal defects (ASDs) (see Epidemiological Data section of this letter for further details).

Some information contained in this response may be outside the approved Prescribing Information. This response is not intended to offer recommendations for administering in a manner inconsistent with its approved labeling. This product is designated Pregnancy Category D. If you become aware of patients who have received this product at any time during their pregnancy, we encourage healthcare professionals to report such information to the company.

In order for GlaxoSmithKline to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 888-825-5249. Please consult the attached Prescribing Information.

This response was developed according to the principles of evidence-based medicine and, therefore, references may not be all-inclusive.

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