BMJ

RESEARCH

Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study

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Cite this as: *BMJ* 2009;339:b3569
doi:10.1136/bmj.b3569

ABSTRACT

Objective To investigate any association between selective serotonin reuptake inhibitors (SSRIs) taken during pregnancy and congenital major malformations.

Design Population based cohort study.

Participants 493 113 children born in Denmark, 1996-2003.

Main outcome measure Major malformations categorised according to Eurocat (European Surveillance of Congenital Anomalies) with additional diagnostic grouping of heart defects. Nationwide registers on medical redemptions (filled prescriptions), delivery, and hospital diagnosis provided information on mothers and newborns. Follow-up data available to December 2005.

Results Redemptions for SSRIs were not associated with major malformations overall but were associated with septal heart defects (odds ratio 1.99, 95% confidence interval 1.13 to 3.53). For individual SSRIs, the odds ratio for septal heart defects was 3.25 (1.21 to 8.75) for sertraline, 2.52 (1.04 to 6.10) for citalopram, and 1.34 (0.33 to 5.41) for fluoxetine. Redemptions for more than one type of SSRI were associated with septal heart defects (4.70, 1.74 to 12.7)). The absolute increase in the prevalence of malformations was low—for example, the prevalence of septal heart defects was 0.5% (2315/493 113) among unexposed children, 0.9% (12/1370) among children whose mothers were prescribed any SSRI, and 2.1% (4/193) among children whose mothers were prescribed more than one type of SSRI.

Conclusion There is an increased prevalence of septal heart defects among children whose mothers were prescribed an SSRI in early pregnancy, particularly sertraline and citalopram. The largest association was found for children of women who redeemed prescriptions for more than one type of SSRI.

INTRODUCTION

Depression affects up to a fifth of pregnant women,[1 2] and medical treatment must balance maternal health with potential adverse fetal effects such as congenital malformations. Until 2005, most studies on selective serotonin reuptake inhibitors (SSRIs) found no association with major malformations,[3-7] but recent studies have indicated an increased prevalence of, for example, omphalocele,[8] craniosynostosis,[8] and, more consistently, heart defects.[8-14] The results on specific types of SSRI are conflicting,[8-10 12-14] but some research has suggested an increased risk of heart defects, especially with paroxetine[9 12 14] but also sertraline, fluoxetine, and citalopram.[6 9 13] The suspected risk of congenital heart defects was responsible for the 2005 warning by the US Food and Drug Administration related to the use of paroxetine during pregnancy.[15] We evaluated associations between SSRIs during the first trimester of pregnancy and major malformations in a large population based cohort study.

METHODS

We used data from four Danish nationwide registries: the medical birth registry,[16] the national register of medicinal product statistics, the fertility database,[17] and the national hospital register.[18] The registries were linked by the use of the unique personal identifier of 10 digits assigned to all citizens at birth.

The medical birth registry[16] stores data on all deliveries, including maternal age, maternal smoking status during pregnancy, parity, date of delivery, gestational age, birth weight, sex of newborn, and information on multiple pregnancy. Information on gestational age at birth is usually estimated from ultrasound measures during early pregnancy. In case of no ultrasound measure the last menstrual period is used. The initiation of pregnancy was calculated by subtracting day of birth by gestational age in days.

The register of medicinal product statistics holds information on therapeutic drug sales, the personal identifier, specification of the medication, and drug classification code (the anatomical therapeutic chemical (ATC) classification system, World Health Organization).[19] On redemption (that is, the filling of a prescription), information from each prescription, including date of redemption, is stored with the purpose of financial compensation. All drugs included in this study are sold by certified pharmacies according to prescriptions written by a doctor, and every pharmacy in Denmark reports to the register.

The fertility database[17] includes demographic information on every person in the fertile age group in

Denmark and their children. We calculated the combined income of the mother and father during the year of their child's birth based on information in the database. If information on income for both parents was missing we used data from the previous calendar year.

The national hospital register[18 20] holds information on all admissions and outpatient hospital contacts in the country. Each patient has a date of admittance and ICD-10 (international classification of disease, 10th revision) coded diagnoses from the study period. We included information from 1 January 1996 to 31 December 2005. Malformations were coded according to the Eurocat categorisation,[21] and congenital heart defects were further categorised in developmentally based subgroups as suggested by Louik et al.[13] As information on malformations in stillborn children is incompletely registered we included only liveborn children in the analyses. We considered only malformations detected at birth or within the first year after birth. We also performed additional analyses with truncation after two years to investigate for potential differences in time of diagnosis.

The exposure window was defined as 28 days before to 112 days after the beginning of gestation. Exposure was defined as two or more redemptions of an SSRI in this time period (ATC codes N06AB). Women with only a single redemption in the exposure window were included in later analyses. We excluded women with any redemption of insulin or antihypertensive medications in a period of three months before the estimated beginning of gestation and those with any redemption during the exposure window to other psychotropic medications, such as antiepileptic medication, antipsychotics, and anxiolytics. Antidepressants other than SSRIs, such as tricyclic antidepressants and venlafaxine, were excluded from the main analyses but included in later sensitivity analyses.

We thus constructed a cohort consisting of all liveborn children in Denmark between 1 January 1996 and 31 December 2003 based on information from the medical birth registry (n=553 689). From these we excluded 1213 children because of coding errors, 22 045 because of emigration, 8388 because of exposure to other psychoactive or antidiabetic drugs as described above, and 21 653 multiple births and 3509 stillbirths. The final study population comprised 496 881 singleton liveborn children.

Statistical analyses were performed with Stata (version 9, StataCorp, Texas, USA). We conducted multiple logistical regressions on dichotomous outcomes adjusted for maternal age (<20, 20-24, 25-29, 30-34, ≥35), calendar time (1996-8, 1999-2001, 2002-3), marital status (unmarried, married, divorced, widow), income (three categories), and smoking (no/yes). Less than 1% had missing values in these variables except for smoking (17% missing), and we performed sensitivity analyses without the smoking variable. Significance was defined as a two sided P value <5% and adjusted odds ratios are provided with 95% confidence intervals. Odds ratios were used to estimate relative prevalence rate ratios. We used causal diagrams (directed acyclic graphs) to guide the selections of potential confounders to be controlled.[22] No adjustments were made for multiple comparisons.

Table 1 | Odds ratios for malformations according to two or more redemptions for selective serotonin reuptake inhibitors (SSRIs)

Birth defects	No of unexposed infants (n=493 113)	SSRI (n=1370)	
		No of infants	OR* (95% CI)
Minor	7373	39	0.88 (0.54 to 1.41)
Major	15 518	55	1.21 (0.91 to 1.62)
Central nervous system	597	1	—
Neural tube defects	180	0	—
Eye	418	1	—
Major cardiac malformations:			
All	3988	16	1.44 (0.86 to 2.40)
Conotruncal heart defects	342	0	—
Right ventricular outflow tract obstructions	331	1	—
Left ventricular outflow tract obstructions	261	1	—
Septal heart defects	2315	12	1.99 (1.13 to 3.53)
Atrioventricular defects	198	0	—
Cleft lip with or without cleft palate	705	4	1.61 (0.60 to 4.30)
Cleft palate alone	300	2	2.65 (0.66 to 10.68)
Gastrointestinal	1260	3	0.92 (0.29 to 2.84)
Genital†	1144	1	—
Omphalocele	62	0	—
Diaphragmatic hernia	2	0	—
Gastroschisis	83	0	—
Craniosynostosis	370	2	0.96 (0.13 to 6.83)

*Adjusted for age, calendar year, income, marriage status, tobacco smoking.
†Hypospadia and undetermined sex.

RESULTS

The final study population comprised 496 881 liveborn singletons. For these children, 1370 mothers had two or more redemptions for individual SSRIs in the exposure window. These pregnancies were regarded as exposed. In keeping with a previous study,[8] women taking an SSRI were more likely to be older, living alone, unmarried, and smokers (data not shown).

The combined prevalence of major malformations (odds ratio 1.21, 95% confidence interval 0.91 to 1.62) or non-cardiac malformations (1.12, 0.79 to 1.59) was not significantly higher among exposed children, but SSRI use was associated with an increased prevalence of septal heart defects (1.99, 1.13 to 3.53) (table 1).

No specific SSRI was significantly associated with major malformations overall or non-cardiac malformations (table 2). There was an increased prevalence of septal heart defects for children of women who used sertraline (3.25, 1.21 to 8.75) and citalopram (2.52, 1.04 to 6.10), but not fluoxetine (1.34, 0.33 to 5.41). Among the 299 exposed to paroxetine we found one septal heart malformation (crude odds ratio 0.76). Redemption of more than one type of SSRI in the exposure window was associated with heart malformations (3.42, 1.40 to 8.34), particularly septal heart defects (4.70, 1.74 to 12.7) (table 2).

In women with no recorded use of antidepressants, 1.2% redeemed a prescription for psychotropic medication, compared with 16% of women who had been prescribed an SSRI. The estimates remained virtually unchanged, however, when these women were included in the analyses—for example, SSRI use was still associated with septal heart defects (2.00, 1.41 to 2.85).

We found 84 women with two or more redemptions for tricyclic antidepressants and 91 for venlafaxine in the exposure window. The numbers were too small to allow for informative adjusted analyses—for instance, we found three major malformations among the children exposed to tricyclic antidepressants (crude odds ratio 1.14, 0.23 to 3.45) and one among those exposed to venlafaxine (0.35).

In subanalyses, we included women with one or more redemptions for antidepressants. We found that 3010 women redeemed one or more SSRI, 265 for tricyclic antidepressants, and 150 for venlafaxine. None of the antidepressants were associated with the combined prevalence of major malformations with the less strict exposure definition (see table A on bmj.com). Septal heart defects were associated with any SSRI use (1.83, 1.22 to 2.75), in particular citalopram (2.16, 1.12 to 4.17) and sertraline (2.01, 0.83 to 4.86), albeit the estimates of sertraline did not reach significance (see table B on bmj.com). In eight women prescribed fluvoxamine there were no reported malformations. Again, the numbers were too small to allow investigation of associations between tricyclic antidepressants or venlafaxine and specific malformations (table A on bmj.com).

Analyses excluding information on smoking had comparable results—for example, septal heart malformations were associated with sertraline (3.18, 1.18 to 8.56) and more than one SSRI (4.45, 1.65 to 12.0), but the confidence interval for citalopram included zero (2.36, 0.98 to 5.71).

Follow-up of the children for two years after birth with regards to congenital malformation resulted in similar results to the one year follow-up—for example, an odds ratio of 1.70 (1.13 to 2.55) for SSRI and septal heart malformations.

As expected, the absolute differences in prevalence of birth defects were limited. We found septal heart defects in 12 (0.9%) children of women with one or more redemption of SSRI, four (2.1%) children of women who redeemed more than one type of SSRI (2.1%), and 2315 (0.5%) children of unexposed women. The prevalence of septal heart defects among the children exposed to a specific SSRI was 0.6% for fluoxetine, 1.1% for citalopram, and 1.5% for sertraline (table 2). Thus, the prevalence of septal heart defects was 0.4 percentage points higher for children of women with one or more redemption of SSRI compared with children of unexposed women, corresponding to a number needed to treat to harm (NNH) of 246. The corresponding number for children of women who redeemed more than one type of SSRI was 62.

Table 2 | Odds ratios for malformations according to two or more prescriptions for individual selective serotonin reuptake inhibitors (SSRIs)*

Birth defects	No of unexposed infants (n=493 113)	Fluoxetine (n=348)		Citalopram (n=460)		Paroxetine (n=299)		Sertraline (n=259)		More than one type of SSRI (n=193)	
		No of infants	OR† (95% CI)	No of infants	OR† (95% CI)	No of infants	OR† (95% CI)	No of infants	OR† (95% CI)	No of infants	OR† (95% CI)
Minor malformations	7373	4	0.62 (0.20 to 1.93)	7	0.79 (0.33 to 1.91)	6	1.43 (0.64 to 3.22)	3	0.76 (0.24 to 2.37)	4	1.08 (0.34 to 3.38)
Major malformations	15 518	11	1.00 (0.53 to 1.88)	17	1.07 (0.63 to 1.83)	15	1.41 (0.79 to 2.51)	12	1.51 (0.84 to 2.69)	10	1.62 (0.83 to 3.16)
Cardiac malformations	3988	2	0.77 (0.19 to 3.11)	6	1.75 (0.78 to 3.93)	3	0.88 (0.22 to 3.55)	5	2.36 (0.97 to 5.72)	5	3.42 (1.40 to 8.34)
Septal heart defects	2315	2	1.34 (0.33 to 5.41)	5	2.52 (1.04 to 6.10)	1	0.76 (0.11 to 5.43	4	3.25 (1.21 to 8.75)	4	4.70 (1.74 to 12.7)
Non-cardiac malformations	11 530	9	1.08 (0.54 to 2.19)	11	0.83 (0.41 to 1.67)	12	1.59 (0.85 to 2.99)	7	1.18 (0.56 to 2.50)	5	0.95 (0.35 to 2.57)

*Four women used fluvoxamine only with no recorded malformations.
†Adjusted for age, calendar year, income, marriage status, tobacco smoking.

DISCUSSION

In this population based cohort study we found that septal heart defects were more prevalent in children of women who redeemed a prescription for a selective serotonin reuptake inhibitor (SSRI) in the first trimester of pregnancy. Sertraline and citalopram, but not paroxetine or fluoxetine, were associated with septal heart defects, though the largest association was found for redemption of more than one type of SSRI. The suggested associations, if causal, represent limited differences in prevalence. We found no associations between SSRIs and non-cardiac malformations.

Comparison with other studies

The four most commonly used SSRIs (fluoxetine, citalopram, sertraline, and paroxetine) were associated with septal heart defects. The various patterns in existing studies, however, are still confusing. A large US case-control study found that sertraline was associated with septal heart defects,[13] and the agreement with data from a different population with a different study design is reassuring for the validity of our results. A study from Finland found no overall association with major malformation (as in our study) but presented no data on septal heart defects.[6] One population based study reported an increased prevalence of heart defects after use of citalopram in the first trimester.[23] We found no associations between paroxetine and heart defects as shown in previous studies[9 12 14] but the previous finding was based on only one child with septal heart defect and we were unable to take dose into account.[12] As in most previous studies, none of our results for fluoxetine showed an odds ratio above two and none were significant.[13] One recent study, however, found that fluoxetine was associated with cardiovascular anomalies, with an adjusted odds ratio of 4.47 (1.31 to 15.27).[24] In that study over 30% of the women exposed to fluoxetine also used benzodiazepine,[24] and the combination of an SSRI and benzodiazepine has been associated with heart defects in a different study.[23] We excluded from our study women with redemptions of other psychotropic medications.

Use of more than one type of SSRI

We found the highest prevalence of septal heart defects among children of women who redeemed prescriptions for more than one type of SSRI in the exposure window. Redemptions for more than one SSRI might represent a change in type of SSRI or simultaneous use of different SSRIs. Both scenarios might result in more pronounced effects on the serotonin transporter, as change in type of SSRI might also result in a period of overlap. Our result could show an additive effect of the different types of SSRI, although confounding by the indication cannot be ruled out.

Clinical implications

Treatment of depression during pregnancy balances the risk of the medicine with that of the depression, and we investigated only a part of the information needed to make evidence based decisions. The reported odds ratios represent small absolute differences in prevalence, and even if SSRI use is causally related to septal heart defects, these heart defects might not necessarily require treatment and some might resolve spontaneously. Some children with septal heart defects, however, need to undergo an operation, but we were unable to estimate the proportion because, for example, the operation might be performed years after the end of our follow-up period.

Strengths and limitations of study

The information on drugs was recorded by skilled pharmacists when the prescriptions were redeemed. We used these redemptions as proxy measures for exposure, which eliminates recall bias and increases the precision of the information on type of antidepressant. Interview during pregnancy might result in confusion of related names, such as sertraline and Seroxat (paroxetine), and increased focus on one drug could result in bias. This precision is essential for the differentiation between specific types of SSRI and would have been difficult if we had relied on women's reports. Our results, however, depend on a correlation between redemptions of prescriptions and drug use. Non-compliance might be a problem for this type of exposure definition and could mask true associations if some of the "exposed" were in fact unexposed. We considered two or more redemptions as an indication of more certain exposure than one prescription only. The main analyses with this more strict exposure definition resulted in slightly stronger estimates with the same pattern related to septal heart defects, which is as expected if the drug had the side effects under study. Use of antidepressant drugs without prescription is unlikely and, if present, would result in underestimation of a true association.

Our choice of the exposure window allowed sufficient time for two or more redemptions and was identical to the exposure window in the study by Louik et al.[13] Additionally, our study was designed to investigate the potential association with various malformations with different windows of susceptibility, and as a result the exposure window was wider than needed for most malformations. With an exposure window wider than the susceptible period for conditions such as heart defect, the women defined as exposed might actually have been unexposed in the critical periods, which could result in an underestimation of true associations for various malformations. It does not explain the reported associations with septal heart defects.

The disentanglement of the effects of treatment from the effect of the disease is a profound problem in pharmacoepidemiological studies. We had no information on the severity of the depression, and potential confounding by indication is impossible to rule out in a non-randomised design. We were unable to carry out comparisons with children of untreated depressed women or of women with a prescription for an SSRI that was not redeemed. Variation in the disease severity, however, is unlikely to explain our observed

WHAT IS ALREADY KNOWN ON THIS TOPIC

Use of an SSRI during pregnancy is common and increasing

The teratogenic effects of specific SSRIs are unconfirmed

WHAT THIS STUDY ADDS

Sertraline and citalopram were associated with an increased prevalence of septal heart defects

Use of more than one type of SSRI during the first trimester was associated with a fourfold increase in prevalence of septal heart defects

differences between the specific types of SSRI as we believe that the disease characteristics of women who use different SSRIs are likely to be comparable in the study period. The warning on paroxetine from the US Food and Drug Administration was published after the exposure period of this study.[15] After this warning the pattern of SSRIs used during pregnancy is likely to have changed.

We adjusted for potential confounding factors, including maternal age and smoking, but all potential confounders were considered in crude categories. Residual confounding or unmeasured confounding might still be present, but the association between the confounder and heart malformation needs to be strong and specific for individual SSRIs to explain our findings; we don't know of any such factors.

We used nationwide registries with almost complete follow-up of liveborn infants. Induced or spontaneous abortions might have introduced selection bias if the drug reduces the survival of a fetus or if exposed women undergo more intensive screening. For instance, more intense surveillance among drug users could result in more prenatal diagnoses and subsequent induced abortions. This could obscure a true teratogenic effect in studies of liveborn children and bias our results towards no effect. Late abortion (after 12 weeks of pregnancy) because of septal heart defects, however, would not be granted in Denmark.

The information on malformations from the hospital registry is subject to some misclassification. The sensitivity of detection of malformation is expected to be higher for severe and visible malformations. If the misclassification was unrelated to exposure it would in most cases lead to bias towards no association. If children of women with depression or with a specific pharmacological treatment for a depression were likely to be examined more thoroughly than other children, however, we might have overestimated specific associations. The similar overall prevalence of malformations by the different exposures indicates no such detection problem.

We used data from a period with an almost fourfold increase in the proportion of pregnant women who were prescribed an SSRI. A parallel change in the detection of septal heart defects could lead to bias if calendar time was not considered—for example, an increased or improved use of ultrasonography before or after birth could lead to a false association between SSRIs and heart defects. The estimates changed only slightly, however, when we adjusted for calendar time in the multivariate analyses. Additionally, we found only a small increase in the prevalence of septal heart defects in the period that did not parallel the much larger increase in the use of SSRIs (see figure on bmj.com).

The study was designed to investigate the potential association between SSRIs and several malformations with no adjustment for multi-hypotheses testing, and the findings could potentially have occurred by chance. Our results, however, are in accordance with those of previous studies that used different methods in other populations. In this light we find that random error is unlikely to be the only explanation of the results.

Conclusion and policy implications

SSRIs, particularly citalopram or sertraline, were associated with an increased prevalence of congenital septal heart defects. The largest prevalence was found after redemptions of more than one type of SSRI in the exposure window, and simultaneous use of different SSRIs or change in type of SSRI during early pregnancy might be problematic. Our results suggest a class effect of the SSRI on heart defects, and the equivocal results from existing studies could represent differences in doses or study population. The associations, if causal, represent limited risks of an exposed child having congenital heart defects. Future studies need much larger sample sizes, preferably with sufficient power to further investigate potential associations with more severe malformations.

Contributors: LHP, TBH, MV, JO, and BHB were responsible for study concept and design, analysis and interpretation of data, drafting the manuscript and revising it for important intellectual content, and study supervision. LHP, JO, and BHB acquired the data. HP, TBH, and JO obtained funding. LHP and BHB analysed the data. LHP, JO, and BHB gave administrative, technical, or material support. LHP is guarantor.
Funding: This work was funded by a grant from the Lundbeck Foundation (grant No 95092485, sted 2214), an independent foundation supported by the pharmaceutical company Lundbeck, and has received support from the National Danish Research Foundation, the University of Aarhus, the Danish Society of Obstetrics and Gynaecology, the Ville Heise Foundation, and the Rosalie Petersen Foundation. Part of the work was done during LHP's employment at the Centre for Clinical Pharmacology, University Hospital of Aarhus, Aarhus, Denmark. JO has received grants from the Lundbeck Foundation.
Role of the sponsor: The Lundbeck Foundation had no role in the design and conduct of the study; the collection, analysis, interpretation of the data; or the preparation, review, or approval of the manuscript.
Competing interests: None declared.
Ethical approval: The study was conducted in accordance with the rules of the Danish Data Protection Board and with "Good Epidemiological Practice."[25] Patients' data were anonymised. Part of the study was done at University of California, Los Angeles, and the study has been subject to approval by the UCLA Institutional Review Board (IRB #G06-04-004-01).

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Accepted: 6 June 2009