First-Trimester Use of Paroxetine and Congenital Heart Defects: A Population-Based Case-Control Study

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BACKGROUND: There is a need for case-control studies of the effect of paroxetine on the occurrence of specific heart defects. **METHODS:** We performed a case-control study with data from a population-based birth defects registry in the Netherlands. All the children born between 1997 and 2006 were selected. Cases were defined as fetuses and children with isolated heart defects, and the controls were fetuses and children with a genetic disorder with no heart defect. We excluded children for whom there was no information on maternal medication use and deceased children and fetuses who were not examined postmortem. First-trimester exposure to paroxetine was compared between cases and controls by calculating adjusted odds ratios (AOR). **RESULTS:** We included 678 cases with isolated heart defects and 615 controls. The first trimester exposure rate was 1.5% for cases and 1.0% for controls. After excluding mothers who used paroxetine outside the first trimester, or who had used another SSRI, we found no significantly increased risk for heart defects overall (10 exposed cases; AOR, 1.5; 95% confidence interval [CI], 0.5–4.0), but we did find a significantly increased risk for atrium septum defects (three exposed cases; AOR, 5.7; 95% CI, 1.4–23.7). **CONCLUSIONS:** Our results suggest that the use of paroxetine in early pregnancy is associated with an increased risk of atrium septum defects. The results stress the importance of studying possible teratogenic effects of a drug, preferably in regard to well-specified malformations. *Birth Defects Research (Part A) 88:94–100, 2010.* © 2009 Wiley-Liss, Inc.

Key words: congenital heart defects; atrium septum defects; selective serotonin reuptake inhibitors; paroxetine; case-control study

INTRODUCTION

Selective serotonin reuptake inhibitors (SSRIs) are currently the most widely prescribed drugs for depression and depressive symptoms, and since 1995 the use of SSRIs among pregnant women in the Netherlands has increased from 1% to almost 3% (Bakker et al., 2008). This increase runs parallel with an increase in SSRI use by women of child-bearing age. The use of SSRIs in early pregnancy has recently been associated with an increased risk of congenital anomalies. In 2005, the manufacturer of paroxetine, a frequently used SSRI, issued a warning that preliminary analyses from safety data showed an increased risk of cardiovascular anomalies after use of paroxetine compared with use of other antidepressants (GlaxoSmithKline Clinical Trial Register, 2005). After this warning, several cohort studies were published on this association, but the results are inconclusive (Cole et al., 2007; Kallen and Otterblad 2007; Diav-Citrin et al., 2008; Merlob et al., 2009; Pedersen et al., 2009). Together, these cohort studies indicate that SSRIs do not have a major teratogenic effect.

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Because case-control studies have more statistical power, these studies are preferred over cohort studies to detect moderately increased risks for specific birth defects. In 2007, two case-control studies were published that used data from two large surveillance studies in the United States (Alwan et al., 2007; Louik et al., 2007). These studies investigated SSRI use in association with various groups of specific birth defects. Some of the results from the study based on National Birth Defects Prevention Study (NBDPS) could not be replicated by the study based on data from the Slone Epidemiology Centre Birth Defects study, but both studies found an increased risk of right ventricular outflow tract obstruction defects after the use of paroxetine. In a third study, designed as a nested case-control study that used data from a medication and pregnancy database in Canada, an increased risk was found for major cardiovascular malformations after a dose of more than 25 mg paroxetine per day, using a reference group of mothers who took other antidepressants in the first trimester (Berard et al., 2007).

Currently, no case-control study on the use of paroxetine in pregnancy and the risk of specific cardiovascular malformations has been published; therefore, we investigated the possible association between the use of paroxetine in early pregnancy and the occurrence of specific heart defects, using a case-control study design.

METHODS

Setting

The study was designed as a case-control study. Cases and controls were derived from the Eurocat Northern Netherlands database, a population-based birth defects registry for the northern part of the Netherlands. The annual number of births covered is approximately 19,000. The registry is notified of infants and fetuses with a congenital malformation by physicians and midwifes on a voluntary basis. Reports are actively collected from obstetric and pediatric hospital departments, cytogenetic laboratories, and pathology departments. Miscarriages and terminations of pregnancy after prenatal diagnosis are included, but the child has to be added to the registry before 16 years of age. Cases are registered only after informed consent has been obtained from the parents. The overall response rate is approximately 80%. Information on malformations is obtained from the medical files and is coded by trained research staff. For births through 2001, the ninth revision of the International Classification of Diseases with modification from the British Pediatric Association is used, for births starting in 2002 the tenth revision is used. A clinical geneticist reviews cases with multiple anomalies. Since 1997, parents have provided information by answering a questionnaire regarding the course of the pregnancy, prenatal screening and diagnostic procedures, exposure to occupational hazards, smoking and drinking habits, and socioeconomic background. Information regarding medications dispensed before and during pregnancy is obtained from community pharmacies which keep complete records of dispersed medications. The use of the prescribed medications and the possible use of over-the-counter medication is verified in a telephone interview with the mother.

Case Definition

With a prevalence of approximately 8 per 1000 births, cardiac anomalies are the most common birth defects (Hoffman and Kaplan, 2002; Reller et al., 2008); they appear as isolated defects, but also occur frequently in children with genetic or other syndromes. Teratogenic effects will most likely not cause an increase in all birth defects, but only in specific birth defects. Therefore, we defined our cases as fetuses or children born between 1997 and 2006 with isolated congenital heart defects. Our definition included fetuses or children with simple or complex heart defects only and excluded fetuses or children with associated genetic or other syndromes or those with extracardiac malformations. Children with minor heart anomalies, such as a persistent ductus Botalli in those born before 37 weeks' gestation, a single umbilical artery, or a functional or nonspecified cardiac murmur were not included. A clinical geneticist (W.S.K-F.) reviewed the cases and classified them into phenotypic subgroups based on embryologic origin.

Control Definition

The Eurocat Northern Netherlands database does not collect information on non-malformed controls. We therefore used fetuses and children with a chromosomal or single gene disorder as controls. The reason for choosing this control group was that medication use was not related to the genetic disorder, and sampling from the source population was done independently of exposure status. From a previous study (Bakker et al., 2007), we concluded that the first-trimester use of prescription drugs among mothers of children with a genetic condition did not differ significantly from the source population consisting of all pregnant women.

Genetic disorders are frequently associated with a heart defect. The risk of developing a heart defect is greater for children with certain chromosomal or other genetic disorders (for example, trisomy 21, del 22q11) than for children without such genetic anomalies (Cleves et al., 2007), but it is still not known why some children suffering from such a disorder develop a heart defect while others do not. Because a relationship between drug exposure and development of a heart defect in a child with a genetic disorder cannot be ruled out, we excluded children with an associated heart defect from the control group. Stillbirths, neonatal deaths, and terminations of pregnancy without a postmortem examination were also excluded from the controls, to ensure there were no heart defects present in the control group that could lead to misclassification. Because this excluded many controls, we performed chi-square or Fisher Exact tests to determine whether the excluded controls represented a selection bias in terms of year of birth or paroxetine use.

Exposure Definition

The estimated prevalence of SSRI use in the year before delivery was 2.5%, according to a population-based cohort study using data from a prescription database. Paroxetine is most commonly used with approximately 60% of SSRIs (Bakker et al., 2008). Children were considered to have been exposed if the mother used paroxetine at some point in the period from 4 weeks before conception through the 12th week of her

pregnancy. We will refer to this whole period as *first trimester*. The remaining children were considered not exposed if the mother had not used paroxetine in pregnancy or any other SSRI at any time during the pregnancy. If the mother used paroxetine outside the first trimester, or at an unknown time in the pregnancy, or if the mother used another type of SSRI during the pregnancy, the child was excluded from the case-control analyses.

Analyses

We accounted for the following possible confounders: year of birth, pregnancy outcome, maternal age, gravidity, mother's educational level, smoking, use of alcohol, body mass index calculated as weight before pregnancy divided by height squared, use of folic acid, and preexisting maternal diabetes or epilepsy. Cases and controls, and exposed and unexposed groups, were described according to these characteristics, and chi-square and Fisher Exact tests were used to determine which characteristics differed between the cases and controls and between the exposed and unexposed groups. The mean maternal age was compared using Student's t test. We calculated crude and adjusted odds ratios (AORs) using logistic regression for all heart defects and for specific heart defects. Analyses were performed using SPSS 16.0 for Windows (SPSS, Inc.,Chicago, IL).

RESULTS

On April 1, 2008, the Eurocat database contained 5125 registrations of children with congenital anomalies born between 1997 and 2006. Of these, 775 children and fetuses were registered with isolated heart defects and 1097 children and fetuses with a genetic disorder, including 628 with a chromosomal disorder and 469 with a monogenetic disorder. A total of 97 cases (12.5%) and 149 (13.6%) controls were excluded because information on maternal medication use was missing. These proportions are not significantly different ($p = 0.50$). Thus, the remaining case group consisted of 678 children and fetuses with an isolated heart defect. Among the remaining 948 controls, 158 had a major heart defect (131 associated with a chromosomal disorder and 27 with a monogenetic disorder). For another 175 deceased children and fetuses, it was uncertain whether they had a heart defect, because no postmortem examination had been performed or the information on the postmortem examination was missing. After excluding the children and fetuses with a genetic disorder associated with a heart defect, or without post mortem examination data, we had 615 controls, consisting of 272 with a chromosomal disorder and 343 with a monogenetic disorder.

Table 1 presents the characteristics of our cases and controls. Significant differences can be observed for year of birth (cases more often came from the period of 2002–2006), maternal age (higher among controls), mother's educational level (more highly educated mothers among controls) and pregnancy outcome (more terminations, miscarriages, and stillbirths among the controls). The excluded controls more often came from the period of 2002–2006 than did the included controls (55.6 vs. 39.7%; $p = 0.000$) and comprised fewer live births (30.3 vs. 86.5%; $p = 0.000$). The difference in pregnancy outcome between included and excluded controls remained after stratifying for year of birth.

A total of 27 mothers had taken an SSRI during pregnancy. Of these, 10 case mothers (1.5%) and six mothers from the control group (1.0%) had used paroxetine in the first trimester. Mothers who used another type of SSRI (n = 5) or who used paroxetine outside the first trimester or at an unknown time in pregnancy (n = 6), were excluded from the case-control analyses. Table 2 presents the characteristics of the 16 exposed children and the 1266 nonexposed children. Significant differences were observed for year of birth (exposed pregnancies were more often from the period 2002–2006) and maternal smoking (more smokers among exposed pregnancies). Mean maternal age did not differ significantly between the exposed and nonexposed children. The use of paroxetine in the first trimester did not differ significantly between excluded and included controls (0.6 vs. 1.0%; $p = 0.72$).

Table 3 presents the 10 exposed cases and lists the type of heart defect and daily dose of medication taken. For most of the exposed cases and controls, the prescribed daily dose was 20 mg. The mother of one case took 10 mg per day, and the mother of another case took 30 mg per day. Among the controls, one mother took 40 mg per day.

Because only year of birth differed between cases and controls and exposed and non-exposed subjects, we adjusted for year of birth in the case-control analyses. Table 4 shows the crude and AORs for the occurrence of heart defects after use of paroxetine. Whereas no significantly increased odds ratio (OR) was found for heart defects overall (adjusted OR, 1.5; 95% confidence interval [CI], 0.5–4.0), a significantly increased OR was found specifically for atrial septal defects (ASDs; AOR, 5.7; 95% CI, 1.4–23.5) after use of paroxetine during the first trimester of pregnancy. Among the three exposed cases with an ASD, one had an ASD sinus venosus superior type. Because this type of ASD is anatomically different from the ASD secundum type, we repeated the analyses for ASD secundum only. The OR decreased slightly and was borderline significant (AOR, 5.1; 95% CI, 1.0–26.1).

DISCUSSION

Our study represents a case-control study on the use of paroxetine during the first trimester of pregnancy and its possible association with specific congenital heart defects. After use of paroxetine, we found a significantly increased OR for ASD, not for the occurrence of isolated heart defects in general.

Heart defects, as a group, are heterogeneous: the development of the heart is a complex process and a wide variety of heart defects can occur. Heart defects can be highly complex, involving several parts of the heart, or relatively simple, such as ventricular septal defects (VSD). Sometimes the heart is affected by two or more separate defects, or extracardiac defects are also present. A specific exposure is not expected to increase the risk for congenital heart defects in general. In studying risk factors, it is therefore important to create homogeneous groups. In this study, by including only cases with isolated heart defects, we tried to create a case group that was as homogeneous as possible. Moreover, we performed subanalyses on specific

Table 1
Characteristics of Cases (Children and Fetuses with Isolated Heart Defects) and Controls (Children and Fetuses with Genetic Disorders without Heart Defects)

		Cases Isolated heart defects		Controls Genetic disorders		
		n = 678	%	n = 615	%	*p*
Year of birth	1997–2001	362	53.4	371	60.3	0.01
	2002–2006	316	46.6	244	39.7	
Maternal age	Mean (SD)	30.3 (4.7)		31.1 (4.9)		0.01
	Missing	28		21		
Educational level	Low	78	12.3	82	14.6	0.02
	Middle	325	51.1	240	42.8	
	High	233	36.6	239	42.6	
	Missing	42		54		
Smoking	Yes	163	25.2	133	23.0	0.38
	No	483	74.8	445	77.0	
	Missing	32		37		
Alcohol	Yes	164	25.5	130	22.4	0.21
	No	479	74.5	450	77.6	
	Missing	35		35		
Gravidity	1	243	37.4	205	34.7	0.32
	>1	407	62.6	386	65.3	
	Missing	28		24		
Pregnancy outcome	Live birth	582	85.8	532	86.5	0.00
	Live birth, but died	97	11.7	21	3.4	
	Termination	1	0.1	11	1.8	
	Miscarriage	6	0.9	35	5.7	
	Stillbirth	10	1.5	16	2.6	
Body mass index	<19	46	7.3	31	5.6	0.24
	19–24	312	49.8	299	54.1	
	>24	269	42.9	223	40.3	
	Missing	51		62		
Correct use of folic acid	Yes	236	35.7	219	37.1	0.62
	No	425	64.3	372	62.9	
	Missing	17		24		
Diabetes	Yes	5	0.7	3	0.5	0.73[a]
	No	667	99.3	591	99.5	
	Missing	6		21		
Epilepsy	Yes	8	1.2	8	1.3	0.8
	No	664	98.8	586	98.7	
	Missing	6		21		

[a]*p* value calculated with Fisher's exact test.

phenotypes of heart defects. The finding of an increased risk for ASDs only and not for all heart defects as a group may be the result of multiple testing, but is in line with the expected specificity of teratogenic effects. However, because the number of exposed cases and controls was relatively small, the 95% confidence intervals are wide and the results need to be interpreted carefully.

Most cohort studies on risks of maternal SSRI and paroxetine use have evaluated the association with heart defects in general. Cole et al. (2007) observed an increased risk for all malformations after the use of paroxetine (OR, 1.76; 95% CI, 1.18–2.64), but not for cardiovascular malformations (OR, 1.46; 95% CI, 0.74–2.88); they used an administrative database from a health care insurer and compared malformation rates with a cohort of mothers using other antidepressants. Only liveborn children with malformations were included in the study. In another cohort study by Kallen and Otterblad (2007), an increased risk for cardiovascular malformations after first trimester use of paroxetine was found (OR 1.63 95% CI 1.05-2.53). After excluding women with putative confounding characteristics such as high body mass index and use of specific other drugs, an increased OR for VSD and/or ASD after maternal use of paroxetine was found (7 exposed cases; OR, 3.23; 95% CI, 1.30–6.65), but no association for other SSRIs with cardiovascular defects was found. Both these cohort studies were included in a metaanalysis of six cohort studies and three case-control studies that concluded that the rate of heart defects in exposed and nonexposed infants closely approximated the rate found in the general population (O'Brien et al., 2008). In a cohort study in British Columbia in which data from several databases, including maternal health and prescription databases, were linked to neonatal records, an increased incidence for ASDs was found when serotonin reuptake inhibitor monotherapy was compared with no exposure (adjusted risk difference, 0.21; 95% CI, 0.05–0.36; Oberlander et al., 2008). Paroxetine was the most commonly used SSRI, but the investigators did not analyze the use of paroxetine in particular and the occurrence of ASDs. Results from a recent population-based cohort study from Denmark found an increased risk for septal heart defects after the

Table 2
Characteristics of Children and Fetuses Exposed to Paroxetine In Utero in the First Trimester and of Nonexposed Children and Fetuses

		Exposed to paroxetine in first trimester		Not exposed		
		n = 16	%	n = 1266	%	*p*
Year of birth	1997–2001	5	31.2	721	57.0	0.039
	2002–2006	11	68.8	545	43.0	
Maternal age	Mean (SD)	32.0 (6.4)		30.7 (4.8)		0.289
	Missing	1		48		
Educational level	Low	2	13.3	155	13.2	Low/middle vs
	Middle	4	26.7	558	47.6	high 0.101
	High	9	60.0	459	39.2	
	Missing	1		94		
Smoking	Yes	8	53.3	285	23.8	0.013[a]
	No	7	46.7	913	76.2	
	Missing	1		68		
Alcohol	Yes	4	26.7	289	24.1	0.767[a]
	No	11	73.3	908	75.9	
	Missing	1		69		
Gravidity	1	4	26.7	441	36.3	0.440
	>1	11	73.3	774	63.7	
	Missing			51		
Pregnancy outcome	LB	14	87.5	1189	93.9	0.259[a]
	T, M, SB	2	12.5	77	6.1	
Body mass index	<19	1	6.7	76	6.6	Low/middle vs
	19–24	7	46.7	597	51.7	high 0.700
	>24	7	46.7	482	41.7	
	Missing	1		111		
Correct use of folic acid	Yes	5	31.2	448	36.6	0.660
	No	11	68.8	777	63.4	
	Missing			41		
Diabetes	Yes	1	6.2	7	0.6	0.098[a]
	No	15	93.2	1232	99.4	
	Missing			27		
Epilepsy	Yes	0	0	16	1.3	1.000[a]
	No	16	100	1223	98.7	
	Missing			27		

[a]*p* value calculated with Fisher's exact test.
LB, live birth including children who died after birth; T, termination of pregnancy; M, miscarriage; SB, stillbirth.

Table 3
Cases with an Isolated Heart Defect after Maternal Exposure to Paroxetine in the First Trimester of Pregnancy Showing Year of Birth and the Daily Dose Taken by the Mother, Period of Use, Diagnosis and Phenotypic Subgroup

Case no.	Year of birth	Daily dose (mg)	Diagnosis	Phenotypic subgroup
1	1998	30	ASD II	ASD
2	1999	20	Transposition of great arteries, AVSD and heart in right thorax	Other
3	2000	20	Patent ductus arteriosus (surgically corrected)	Other
4	2000	20	Coarctation of aorta	Left-sided defects
5	2002	20	VSD, muscular	VSD
6	2003	20	ASD, sinus venosus superior type	ASD
7	2003	20	ASD II	ASD
8	2003	10	Pulmonary valve stenosis	Right-sided defects
9	2004	20	Aortic valve stenosis	Left-sided defects
10	2004	20	Coarctation of aorta	Left-sided defects

ASD atrial septal defect; AVSD, atrioventricular septal defect; VSD ventricular septal defect.

Table 4
Comparison of Crude and Adjusted Odds Ratios for Congenital Heart Defects in Cases and Controls after Maternal Exposure to Paroxetine in the First Trimester

	Exposed	Non-exposed	OR	95% CI	AdjOR[a]	95% CI	p-value[b]
Controls	6	605	ref				
All heart defects	10	661	1.5	(0.6-4.2)	1.5	(0.5-4.0)	0.476
VSD	1	182	0.6	(0.1-4.6)	0.5	(0.1-4.2)	0.528
ASD	3	53	5.7	(1.4-23.5)	5.7	(1.4-23.7)	0.016
Septal defects[c] (ASD and VSD)	4	245	1.6	(0.5-5.9)	1.6	(0.4-5.6)	0.493
Right-sided defects	1	101	1.0	(0.1-8.3)	0.9	(0.1-7.6)	0.926
Left-sided defects	3	126	2.4	(0.6-9.7)	2.1	(0.5-8.7)	0.292
Other defects	2	189	1.1	(0.2-5.3)	1.0	(0.2-5.2)	0.967

[a]Odds ratio adjusted for year of birth.
[b]p value obtained from logistic regression.
[c]Septal defects also include children and fetuses with both a VSD and an ASD.
OR, odds ratio; CI, confidence interval; AOR, adjusted odds ratio; VSD, ventricular septal defect; ASD, atrial septal defect; OR.

use of SSRIs and more specifically for sertraline and citalopram and after the use of more than one type of SSRI, but not for paroxetine (Pedersen et al., 2009).

As mentioned in the Introduction, case-control studies have more statistical power to detect moderately increased risks for specific birth defects. Using data from two birth defects surveillance systems, two large case-control studies investigated the use of SSRIs in relation to several congenital anomalies (Alwan et al., 2007; Louik et al., 2007). Both studies found an increased risk for right ventricular outflow tract obstruction defects after the use of paroxetine (the NBDPS study covered seven exposed cases [AOR, 2.5; 95% CI, 1.0–6.0], whereas the Slone study covered six exposed cases [OR, 3.3; 95% CI, 1.3–8.8]). Both studies used nonmalformed controls, and the use of medication shortly before and during pregnancy was retrospectively determined with a telephone interview with the mother. Neither study made a statistical adjustment for multiple testing. In our study we could not find a significantly increased risk for right-sided defects, because we had only one paroxetine-exposed case with such a heart defect. A case-control study by Berard et al. (2007), who used data from health care databases on malformations and medication, found an association between paroxetine and cardiac malformations only when a daily dose of more than 25 mg was taken (five exposed cases; AOR, 3.07; 95% CI, 1.00–9.42). They included only liveborn children, and the mother's actual use of the medication was not verified. No analyses were performed for specific heart defects.

In conclusion, results from our study and other epidemiologic studies on paroxetine and heart defects are difficult to compare because of differences in study design, exposure, and outcome definition. Results from a recent metaanalysis including 20 publications indicate an increased prevalence of combined heart defects associated with first-trimester paroxetine use (Wurst et al., 2009). They also found that variability among individual study findings might be associated with data source, type of publication, and age at ascertainment.

Cardiac defects are, however, also associated with several chromosomal and monogenetic disorders. Ongoing research has demonstrated that the genetic basis for heart defects is larger than previously expected (Pierpont et al., 2007). It is possible that, in our study population, we may have a case (or cases) with an isolated heart defect, suffering from a chromosomal or monogenetic disorder that has not yet been discovered or diagnosed. In selecting the case group, the criterion requiring a postmortem examination was not applied. Therefore, we cannot fully exclude the possibility that we may have included deceased cases with a heart defect and extracardiac defects in the case group. However, any misclassification of cases with an undiagnosed genetic disorder or extracardiac anomalies will bias the OR toward no effect.

For the controls, we excluded all children with a genetic disorder and an associated heart defect, and all children in whom the absence of a heart defect was not sufficiently well demonstrated. Because the rate of pregnancy terminations for genetic disorders is increasing over time in the Netherlands, the excluded controls came more often from the birth years 2002 to 2006 and included more terminations, miscarriages, and stillbirths than the included controls. There was, however, no association with the use of paroxetine. Thus, excluding controls with a heart defect or without a postmortem examination will not bias our results. The included controls more often came from the birth years 1997 to 2001 than did the cases. The mean maternal age was higher for the controls than for the cases, because maternal age is a risk factor for chromosomal anomalies. Because certain chromosomal and monogenetic disorders are lethal and subject to prenatal screening, there were more terminations, miscarriages, and stillbirths among the controls. Maternal age and pregnancy outcome was not associated with exposure status, so we calculated ORs adjusted for year of birth alone. The AORs were similar to the crude ORs, indicating that year of birth was not a strong confounder. We did not calculate ORs adjusted for other potential confounders such as smoking, maternal disease, or use of other (teratogenic) drugs because of the relatively small sample size. In addition, it was not possible to account for any confounding by indication, because good information on depression status of women not using antidepressants was not available.

Depression is associated with several life style factors that are risk factors for birth defects. Although we did not find significant differences for several of these lifestyle factors, such as drinking habits, we cannot rule out the presence of unidentified confounding factors. Alternatively, there may be a plausible biologic

explanation for the possible teratogenic effect of paroxetine. SSRIs inhibit the reuptake of serotonin (5-hydroxytryptamine) by binding to the serotonin uptake sites (transporters), which results in an increase of synaptic serotonin levels. Serotonin is known to mediate a wide variety of physiologic effects, including developmental functions. Animal studies have shown that serotonin also plays a role in mouse cardiovascular morphogenesis (Nebigil and Maroteaux, 2001). It is possible that the properties of paroxetine that distinguish it from other SSRIs are associated with the specific teratogenic effects. The specific SSRIs differ in their pharmacokinetic properties (Hiemke and Hartter, 2000). Paroxetine is the most potent serotonin reuptake blocker available, but its half-life varies depending on dose and duration of use. The cytochrome P450 isoenzymes play an important role in the extensive metabolism of paroxetine, with a high interindividual variability.

In this study, we used prospectively collected pharmacy data and verified the actual use with the mother. Misclassification of exposure might still have occurred if the mother obtained her medication through other sources than her pharmacist and did not reveal this in the telephone interview. However, because we used malformed controls and the same procedure for data collection for cases and controls, any misclassification bias will most likely be nondifferential. Misclassification of exposure might also have occurred because of the broadly defined exposure window that was not restricted to the period of cardiac development to allow for uncertainty in date of conception and period of medication use. The actual exposure time could also be longer than the period of use, because it may take some time for the drug to be eliminated from the body. For these reasons, a strictly defined exposure window might also introduce misclassification bias. Moreover, the actual exposure of the fetus to paroxetine is unknown. Measuring serum levels of paroxetine in the developing fetus is not a feasible option. A more appropriate approach might be to include genotypic factors indicating the metabolizing properties of mother and child in studies on teratogenic effects.

In conclusion, we found an increased OR for isolated ASDs after maternal use of paroxetine in the month before conception and/or the first trimester, but not for isolated heart defects in general; however, the absolute risk for ASDs remains small. Our results stress the importance of studying possible teratogenic effects of a specific drug on specific birth defects. Results from studies on the use of paroxetine and a possible association with heart defects have not been conclusive, possibly owing to methodological differences or overlooking biologic factors. We recommend that future studies should also include the analysis of biologic factors, such as drug eliminating or metabolizing properties, to obtain more specific information on the teratogenic risks of paroxetine and other SSRIs.

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