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Selective serotonin reuptake inhibitor antidepressant use in first trimester pregnancy and risk of specific congenital anomalies: a European register-based study

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Abstract Evidence of an association between early pregnancy exposure to selective serotonin reuptake inhibitors (SSRI) and congenital heart defects (CHD) has contributed to recommendations to weigh benefits and risks carefully. The objective of this study was to determine the specificity of association between first trimester exposure to SSRIs and specific CHD and other congenital anomalies (CA) associated with SSRI exposure in the literature (signals). A population-based case-malformed control study was conducted in 12 EUROCAT CA registries covering

2.1 million births 1995–2009 including livebirths, fetal deaths from 20 weeks gestation and terminations of pregnancy for fetal anomaly. Babies/fetuses with specific CHD ($n = 12,876$) and non-CHD signal CA ($n = 13,024$), were compared with malformed controls whose diagnosed CA have not been associated with SSRI in the literature ($n = 17,083$). SSRI exposure in first trimester pregnancy was associated with CHD overall (OR adjusted for registry 1.41, 95 % CI 1.07–1.86, fluoxetine adjOR 1.43 95 % CI 0.85–2.40, paroxetine adjOR 1.53, 95 % CI 0.91–2.58) and with severe CHD (adjOR 1.56, 95 % CI 1.02–2.39), particularly Tetralogy of Fallot (adjOR 3.16, 95 % CI 1.52–6.58) and Ebstein's anomaly (adjOR 8.23, 95 % CI

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2.92–23.16). Significant associations with SSRI exposure were also found for ano-rectal atresia/stenosis (adjOR 2.46, 95 % CI 1.06–5.68), gastroschisis (adjOR 2.42, 95 % CI 1.10–5.29), renal dysplasia (adjOR 3.01, 95 % CI 1.61–5.61), and clubfoot (adjOR 2.41, 95 % CI 1.59–3.65). These data support a teratogenic effect of SSRIs specific to certain anomalies, but cannot exclude confounding by indication or associated factors.

Keywords Congenital anomaly · SSRI · Medication · Depression · Epidemiology · Registry

Introduction

In Europe, between 3 and 11 % of women have been estimated to have major depression in any 1 year [1–4]. Untreated depression in pregnancy impacts negatively on both the mother and the developing fetus, increasing the risk of premature delivery, low birth weight, small for gestational age and child developmental outcomes [5, 6]. Pharmacotherapy is a popular treatment approach but the safety in pregnancy of most antidepressant medications is uncertain [7]. Therefore, guidelines recommend that pharmacotherapy should be avoided if possible in pregnancy in favour of non-pharmaceutical treatments except in the case of severe depression where benefits outweigh risks [8]. However, the critical period of organogenesis is early in pregnancy and pregnancies may be inadvertently exposed to antidepressant medication before women become aware they are pregnant, or there may not be sufficient time to change medication or treatment approach for women receiving treatment for depressive disorders who become pregnant.

Antidepressant use in first trimester pregnancy has been estimated at 2.0–10.0 % [9–14]. Selective serotonin reuptake inhibitor (SSRI) antidepressants are widely prescribed for treating major depression, including in pregnancy [13–16]. Prior to 2005, SSRIs were regarded to be safe in pregnancy, based mostly on prospective cohort studies with limited sample sizes [17–21]. Thereafter, starting with paroxetine [22], the SSRIs have come under scrutiny particularly in relation to congenital heart defects (CHD) [22–37]. Although not all studies have supported this association [38–45], meta-analyses have found positive overall evidence [46–50]. Some non-CHD congenital anomalies have also been linked to SSRI exposure in first trimester pregnancy [24, 29, 32, 34, 35] although this literature is much smaller. Inconsistencies in the literature can be expected due to different sources of bias, for example the non-inclusion of terminations of pregnancy for fetal anomaly in many studies, different levels of accuracy in recording the diagnosis of CHD and other CA, use of different exposure window definitions [51] and small study

population sizes which have meant that statistically significant risks appear to relate to the more common congenital anomalies (such as septal heart defects) or the more commonly used SSRIs.

The biologic plausibility of a teratogenic effect of SSRIs in humans is based on studies of drug and metabolite levels in amniotic fluid and cord blood combined with evidence from animal studies [52]. Most SSRIs have a short half-life (approximately 1 day). Fluoxetine has a half-life of approximately 1–4 days and its metabolite norfluoxetine a half-life of 7–15 days [53]. Serotonin acts as an important signalling molecule in progenitor heart cells during the establishment of laterality, formation of the outflow tract, myocardial cell differentiation, and septation of the heart chambers [54] and abnormal levels during these critical periods e.g., through the activity of serotonin reuptake inhibitors, has been shown to lead to faulty morphogenesis in animal models [55, 56].

There remains, however, some controversy about the nature of the causal association in human epidemiological studies. It has been suggested that the apparent excess risk of less severe CHDs might reflect ascertainment bias due to greater likelihood of exposed babies receiving special neonatal care [48, 57, 58]. Other studies have focused on confounding by indication or co-exposures including co-medications [23, 33, 59] finding evidence of attenuation of CHD risk.

European Surveillance of Congenital Anomalies (EUROCAT) is a large congenital anomaly surveillance system [60] with a central database which has previously been used to study risks of antiepileptic drug exposure [61]. Using the considerable statistical power provided, we examined the specificity of association between first trimester exposure to SSRIs and specific CHD and non-CHD anomaly subgroups.

Materials and methods

Study design

Case-malformed control study based on EUROCAT population-based congenital anomaly registries. Cases were babies with CHD, or with congenital anomalies other than CHD identified as significantly associated with SSRI exposure (“signals”) in at least one previous study. Controls were all other registrations. Genetic conditions were excluded from both cases and controls.

Setting and data source

EUROCAT registries were included if they had a recorded antidepressant exposure of at least 3 per 1000 and at least 5 exposed registrations in designated 5 years periods:

1995–1999, 2000–2004, 2005–2009. Twelve registries in 12 European countries were included for all or part of 1995–2009 (Table 1). The data from Northern Netherlands registry 1997–2006 have been previously published limited to paroxetine use [36]. The 12 registries registered 70,117 babies/fetuses with congenital anomaly from a population of 2,177,977 births.

Data were extracted from the central database of EUROCAT [60]. EUROCAT registries collect data on live births, stillbirths and late fetal deaths from 20 weeks gestation, and terminations of pregnancy for fetal anomaly (TOPFAs). Registries use multiple sources of information: maternity, neonatal, and paediatric records; fetal medicine, cytogenetic, pathology, and medical genetics records; paediatric cardiology services; and hospital discharge and child health records [62]. Eleven of the 12 registries register children with congenital anomalies up to age 1 year or more. A registrant can have up to 8 malformations and one syndrome recorded. Congenital anomalies are coded to the International Classification of Diseases (ICD) version 9 or 10 with 1-digit BPA extension. These codes are classified into the standard EUROCAT malformation subgroups [63] (see ESM Appendix). The severe CHD subgroup as defined by EUROCAT included all CHD subgroups with higher perinatal mortality (see ESM Appendix) [64]. Babies/fetuses with only congenital anomalies categorised as minor according to EUROCAT definitions were excluded [63].

Cases and controls

Cases and controls were defined as livebirths, fetal deaths from 20 weeks, and terminations of pregnancy for fetal

anomaly following prenatal diagnosis with non-genetic major CA. 7813 genetic registrations (chromosomal or single gene disorders) identified using the EUROCAT multiple malformation algorithm [65] were excluded as having a different preconceptional aetiology [66, 67]. 201 cases/controls with teratogenic syndromes were also excluded as of known cause. To avoid terminological confusion, we refer to any baby with congenital anomaly as a “registration”, covering both cases and controls and excluded babies.

Cases of CHD

ICD codes Q20-26 (ICD10) and 745, 746, and 7470–7474 (ICD9-BPA), with or without extra-cardiac anomalies. Excluded from CHD were preterm deliveries (<37 weeks) with only patent ductus arteriosus (Q250 or 7470), and all cases with only patent foramen ovale (Q2111) [62]. CHDs were classified into EUROCAT CHD subgroups [63] (see ESM Appendix).

Cases of non-CHD “signals”

Cases were 13 standard EUROCAT congenital anomaly subgroups (and organ system subgroups including those anomalies) which had shown statistically significant associations with one or more SSRI types in the literature (accessed via Pubmed and Embase up to June 2012) [24, 29, 32, 34, 35]:

- Neural tube defects—paroxetine [35]
- anencephaly (part of neural tube defects)—SSRI, paroxetine [34]

Table 1 Registry, population (births), number of congenital anomaly (CA) registrations, and number and % SSRI exposure

Registry	Birth years	Births	CA	SSRI (N)	SSRI (%)
Antwerp (Belgium) ^M	2000–2004	61,585	1776	5	0.30
Basque country (Spain) ^M	2005–2009	103,040	1188	8	0.70
Cork and Kerry (Ireland) ^M	1996–2004	71,625	1086	10	0.90
Malta ^M	1995–1999	23,368	615	1 [^]	0.20
Northern Netherlands ^{M,I,P}	1995–2009	288,971	5217	53	1.00
Norway ^M	2000–2009	590,747	15,347	82	0.50
Odense (Denmark) ^M	2000–2009	53,491	932	21	2.30
Paris (France) ^M	2000–2009	278,435	5104	15	0.30
Saxony-Anhalt (Germany) ^{M,I}	2005–2009	86,662	1605	7	0.40
Tuscany (Italy) ^I	2005–2009	152,137	778	7	0.90
Vaud (Switzerland) ^M	2000–2009	73,522	1657	6	0.40
Wales (UK) ^M	1998–2009	394,394	7678	113	1.50
Total		2,177,977	42,983	328	0.76

[^] Malta fulfilled inclusion criteria of 5 exposed CA registrations before specific exclusions were made

^M Medication ascertainment from prospective maternal medical/midwifery notes

^I Information on medication exposure taken from or confirmed through maternal interviews after birth

^P Information available on maternal prescriptions

eye defects—paroxetine [24]
 ear/face/neck defects—fluoxetine [32]
 respiratory defects—sertraline [32]
 digestive system defects—fluoxetine [32]
 ano-rectal atresia and stenosis (part of digestive system)—sertraline [35]
 gastroschisis—paroxetine [34]
 omphalocele—SSRI, paroxetine, sertraline [34, 35]
 renal dysplasia—SSRI [29, 32]
 hypospadias—paroxetine [29]
 limb reduction—sertraline [35]
 lower limb reduction (part of limb reduction)—SSRI [32]
 clubfoot—SSRI, paroxetine [35]
 craniosynostosis [34]

Cases where any of the above were associated with CHD were analysed only as CHD cases.

Controls

Controls were the remaining congenital anomaly registrations, after excluding all registrations with CHD or with a non-CHD “signal” congenital anomaly subgroup.

An exploratory analysis was conducted within the control group to determine whether any of the component anomalies were more commonly exposed to SSRI than other controls, adjusting odds ratios for registry.

Exposure ascertainment

For the most part, our medication exposure information came from maternal medical/midwifery notes, created prospectively [68]. Other additional data sources include paediatrician records (postnatal), medical geneticist records (postnatal), GP records of mother (prenatal), and maternal interviews (postnatal) (see Table 1). One registry accesses a prescription database as its primary source and verifies use of prescribed medications through postnatal telephone interviews with the mothers. Data sources per registry are shown in Table 1. Data sources were unbiased with respect to case/control status. Medication exposure was ascertained similarly for all types of pregnancy outcomes, except for one registry which did not obtain medication data for TOPFA (TOPFA for that registry were excluded from the dataset). Drug data are coded to the Anatomical Therapeutic Chemical (ATC) code [69]. Maternal illness before and during pregnancy is coded to ICD codes (ICD-9 or ICD-10).

Exposure was defined as use of SSRI (ATC N06AB) without use of any other type of antidepressant. The first trimester of pregnancy was defined as the period from the first day of the last menstrual period up to the 12th week of

gestation [63]. Women were excluded from the dataset if they took non-SSRI antidepressants ($n = 121$) or unspecified antidepressants ($n = 39$), and for the specific SSRI analyses, if they took more than one specific SSRI ($n = 1$, citalopram + fluoxetine). Women were considered unexposed if the registry did not record use of any antidepressants in first trimester pregnancy. When using maternity records to ascertain medication usage, it is not always possible to distinguish no usage of the medication from no reported usage—unknown medication use mainly indicated that the sources of medication information for the case were not available to the register, while no exposure indicated that the usual sources had been consulted but no exposure was recorded. Two registries (Antwerp and Tuscany) did not distinguish these two situations, and all of their cases without recorded exposure were considered unexposed. Six SSRI antidepressants were recorded: Fluoxetine (N06AB03), Citalopram (N06AB04), Paroxetine (N06AB05), Sertraline (N06AB06), Fluvoxamine (N06AB08), and Escitalopram (N06AB10). All were analysed individually except Fluvoxamine to which only six women were exposed. Where a significant association was found, exposed cases were checked with registries to verify first trimester exposure and drug type, and these case lists were also examined for evidence that co-exposure to other medications might constitute a significant source of confounding. The atrial septal defect (ASD) cases exposed to SSRIs were in addition checked with the registries to determine whether they had been infants in specialist neonatal care who may have been examined more intensively, which could lead to diagnostic bias.

To avoid misclassification of antidepressant exposure status, women with drug use unknown or missing ($n = 17,869$, including all TOPFA from one of the registries) or those with a record of depression diagnosis with no record of antidepressant use ($n = 20$) were excluded. To avoid confounding by co-exposure to identifiable teratogenic medications/condition, cases/controls were excluded if they had a record of exposure to antiepileptic medication ($n = 374$), or antidiabetic medication/diabetes ($n = 697$), or they had teratogenic syndromes ($n = 201$).

After all exclusions, the study was based on the remaining 42,983 registrations.

Statistical analysis

Logistic regression analysis was used to estimate odds ratios and 95 % confidence intervals using Stata version 9.0 (Statacorp LP, College Station, TX, USA). Analysis was limited to congenital anomaly subgroups with at least 3 exposed cases as it was considered that odds ratios based on 1 or 2 cases could not be meaningfully interpreted. In cases where a statistically significant association was detected between SSRI (combined) and any congenital

anomaly subgroup, results for specific SSRIs are presented even when the number of exposed cases was <3 to facilitate assessment of specificity of association between specific SSRIs and specific congenital anomalies. Analyses were adjusted for registry in order to adjust for confounding that may arise if registries differ in both exposure and outcome prevalences. As recommended for observational epidemiological studies, no statistical adjustment was performed for multiple testing [70], but design and interpretation took into account presence of a prior hypothesis.

Ethics approval

EUROCAT has approval from the Ulster University Research Ethics Committee. Additionally, all registries have ethical approval appropriate to their national and local ethics guidelines.

Results

A total of 42,983 non-genetic congenital anomaly registrations consisting of 12,876 with CHD, 13,024 with one or more of the 15 “signal” subgroups, and 17,083 controls were included in the analysis. Exposure to SSRIs in first trimester pregnancy among all registrations was 0.76 % (328/42,983) (Table 1); 0.68 and 0.66 % of the CA registrations were exposed to SSRIs in 1995–1999 and 2000–2004 respectively with the exposure increasing to 0.90 % 2005–2009 ($\chi^2 = 7.65$, $df = 2$, $p = 0.022$). By type of birth, 0.76 % of livebirths, 0.79 % of TOPFA and 0.87 % of stillbirths were exposed to SSRIs ($\chi^2 = 0.11$, $df = 2$, $p = 0.945$). 14.6 % of the women who had SSRI prescriptions also had prescriptions for psycholeptic medications.

Among the controls, 99 registrations were exposed to SSRIs, of which 27 were to fluoxetine, 27 to paroxetine, 20 to citalopram, 14 to sertraline, 9 to escitalopram and 1 to fluvoxamine.

Congenital heart defects

SSRI (combined) exposure was significantly associated with CHD (OR 1.41, 95 % CI 1.07–1.86, Table 2); the association was similar or slightly stronger for severe CHD (OR 1.56, 95 % CI 1.02–2.39, Table 2) while the association with the main other CHD group, septal defects, was slightly lower and of borderline statistical significance (OR 1.36, 95 % CI 0.99–1.87, Table 2). Assessing specific SSRIs for CHD combined, the raised odds does not appear to be specific to any one SSRI—odds ratios were between

1.43 and 1.53 with overlapping confidence intervals for the four most common SSRIs, and a lower OR with a wide confidence interval was found only for escitalopram (OR 1.10, 95 % CI 0.41–2.95). Assessing specificity of association for specific SSRIs and severe CHD also did not reveal raised odds limited to any one SSRI (Table 2).

Statistically significant associations were detected between SSRI and Tetralogy of Fallot (TOF) (OR 3.16, 95 % CI 1.52–6.58, 8 exposed cases, Table 2). The TOF association was not limited to any one specific SSRI (Table 2).

The strongest association with SSRI exposure was for Ebstein’s anomaly (OR 8.23, 95 % CI 2.92–23.16), with 4 exposed cases distributed across 4 different types of SSRIs (Table 2). Examination of the exposed case list showed that no cases were co-exposed to lithium. Although the strongest evidence for severe CHD types was for TOF and Ebstein’s anomaly, other subgroups either showed non-significant raised odds ratios (e.g. Atrioventricular septal defect with OR 2.08) or odds ratios closer to 1 but with wide confidence intervals.

The association between SSRIs and septal defects was of borderline significance (Table 2). Odds ratios were generally higher for the septal defect subtype ASD (OR 1.71, 95 % CI 1.09–2.68, Table 2) than VSD, except for a VSD-paroxetine association (OR 1.90, 95 % CI 1.04–3.48, Table 2). Among the 25 SSRI exposed ASD cases, 7 were in neonatal intensive units, 5 were not and there is no information on the remaining 13 infants.

Non-CHD signals

There were 121 SSRI exposed babies with anomalies belonging to the 15 “signal” subgroups (Table 3). For five of these subgroups, a statistically significant association was found with SSRI combined, or a specific SSRI type. Exposure to SSRI was associated with increased odds of ano-rectal atresia and stenosis (OR 2.46, 95 % CI 1.06–5.68, Table 3), but there were no exposures to sertraline, the origin of the signal (Table 3).

Gastroschisis was associated with SSRI exposure (OR 2.42, 95 % CI 1.10–5.29, Table 3), but was associated with SSRIs other than paroxetine (Table 3).

Renal dysplasia was associated with SSRI exposure (OR 3.01, 95 % CI 1.61–5.61, Table 3), particularly fluoxetine (OR 5.76, 95 % CI 2.54–13.08).

A significant association was found between hypospadias and citalopram (OR 3.21, 95 % CI 1.56–6.60, Table 3), while a non-significant modestly elevated OR of 1.34 (95 % CI 0.58–3.09) was found with paroxetine (Table 3).

Table 2 Number (N) and OR of maternal exposure to SSRIs, combined and by SSRI type, comparing CHD subgroups with controls, 12 EUROCAT registries 1995–2009

CA	SSRI		Fluoxetine		Paroxetine		Citalopram		Sertraline		Escitalopram	
	N	Adj* OR (95 % CI)	N	Adj* OR (95 % CI)	N	Adj* OR (95 % CI)	N	Adj* OR (95 % CI)	N	Adj* OR (95 % CI)	N	Adj* OR (95 % CI)
CHD	12,876	1.08	31	1.43 (0.85–2.40)	31	1.53 (0.91–2.58)	23	1.45 (0.79–2.65)	16	1.51 (0.73–3.12)	7	1.10 (0.41–2.95)
Severe CHD	2935	28	8	1.46 (1.02–2.39)	6	1.08 (0.66–3.23)	6	1.85 (0.73–4.66)	6	2.88 (1.09–7.61)	2	1.65 (0.35–7.81)
Transposition great vessels	615	3	0	0.79 (0.25–2.52)	1	–	0	–	1	–	1	–
Tetralogy of fallot	428	8	4	3.16 (1.52–6.58)	0	–	2	4.41 (1.02–19.15)	1	3.33 (0.43–25.68)	1	5.85 (0.73–47.09)
Atrioventricular septal defect	290	4	2	2.08 (0.76–5.73)	1	–	0	–	1	–	0	–
Ebstein's anomaly	93	4	0	8.23 (2.92–23.16)	1	6.43 (0.85–48.54)	1	12.36 (1.61–95.15)	1	16.42 (2.10–128.38)	1	34.19 (4.09–286.04)
Hypoplastic left heart	398	3	1	1.22 (0.38–3.88)	1	–	1	–	0	–	0	–
Coarctation of aorta	570	4	0	1.12 (0.41–3.07)	0	–	0	–	2	–	0	–
Septal defects	8131	64	16	1.36 (0.99–1.87)	23	1.92 (1.09–3.37)	9	0.88 (0.40–1.94)	9	1.33 (0.57–3.09)	7	1.62 (0.60–4.36)
Atrial septal defect (ASD)	2691	25	6	1.71 (1.09–2.68)	5	1.38 (0.68–4.11)	4	1.28 (0.43–3.75)	5	2.02 (0.71–5.71)	5	3.31 (1.11–9.90)
ASD without severe CHD	2378	20	5	1.54 (0.94–2.52)	5	1.65 (0.62–4.42)	3	1.07 (0.31–3.61)	2	–	5	3.62 (1.21–10.83)
Ventricular septal defect (VSD)	6167	41	10	1.12 (0.77–1.61)	18	1.90 (1.04–3.48)	5	0.63 (0.24–1.70)	6	1.15 (0.44–3.01)	2	–
VSD without severe CHD	5511	36	10	1.12 (0.76–1.65)	17	2.12 (1.15–3.92)	5	0.71 (0.26–1.90)	4	0.84 (0.27–2.57)	0	–
Pulmonary valve stenosis	772	7	3	1.30 (0.60–2.83)	1	–	2	–	1	–	0	–

OR italicised are reported even though the number of exposed cases was <3 to help assess specificity of effect

The EUROCAT severe CHD subgroups truncus arteriosus, single ventricle, tricuspid atresia, total anomalous pulmonary venous return, hypoplastic right heart, aortic stenosis, and pulmonary atresia have <3 SSRI exposed cases each and therefore not reported separately, but included in totals

* ORs were adjusted for registry

Table 3 Number (N) and OR of maternal exposure to SSRIs, combined and by SSRI type, comparing non-CHD signal subgroups with controls, 12 EUROCAT registries 1995–2009

CA	N	SSRI		Fluoxetine		Paroxetine		Citalopram		Sertraline		Escitalopram	
		N	Adj* OR (95 % CI)	N	Adj* OR (95 % CI)	N	Adj* OR (95 % CI)	N	Adj* OR (95 % CI)	N	Adj* OR (95 % CI)	N	Adj* OR (95 % CI)
Neural tube ^{s,p,c}	1322	8	0.90 (0.43–1.88)	3	0.99 (0.30–3.29)	0	–	2	–	1	–	1	–
Anencephaly ^s	473	3	0.89 (0.28–2.84)	2	–	0	–	1	–	0	–	0	–
Eye ^p	828	7	1.13 (0.52–2.47)	1	–	3	1.37 (0.41–4.59)	2	–	0	–	1	–
Ear, face and neck ^f	746	3	0.71 (0.22–2.25)	2	–	0	–	0	–	0	–	1	–
Respiratory system ^{s*}	983	7	1.08 (0.50–2.35)	1	–	0	–	2	–	2	–	0	–
Digestive system ^f	2739	19	1.13 (0.69–1.87)	5	0.96 (0.36–2.51)	7	1.25 (0.54–2.90)	2	–	1	–	2	–
Ano–rectal atresia and stenosis ^{s*}	392	6	2.46 (1.06–5.68)	2	2.55 (0.60–10.91)	2	2.82 (0.66–11.96)	1	2.19 (0.29–16.63)	0	–	1	6.02 (0.73–49.62)
Gastroschisis ^p	413	7	2.42 (1.10–5.29)	2	2.28 (0.53–9.82)	0	–	3	5.10 (1.46–17.75)	1	2.69 (0.34–21.05)	1	5.05 (0.62–40.90)
Renal dysplasia ^s	618	12	3.01 (1.61–5.61)	8	5.76 (2.54–13.08)	2	1.62 (0.38–6.95)	1	1.40 (0.18–10.86)	0	–	0	–
Hypospadias ^p	3041	25	1.34 (0.86–2.09)	2	–	7	1.34 (0.58–3.09)	12	3.21 (1.56–6.60)	2	–	2	–
Limb reduction ^{s*}	784	6	1.15 (0.50–2.65)	2	–	3	1.86 (0.56–6.17)	0	–	0	–	1	–
Clubfoot ^{s,p}	1992	30	2.41 (1.59–3.65)	6	1.65 (0.68–4.03)	10	2.99 (1.44–6.21)	5	1.91 (0.71–5.11)	5	3.05 (1.09–8.52)	4	3.88 (1.19–12.69)
Craniosynostosis ^s	307	5	2.48 (0.99–6.22)	2	–	1	–	1	–	1	–	0	–

Omphalocele and lower limb reduction anomaly have 1 SSRI exposed case each and therefore not separately reported

OR italicised are reported even though the number of exposed cases was <3 to help assess specificity of effect

Signal source: *s* SSRI, *f* fluoxetine, *p* paroxetine, *c* citalopram, *s** sertraline

* ORs were adjusted for registry

Clubfoot was associated with SSRI exposure (OR 2.41, 95 % CI 1.59–3.65), particularly with paroxetine, sertraline and escitalopram where point estimates were close to or above 3.

The OR for SSRI and craniosynostosis was of borderline statistical significance (OR 2.48, 95 % CI 0.99–6.22). Odds ratios close to one were found for neural tube defects, anencephaly, and eye, ear/face/neck, respiratory system defects, digestive system defects, and limb reduction defects (Table 3). There were <3 exposed cases of omphalocele which was not analysed separately.

Subgroups included within the controls

There were 99 SSRI exposed controls. Eleven EUROCAT subgroups had at least 3 SSRI exposed registrations and

were analysed in comparison with all other controls combined. A statistically significant association was observed for SSRI and microcephaly (OR 4.15, 95 % CI 1.60–10.78) with 5 cases distributed across 4 SSRI types (online appendix).

Sensitivity analyses in which women with missing/unknown drug exposure were classified with the unexposed group yielded comparable odds ratios to those reported in the main analysis. We did not formally take into account multiple pregnancies per woman in the statistical analysis. However, we looked for twin and sibling pairs among the SSRI exposed. We found three sets of sibling/twin pairs whose mothers were exposed to SSRIs. One set of twins had very different congenital anomalies (one non-severe cardiac, one genital), one set of siblings born 10 years apart and exposed to different SSRIs both had isolated

congenital hip dislocation and one sibling pair born 1 year apart with the same exposure, both had CHD anomalies one of which was a severe CHD. Taking siblings into account therefore does not change the results substantially.

Discussion

This is the first study to have systematically examined the full range of congenital anomalies in a large population. We found a statistically significant association between SSRIs as a class and CHD overall supporting previous reports of this association [22–37, 46, 47, 68]. We have been able to show in addition that the association is stronger for severe CHD and, therefore, is unlikely to be explained as neonatal examination bias or more frequent echocardiograms or other screening/diagnostic procedures for SSRI exposed infants [48, 57, 58]. We have also shown that the association is not specific to any one SSRI type, although the power of the study to estimate differences between the effects associated with specific SSRIs was limited. This suggests switching from one specific SSRI to another before or in pregnancy is not an effective strategy to reduce the risk of CHD. Our finding of non-specificity by SSRI type is compatible with the mechanism of teratogenic action being one that is common to all SSRIs and is also compatible with confounding by depression as indication or other associated factors/exposures.

Recent studies have suggested that the association between SSRI and CHD may be explained by confounding [23, 33, 59]. A Danish healthcare database study of livebirths found a higher risk of CHD both among women exposed to SSRI in the first trimester, and those who paused SSRI use during pregnancy, suggesting confounding by underlying depression or factors associated with depression [33]. A British healthcare database study of livebirths found a small excess risk of CHD (14 %) with SSRI exposure, and a similarly small excess risk (10 %) for women with unmedicated depression, and for individual SSRIs found a significantly elevated risk only for paroxetine when compared to unmedicated depression [23]. A US health insurance database study found that in an analysis restricted to women with a diagnosis of depression, controlling for co-exposures to other medications attenuated the CHD risks [59]. In our study we did not have full information on depression diagnosis, but we excluded women with diabetes/insulin or antiepileptic exposures where the main risk of confounding lies and, since the numbers of exposed cases are very small for statistical adjustment for confounding by co-medication, we examined case lists for evidence of potential confounding by co-medications and found none. We also used validated

registry CA diagnoses, including TOPFA, rather than relying on the problematic recording of CA in healthcare databases [71]. Further investigation of the hypothesis that the causal association is with the underlying depression is necessary, taking into account the specificity we find in relation to types of CHD and other CA. Moreover, the evidence that maternal depression increases congenital anomaly risk is lacking [6], although there are known associations with stress [72], and this requires further research.

We found previously unreported associations between SSRI and TOF (OR 3.16, 95 % CI 1.52–6.58) and Ebstein's anomaly (OR 8.23, 95 % CI 2.92–23.16). The finding relating to Ebstein's anomaly is of particular interest given that it has previously been reported to be associated with the antipsychotic drug lithium [73] which has led to avoidance of lithium use in pregnancy, although the evidence remains controversial [74]. None of the SSRI exposed Ebstein's anomaly cases in our data also had lithium exposure and the SSRI association appears to be an independent finding.

Our findings support an association between SSRIs and ASD, but we found no evidence that this was specific to paroxetine as previously reported [32, 33] and we did find some evidence that exposed cases of ASD tended to have been cared for in neonatal units and thus biased ascertainment of ASD is possible. We found a previously unreported association between paroxetine and VSD, which did appear to be specific only to paroxetine.

Among 15 non-CHD signals in the literature, 5 were supported by statistically significant associations with OR above 2 in our data (ano-rectal atresia and stenosis, gastroschisis, renal dysplasia, clubfoot and hypospadias). Craniosynostosis was also of borderline significance. Except for hypospadias, these associations were not confined to any one SSRI, and often not the SSRI type of the original signal [24, 29, 32, 34, 35]. Gastroschisis is strongly associated with socio-economic deprivation and lifestyle exposures, including smoking and recreational drugs [75], and confounding or cumulative or interacting exposure effects should also be considered as an explanation for its association with SSRI use. For other anomalies, the evidence concerning factors such as obesity [76], smoking [77], and alcohol use [78] would suggest that confounding would be unlikely to be strong enough to explain ORs above 2.

For the other signal subgroups (neural tube defects/anencephaly, eye, ear/face/neck, respiratory system, digestive system, omphalocele, limb reduction) our data do not support associations with SSRI, but generally wide confidence intervals cannot exclude moderate associations. Folic acid could have been an unmeasured confounder in our analyses—the absence of an association between SSRI and neural tube defects (the congenital anomaly most

strongly associated with folic acid), suggests that either SSRI users are as likely to use folic acid as other mothers, or that SSRI users take more folic acid but folic acid protects against the teratogenic effects of SSRI.

The finding in the exploratory analysis of a significant association with microcephaly is of interest given the wide range of teratogenic exposures associated with microcephaly [79] but confounding and the likelihood of spurious chance associations due to multiple testing mean that this should be very cautiously interpreted until confirmed by other studies.

Strengths and limitations

This study has several strengths. It used data from a large population-based congenital anomaly surveillance system covering approximately 2 million births in 12 European countries providing the opportunity to study some rare CHD types and other congenital anomalies. Importantly, the database has information on TOPFA following prenatal diagnosis which constituted about 5.9 % of all (non-genetic) registrations, a much higher proportion for more severe CAs. Inclusion of TOPFA is particularly important since uptake of prenatal diagnosis and TOPFA may be associated with depression, SSRI use or socioeconomic correlates. For most of the registries, exposure data were recorded prospectively before outcome was known eliminating the possibility of recall bias, but in addition the use of malformed controls meant that there was little opportunity for recall bias.

The main limitation of the study relates to exposure classification. There was undoubtedly underascertainment of antidepressant use, as shown by the relatively low exposure prevalence of 0.8 % overall, when compared to population-based estimates among pregnant women [9, 12–15, 79]. SSRI exposure is difficult to ascertain accurately, and even comparisons between research birth cohorts and prescription databases have shown considerable unexplained discrepancies [51, 80]. One quarter of registrations had missing exposure information. While there is no reason to believe this exposure misclassification was differential across cases and controls and thus would lead to bias, the low exposure prevalence did decrease the statistical power of the study. There was no information on dosage or length of exposure to SSRIs—Berard et al. [37] suggested that the teratogenic effect of paroxetine may be limited to higher doses (25 mg/day). We assumed, as is customary, that the relevant exposure window was the first trimester (as these are the available EUROCAT data) but this window is wider than the sensitive period for many congenital anomalies, some congenital anomalies may occur after later exposures [81]. On the other hand, some of the exposures recorded do not specify timing precisely and may be misattributed to the

first trimester, although we verified timing for anomalies where significant associations were found. In general, misclassification of exposure is likely to have led to underestimation of odds ratios.

Use of malformed controls could lead to underestimation of the odds ratio if the SSRIs under study also caused malformations that are included in the controls. However, by design, we excluded all known non-CHD “signals” from the control group and an exploratory analysis carried out on the control group found only one anomaly subgroup (microcephaly) to be disproportionately represented among the SSRI exposed. We excluded chromosomal syndromes from both cases and controls. Further research could examine whether a fetus with a chromosomal syndrome has a greater sensitivity to the teratogenic effect of SSRIs, but our study did not have the statistical power to do this.

Multiple comparisons were carried out and some of the significant associations might be due to chance, although we tried to minimise this problem by clear specification of prior hypotheses. Data were unavailable on possible confounding co-exposures as already discussed.

Implications for practice

Our data cannot resolve whether the association between SSRI use and congenital anomalies is a causal one. We have however been able to show the range of congenital anomalies associated with SSRI use includes severe CHD and also goes beyond CHD, we have estimated the strength of association for each anomaly, and shown that the risks are found across a range of specific SSRI types. In a population of 100,000 pregnant women, of whom 4 % [14] take SSRIs during the first trimester (4000 women), we can estimate from our data, using EUROCAT congenital anomaly prevalence estimates, that an extra 28 cases would be born with major congenital anomalies to these women, of which under half would be cardiac defects. On a population basis, this strongly reinforces the importance of population measures to prevent depressive illness prior to and during pregnancy, to make readily available the choice of non-pharmacological treatments, and to prioritise further research on both depression and antidepressants. On an individual basis, the additional risk of congenital anomaly (approximately 0.5 %) is very low. These low estimated risks, which should however be considered together with adverse effects of later pregnancy exposures such as poor neonatal adaptation syndrome, newborn pulmonary hypertension and possible neurodevelopmental effects [6], must be balanced for each individual woman against the benefits of choosing SSRI treatment, benefits which can be vital for both mother and baby in case of severe depression [6].

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Compliance with Ethical Standards

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Conflict of interest The congenital anomaly registries and institutions where EG, MKB, DT, BK, VN, MoM, AP, MG, MCA, AR, LA, LdJvdB and HD are employed have previously received funding from Glaxo Smith Kline for a study of safety of antiepileptic lamotrigine use in pregnancy. No author has had any association with or interest in any antidepressant manufacturer in relation to the current study.

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