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Paroxetine and fluoxetine in pregnancy: a prospective, multicentre, controlled, observational study

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- In recent years there has been concern regarding the possibility that selective serotonin reuptake inhibitors (SSRIs) cause an increased rate of congenital cardiovascular anomalies.
- As of today, there is still debate in the literature as to the possible effects of paroxetine and fluoxetine on the embryonic cardiovascular system.

WHAT THIS STUDY ADDS

- Based on prospective data from three Teratogen Information Services, we have demonstrated an increased rate of congenital cardiovascular anomalies among the offspring of fluoxetine- and paroxetine-treated mothers.

AIMS

Recent studies have suggested a possible association between maternal use of selective serotonin reuptake inhibitors (SSRIs) in early pregnancy and cardiovascular anomalies. The aim of the present study was to evaluate the teratogenic risk of paroxetine and fluoxetine.

METHODS

This multicentre, prospective, controlled study evaluated the rate of major congenital anomalies after first-trimester gestational exposure to paroxetine, fluoxetine or nonteratogens.

RESULTS

We followed up 410 paroxetine, 314 fluoxetine first-trimester exposed pregnancies and 1467 controls. After exclusion of genetic and cytogenetic anomalies, there was a higher rate of major anomalies in the SSRI groups compared with the controls [paroxetine 18/348 (5.2%), fluoxetine 12/253 (4.7%) and controls 34/1359 (2.5%)]. The main risk applied to cardiovascular anomalies [paroxetine 7/348 (2.0%), crude odds ratio (OR) 3.47, 95% confidence interval (CI) 1.13, 10.58; fluoxetine 7/253 (2.8%), crude OR, 4.81 95% CI 1.56, 14.71; and controls 8/1359 (0.6%)]. On logistic regression analysis only cigarette smoking of $\geq$10 cigarettes day^{-1} and fluoxetine exposure were significant variables for cardiovascular anomalies. The adjusted ORs for paroxetine and fluoxetine were 2.66 (95% CI 0.80, 8.90) and 4.47 (95% CI 1.31, 15.27), respectively.

CONCLUSION

This study suggests a possible association between cardiovascular anomalies and first-trimester exposure to fluoxetine.

Introduction

Selective serotonin reuptake inhibitors (SSRIs) are widely prescribed for the treatment of depression and other disorders. Estimates suggest that the lifetime risk for depression ranges from 10 to 25% for women, with a peak prevalence occurring between the childbearing ages of 25 and 44 years [1]. Others have suggested that 9–14% of all pregnant women display signs of depression and/or have illnesses that fulfil research diagnostic criteria for depression, [2–4]. In Europe, <1% of pregnant women [5, 6] have been reported to use antidepressants. In the USA, SSRI use during pregnancy increased from 1.5% in 1996 to 6.4% in 2004 [7]. Fluoxetine and paroxetine readily cross the human placenta [8]. Fluoxetine is the first marketed SSRI that has been extensively studied in pregnancy [9–13]. Initial studies on the safety of paroxetine in pregnancy were reassuring [8, 13–18]. However, there has recently been discussion of whether the use of SSRIs in pregnancy, paroxetine in particular, may increase the risk of malformations, mainly cardiac [19–25]. Some of these studies are retrospective and burdened with recall and selection bias. GlaxoSmithKline, the manufacturer of PAXIL® (paroxetine HCl), revised their paroxetine label in September 2005 [26] and added a warning to the pregnancy precautions suggesting a risk of cardiac defects. In December 2005 the label was further revised and the pregnancy category was reclassified to D, which means that there is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk [27].

Neonatal symptoms have been described initially with fluoxetine and later on with paroxetine and other SSRIs [10, 28–35]. Neonatal toxicity or discontinuation (withdrawal, abstinence) syndromes associated with SSRIs are characterized by irritability, abnormal crying, tremor, convulsions and poor neonatal adaptation including respiratory distress, tachypnoea, jitteriness, lethargy, and poor tone or colour. Recent data also suggest an association between the maternal use of SSRIs and persistent pulmonary hypertension of the newborn [36].

The primary objective of the present study was to evaluate prospectively the rate of major congenital anomalies after pregnancy exposure to paroxetine compared with fluoxetine, with more data on its safe use in pregnancy, and with a control group of pregnant women exposed to nonteratogens. Secondary end-points of interest were pregnancy outcome, birth weight, gestational age at delivery and neonatal complications.

Materials and methods

Our prospective, controlled, multicentre, observational study enrolled pregnant women who contacted the Israeli Teratology Information Service (TIS) (Jerusalem, Israel), Servizio di Informazione Teratologica (Padua, Italy) or Pharmakovigilanz-und Beratungszentrum für Embryonaltoxikologie (Berlin, Germany) with regard to gestational exposure to paroxetine or fluoxetine between the years 1994 and 2002 in Israel and Italy, and between 2002 and 2005 in Germany. The three TISes are members of the European Network of Teratology Information Services, an organization of counselling services with regard to environmental exposure during pregnancy, and use a similar methodology [37, 38]. The exposed groups were compared with a control group of women who contacted one of the three participating centres during pregnancy regarding exposures known not to be teratogenic in similar time frames. The common exposures for which control women contacted the TISes were antibiotics (e.g. penicillins, cephalosporins), oral contraceptives taken no later than the first 4–5 weeks of pregnancy, low-dose diagnostic irradiation, topical preparations with negligible systemic absorption, paracetamol, hair dye and housecleaning agents, iron supplementation, and thyroxine replacement [39, 40].

Details of exposure were collected at the initial contact with the TIS and before pregnancy outcome was known using a structured questionnaire (available from the authors by request). Verbal (Jerusalem, Germany) or written (Italy) consent to participate in the study was given by the woman at initial contact. In addition, the following information was recorded: maternal demographics, medical and obstetrical histories, exposure details (dose, duration and timing in pregnancy). Retrospective cases were not included. After the expected date of delivery we actively sought after pregnancy outcome in the exposed and control groups. Follow-up was conducted by a telephone interview or mailed questionnaire to the woman or the child's paediatrician to obtain details of the pregnancy outcome, gestational age at delivery, birth weight, congenital anomalies and neonatal complications. In addition, SSRIs and other exposures were ascertained. The offspring follow-up was performed between the neonatal period and 6 years of age. However, in most cases it was carried out within the first 2 years of life. Data collection was similar in the exposed and control groups.

Major anomalies were defined as structural abnormalities in the offspring that have serious medical, surgical or cosmetic consequences. Ventricular septal defects (VSDs) are structural anomalies of the heart. Any VSD carries a risk of infectious endocarditis and requires prophylactic antibiotics before invasive procedures. They were therefore considered major anomalies. Significant neurodevelopmental or functional problems were also considered as major anomalies, even in the absence of a structural abnormality, when they required special education or interventions. In the case of multiple births, each live-born offspring was included in the analysis.

Statistical analysis

Categorical data were compared by χ^2 or Fisher's exact tests. Continuous data did not follow normal distribution and were compared using the Kruskal–Wallis (for three groups) or Mann–Whitney tests (for two groups). The data are expressed as ratios or percentages for categorical data. Continuous data are presented using median with interquartile range. The *P*-values presented in the tables are for a comparison between the three groups. Logistic regression analysis was used to evaluate the relative contribution of various predictors to the differences in the miscarriage rate and the rate of cardiovascular anomalies. Statistical calculations were done using SPSS Version 13 (SPSS Inc., Chicago, IL, USA).

Results

General characteristics of the study group

A total of 463 paroxetine-exposed and 346 fluoxetine-exposed pregnancies were prospectively followed up by the three participating centres [304/237 (paroxetine/fluoxetine) in Jerusalem, 81/49 in Padua and 78/60 in Berlin]. The follow-up rate in the SSRI-exposed groups was 60.3%/44.2% (paroxetine/fluoxetine) in the Israeli TIS, 77.9%/69.0% in Padua and 91.1%/87.1% in Berlin. In 410/463 paroxetine-exposed (88.6%) and in 314/346 fluoxetine-exposed pregnancies (90.8%) the exposure was at least in the first trimester (women who took paroxetine between weeks 3 + 3 and 13 or fluoxetine between weeks 2–13 after the last menstrual period, taking into account the elimination half-life). The medication was taken throughout pregnancy in 211/463 paroxetine-exposed pregnancies (45.6%) and in 151/347 fluoxetine-exposed pregnancies (43.5%). The control group included 1467 pregnancies with exposures known not to be teratogenic from the three participating centres.

The exposed groups

The median daily dose [interquartile range (IQR) between the 25–75th percentiles] of paroxetine and fluoxetine was 20 mg (IQR 20–20) and 20 mg (IQR 20–40), respectively. The median duration of treatment was 224 days (IQR 56–280) in the paroxetine and 240 days (IQR 49–280) in the fluoxetine groups. The indication for therapy was reported in 59.0% of the paroxetine and in 52.7% of the fluoxetine groups. The reported common indications for treatment in the exposed groups were depression, anxiety, obsessive compulsive disorder, manic depressive disorder, schizoaffective disorder and eating disorder. Concomitant psychiatric medications were used by 40.3% of the paroxetine-treated women (in 29.9% the combination was with a benzodiazepine) and by 45.7% of the fluoxetine-treated women (in 31.5% the combination was with a benzodiazepine).

Maternal characteristics

A comparison of maternal characteristics and obstetrical history between the paroxetine-exposed, fluoxetine-exposed and control groups is presented in Table 1. The median maternal age in both SSRI-exposed groups was 1

Table 1

Maternal characteristics and obstetrical history

	Paroxetine *n* = 463	Fluoxetine *n* = 346	Control *n* = 1467	*P*-value
Maternal age (years) median (IQR)	32* (28–36)	32* (28–36)	31 (27–34)	<0.001
Gravidity (%)				
1	119/417 (28.5)	89/312 (28.5)	384/1411 (27.2)	0.812
2–4	233/417 (55.9)	167/312* (53.5)	846/1411 (60.0)	0.063
≥5	65/417 (15.6)	56/312* (17.9)	181/1411 (12.8)	0.040
Parity (%)				
0	143/423 (33.8)	110/315 (34.9)	474/1410 (33.6)	0.907
1–3	250/423 (59.1)	177/315 (56.2)	850/1410 (60.3)	0.403
≥4	30/423 (7.1)	28/315 (8.9)	86/1410 (6.1)	0.189
Previous miscarriage (%)				
0	332/416 (79.8)	255/305 (83.6)	1135/1402 (81.0)	0.423
1	58/416 (13.9)	30/305 (9.8)	194/1402 (13.8)	0.159
≥2	26/416 (6.3)	20/305 (6.6)	73/1402 (5.2)	0.530
Previous ETOP ≥1 (%)	50/416 (12.0)	55/308* (17.9)	126/1402 (9.0)	<0.001
Previous stillbirth ≥1 (%)	5/415 (1.2)	2/303 (0.7)	12/1401 (0.9)	0.719
Gestational age at initial contact median (IQR)	8* (6–13)	8* (6–13)	9 (7–15)	<0.001
Cigarette smoking (%)				
Nonsmokers	295/372* (79.3)	234/293* (79.9)	978/1057 (92.5)	<0.001
<10 cig day^{-1}	25/372* (6.7)	23/293* (7.8)	33/1057 (3.1)	<0.001
≥10 cig day^{-1}	52/372* (14.0)	36/293* (12.3)	46/1057 (4.4)	<0.001

*$P < 0.05$ exposed *vs.* controls. ETOP, elective termination of pregnancy; IQR, interquartile range.

year older than in the control group. A higher proportion of the fluoxetine-treated women had a history of an elective termination of pregnancy compared with the control group. The gestational age at initial contact was earlier in both exposed groups compared with the control group. The rate of cigarette smokers was higher in both SSRI-exposed groups.

Pregnancy outcome

General A comparison of pregnancy outcome between the groups is presented in Table 2. To evaluate the relative contribution of various predictors to the differences in the miscarriage rate, logistic regression was performed (Table 3). After the adjustment the difference became

Table 2

Pregnancy outcome

	Paroxetine (n = 463)	Fluoxetine (n = 346)	Control (n = 1467)
Live-born infants	402	284	1350
Multiple gestations	7 twin sets	7 twin sets, 1 triplet	30 twin sets, 2 triplets
Delivery (%) resulting in live-born	395/463 (85.3)*	276/346 (79.8)*†	1318/1467 (89.8)
Miscarriage (%)	42/463 (9.1)	41/346 (11.8)*	97/1467 (6.6)
ETOP (%)	22/463 (4.8)	27/346 (7.8)*	43/1467 (2.8)
Stillbirth (%)	4/463 (0.9)	1/346 (0.3)	8/1467 (0.5)
Ectopic pregnancy (%)	0/463 (0.0)	1/346 (0.3)	1/1467 (0.1)
Major anomalies‡ (%)	21/403* (5.2)	18/286* (6.3)	40/1359 (2.9)
Major anomalies, first trimester‡ (%)	19/348* (5.5)	15/253* (5.9)	40/1359 (2.9)
Major anomalies without chromosomal or genetic, first trimester‡ (%)	18/348* (5.2)	12/253* (4.7)	34/1359 (2.5)
Major cardiovascular anomalies, first trimester‡ (%)	7/348* (2.0)	7/253* (2.8)	8/1359 (0.6)
Major noncardiovascular anomalies, first trimester‡ (%)	12/348 (3.4)	8/253 (3.2)	32/1359 (2.4)
Gestational age at delivery weeks median (IQR)	n = 381/395 39* (38–40)	n = 266/277 40* (38–40)	n = 1306/1318 40 (39–41)
Preterm delivery, ≤ 36 (%)	33/381 (8.7)	24/266 (9.0)	84/1306 (6.4)
Birth weight g median (IQR)	n = 388/402 3250* (2881–3600)	n = 277/285 3200* (2855–3525)	n = 1330/1350 3300 (2984–3641)

*P < 0.05 exposed *vs.* controls. †P < 0.05 paroxetine *vs.* fluoxetine. ‡Including ETOPs (elective termination of pregnancy) due to prenatally diagnosed anomalies: one in the paroxetine, one in the fluoxetine, nine in the control group (four chromosomal or genetic). IQR, interquartile range.

Table 3

Logistic regression analysis for miscarriage rate and cardiovascular anomalies

Parameters	Miscarriages Crude OR (CI)	Adjusted‡ OR (CI)	Cardiovascular anomalies Crude OR (CI)	Adjusted‡ OR (CI)
Type of exposure				
Paroxetine	1.41 (0.95, 2.09)	0.85 (0.52, 1.40)	3.47 (1.13, 10.58)	2.66 (0.80, 8.90)
Fluoxetine	1.90 (1.27, 2.84)	1.27 (0.76, 2.13)	4.81 (1.56, 14.71)	4.47 (1.31, 15.27)
GA at call		0.78 (0.73, 0.83)		
Maternal age		1.07 (1.03, 1.10)		1.00 (0.92, 1.10)
Smoking				
<10 cig day^{-1}*		1.23 (0.58, 2.59)		2.75 (0.58, 13.00)
≥10 cig day^{-1}*		2.04 (1.19, 3.52)		5.40 (1.76, 16.54)
Previous miscarriages		1.02 (0.83, 1.26)		
TIS origin				
Padua/Jerusalem		1.27 (1.03, 4.67)		0.90 (0.11, 7.57)
Berlin/Jerusalem		0.86 (0.57, 1.31)		1.24 (0.42, 3.69)
Concomitant psychiatric medications				
Benzodiazepines†		0.73 (0.39, 1.35)		1.06 (0.30, 3.82)
Other psychiatric drugs†		1.51 (0.71, 3.22)		0.60 (0.07, 5.24)
Multi-fetal gestation				1.63 (0.21, 12.83)
SSRI dose				1.00 (0.99, 1.01)

‡All the variables in the model have been used in the adjusted ORs. *Compared with nonsmokers. †Compared with cases with no concomitant psychiatric medications. CI, 95% confidence interval; GA, gestational age; OR, odds ratio; TIS, Teratology Information Service; GA, gestational age.

insignificant. The only significant predictors were gestational age at initial contact (with higher miscarriage rate in women calling early during gestation), maternal age, smoking ≥10 cigarettes day^{-1} and origin of cases (Padua/Jerusalem).

Risk of congenital anomalies There was an approximately twofold increase in the overall rate of congenital anomalies in the groups exposed to paroxetine or fluoxetine during the first trimester compared with the control group, when the analysis was performed without chromosomal or genetic disorders (Table 2). The main risk applied to cardiovascular anomalies. There were no significant differences between the three groups when the noncardiovascular anomalies were compared. To evaluate the relative contribution of various predictors to the risk of cardiovascular anomalies, logistic regression analysis was performed (Table 3). The only significant predictors were smoking of ≥10 cigarettes day^{-1} and exposure to fluoxetine.

Gestational age and birth weight Birth weight was slightly lower and gestational age at delivery was earlier in both SSRI-exposed groups compared with the control group. However, the rate of preterm deliveries was comparable between the three groups (Table 2).

Perinatal complications Perinatal complications in full-term infants were present in 42/206 (20.4%) of the paroxetine and in 20/116 (17.2%) of the fluoxetine live-born neonates exposed near term. Common perinatal effects in the exposed group were respiratory problems, sleepiness, decelerations on fetal monitor, excessive crying, tremor, meconium-stained amniotic fluid, floppy infant, and jitteriness. The most serious complication was convulsions [4/206 (1.9%) in the paroxetine group, 1/116 (0.9%) in the fluoxetine group and 1/961 (0.1%) in the control group].

Congenital anomalies The list of major congenital anomalies is presented in Table 4 (cardiovascular anomalies) and Table 5 (noncardiovascular anomalies). Table 4 includes data on additional medications and on smoking status. In two cardiovascular anomalies the women were co-exposed to human teratogens (carbamazepine in one case and alcohol in another). In a case of trisomy 21 in the fluoxetine group, the woman had also been treated with valproic acid 1200 mg day^{-1} and olanzapine 10 mg day^{-1} until the 20th gestational week. In all other cases of congenital anomalies no known teratogenic concomitant exposures were reported. When the analysis of cardiovascular anomalies was performed, it did not include the two cases with cardiovascular anomalies, where the primary problem was chromosomal (trisomy 21).

Discussion

This prospective, controlled, observational study from three TISes followed up 463 paroxetine-exposed pregnancies and 346 fluoxetine-exposed pregnancies.

Elective terminations of pregnancy

There was a higher rate of elective terminations of pregnancy (ETOPs) in the fluoxetine-exposed group. This could be related to many factors, e.g. the underlying psychiatric disease, fear of medication effect on pregnancy outcome, but similar factors should play a role in the paroxetine group, where no significant difference was found compared with the control group. In the fluoxetine group, a higher proportion of women had one or more previous ETOPs. It seems, therefore, that the women in this group were more prone to terminate their pregnancy *a priori*.

Perinatal complications

In the present study, there was no case of persistent pulmonary hypertension of the newborn reported in the SSRI-exposed groups. However, the power of the present study was insufficient to detect specific rare complications. Neonates exposed to SSRIs close to term should be carefully followed up for discontinuation or toxicity syndromes.

Risk of cardiovascular anomalies

The major finding of this study was a higher rate of major anomalies in the SSRI groups exposed in the first trimester compared with the controls, after exclusion of genetic and cytogenetic anomalies. Specifically, the rate of cardiovascular anomalies was higher in the SSRI groups exposed in the first trimester compared with the controls. As can be seen in Table 4, the anomalies reported in the cardiovascular section in the SSRI groups are quite varied. This diversity of cardiovascular anomalies argues against a plausible common underlying mechanism, but one cannot rule it out with certainty. One should keep in mind that in the present study VSDs were considered as major anomalies, even when they spontaneously closed. After adjustment for potential confounders, the odds ratio remained significant only for fluoxetine and smoking of ≥10 cigarettes. The confidence intervals for these predictors are wide, and the results should therefore be interpreted with caution. Cardiovascular anomalies are common malformations in the general population. Large human studies on fluoxetine in pregnancy have not observed any association with cardiovascular anomalies. Initial small human studies on paroxetine in pregnancy have not observed an association with cardiovascular anomalies; however, recent large epidemiological studies with different methodologies support such an association, especially with paroxetine. Preliminary data of the present study did not show a significant difference [41], but turned significant when the number of cases was increased [42]. Studies with relatively small sample size

Table 4

List of cardiovascular major anomalies

Paroxetine ($n = 8$)	Additional medications	Fluoxetine ($n = 9$)	Additional medications	Control ($n = 8$)
ASD, VSD and coarctation of aorta (operated at 16 days)	Oxazepam, diclofenac inj. 8th week, nifedipine, atenolol 3rd trim.[a]	VSD and TGA†[b]	None	RBBB and moderate TR (present at 2 years, needs catheterization)[a]
Unspecified CHD (operated at 2 months)	Oxazepam, dipyrone, ibuprofen 7th week, penicillin V-K[c]	Small muscular VSD (diagnosed at 6 months, closed by 1 year)*[a]	Enoxaparin throughout pregnancy	VSD (closed by 11 months)[c]
Hypoplastic left heart, 2 VSDs, large ASD and small mitral valve (died at 1 year)*	Clonazepam from 22nd week[a]	Pulmonary valve stenosis (perinatally diagnosed)[a]	None	Small muscular VSD (prenatally diagnosed, present at 3 months)[a]
Left mild pulmonary artery stenosis, PFO and mild left ventricular distension	None[a]	Unspecified CHD[a]	Carbamazepine, clonazepam, erythromycin, ethinylestradiol + levonorgestrel	PDA (diagnosed on 3rd day, present at 1 month)[a]
Pulmonary valve stenosis (perinatally diagnosed)	None[a]	Mild pulmonary artery stenosis (perinatally diagnosed, present at 4 years)*[d]	Clonazepam	PR and VSD (closed at 7 months)[a]
Clinically significant TR	Diazepam until week 7, dipyrone[a]	ASD (diagnosed before 5 months)[b]	None	VSD and ASD[a]
Small VSD and PFO (perinatally diagnosed)	Clotrimazole 36th week[a]	ASD (needs catheterization)[a]	None	Small PDA (perinatally diagnosed, closed), pulmonary hypertension[c]
Pulmonary artery stenosis, PFO and pes calcaneus (perinatally diagnosed)	Alcohol abuse 70 g day^{-1} until the 12th week, smoking cannabis 1 g day^{-1}, occasionally heroin abuse and opipramol, promethazine, clobutinol and acetylcysteine in 1st trim.[c]	Critical aortic valve stenosis with dysplastic bicuspid aortic valve (perinatally diagnosed, dilated)[c]	None	ASD (perinatally diagnosed)[a]
		VSD (perinatally diagnosed, closed)[a]	Metronidazole (vaginally)	

*Exposure not during the first trimester of pregnancy. †Electively terminated pregnancy. ASD, atrial septal defect; CHD, congenital heart defect; PDA, patent ductus arteriosus; PFO, patent foramen ovale; PR, pulmonic regurgitation; RBBB, right bundle branch block; TGA, transposition of great arteries; TR, tricuspid regurgitation; VSD, ventricular septal defect. [a,b,c,d]Smoking status ([a]none, [b]<10 cig day^{-1}, [c]≥10 cig day^{-1}, [d]unknown)

Table 5

List of noncardiovascular major anomalies

Anomalies	Paroxetine	Fluoxetine	Control
Genitourinary	2 Prune belly syndrome with open urachus (operated) Multicystic renal dysplasia	3 Pelvic kidney (prenatally diagnosed) Abdominal testes Urinary tract anomaly	8 Undescended testes (perinatally diagnosed, operated) Mild hypospadias and urethral stenosis (operated) Right pelvic kidney (prenatally diagnosed) Hydronephrosis (operated at 10 months) Hydronephrosis (operated) Bilateral agenesis of kidneys† Unilateral agenesis of kidney Potter syndrome (1 of twins, died 8 min after birth)
CNS	2 Agenesis of corpus callosum Hydrocephalus and cerebrovascular thrombosis†		1 Dandy Walker syndrome†
Gastrointestinal		1 Pyloric stenosis (operated)*	1 Pyloric stenosis (operated)
Oral clefts			2 Cleft palate (operated) Cleft lip and palate†
Herniae	3 Inguinal (bilateral) (operated at 3 weeks) Inguinal (operated) and epigastric (perinatally diagnosed) Epigastric (needs operation)		4 Inguinal (bilateral) (operated) Inguinal (diagnosed at 5 weeks, operated) Inguinal (operated at 4 months) Diaphragmatic (prenatally diagnosed, operated on 2nd day)
DDH			4 With Pavlik braces With Pavlik braces With Pavlik braces With Pavlik braces, operated tendon and casting
Neuro-developmental	2 Delay (special education day care at 18 months) Severe mental retardation (noted at 13 months)	1 ADHD (special education at age 5.5 years)	1 PDD (neurodevelopmental problems noted at 1 year, PDD diagnosed before age 3 years)
Congenital tumours	1 Sacrococcygeal teratoma (fully resected on 1st day of life)		
Chromosomal	1 Trisomy 21*	3 Trisomy 21with PFO Trisomy 21 with Ebstein's anomaly Trisomy 21†	3 Trisomy 21† Unspecified chromosomal anomaly† Unspecified chromosomal anomaly†
Genetic	1 External hydrocephalus (familial)		3 Neurofibromatosis† Haemophilia B X-linked ichthyosis
Other	1 Sagittal craniosynostosis (operated)	1 Clubfoot (operated)	5 Widespread haemangiomas Multiple anomalies† Congenital strabismus, left VI cranial nerve paralysis Omphalocoele† Unilateral defect of leg and foot

*Exposure not during the first trimester of pregnancy. †Electively terminated pregnancy. ADHD, attention deficit hyperactivity disorder; CNS, central nervous system; DDH, developmental dyplasia of hip; PDD, pervasive developmental disorder.

should be interpreted with caution. The finding of increased risk for cardiovascular anomalies may be an artefact. It can still be coincidental. Alternatively, SSRI-exposed fetuses/neonates may be examined more thoroughly before and after birth than control infants because of the frequent occurrence of neonatal problems in this group and the underlying anxiety of their mothers. It may allow less severe cardiac malformations to be ascertained more frequently, and therefore increase their number. However, in our study the noncomplex, less severe cardiovascular malformations were similarly distributed among the three groups.

A recent meta-analysis [43] has suggested that detection bias cannot be ruled out as contributing to the apparent increased risk of cardiovascular malformations with paroxetine. In addition, a most recent survey [44] of data from published and unpublished studies related to the rate of congenital cardiovascular anomalies in infants born to mothers treated with paroxetine during pregnancy has found that in the published data (on 2205 exposed infants), the rate of cardiovascular anomalies was 1.5%, whereas in the 1174 unpublished cases the rate was only 0.7%. Taking all data together, the rate was not significantly higher than expected in a control population. In a recent population-based study [45] an increased risk of cardiovascular anomalies was found following combined prenatal exposure to SSRIs and benzodiazepines ($n = 359$) compared with no exposure even after controlling for maternal illness characteristics. SSRI monotherapy ($n = 2625$) was not associated with an increased risk for major congenital anomalies or overall cardiovascular congenital anomalies, but was associated with an increased incidence of an atrial septal defect.

Animal studies in rodents exposed to paroxetine or fluoxetine in pregnancy have shown no increase in the rate of congenital anomalies [46–48]. However, the neurotransmitter serotonin may play a role in cardiac morphogenesis during endocardial cushion formation as suggested by *in vitro* animal studies [49]. The blockade of serotonin uptake by SSRIs (paroxetine, fluoxetine and sertraline) inhibited proliferation of cardiac cells [49, 50].

The underlying illness (psychiatric or other) is a potential confounder; however, women in both SSRI groups had underlying psychiatric conditions. Depression and anxiety have been previously linked with preterm delivery [51–53], but not with congenital anomalies. Another potential confounder is co-administered medications. In two cardiovascular anomalies co-exposure to human teratogens (carbamazepine in one case and alcohol in another) could have explained the effect. In all other cases of congenital anomalies without chromosomal or genetic ones, no known teratogenic concomitant exposures were reported.

Cigarette smoking has previously been associated with cardiovascular defects in several studies [54–58]. Every effort should be made to encourage women to quit smoking in pregnancy, especially if they are treated with an SSRI. It is important to control for cigarette smoking in future studies dealing with potential teratogenic effects. Another potential confounder may be alcohol consumption. However, in the Israeli TIS database, which contributed the majority of cases, alcohol consumption is reported in <0.5%; alcohol use is therefore not a significant problem. It is well known that discontinuation of antidepressants carries serious risks to the women who need them [59, 60]. When making a decision on the continuation of paroxetine or fluoxetine during pregnancy, all factors should be weighed, from the risk of malformations to the risk of neonatal complications, as well as the risk of disease relapse during pregnancy and the effects of untreated disease on fetal and maternal well-being.

Advantages and limitations

The present study has advantages and limitations. The response rate was <100%. However, it is important to note that the cases lost to follow-up were due to technical reasons, e.g. telephone disconnection, recording wrong number at initial call, or change of address, and not due to refusal to fill the questionnaire. We compared initial available data between those with and without follow-up in the SSRI-exposed group from the Israeli TIS database. There were no significant differences between the two groups in maternal age, gestational age at initial contact or pregnancy number. We therefore believe that it does not introduce a significant selection bias. Other limitations of the study are: reliance on maternal interview as a source for outcome data in most cases, lack of direct physical examination of the offspring, variation in timing of follow-up, combining data from three TISes, lack of data on socioeconomic status, a nonrandomized design with no blindness to exposure, and limited power for specific rare defects. However, applying the same procedure to all arms of the study and the prospective nature minimize the potential biases. Finally, the relatively large number of SSRI-exposed cases gives reasonable power.

Future directions

Other studies are needed to verify the possible association between cardiovascular anomalies and paroxetine or fluoxetine exposure, as well as the possible association between cardiovascular anomalies and cigarette smoking. Further research is required to evaluate the safety of other SSRIs in pregnancy.

Previous presentations of preliminary data were given at the 42nd Annual Meeting of the Teratology Society and 15th International Conference of the Organization of Teratology Information Services (OTIS), Scottsdale, Arizona, USA 2002 and at the 16th European Network of Teratology Information Services (ENTIS) meeting, Haarlem, the Netherlands, 2005.

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