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EXPOSURE TO SELECTIVE SEROTONINE REUPTAKE INHIBITORS AND THE RISK OF CONGENITAL MALFORMATIONS: A NATION-WIDE COHORT-STUDY

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ABSTRACT

Objectives

To analyse the relation between selective serotonine reuptake inhibitor (SSRI) use and major congenital malformations, with focus on malformations of the heart.

Design

Register based retrospective nation-wide cohort study, using the Danish Medical Birth Registry.

Setting

Denmark

Participants

Pregnant women in Denmark between 1997 and 2009 and their offspring.

Primary outcome measures

For each SSRI odds ratios for major congenital malformations were estimated using multivariable logistic regression models for women exposed to an SSRI during the first trimester and for women pausing exposure during pregnancy.

Results

We identified 848 786 pregnancies; 4183 were exposed to an SSRI throughout the first trimester, and 806 pregnancies paused exposure during pregnancy. Risks of congenital malformations of the heart were similar for pregnancies exposed to an SSRI throughout the first trimester; adjusted OR 2.01 (95% CI 1.60-2.53) and for pregnancies pausing SSRI treatment during pregnancy; adjusted OR 1.85 (95% CI 1.07-3.20). P-value for difference: 0.94. We found similar increased risks of

specific congenital malformations of the heart for the individual SSRIs. Furthermore, we found no association with dosage.

Conclusions

The apparent association between SSRI use and congenital malformations of the heart may be confounded by indications. The moderate absolute risk increase combined with uncertainty for causality still requires the risk versus benefit to be evaluated in each individual case.

ARTICLE SUMMARY

Article focus

- Relation between SSRIs and congenital malformations
- Focus on malformations of the heart
- Focus on women pausing treatment during pregnancy

Key messages

- Risks of congenital malformations of the heart are increased for infants whose mothers were exposed to an SSRI during the first trimester.
- Risks of congenital malformations of the heart are not different for pregnancies exposed during the first trimester as for pregnancies pausing treatment during pregnancy.
- The found risk increases are moderate in absolute terms.

Strengths and limitations of this study

- Observational study – no causal relations.
- Nation-wide study, including all live births in the study period.
- Register based study - no recall bias.

ARTICLE

Introduction

Depression is common during pregnancy and up to 15% of pregnant women suffer from depression or depressive symptoms.[1;2] The most used pharmacological treatment for pregnant women is selective serotonine reuptake inhibitors (SSRIs).[3-6] Treatment with SSRIs during pregnancy in Denmark has doubled over a short span of time with 1.4% of pregnancies treated in 2004 compared to 2.4% in 2007. This rapid increase has also been observed in other countries where the proportion of pregnant women treated with an SSRI is reported to be even higher than in Denmark.[4-8] Several studies have analysed the consequences of this treatment on pregnancy outcomes, and indicated an increased risk of congenital malformations[9;10], and more notably heart defects.[11-21] However, the data are conflicting and studies including up to a million pregnancies indicate little risk of congenital malformations.[11;13;16-18;22-32] None of these studies have successfully managed to differentiate between the consequences of the drugs themselves and the underlying disease. Given the uncertainty of safety and the common use, we performed a nationwide study of the relation between SSRI use and congenital malformations with focus on congenital heart defects, and comparison with paused use during pregnancy to account for special characteristics of women using antidepressants.

Materials and methods

Through the Danish Medical Birth Registry we identified all pregnancies in Denmark between 1997 and 2009. Their drug redemptions were identified using the Register of Medicinal Product Statistics. We calculated the associations between exposure to SSRIs and congenital malformations using multivariable logistic regression adjusted for maternal characteristics.

Study Population

At birth, all Danish citizens are given a unique permanent identification number [33], which enables personalized information to be linked across databases.. Using The Danish Medical Birth Registry we identified 854,008 births between 1997 and 2009. We excluded 5,222 records with missing data on date of birth and pregnancy length. The final cohort consisted of 848,786 pregnancies (99.4 % of all pregnancies). The Danish Medical Birth Registry includes data on all births in Denmark since 1973[34] and the following information is contained: unique identification numbers of mother and child as well recorded time of gestation, which is based on last menstrual period and ultrasound estimates. We obtained medical treatment from the Danish Register of Medicinal Product Statistics, which, since 1995, has recorded drugs dispensed from Danish pharmacies. Registration is close to perfect due to partial reimbursement by health-care authorities. [35] For this reason, direct importing by patients is nearly non-existent. The register contains type of drug (International Anatomical Therapeutic Coding (ATC)), date of redemption, quantity dispensed and strength.[36] Information on smoking was gathered from the Danish Medical Birth Registry. Individual information on household income and highest attained level of education was gathered from Statistics Denmark.[37]

Outcome Measures

Congenital malformations were identified through the Danish National Hospital Register.[38] We identified children with congenital malformation within one year of birth and the corresponding grouping according to the European Surveillance of Congenital Anomalies (EUROCAT) classification system guide 1.3.[39]

Identification of Exposure

Exposure to the following SSRIs (ATC codes) was identified in the present study: fluoxetine (N06AB03), citalopram (N06AB04), paroxetine (N06AB05), sertraline (N06AB06), and escitalopram (N06AB10). Other SSRIs were not included because of low incidence of use (n<50).

SSRI prescriptions redeemed during the study period were identified through the Register of Medicinal Product Statistics. Using the date of prescription, strength and number of tablets prescribed we performed an estimation of exposure periods and dosages of the individual SSRIs. We calculated dosage as the average of up to seven prescriptions based on the standard dose of the individual antidepressant. Calculation of drug exposure periods using this method has been described previously.[40]

We identified all pregnancies exposed to an SSRI during the first trimester with a continuous exposure before pregnancy by defining it as exposure between at least one month before conception and day 84 of pregnancy (last day of the first trimester). Women changing exposure to another SSRI during the first trimester were not included in the study (n=646). In order to address a possible confounding by indication we compared our cohort exposed during the first trimester with a control cohort comprised of women pausing exposure during pregnancy. We defined women with paused exposure as exposure to an SSRI three to twelve months before conception and one to twelve months after giving birth, but with no exposure to an SSRI between three months before conception to one month after giving birth. In addition, they had to be exposed to the same individual SSRI before and after pregnancy.

We divided the study population into pregnancies exposed to high or low SSRI dose based on the daily dose values of the individual SSRIs during pregnancy. Doses over the following

cut-off values were considered as high doses; 20 mg for citalopram, 10 mg for escitalopram, 20 mg for fluoxetine, 10 mg for paroxetine and 50 mg for sertraline.

Statistical Analysis

Baseline characteristics were compared with chi-square tests for chategorical variables. Risks of malformations were examined with linear logistic regression models. In multiavariable analyses we included the mother's age divided into 5 categories: <20, 20-25, 25-30, 30-35, >35 years (0% missing values). Annual gross household income was divided into quartiles (<1% missing values). The highest obtained level of education attained was divided into three groups: low, medium and high, resulting in 4.3% missing values. The number of prior births (parity), including stillbirths, was divided into four classes: 1, 2, 3 and >3 births (<1% missing values). Year of conception was divided into 5 categories (1995-97, 1998-2000, 2001-03, 2004-06, and 2007-09). Smoking was divided into five categories according to the number of daily cigarette: 0, 1-10, 11-20, >20 and unknown (<1% missing values). Body mass index (BMI) was divided into 5 group (<21, 21-25, 26-30, >30). Information on BMI was only available from January 1st 2004, and includes 7% missing values in the period 2004-2009. (Table 1) Records with missing values in the above mentioned categories were not included in the multivariable analyses.

Ethics

The present study has been approved by The Danish Data Protection Agency (No. 2008-41-2517). Retrospective register studies do not require ethical permission in Denmark. Our findings are reported according to strengthening the reporting of observational studies in epidemiology (STROBE).[41]

Results

We identified 4183 pregnancies exposed to an SSRI throughout the first trimester, 806 pregnancies with paused exposure, and 843 797 pregnancies not exposed to an SSRI. 83% of pregnancies exposed to an SSRI throughout the first trimester went on to redeem a prescription of an SSRI during the third trimester. Table 1 shows the basic characteristics for women exposed and to an SSRI, and for unexposed women. Table 2 presents the association between exposure to SSRIs and major congenital malformation with more than 10 cases, and specific septal congenital defects of the heart. For information on risks associated with the remaining congenital malformations please refer to supplement A.

Table 1. Maternal characteristics of women exposed to an SSRI and unexposed

	Exposed to SSRIs			Unexposed	
Characteristic	First trimester N=4 183	Paused during pregnancy N=806		N=843 797	
	N (%)	N (%)	p-value[a]	N (%)	p-value[a]
Education			<0.01		<0.001
short	1731 (41.38)	372 (46.15)		280447 (33.24)	
medium	1119 (26.75)	225 (27.92)		254194 (30.13)	
long	1262 (30.17)	193 (23.95)		272380 (32.28)	
Missing values	71 (1.7)	16 (1.99)		36776 (4.36)	
Annual household income			0.12		<0.001
less than $ 58 335	1320 (31.56)	264 (32.75)		210290 (24.92)	
$ 58 335 - $ 93 656	1101 (26.32)	222 (27.54)		212110 (25.14)	
$ 93 656 - $ 119 082	906 (21.66)	185 (22.95)		211436 (25.06)	
$ 119 082 or greater	856 (20.46)	135 (16.75)		207247 (24.56)	
Missing values	0 (-)	0 (-)		2714 (0.32)	
Age (years)			<0.001		<0.001
<20	70 (1.67)	20 (2.48)		23324 (2.76)	
21-25	555 (13.27)	122 (15.14)		129059 (15.3)	
26-30	1364 (32.61)	269 (33.37)		318664 (37.77)	
31-35	1423 (34.02)	295 (36.6)		268959 (31.87)	
>35	771 (18.43)	100 (12.41)		102791 (12.18)	

Missing values	0 (-)	0 (-)		0 (-)	
Parity			<0.001		<0.001
1	1983 (47.41)	282 (34.99)		368168 (43.63)	
2	1320 (31.56)	310 (38.46)		308992 (36.62)	
>2	833 (19.91)	208 (25.81)		162030 (19.2)	
Missing values	47 (1.12)	6 (0.74)		4607 (0.55)	
Daily cigarettes			0.53		<0.001
0	2810 (67.18)	532 (66)		660888 (78.32)	
1-10	1049 (25.08)	211 (26.18)		128269 (15.2)	
11-20	66 (1.58)	11 (1.36)		5294 (0.63)	
>20	138 (3.3)	34 (4.22)		20967 (2.48)	
No information	118 (2.82)	18 (2.23)		27580 (3.27)	
Missing values	2 (0.05)	0 (-)		799 (0.09)	
Pre-pregnancy BMI[b]			0.89		<0.001
<21	391 (12.23)	66 (12.6)		53500 (13.95)	
21-25	1393 (43.59)	233 (44.47)		186428 (48.62)	
26-30	705 (22.06)	117 (22.33)		74673 (19.48)	
>30	493 (15.43)	74 (14.12)		41652 (10.86)	
Missing values	214 (6.7)	35 (6.68)		27161 (7.08)	

Data indicate number of pregnancies (N) and percentage (%). [a]Chi square tests were used to assess the overall p value for the group comparison with pregnancies exposed to an SSRI during the first trimester. [b]BMI=body mass index. Information on pre-pregnancy BMI was only available for women giving birth after 1. January 2004. Thus this cohort comprises 387 142 pregnancies

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Table 2. Risk of congenital malformations among women exposed to an SSRI vs. women with no exposure

	Exposed to any SSRI					No exposure
	First trimester N=4183		Paused during pregnancy N=806			N=843 797
Outcome	**N (%)**	**OR (96% CI)**	**N (%)**	**OR (96% CI)**	**p-value[a]**	**N (%)**
Major malformations	208 (4.97)	1.33 (1.16-1.53)	36 (4.47)	1.27 (0.91-1.78)	0.90	29703 (3.52)
Congenital malformations of the heart	77 (1.84)	2.01 (1.60-2.53)	13 (1.61)	1.85 (1.07-3.20)	0.94	7755 (0.92)
Septal defects	49 (1.17)	2.04 (1.53-2.72)	11 (1.36)	2.56 (1.41-4.64)	0.35	4826 (0.57)
Ventricular septal defects	21 (0.50)	1.62 (1.05-2.50)	9 (1.12)	3.74 (1.93-7.23)	0.97	2803 (0.33)
Atrial septal defects	34 (0.81)	2.60 (1.84-3.68)	6 (0.74)	2.61 (1.17-5.84)	0.74	2490 (0.30)
Congenital malformations of the digestive system	13 (0.31)	1.80 (1.04-3.12)	1 (0.12)	0.75 (0.11-5.35)	0.59	1545 (0.18)
Congenital malformations of the internal urinary system	11 (0.26)	0.84 (0.45-1.57)	-	-	-	2333 (0.28)
Congenital malformations of the external genital organs	19 (0.45)	1.55 (0.99-2.44)	2 (0.25)	0.89 (0.22-3.59)	0.46	2504 (0.30)
Congenital malformations of the limbs	53 (1.27)	0.93 (0.71-1.23)	14 (1.74)	1.37 (0.80-2.32)	0.18	11785 (1.40)

Estimates are presented as Odds Ratios (OR) with 95% confidence intervals (95% CI) [a]P-value for comparison of odds ratios between pregnancies exposed throughout the first trimester and pregnancies with paused exposure during pregnancy. [b]Multivariable logistic regressions are adjusted for mother's age, parity, income, education, smoking and year of conception.

First trimester exposure to any SSRI vs. no exposure

The rate of major congenital malformations among pregnancies exposed to any SSRI throughout the first trimester was 50 per 1000 pregnancies, compared to 35 pr 1000 unexposed pregnancies (Figure 1). We found an association between SSRI exposure and major congenital malformations; adjusted OR=1.33 (95% CI, 1.16-1.53) (table 2).

When analysing the association between exposure to any SSRI and the different major malformations according to the EUROCAT classification we found a statistically significant association between exposure to an SSRI and congenital malformations of the heart; adjusted OR=2.01 (95% CI, 1.60-2.53), and congenital malformations of the digestive system; adjusted OR=1.80 (95% CI, 1.04-3.12), but not the remaining major congenital malformations (table 2).

Paused exposure vs. unexposed

The rate of major congenital malformations among pregnancies pausing exposure during pregnancy was 45 per 1000 pregnancies (Figure 1). The risk of any major malformation when pausing exposure to an SSRI during pregnancy was; adjusted OR=1.27 (95% CI, 0.91-1.78) compared to unexposed pregnancies. When estimating the risk of specific major congenital malformations we found that paused exposure was associated with congenital malformations of the heart; adjusted OR 1.85 (95% CI, 1.07-3.20) (table 2).

Figure 1.Rates per 1000 pregnancies of major congenital malformations for infants exposed to selective serotonine reuptake inhibitors in utero

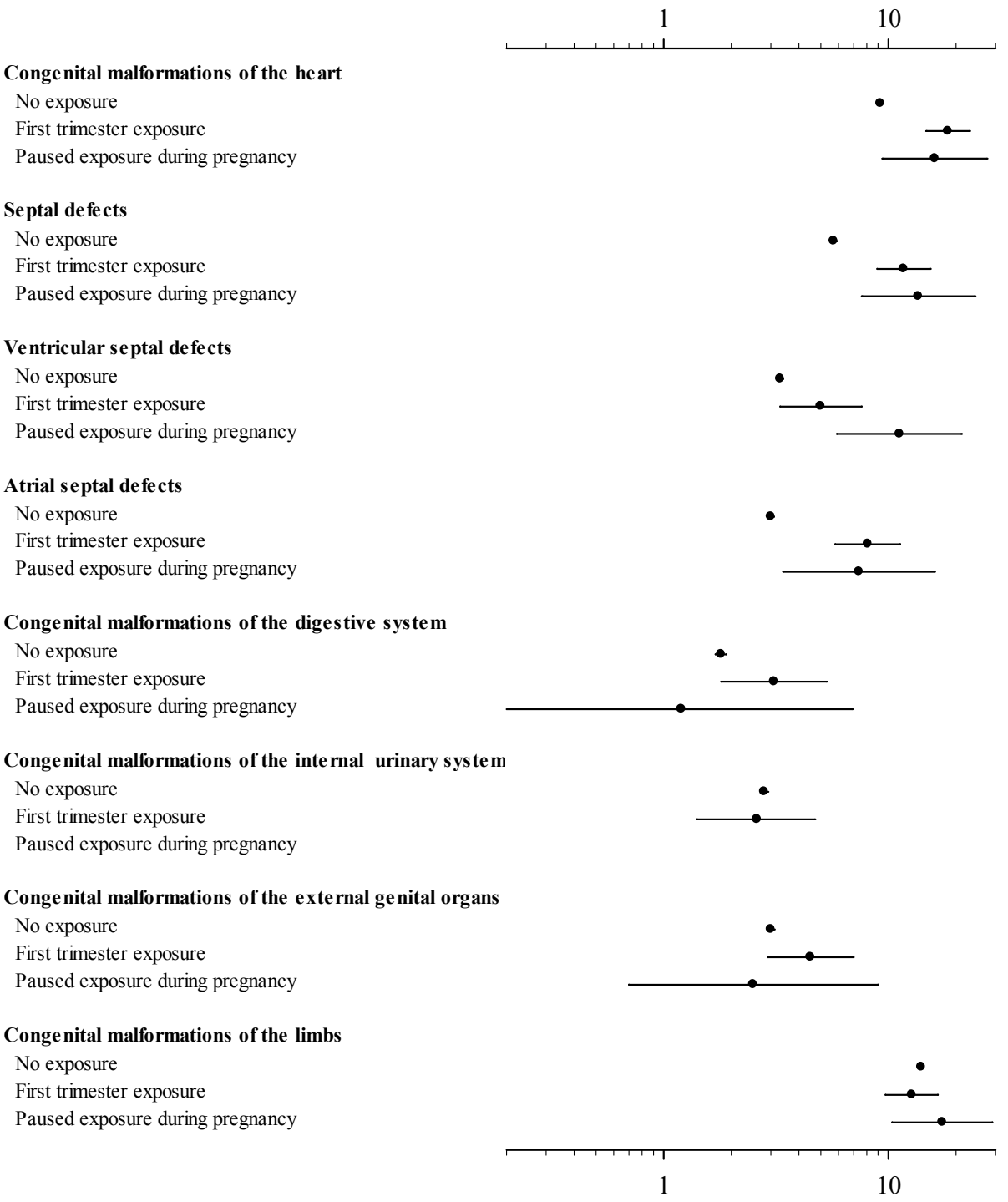

Figure shows number of infants diagnosed with a major malformation per 1000 births. Rates are shown with 95 % confidence intervals.

Other Analyses

Exposure to individual SSRIs

We found a significant association between major congenital malformations and exposure to citalopram; adjusted OR=1.51 (95% CI, 1.21-1.87), and sertraline; adjusted OR=1.41 (95% CI, 1.03-1.92). Furthermore, we found an association between congenital malformations of the heart and exposure to citalopram; adjusted OR=1.91 (95% CI, 1.31-2.77), fluoxetine; adjusted OR=2.05 (95% CI, 1.27-3.31), and sertraline; adjusted OR=2.73 (95% CI, 1.75-4.26). Associations for the remaining major congenital malformations are presented in supplement A.

Specific heart defects

We performed a sub analysis of the specific congenital septal defects of the heart and their association with exposure to SSRIs and found an association between exposure to any SSRI and septal heart defects; adjusted OR=2.04 (95% CI, 1.53-2.72) (table 2).Specifically, ventricular septal defects and atrial septal defects were associated with an increased risk. Increased risk of congenital septal defects was also found for pregnancies with paused exposure; adjusted OR=2.56 (95% CI, 1.41-4.64) (table 2).

For the individual SSRIs we found an association between exposure to all SSRIs, except for escitalopram, and atrial septal defects. Ventricular septal defects was only associated with exposure to sertraline; adjusted OR=3.60 (95% CI, 1.86-6.96), and not the remaining individual SSRIs (supplement A).

Other congenital defects

Studies have reported a possible association between exposure to an SSRI during pregnancy and omphalocele, anencephaly and craniosynostosis.[9;10] We found an association for exposure to an SSRI in the first trimester and craniosynostosis (n=9); adjusted OR=1.94 (95% CI, 1.00-3.76), but not for omphalocele or anencephaly. For pregnancies with paused exposure, the association with craniosynostosis (n=3) was; adjusted OR=3.64 (95% CI, 1.17-11.34).

Dosage

We found an adjusted odds ratio for major malformations: OR 1.39 (95% CI, 1.14-1.68) for low dose exposure and 1.27 (95% CI, 1.03-1.56) for high dose exposure (p for difference=0.29).

For the individual major malformations we found similar associations for pregnancies exposed to low dose and pregnancies exposed to high dose, as for the whole cohort (Table 3). Analysing the effect of dose as a continuous variable yielded no dose-response association.

Table 3. Odds Ratios (OR) and 95% confidence intervals (95% CI) for association between congenital malformations among women exposed to low and high doses SSRI during pregnancy.

Outcome	Low dose SSRI (n=2588)		High dose SSRI (n=1603)		
	N (%)	OR (95% CI)[a]	N (%)	OR (95% CI)[a]	p-value[b]
Major malformations	121 (4.68)	1.26 (1.05-1.51)	87 (5.43)	1.44 (1.15-1.79)	0.29
Congenital malformations of the heart	44 (1.7)	1.83 (1.35-2.48)	33 (2.06)	2.26 (1.60-3.19)	0.41
Congenital malformations of the digestive system	8 (0.31)	1.78 (0.89-3.58)	5 (0.31)	1.80 (0.75-4.35)	0.99
Congenital malformations of the internal urinary system	6 (0.23)	0.82 (0.37-1.83)	5 (0.31)	0.88 (0.33-2.34)	0.63
Congenital malformations of the external genital organs	10 (0.39)	1.32 (0.71-2.46)	9 (0.56)	1.91 (0.99-3.68)	0.42

Congenital malformations of the limbs	33 (1.28)	0.94 (0.67-1.33)	20 (1.25)	0.91 (0.59-1.42)	0.93

[a]Multivariable logistic regressions are adjusted for mother's age, parity, income, education, smoking and year of conception. [b]P-value for comparison of odds ratios between pregnancies exposed to low dose SSRI and high dose SSRI.

Additional adjustments

In order to identify possible unaccounted confounders we performed additional multivariable analyses including co-medication (psycholeptics, benzodiazepins and antidiebetics) as independent variables in our model. The results showed no considerable change in the estimates or their level of significance compared to our primary analysis.

When including body mass index (BMI) as an independent variable in our multivariable model we found the same statistically significant associations for exposure to any SSRI or individual SSRIs, and the specific congenital malformations as our multivariable model not adjusted for BMI. Information on BMI was only available for pregnancies after January 1st 2004, which reduced our cohort to 3196 pregnancies exposed to an SSRI and 383 946 with no exposure.

Non-SSRI antidepressants

The association between congenital malformations and exposure to non-SSRI antidepressants: tricyclic antidepressants (ATC N06AA, n=223) and other antidepressants (ATC N06AX, n=831) was; adjusted OR=1.04 (95% CI, 0.53-2.03) and; adjusted OR=0.70 (95% CI, 0.47-1.05), respectively. The associations with congenital malformations of the heart were; adjusted OR=1.33 (95% CI, 0.42-4.15) for tricyclic antidepressants and adjusted OR=0.99 (95% CI 0.51-1.91) for other antidepressants.

Discussion

We performed a retrospective nation-wide cohort study analysing the association between redemption of an SSRI during pregnancy and major congenital malformations. We found an association between exposure to an SSRI during the first trimester and major congenital malformations. More specifically; congenital malformations of the heart (ventricular septal defects and atrial septal defects) and congenital malformations of the digestive system. Furthermore, we found an association between women pausing SSRI exposure during pregnancy and congenital malformations of the heart. Based on findings described in the published literature we will centre the following discussion on major congenital malformations and congenital malformations of the heart for pregnancies exposed to SSRIs.

Our study's results are in accordance with two earlier Danish studies[20;42] based on cohorts comprising only part of the entire nation. A third Danish nation-wide study by Pedersen et al found an increased estimate for major congenital malformations and congenital malformations of the heart, though not statistically significant, in the studied period 1996-2004.[17] The number of exposed women in their study was 1370, compared to ours 4183, which could explain why our estimates reached statistical significance. The study concludes that there is a class effect of SSRIs on heart defects.

Several studies have not found an association between exposure to any SSRI and major malformations.[11;13;16;18;22-32] We find that some of these study are not comparable to ours because most of them are case-control studies, and with cohorts much smaller than ours.[13;22-29;31] Five of the studies are though similar to ours; based on nation-wide cohorts and

national registers, and cohort-sizes comparable to ours. Four are based on Swedish data and are successive updates [16;18;30;31], and one on Finnish data.[11]

The latest update of Swedish data found an increased risk of cardiovascular congenital malformations for pregnancies exposed to paroxetine, but not for the remaining individual SSRIs, or SSRI as a group.[18] Information on SSRI exposure was partly based on antenatal interviews which could give rise to recall bias. Furthermore, their analyses were adjusted for BMI. Adjusting our multivariable analysis for BMI had little effect the estimates.

The Finnish study found an increased risk of ventricular septal defects for pregnancies exposed to fluoxetine, but not for the remaining individual SSRIs, or SSRI as a group.[11] The study is completely based on national registers, like our study. Exposure was though defined as redemption of at least one prescription between one month before pregnancy and birth. This could overestimate the number of exposed women and push estimates towards unity, and explain the lack of association with major congenital malformations, and specifically atrial septal defects.

None of the above mentioned studies assessed the risk of congenital malformations for women pausing exposure during pregnancy and thereby addressing the possibility of confounding by indication. Furthermore, neither the Swedish nor the Finnish studies adjusted their analyses for socioeconomic factors which in our study are unevenly distributed between our exposed and unexposed population. Importantly, we believe there are sociodemographic differences between the populations included in these Scandinavian studies compared to ours. Although Denmark resembles both Sweden and Finland, differences in culture and health care policies could account for the discrepancies in our

results. Discrepancies between published studies could also be due to the low number of cases, where each case can have a significant effect on the estimate.

Congenital malformations of the heart have been associated with exposure to SSRIs in some studies [10-12;15-18;27;31;42], in contrast to studies not identifying this association.[9;13;19;26] Our analyses showed an increased risk of congenital heart defects for the individual SSRIs. Risks of atrial septal defects were furthermore associated with exposure to all individual SSRIs, except for escitalopram. The lack of statistical significance with escitalopram exposure could be due to low statistical power. We found the same increased risks for heart defects for those with paused exposure during pregnancy, which strengthens the assumption of confounding by indication.

Although statistically significant, the increased risks associated with SSRI exposure are small in absolute terms. For example, the populations' background risk of atrial septal defects is 0.26 %, and even if we estimate a two-fold risk increase associated with exposure to any SSRI the risk of giving birth to a child with this congenital malformation would be approximately 5 cases for every 1000 births (Figure 1).

Strengths and limitations

The main weakness is the observational design. We had access to important covariates but it cannot be excluded that unaccounted confounder explain the results. Our study could furthermore be affected by a possible detection bias. Pregnant women exposed to SSRIs are reported to have increased rates of observed malformations, due to increased rates of ultrasound examinations compared to women not treated with SSRIs.[43] In contrast, detection of a malformation during an ultrasound examination could lead to pregnancy termination, and thereby decreased rates of malformations among the SSRI exposed. On the

other hand, infants of women redeeming prescriptions for SSRIs undergo, in the first year of life, approximately twice as many echocardiograms compared with infants of unexposed women.[43] More frequent echocardiograms could increase the risk of heart defect detection, it could also however indicate symptoms of the infant.

There is a possibility that we have overestimated SSRI treatment periods, since we cannot adjust for lack of compliance, or the patients' intention of commencing a treatment shortly after drug redemption. However, it has been estimated that the majority of redeemed prescriptions by pregnant women are taken[44], and compliance in Denmark has been estimated to be 80% for antidepressant treatment during pregnancy.[45] Furthermore, an overestimation of treatment periods would bias our estimates towards unity. We performed additional analyses defining exposure as redemption of 2 SSRI prescriptions during pregnancy. The results of these analyses, which are not presented, yielded the same statistically significant association as our primary analyses.

A main strength is the complete national design including nearly all births in Denmark and the mothers' drug redemptions in the study period. The Register of Medicinal Product Statistics includes approximately 97.5% of all redeemed prescriptions.[35] Danish pharmacies are, by law, required to register all redeemed prescriptions as part of the national health care reimbursement scheme. All prescriptions have been redeemed and paid for, which increases the probability of exposure. Recall bias is eliminated since information was recorded prospectively and not based on questionnaires or interviews. Furthermore, to our knowledge, this is the first study to address a possible confounding by indication by assessing risks associated with paused exposure to SSRIs during pregnancy.

Conclusion

Our study shows with high confidence a relation between exposure to an SSRI during the first trimester and risk of congenital malformations of the heart. In addition, we found a nearly identical risk for women who used an SSRI before and after pregnancy but discontinued use during pregnancy. We find both associations strong enough to conclude that risks related to SSRI use during the first trimester are a result of an unaccounted confounder associated to the redemption of an SSRI prescription. This was sustained by the lack of relation between dose and risk. However, based on our study's design we cannot rule out an actual causal relation between redemption of an SSRI and congenital malformations. We found no relation with non-SSRI antidepressants, which may indicate a particular risk with SSRIs, but which may also be explained by lack of power.

We therefore conclude that the apparent association between SSRI use and congenital malformations of the heart may be confounded by indications. The moderate absolute risk increase combined with uncertainty for causality still requires the risk versus benefit to be evaluated in each individual case.

Acknowledgments

None to declare.

Competing interests

All authors declare no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Reference List

(1) Bennett HA, Einarson A, Taddio A, et al. Prevalence of depression during pregnancy: systematic review. *Obstet Gynecol* 2004;**103**(4):698-709.

(2) Chatillon O, Even C. [Antepartum depression: Prevalence, diagnosis and treatment.]. *Encephale* 2010;**36**(6):443-451.

(3) Ververs T, Kaasenbrood H, Visser G, et al. Prevalence and patterns of antidepressant drug use during pregnancy. *Eur J Clin Pharmacol* 2006;**62**(10):863-870.

(4) Cooper WO, Willy ME, Pont SJ, et al. Increasing use of antidepressants in pregnancy. *Am J Obstet Gynecol* 2007;**196**(6):544-545.

(5) Andrade SE, Raebel MA, Brown J, et al. Use of antidepressant medications during pregnancy: a multisite study. *Am J Obstet Gynecol* 2008;**198**(2):194-195.

(6) Alwan S, Reefhuis J, Rasmussen SA, et al. Prevention Study TNBD. Patterns of Antidepressant Medication Use Among Pregnant Women in a United States Population. *J Clin Pharmacol* 2011;**51**(2):264-70.

(7) Bakker MK, Kolling P, van den Berg PB, et al. Increase in use of selective serotonin reuptake inhibitors in pregnancy during the last decade, a population-based cohort study from the Netherlands. *Br J Clin Pharmacol* 2008;**65**(4):600-606.

(8) Wichman CL, Fothergill A, Moore KM, et al. Recent trends in selective serotonin reuptake inhibitor use in pregnancy. *J Clin Psychopharmacol* 2008;**28**(6):714-716.

(9) Alwan S, Reefhuis J, Rasmussen SA, et al. Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. *N Engl J Med* 2007;**356**(26):2684-2692.

(10) Louik C, Lin AE, Werler MM, et al. First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. *N Engl J Med* 2007;**356**(26):2675-2683.

(11) Malm H, Artama M, Gissler M, et al. Selective serotonin reuptake inhibitors and risk for major congenital anomalies. *Obstet Gynecol* 2011;**118**(1):111-120.

(12) Bakker MK, Kerstjens-Frederikse WS, Buys CH, et al. First-trimester use of paroxetine and congenital heart defects: a population-based case-control study. *Birth Defects Res A Clin Mol Teratol* 2010;**88**(2):94-100.

(13) Berard A, Ramos E, Rey E, et al. First trimester exposure to paroxetine and risk of cardiac malformations in infants: the importance of dosage. *Birth Defects Res B Dev Reprod Toxicol* 2007;**80**(1):18-27.

(14) Cole JA, Ephross SA, Cosmatos IS, et al. Paroxetine in the first trimester and the prevalence of congenital malformations. *Pharmacoepidemiol Drug Saf* 2007;**16**(10):1075-1085.

(15) Diav-Citrin O, Shechtman S, Weinbaum D, et al. Paroxetine and fluoxetine in pregnancy: a prospective, multicentre, controlled, observational study. *Br J Clin Pharmacol* 2008;**66**(5):695-705.

(16) Kallen BA, Otterblad OP. Maternal use of selective serotonin re-uptake inhibitors in early pregnancy and infant congenital malformations. *Birth Defects Res A Clin Mol Teratol* 2007;**79**(4):301-308.

(17) Pedersen LH, Henriksen TB, Vestergaard M, et al. Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study. *BMJ* 2009;**339**:b3569.

(18) Reis M, Kallen B. Delivery outcome after maternal use of antidepressant drugs in pregnancy: an update using Swedish data. *Psychol Med* 2010 Oct;**40**(10):1723-33

(19) Wichman CL, Moore KM, Lang TR, et al. Congenital Heart Disease Associated With Selective Serotonin Reuptake Inhibitor Use During Pregnancy. *Mayo Clinic Proceedings* 2009;**84**(1):23-27.

(20) Wogelius P, Norgaard M, Gislum M, et al. Maternal use of selective serotonin reuptake inhibitors and risk of congenital malformations. *Epidemiology* 2006;**17**(6):701-704.

(21) Wurst KE, Poole C, Ephross SA, et al. First trimester paroxetine use and the prevalence of congenital, specifically cardiac, defects: a meta-analysis of epidemiological studies. *Birth Defects Res A Clin Mol Teratol* 2010;**88**(3):159-170.

(22) Malm H, Klaukka T, Neuvonen PJ. Risks associated with selective serotonin reuptake inhibitors in pregnancy. *Obstet Gynecol* 2005;**106**(6):1289-1296.

(23) Kulin NA, Pastuszak A, Sage SR, et al. Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors: a prospective controlled multicenter study. *JAMA* 1998;**279**(8):609-610.

(24) Ramos E, St-Andre M, Rey E, et al. Duration of antidepressant use during pregnancy and risk of major congenital malformations. *The British Journal of Psychiatry* 2008;**192**(5):344-350.

(25) Einarson A, Choi J, Einarson TR, et al. Incidence of major malformations in infants following antidepressant exposure in pregnancy: results of a large prospective cohort study. *Can J Psychiatry* 2009;**54**(4):242-246.

(26) Davis RL, Rubanowice D, McPhillips H, et al. Risks of congenital malformations and perinatal events among infants exposed to antidepressant medications during pregnancy. *Pharmacoepidemiol Drug Saf* 2007;**16**(10):1086-1094.

(27) Oberlander TF, Warburton W, Misri S, et al. Major congenital malformations following prenatal exposure to serotonin reuptake inhibitors and benzodiazepines using population-based health data. *Birth Defects Res B Dev Reprod Toxicol* 2008;**83**(1):68-76.

(28) Simon GE, Cunningham ML, Davis RL. Outcomes of Prenatal Antidepressant Exposure. *Am J Psychiatry* 2002;**159**(12):2055-2061.

(29) Wen SW, Yang Q, Garner P, et al. Selective serotonin reuptake inhibitors and adverse pregnancy outcomes. *Am J Obstet Gynecol* 2006;**194**(4):961-966.

(30) Ericson A, Kallen B, Wiholm B. Delivery outcome after the use of antidepressants in early pregnancy. *Eur J Clin Pharmacol* 1999;**55**(7):503-508.

(31) Kallen B, Otterblad Olausson P. Antidepressant drugs during pregnancy and infant congenital heart defect. *Reproductive Toxicology* 2006;**21**(3):221-222.

(32) Lennestal RM, Kallen BM. Delivery Outcome in Relation to Maternal Use of Some Recently Introduced Antidepressants. [Article]. *Journal of Clinical Psychopharmacology* 2007;**27**(6):607-613.

(33) Pedersen CB, Gotzsche H, Moller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull* 2006;**53**(4):441-449.

(34) Knudsen LB, Olsen J. The Danish Medical Birth Registry. *Dan Med Bull* 1998;**45**(3):320-323.

(35) Sorensen HT, Hansen I, Ejlersen E, et al. Identification of patients treated with strong analgesics: an assessment of two Danish information systems with respect to epidemiological research. *J Med Syst* 1996;**20**(1):57-65.

(36) Gaist D, Sorensen HT, Hallas J. The Danish prescription registries. *Dan Med Bull* 1997;**44**(4):445-448.

(37) Statistics Denmark. Containing detailed statistical information on the Danish Society. Available at: http://www.dst.dk/en. Accessed March, 2012.

(38) Andersen TF, Madsen M, Jorgensen J, et al. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999;**46**(3):263-268.

(39) European Surveillance of Congenital Anomalies. EUROCAT Guide 1.3 and reference documents. Newtownabbey Co Antrim: University of Ulster; 2005.Available at: http://www.eurocat-network.eu/content/EUROCAT-Guide-1.3.pdf. Accessed March 2012.

(40) Fosbol EL, Gislason GH, Jacobsen S, et al. The pattern of use of non-steroidal anti-inflammatory drugs (NSAIDs) from 1997 to 2005: a nationwide study on 4.6 million people. *Pharmacoepidemiol Drug Saf* 2008;**17**(8):822-833.

(41) von Elm E, Altman DG, Egger M, et al.The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007;**370**(9596):1453-1457.

(42) Kornum JB, Nielsen RB, Pedersen L, et al. Use of selective serotonin-reuptake inhibitors during early pregnancy and risk of congenital malformations: updated analysis. *Clin Epidemiol* 2010;**2**:29-36.

(43) Bar-Oz B, Einarson T, Einarson A, et al. Paroxetine and congenital malformations: meta-Analysis and consideration of potential confounding factors. *Clin Ther* 2007;**29**(5):918-926.

(44) de Jong van den Berg LT, Feenstra N, Sorensen HT, et al.. Improvement of drug exposure data in a registration of congenital anomalies. Pilot-study: pharmacist and mother as sources for drug exposure data during pregnancy. EuroMAP Group. Europen Medicine and Pregnancy Group. *Teratology* 1999;**60**(1):33-36.

(45) Olesen C, Sondergaard C, Thrane N, et al. Do pregnant women report use of dispensed medications? *Epidemiology* 2001;**12**(5):497-501.

Supplement A. Odds Ratios (OR) and 95% confidence intervals (95% CI) for the incidence and risk of congenital malformations among women exposed to individual SSRIs vs. women with no exposure

	SSRI (n=4183)		Citalopram (n=1606)		Escitalopram (n=293)		Fluoxetine (n=928)		Paroxetine (n=568)		Sertraline (n=817)	
Congenital malformations	**N (%)**	**OR (95% CI)[a]**	**N (%)**	**OR (95% CI)[a]**	**N (%)**	**OR (95% CI)[a]**	**N (%)**	**OR (95% CI)[a]**	**N (%)**	**OR (95% CI)[a]**	**N (%)**	**OR (95% CI)[a]**
Major	208 (4.97)	1.33 (1.16-1.53)	89 (5.54)	89 (5.54-1.51)	8 (2.73)	0.69 (0.34-1.4)	41 (4.42)	1.18 (0.86-1.61)	26 (4.58)	1.25 (0.84-1.85)	44 (5.39)	1.41 (1.03-1.92)
Of the nervous system	7 (0.17)	1.13 (0.54-2.39)	2 (0.12)	2 (0.12-0.84)	1 (0.34)	2.25 (0.32-16.05)	2 (0.22)	1.44 (0.36-5.79)	1 (0.18)	1.19 (0.17-8.45)	1 (0.12)	0.85 (0.12-6.07)
Neural Tube Defects	1 (0.02)	0.73 (0.1-5.21)	-	-	0 (0)	-	1 (0.11)	3.22 (0.45-23.03)	0 (0)	-	0 (0)	-
Of the eye	7 (0.17)	1.43 (0.68-3.01)	5 (0.31)	5 (0.31-2.62)	0 (0)	-	1 (0.11)	0.93 (0.13-6.63)	0 (0)	-	1 (0.12)	1.05 (0.15-7.45)
Of the ear, face and neck	2 (0.05)	2.36 (0.58-9.61)	0 (0)	-	0 (0)	-	0 (0)	-	1 (0.18)	8.32 (1.16-59.81)	1 (0.12)	6.13 (0.85-44.05)
Of the heart	77 (1.84)	2.01 (1.6-2.53)	28 (1.74)	28 (1.74-1.91)	3 (1.02)	1.06 (0.34-3.3)	17 (1.83)	2.05 (1.27-3.31)	8 (1.41)	1.54 (0.77-3.1)	21 (2.57)	2.73 (1.75-4.26)
Septal defects	49 (1.17)	2.04 (1.53-2.72)	17 (1.06)	17 (1.06-1.86)	2 (0.68)	1.12 (0.28-4.51)	9 (0.97)	1.73 (0.89-3.33)	6 (1.06)	1.89 (0.85-4.23)	15 (1.84)	3.09 (1.82-5.25)
Ventricular septal defects	21 (0.5)	1.62 (1.05-2.5)	7 (0.44)	7 (0.44-1.41)	0 (0)	0 (0-0)	3 (0.32)	1.03 (0.33-3.2)	2 (0.35)	1.13 (0.28-4.54)	9 (1.1)	3.6 (1.86-6.96)
Atrial septal defects	34 (0.81)	2.6 (1.84-3.68)	12 (0.75)	12 (0.75-2.41)	1 (0.34)	1.01 (0.14-7.23)	7 (0.75)	2.53 (1.2-5.32)	6 (1.06)	3.51 (1.57-7.87)	8 (0.98)	2.85 (1.35-5.99)
Atrioventricular septal	2 (0.05)	1.25 (0.31-5.02)	0 (0)	-	1 (0.34)	8.71 (1.21-62.64)	0 (0)	-	0 (0)	-	1 (0.12)	3.22 (0.45-23.03)
Of the respiratory system	7 (0.17)	1.41 (0.67-2.98)	2 (0.12)	2 (0.12-1.03)	1 (0.34)	2.66 (0.37-19.02)	1 (0.11)	0.94 (0.13-6.67)	1 (0.18)	1.52 (0.21-10.8)	2 (0.24)	2.09 (0.52-8.38)
Oro-facial clefts	6 (0.14)	1.02 (0.46-2.27)	4 (0.25)	4 (0.25-1.8)	0 (0)	-	1 (0.11)	0.76 (0.11-5.4)	0 (0)	0 (0-0)	1 (0.12)	0.88 (0.12-6.24)
Of the digestive system	13 (0.31)	1.8 (1.04-3.12)	7 (0.44)	7 (0.44-2.5)	0 (0)	-	2 (0.22)	1.25 (0.31-5)	2 (0.35)	2.09 (0.52-8.39)	2 (0.24)	1.43 (0.36-5.74)
Abdominal wall defects	1 (0.02)	1.04 (0.14-7.44)	1 (0.06)	1 (0.06-2.54)	0 (0)	-	0 (0)	-	0 (0)	-	0 (0)	-
Of the internal urinary system	11 (0.26)	0.84 (0.45-1.57)	9 (0.56)	9 (0.56-2.02)	0 (0)	-	0 (0)	-	0 (0)	-	2 (0.24)	0.44 (0.06-3.11)
Of the external genital organs	19 (0.45)	1.55 (0.99-2.44)	8 (0.5)	8 (0.5-1.7)	1 (0.34)	1.08 (0.15-7.67)	3 (0.32)	1.09 (0.35-3.38)	6 (1.06)	3.83 (1.71-8.57)	1 (0.12)	0.41 (0.06-2.93)
Of the limbs	53 (1.27)	0.93 (0.71-1.23)	24 (1.49)	24 (1.49-1.13)	1 (0.34)	0.25 (0.04-1.75)	10 (1.08)	0.76 (0.41-1.42)	7 (1.23)	0.91 (0.43-1.92)	11 (1.35)	1 (0.55-1.81)
Of the musculoskeletal system	8 (0.19)	1.29 (0.64-2.59)	3 (0.19)	3 (0.19-1.25)	1 (0.34)	2.18 (0.31-15.57)	2 (0.22)	1.46 (0.36-5.85)	1 (0.18)	1.2 (0.17-8.55)	1 (0.12)	0.83 (0.12-5.9)
Chromosomal abnormalities	7 (0.17)	1.57 (0.74-3.31)	1 (0.06)	1 (0.06-0.59)	0 (0)	-	1 (0.11)	0.97 (0.14-6.92)	3 (0.53)	4.65 (1.49-14.53)	2 (0.24)	2.35 (0.59-9.45)

Other malformations	9 (0.22)	1.36 (0.68-2.74)	4 (0.25)	4 (0.25-1.32)	0 (0)	-	4 (0.43)	3.08 (1.15-8.23)	0 (0)	-	1 (0.12)	0.88 (0.12-6.28)
And teratogenic syndromes	2 (0.05)	2.78 (0.67-11.6)	1 (0.06)	1 (0.06-3.58)	0 (0)	-	0 (0)	-	0 (0)	-	1 (0.12)	10.13 (1.36-75.44)
Genetic syndromes	1 (0.02)	0.39 (0.06-2.78)	0 (0)	-	0 (0)	-	1 (0.11)	1.79 (0.25-12.76)	0 (0)	-	0 (0)	-

Incidence is presented as number of cases (N) with percentages (%). Estimates of multivariable logistic regressions are presented as Odds Ratios (OR) with 95% confidence intervals (95% CI) [a]Multivariable logistic regressions are adjusted for mother's age, parity, income, education, smoking and year of conception.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-8*
Bias	9	Describe any efforts to address potential sources of bias	7,8
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7,8
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9,10
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	9,10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-16
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14-16
Discussion			
Key results	18	Summarise key results with reference to study objectives	16,17
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-21
Generalisability	21	Discuss the generalisability (external validity) of the study results	21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Exposure to selective serotonine reuptake inhibitors and the risk of congenital malformations: a nation-wide cohort study

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EXPOSURE TO SELECTIVE SEROTONINE REUPTAKE INHIBITORS AND THE RISK OF CONGENITAL MALFORMATIONS: A NATION-WIDE COHORT-STUDY

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Key words: Pregnancy, antidepressive agents, serotonin uptake inhibitors, congenital malformations, pharmacoepidemiology.

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ABSTRACT

Objectives

To analyse the relation between selective serotonine reuptake inhibitor (SSRI) use and major congenital malformations, with focus on malformations of the heart.

Design

Register based retrospective nation-wide cohort study, using the Danish Medical Birth Registry.

Setting

Denmark

Participants

Pregnant women in Denmark between 1997 and 2009 and their offspring.

Primary outcome measures

For each SSRI odds ratios for major congenital malformations were estimated using multivariable logistic regression models for women exposed to an SSRI during the first trimester and for women ~~pausing~~ with paused exposure during pregnancy.

Results

We identified 848 786 pregnancies; 4183 were exposed to an SSRI throughout the first trimester, and 806 pregnancies paused exposure during pregnancy. Risks of congenital malformations of the heart were similar for pregnancies exposed to an SSRI throughout the first trimester; adjusted OR 2.01 (95% CI 1.60-2.53) and for pregnancies ~~pausing~~ with paused SSRI treatment during pregnancy; adjusted OR 1.85 (95% CI 1.07-3.20). P-value for difference: 0.94. We found similar

increased risks of specific congenital malformations of the heart for the individual SSRIs. Furthermore, we found no association with dosage.

Conclusions

The apparent association between SSRI use and congenital malformations of the heart may be confounded by indications. The moderate absolute risk increase combined with uncertainty for causality still requires the risk versus benefit to be evaluated in each individual case.

ARTICLE SUMMARY

Article focus

- Relation between SSRIs and congenital malformations
- Focus on malformations of the heart
- Focus on women ~~pausing~~ with paused treatment during pregnancy

Key messages

- Risks of congenital malformations of the heart are increased for infants whose mothers were exposed to an SSRI during the first trimester.
- Risks of congenital malformations of the heart are not different for pregnancies exposed during the first trimester as for pregnancies ~~pausing~~ with paused treatment during pregnancy.
- The found risk increases are moderate in absolute terms.

Strengths and limitations of this study

- Observational study – no causal relations.
- Nation-wide study, including all live births in the study period.
- Register based study - no recall bias.

ARTICLE

Introduction

Depression is common during pregnancy and up to 15% of pregnant women suffer from depression or depressive symptoms.[1;2] The most used pharmacological treatment for pregnant women is selective serotonine reuptake inhibitors (SSRIs).[3-6] Treatment with SSRIs during pregnancy in Denmark has doubled over a short span of time with 1.4% of pregnancies treated in 2004 compared to 2.4% in 2007. This rapid increase has also been observed in other countries where the proportion of pregnant women treated with an SSRI is reported to be even higher than in Denmark.[4-8] Several studies have analysed the consequences of this treatment on pregnancy outcomes, and indicated an increased risk of congenital malformations[9;10], and more notably heart defects.[11-21] However, the data are conflicting[11;13;16-18;22-32] and studies including up to a million pregnancies indicate little risk of congenital malformations[11,16;18;30;31] ~~[11;13;16-18;22-32]~~. None of these studies have successfully managed to differentiate between the consequences of the drugs themselves and the underlying disease. Given the uncertainty of safety and the common use, we performed a nationwide study of the relation between SSRI use and congenital malformations with focus on congenital heart defects, and comparison with paused use during pregnancy to account for special characteristics of women using antidepressants.

Materials and methods

Through the Danish Medical Birth Registry we identified all pregnancies in Denmark between 1997 and 2009. Their drug redemptions were identified using the Register of Medicinal Product Statistics. We calculated the associations between exposure to SSRIs and congenital malformations using multivariable logistic regression adjusted for maternal characteristics.

Study Population

At birth, all Danish citizens are given a unique permanent identification number [33], which enables personalized information to be linked across databases.. Using The Danish Medical Birth Registry we identified 854,008 births between 1997 and 2009. We excluded 5,222 records with missing data on date of birth and pregnancy length. The final cohort consisted of 848,786 pregnancies (99.4 % of all pregnancies). The Danish Medical Birth Registry includes data on all births in Denmark since 1973[34] and the following information is contained: unique identification numbers of mother and child as well recorded time of gestation, which is based on last menstrual period and ultrasound estimates. We obtained medical treatment from the Danish Register of Medicinal Product Statistics, which, since 1995, has recorded drugs dispensed from Danish pharmacies. Registration is close to perfect due to partial reimbursement by health-care authorities. [35] For this reason, direct importing by patients is nearly non-existent. The register contains type of drug (International Anatomical Therapeutic Coding (ATC)), date of redemption, quantity dispensed and strength.[36] Information on smoking was gathered from the Danish Medical Birth Registry. Individual information on household income and highest attained level of education was gathered from Statistics Denmark.[37]

Outcome Measures

Congenital malformations were identified through the Danish National Hospital Register.[38] We identified children with congenital malformation within one year of birth and the corresponding grouping according to the European Surveillance of Congenital Anomalies (EUROCAT) classification system guide 1.3.[39]

Identification of Exposure

Exposure to the following SSRIs (ATC codes) was identified in the present study: fluoxetine (N06AB03), citalopram (N06AB04), paroxetine (N06AB05), sertraline (N06AB06), and escitalopram (N06AB10). Other SSRIs were not included because of low incidence of use (n<50).

SSRI prescriptions redeemed during the study period were identified through the Register of Medicinal Product Statistics. Using the date of prescription, strength and number of tablets prescribed we performed an estimation of exposure periods and dosages of the individual SSRIs. We calculated dosage as the average of up to seven prescriptions based on the standard dose of the individual antidepressant. Calculation of drug exposure periods using this method has been described previously.[40]

We identified all pregnancies exposed to an SSRI during the first trimester with a continuous exposure before pregnancy by defining it as exposure between at least one month before conception and day 84 of pregnancy (last day of the first trimester). Women changing exposure to another SSRI during the first trimester were not included in the study (n=646). In order to address a possible confounding by indication we compared our cohort exposed during the first trimester with a control cohort comprised of women ~~pausing~~ with paused exposure during pregnancy. We defined women with paused exposure as exposure to an SSRI three to twelve months before conception and one to twelve months after giving birth, but with no exposure to an SSRI between three months before conception to one month after giving birth. In addition, they had to be exposed to the same individual SSRI before and after pregnancy to ensure comparability with women exposed during the first trimester.~~.~~

We divided the study population into pregnancies exposed to high or low SSRI dose based on the recommended daily dose values of the individual SSRIs during pregnancy. Doses over the following cut-off values were considered as high doses; 20 mg for citalopram, 10 mg for escitalopram, 20 mg for fluoxetine, 210 mg for paroxetine and 50 mg for sertraline.

Statistical Analysis

Baseline characteristics were compared with chi-square tests for chategorical variables. Risks of malformations were examined with linear logistic regression models. In multiavariable analyses we included the mother's age divided into 5 categories: <20, 20-25, 25-30, 30-35, >35 years (0% missing values). Annual gross household income was divided into quartiles (<1% missing values). The highest obtained level of education attained was divided into three groups: low, medium and high, resulting in 4.3% missing values. The number of prior births (parity), including stillbirths, was divided into four classes: 1, 2, 3 and >3 births (<1% missing values). Year of conception was divided into 5 categories (1995-97, 1998-2000, 2001-03, 2004-06, and 2007-09). Smoking was divided into five categories according to the number of daily cigarette: 0, 1-10, 11-20, >20 and unknown (<1% missing values). Body mass index (BMI) was divided into 5 group (<21, 21-25, 26-30, >30). Information on BMI was only available from January 1st 2004, and includes 7% missing values in the period 2004-2009. (Table 1) Records with missing values in the above mentioned categories were not included in the multivariable analyses.

Ethics

The present study has been approved by The Danish Data Protection Agency (No. 2008-41-2517). Retrospective register studies do not require ethical permission in Denmark. Our findings are reported according to strengthening the reporting of observational studies in epidemiology (STROBE).[41]

Results

We identified 4183 pregnancies exposed to an SSRI throughout the first trimester, 806 pregnancies with paused exposure, and 843 797 pregnancies not exposed to an SSRI. 83% of pregnancies exposed to an SSRI throughout the first trimester went on to redeem a prescription of an SSRI during the third trimester. Table 1 shows the basic characteristics for women exposed and to an SSRI, and for unexposed women. Table 2 presents the association between exposure to SSRIs and major congenital malformation with more than 10 cases, and specific septal congenital defects of the heart. For information on risks associated with the remaining congenital malformations please refer to supplement A.

Table 1. Maternal characteristics of women exposed to an SSRI and unexposed

	Exposed to SSRIs			Unexposed	
Characteristic	**First trimester N=4 183**	**Paused during pregnancy N=806**		**N=843 797**	
	N (%)	**N (%)**	**p-value[a]**	**N (%)**	**p-value[a]**
Education			<0.01		<0.001
short	1731 (41.38)	372 (46.15)		280447 (33.24)	
medium	1119 (26.75)	225 (27.92)		254194 (30.13)	
long	1262 (30.17)	193 (23.95)		272380 (32.28)	
Missing values	71 (1.70)	16 (1.99)		36776 (4.36)	
Annual household income			0.12		<0.001
less than $ 58 335	1320 (31.56)	264 (32.75)		210290 (24.92)	
$ 58 335 - $ 93 656	1101 (26.32)	222 (27.54)		212110 (25.14)	
$ 93 656 - $ 119 082	906 (21.66)	185 (22.95)		211436 (25.06)	
$ 119 082 or greater	856 (20.46)	135 (16.75)		207247 (24.56)	
Missing values	0 (-)	0 (-)		2714 (0.32)	
Age (years)			<0.001		<0.001
<20	70 (1.67)	20 (2.48)		23324 (2.76)	
21-25	555 (13.27)	122 (15.14)		129059 (15.30)	
26-30	1364 (32.61)	269 (33.37)		318664 (37.77)	
31-35	1423 (34.02)	295 (36.60)		268959 (31.87)	
>35	771 (18.43)	100 (12.41)		102791 (12.18)	

Missing values	0 (-)	0 (-)		0 (-)	
Parity			<0.001		<0.001
1	1983 (47.41)	282 (34.99)		368168 (43.63)	
2	1320 (31.56)	310 (38.46)		308992 (36.62)	
>2	833 (19.91)	208 (25.81)		162030 (19.20)	
Missing values	47 (1.12)	6 (0.74)		4607 (0.55)	
Daily cigarettes			0.53		<0.001
0	2810 (67.18)	532 (66)		660888 (78.32)	
1-10	1049 (25.08)	211 (26.18)		128269 (15.2)	
11-20	66 (1.58)	11 (1.36)		5294 (0.63)	
>20	138 (3.30)	34 (4.22)		20967 (2.48)	
No information	118 (2.82)	18 (2.23)		27580 (3.27)	
Missing values	2 (0.05)	0 (-)		799 (0.09)	
Pre-pregnancy BMI[b]			0.89		<0.001
<21	391 (12.23)	66 (12.60)		53500 (13.95)	
21-25	1393 (43.59)	233 (44.47)		186428 (48.62)	
26-30	705 (22.06)	117 (22.33)		74673 (19.48)	
>30	493 (15.43)	74 (14.12)		41652 (10.86)	
Missing values	214 (6.70)	35 (6.68)		27161 (7.08)	

Data indicate number of pregnancies (N) and percentage (%). [a]Chi square tests were used to assess the overall p value for the group comparison with pregnancies exposed to an SSRI during the first trimester. [b]BMI=body mass index. Information on pre-pregnancy BMI was only available for women giving birth after 1. January 2004. Thus this cohort comprises 387 142 pregnancies

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Table 2. Risk of congenital malformations among women exposed to an SSRI vs. women with no exposure

	Exposed to any SSRI					No exposure
	First trimester N=4183		Paused during pregnancy N=806			N=843 797
Outcome	**N (%)**	**OR (96% CI)**	**N (%)**	**OR (96% CI)**	**p-value[a]**	**N (%)**
Major malformations	208 (4.97)	1.33 (1.16-1.53)	36 (4.47)	1.27 (0.91-1.78)	0.90	29703 (3.52)
Congenital malformations of the heart	77 (1.84)	2.01 (1.60-2.53)	13 (1.61)	1.85 (1.07-3.20)	0.94	7755 (0.92)
Septal defects	49 (1.17)	2.04 (1.53-2.72)	11 (1.36)	2.56 (1.41-4.64)	0.35	4826 (0.57)
Ventricular septal defects	21 (0.50)	1.62 (1.05-2.50)	9 (1.12)	3.74 (1.93-7.23)	0.97	2803 (0.33)
Atrial septal defects	34 (0.81)	2.60 (1.84-3.68)	6 (0.74)	2.61 (1.17-5.84)	0.74	2490 (0.30)
Congenital malformations of the digestive system	13 (0.31)	1.80 (1.04-3.12)	1 (0.12)	0.75 (0.11-5.35)	0.59	1545 (0.18)
Congenital malformations of the internal urinary system	11 (0.26)	0.84 (0.45-1.57)	-	-	-	2333 (0.28)
Congenital malformations of the external genital organs	19 (0.45)	1.55 (0.99-2.44)	2 (0.25)	0.89 (0.22-3.59)	0.46	2504 (0.30)
Congenital malformations of the limbs	53 (1.27)	0.93 (0.71-1.23)	14 (1.74)	1.37 (0.80-2.32)	0.18	11785 (1.40)

Estimates are presented as Odds Ratios (OR) with 95% confidence intervals (95% CI) [a]P-value for comparison of odds ratios between pregnancies exposed throughout the first trimester and pregnancies with paused exposure during pregnancy. [b]Multivariable logistic regressions are adjusted for mother's age, parity, income, education, smoking and year of conception.

First trimester exposure to any SSRI vs. no exposure

The rate of major congenital malformations among pregnancies exposed to any SSRI throughout the first trimester was 50 per 1000 pregnancies, compared to 35 pr 1000 unexposed pregnancies (Figure 1). We found an association between SSRI exposure and major congenital malformations; adjusted OR=1.33 (95% CI, 1.16-1.53) (table 2).

When analysing the association between exposure to any SSRI and the different major malformations according to the EUROCAT classification we found a statistically significant association between exposure to an SSRI and congenital malformations of the heart; adjusted OR=2.01 (95% CI, 1.60-2.53), and congenital malformations of the digestive system; adjusted OR=1.80 (95% CI, 1.04-3.12), but not the remaining major congenital malformations (table 2).

Paused exposure vs. unexposed

The rate of major congenital malformations among pregnancies ~~pausing~~ with paused exposure during pregnancy was 45 per 1000 pregnancies (Figure 1). The risk of any major malformation for women with ~~when~~ paus~~inged~~ exposure to an SSRI during pregnancy was; adjusted OR=1.27 (95% CI, 0.91-1.78) compared to unexposed pregnancies. When estimating the risk of specific major congenital malformations we found that paused exposure was associated with congenital malformations of the heart; adjusted OR 1.85 (95% CI, 1.07-3.20) (table 2).

Figure 1.Rates per 1000 pregnancies of major congenital malformations for infants exposed to selective serotonine reuptake inhibitors in utero

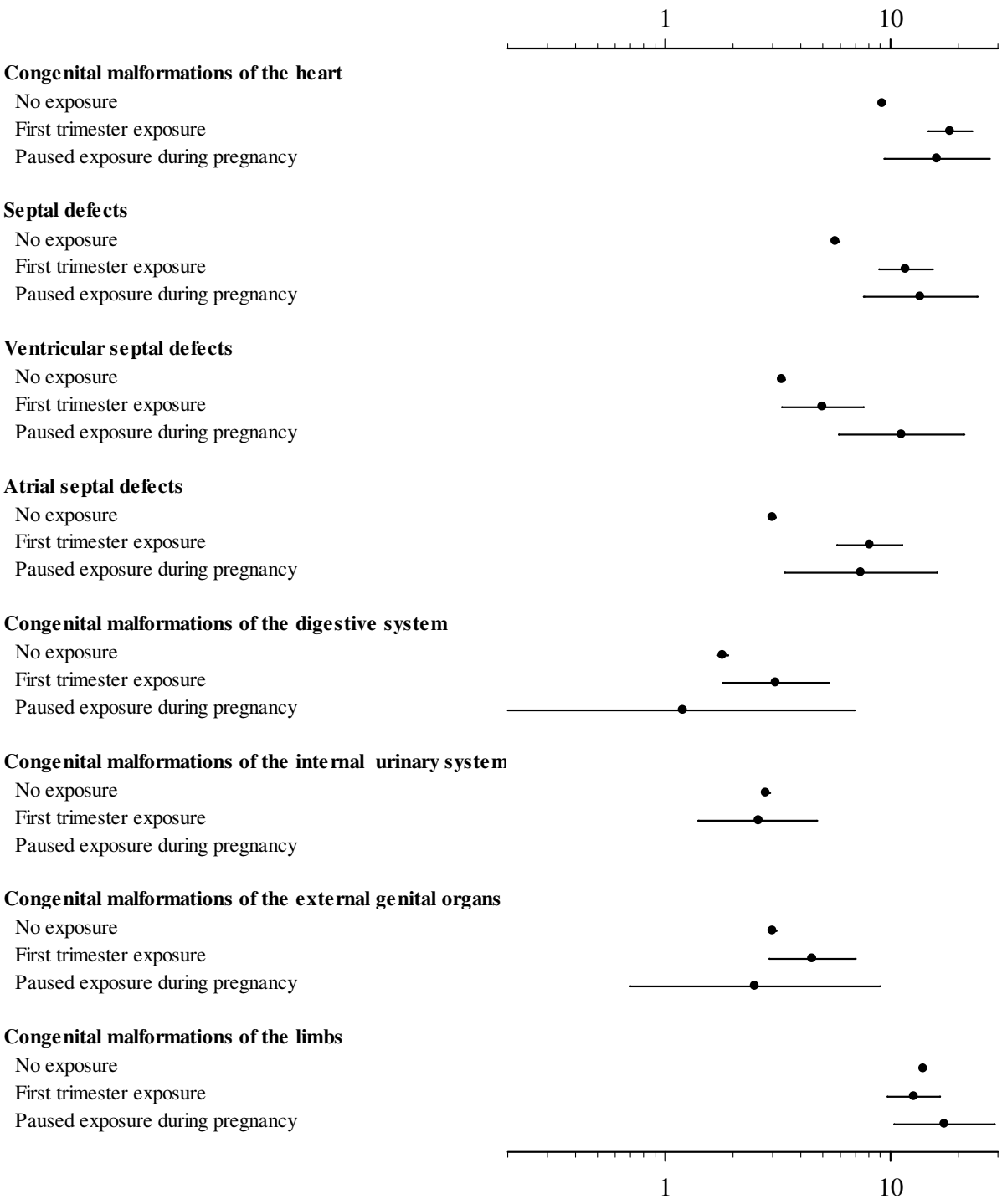

Figure shows number of infants diagnosed with a major malformation per 1000 births. Rates are shown with 95 % confidence intervals.

Other Analyses

Exposure to individual SSRIs

We found a significant association between major congenital malformations and exposure to citalopram; adjusted OR=1.51 (95% CI, 1.21-1.87), and sertraline; adjusted OR=1.41 (95% CI, 1.03-1.92). Furthermore, we found an association between congenital malformations of the heart and exposure to citalopram; adjusted OR=1.91 (95% CI, 1.31-2.77), fluoxetine; adjusted OR=2.05 (95% CI, 1.27-3.31), and sertraline; adjusted OR=2.73 (95% CI, 1.75-4.26). Associations for the remaining major congenital malformations are presented in supplement A.

Specific heart defects

We performed a sub analysis of the specific congenital septal defects of the heart and their association with exposure to SSRIs and found an association between exposure to any SSRI and septal heart defects; adjusted OR=2.04 (95% CI, 1.53-2.72) (table 2).Specifically, ventricular septal defects and atrial septal defects were associated with an increased risk. Increased risk of congenital septal defects was also found for pregnancies with paused exposure; adjusted OR=2.56 (95% CI, 1.41-4.64) (table 2).

For the individual SSRIs we found an association between exposure to all SSRIs, except for escitalopram, and atrial septal defects. Ventricular septal defects was only associated with exposure to sertraline; adjusted OR=3.60 (95% CI, 1.86-6.96), and not the remaining individual SSRIs (supplement A).

Other congenital defects

Studies have reported a possible association between exposure to an SSRI during pregnancy and omphalocele, anencephaly and craniosynostosis.[9;10] We found an association for exposure to an SSRI in the first trimester and craniosynostosis (n=9); adjusted OR=1.94 (95% CI, 1.00-3.76), but not for omphalocele or anencephaly. For pregnancies with paused exposure, the association with craniosynostosis (n=3) was; adjusted OR=3.64 (95% CI, 1.17-11.34).

Dosage

We found an adjusted odds ratio for major malformations: OR 1.39 (95% CI, 1.14-1.68) for low dose exposure and 1.27 (95% CI, 1.03-1.56) for high dose exposure (p for difference=0.29).

For the individual major malformations we found similar associations for pregnancies exposed to low dose and pregnancies exposed to high dose, as for the whole cohort (Table 3). Analysing the effect of dose as a continuous variable yielded no dose-response association.

Table 3. Odds Ratios (OR) and 95% confidence intervals (95% CI) for association between congenital malformations among women exposed to low and high doses SSRI during pregnancy.

Outcome	Low dose SSRI (n=2588)		High dose SSRI (n=1603)		
	N (%)	OR (95% CI)[a]	N (%)	OR (95% CI)[a]	p-value[b]
Major malformations	121 (4.68)	1.26 (1.05-1.51)	87 (5.43)	1.44 (1.15-1.79)	0.29
Congenital malformations of the heart	44 (1.70)	1.83 (1.35-2.48)	33 (2.06)	2.26 (1.60-3.19)	0.41
Congenital malformations of the digestive system	8 (0.31)	1.78 (0.89-3.58)	5 (0.31)	1.80 (0.75-4.35)	0.99
Congenital malformations of the internal urinary system	6 (0.23)	0.82 (0.37-1.83)	5 (0.31)	0.88 (0.33-2.34)	0.63
Congenital malformations of the external genital organs	10 (0.39)	1.32 (0.71-2.46)	9 (0.56)	1.91 (0.99-3.68)	0.42

Congenital malformations of the limbs	33 (1.28)	0.94 (0.67-1.33)	20 (1.25)	0.91 (0.59-1.42)	0.93

[a]Multivariable logistic regressions are adjusted for mother's age, parity, income, education, smoking and year of conception. [b]P-value for comparison of odds ratios between pregnancies exposed to low dose SSRI and high dose SSRI.

Additional adjustments

In order to identify possible unaccounted confounders we performed additional multivariable analyses including co-medication (psycholeptics; ATC code A05, ~~,~~ ~~benzodiazepins~~ and antidiebetics; ATC code A10) as independent variables in our model. The results showed no considerable change in the estimates or their level of significance compared to our primary analysis (Supplement B).

When including body mass index (BMI) as an independent variable in our multivariable model we found the same statistically significant associations for exposure to any SSRI or individual SSRIs, and the specific congenital malformations as our multivariable model not adjusted for BMI. Information on BMI was only available for pregnancies after January 1st 2004, which reduced our cohort to 3196 pregnancies exposed to an SSRI and 383 946 with no exposure.

Non-SSRI antidepressants

The association between congenital malformations and exposure to non-SSRI antidepressants: tricyclic antidepressants (ATC N06AA, n=223) and other antidepressants (ATC N06AX, n=831) was; adjusted OR=1.04 (95% CI, 0.53-2.03) and; adjusted OR=0.70 (95% CI, 0.47-1.05), respectively. The associations with congenital malformations of the heart were; adjusted OR=1.33 (95% CI, 0.42-4.15) for tricyclic antidepressants and adjusted OR=0.99 (95% CI 0.51-1.91) for other antidepressants.

Discussion

We performed a retrospective nation-wide cohort study analysing the association between redemption of an SSRI during pregnancy and major congenital malformations. We found an association between exposure to an SSRI during the first trimester and major congenital malformations. More specifically; congenital malformations of the heart (ventricular septal defects and atrial septal defects) and congenital malformations of the digestive system. Furthermore, we found an association between women ~~pausing~~ with ~~SSRI~~paused SSRI exposure during pregnancy and congenital malformations of the heart. Based on findings described in the published literature we will centre the following discussion on major congenital malformations and congenital malformations of the heart for pregnancies exposed to SSRIs.

Our study's results are in accordance with two earlier Danish studies[20;42] based on cohorts comprising only part of the entire nation. A third Danish nation-wide study by Pedersen et al found an increased estimate for major congenital malformations and congenital malformations of the heart, though not statistically significant, in the studied period 1996-2004.[17] The number of exposed women in their study was 1370, compared to ours 4183, which could explain why our estimates reached statistical significance. The study concludes that there is a class effect of SSRIs on heart defects.

Several studies have not found an association between exposure to any SSRI and major malformations overall.[11;13;16;18;22-32] We find that some of these study are not comparable to ours because most of them are case-control studies, and with cohorts much smaller than ours.[13;22-29;31] Five of the studies are though similar to ours; based on nation-

wide cohorts and national registers, and cohort-sizes comparable to ours. Four are based on Swedish data and are successive updates [16;18;30;31], and one on Finnish data.[11]

The latest update of Swedish data found an increased risk of cardiovascular congenital malformations for pregnancies exposed to paroxetine, but not for the remaining individual SSRIs, or SSRI as a group.[18] Information on SSRI exposure was partly based on antenatal interviews which could, although unlikely, give rise to recall bias. Furthermore, their analyses were adjusted for BMI. Adjusting our multivariable analysis for BMI had little effect the estimates.

The Finnish study found an increased risk of ventricular septal defects for pregnancies exposed to fluoxetine, but not for the remaining individual SSRIs, or SSRI as a group.[11] The study is completely based on national registers, like our study. Exposure was though defined as redemption of at least one prescription between one month before pregnancy and ~~birth~~the end of the first trimester. This could under~~over~~estimate the number of exposed women if prescriptions for an SSRI were redeemed just before and after this chosen period. This could indicate continuous exposure during the first trimester and ~~and~~ push estimates towards unity, and, in theory, explain the lack of association with major congenital malformations, and specifically atrial septal defects.

None of the above mentioned studies assessed the risk of congenital malformations for women ~~pausing~~ with paused exposure during pregnancy and thereby addressing the possibility of confounding by indication. Furthermore, neither the Swedish nor the Finnish studies adjusted their analyses for socioeconomic factors which in our study are unevenly distributed between our exposed and unexposed population. ~~-~~Importantly, we believe there are sociodemographic differences between the populations included in these

Scandinavian studies compared to ours. Although Denmark resembles both Sweden and Finland, differences in culture and health care policies could account for the discrepancies in our results. Discrepancies between published studies could also be due to the low number of cases, where each case can have a significant effect on the estimate.

Congenital malformations of the heart have been associated with exposure to SSRIs in some studies [10-12;15-18;27;31;42], in contrast to studies not identifying this association.[9;13;19;26] Our analyses showed an increased risk of congenital heart defects for the individual SSRIs. Risks of atrial septal defects were furthermore associated with exposure to all individual SSRIs, except for escitalopram. The lack of statistical significance with escitalopram exposure could be due to low statistical power. We found the same increased risks for heart defects for those with paused exposure during pregnancy, which strengthens the assumption of confounding by indication.

Although statistically significant, the increased risks associated with SSRI exposure are small in absolute terms. For example, the populations' background risk of atrial septal defects is 0.26 %, and even if we estimate a two-fold risk increase associated with exposure to any SSRI the risk of giving birth to a child with this congenital malformation would be approximately 5 cases for every 1000 births (Figure 1).

Strengths and limitations

The main weakness is the observational design. We had access to important covariates but it cannot be excluded that unaccounted confounder explain the results. Our study could furthermore be affected by a possible detection bias. Pregnant women exposed to SSRIs are reported to have increased rates of observed malformations, due to increased rates of ultrasound examinations compared to women not treated with SSRIs.[43] In contrast,

detection of a malformation during an ultrasound examination could lead to pregnancy termination, and thereby decreased rates of malformations among the SSRI exposed. On the other hand, infants of women redeeming prescriptions for SSRIs undergo, in the first year of life, approximately twice as many echocardiograms compared with infants of unexposed women.[43] More frequent echocardiograms could increase the risk of heart defect detection and give rise to information bias (diagnostic suspicion bias). This bias could partly explain our findings. On the other hand, more frequent echocardiograms could indicate a more severe symptomatology among the exposed children due to an unaccounted factor. ~~, it could also however indicate symptoms of the infant.~~

Importantly, information on indication for elective termination of pregnancies was not available in our databases. If pregnant women exposed to an SSRI had a higher rate of provoked abortions due to severe malformations it could mask a possible teratogenic effect of the drugs.

There is a possibility that we have overestimated SSRI treatment periods, since we cannot adjust for lack of compliance, or the patients' intention of commencing a treatment shortly after drug redemption. However, it has been estimated that the majority of redeemed prescriptions by pregnant women are taken[44], and compliance in Denmark has been estimated to be 80% for antidepressant treatment during pregnancy.[45] Furthermore, an overestimation of treatment periods would bias our estimates towards unity. We performed additional analyses defining exposure as redemption of 2 SSRI prescriptions during pregnancy. The results of these analyses, which are not presented, yielded the same statistically significant association as our primary analyses.

A main strength is the complete national design including nearly all births in Denmark and the mothers' drug redemptions in the study period. The Register of Medicinal Product Statistics includes approximately 97.5% of all redeemed prescriptions.[35] Danish pharmacies are, by law, required to register all redeemed prescriptions as part of the national health care reimbursement scheme. All prescriptions have been redeemed and paid for, which increases the probability of exposure. Recall bias is eliminated since information was recorded prospectively and not based on questionnaires or interviews. Furthermore, to our knowledge, this is the first study to address a possible confounding by indication by assessing risks associated with paused exposure to SSRIs during pregnancy.

Conclusion

Our study shows with high confidence a relation between exposure to an SSRI during the first trimester and risk of congenital malformations of the heart. In addition, we found a nearly identical risk for women who used an SSRI before and after pregnancy but discontinued use during pregnancy. We find both associations strong enough to conclude that risks related to SSRI use during the first trimester are a result of an unaccounted confounder associated to the redemption of an SSRI prescription. This was sustained by the lack of relation between dose and risk. A possible explanation could be information bias, because children of women redeeming an SSRI are more likely to undergo an echocardiogram during the first year of life. However, based on our study's design we cannot rule out an actual causal relation between redemption of an SSRI and congenital malformations. We found no relation with non-SSRI antidepressants, which may indicate a particular risk with SSRIs, but which may also be explained by lack of power.

We therefore conclude that the apparent association between SSRI use and congenital malformations of the heart may be confounded by indications. The moderate absolute risk increase combined with uncertainty for causality still requires the risk versus benefit to be evaluated in each individual case.

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None to declare.

Competing interests

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Reference List

(1) Bennett HA, Einarson A, Taddio A, et al. Prevalence of depression during pregnancy: systematic review. *Obstet Gynecol* 2004;**103**(4):698-709.

(2) Chatillon O, Even C. [Antepartum depression: Prevalence, diagnosis and treatment.]. *Encephale* 2010;**36**(6):443-451.

(3) Ververs T, Kaasenbrood H, Visser G, et al. Prevalence and patterns of antidepressant drug use during pregnancy. *Eur J Clin Pharmacol* 2006;**62**(10):863-870.

(4) Cooper WO, Willy ME, Pont SJ, et al. Increasing use of antidepressants in pregnancy. *Am J Obstet Gynecol* 2007;**196**(6):544-545.

(5) Andrade SE, Raebel MA, Brown J, et al. Use of antidepressant medications during pregnancy: a multisite study. *Am J Obstet Gynecol* 2008;**198**(2):194-195.

(6) Alwan S, Reefhuis J, Rasmussen SA, et al. Prevention Study TNBD. Patterns of Antidepressant Medication Use Among Pregnant Women in a United States Population. *J Clin Pharmacol* 2011;**51**(2):264-70.

(7) Bakker MK, Kolling P, van den Berg PB, et al. Increase in use of selective serotonin reuptake inhibitors in pregnancy during the last decade, a population-based cohort study from the Netherlands. *Br J Clin Pharmacol* 2008;**65**(4):600-606.

(8) Wichman CL, Fothergill A, Moore KM, et al. Recent trends in selective serotonin reuptake inhibitor use in pregnancy. *J Clin Psychopharmacol* 2008;**28**(6):714-716.

(9) Alwan S, Reefhuis J, Rasmussen SA, et al. Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. *N Engl J Med* 2007;**356**(26):2684-2692.

(10) Louik C, Lin AE, Werler MM, et al. First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. *N Engl J Med* 2007;**356**(26):2675-2683.

(11) Malm H, Artama M, Gissler M, et al. Selective serotonin reuptake inhibitors and risk for major congenital anomalies. *Obstet Gynecol* 2011;**118**(1):111-120.

(12) Bakker MK, Kerstjens-Frederikse WS, Buys CH, et al. First-trimester use of paroxetine and congenital heart defects: a population-based case-control study. *Birth Defects Res A Clin Mol Teratol* 2010;**88**(2):94-100.

(13) Berard A, Ramos E, Rey E, et al. First trimester exposure to paroxetine and risk of cardiac malformations in infants: the importance of dosage. *Birth Defects Res B Dev Reprod Toxicol* 2007;**80**(1):18-27.

(14) Cole JA, Ephross SA, Cosmatos IS, et al. Paroxetine in the first trimester and the prevalence of congenital malformations. *Pharmacoepidemiol Drug Saf* 2007;**16**(10):1075-1085.

(15) Diav-Citrin O, Shechtman S, Weinbaum D, et al. Paroxetine and fluoxetine in pregnancy: a prospective, multicentre, controlled, observational study. *Br J Clin Pharmacol* 2008;**66**(5):695-705.

(16) Kallen BA, Otterblad OP. Maternal use of selective serotonin re-uptake inhibitors in early pregnancy and infant congenital malformations. *Birth Defects Res A Clin Mol Teratol* 2007;**79**(4):301-308.

(17) Pedersen LH, Henriksen TB, Vestergaard M, et al. Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study. *BMJ* 2009;**339**:b3569.

(18) Reis M, Kallen B. Delivery outcome after maternal use of antidepressant drugs in pregnancy: an update using Swedish data. *Psychol Med* 2010 Oct;**40**(10):1723-33

(19) Wichman CL, Moore KM, Lang TR, et al. Congenital Heart Disease Associated With Selective Serotonin Reuptake Inhibitor Use During Pregnancy. *Mayo Clinic Proceedings* 2009;**84**(1):23-27.

(20) Wogelius P, Norgaard M, Gislum M, et al. Maternal use of selective serotonin reuptake inhibitors and risk of congenital malformations. *Epidemiology* 2006;**17**(6):701-704.

(21) Wurst KE, Poole C, Ephross SA, et al. First trimester paroxetine use and the prevalence of congenital, specifically cardiac, defects: a meta-analysis of epidemiological studies. *Birth Defects Res A Clin Mol Teratol* 2010;**88**(3):159-170.

(22) Malm H, Klaukka T, Neuvonen PJ. Risks associated with selective serotonin reuptake inhibitors in pregnancy. *Obstet Gynecol* 2005;**106**(6):1289-1296.

(23) Kulin NA, Pastuszak A, Sage SR, et al. Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors: a prospective controlled multicenter study. *JAMA* 1998;**279**(8):609-610.

(24) Ramos E, St-Andre M, Rey E, et al. Duration of antidepressant use during pregnancy and risk of major congenital malformations. *The British Journal of Psychiatry* 2008;**192**(5):344-350.

(25) Einarson A, Choi J, Einarson TR, et al. Incidence of major malformations in infants following antidepressant exposure in pregnancy: results of a large prospective cohort study. *Can J Psychiatry* 2009;**54**(4):242-246.

(26) Davis RL, Rubanowice D, McPhillips H, et al. Risks of congenital malformations and perinatal events among infants exposed to antidepressant medications during pregnancy. *Pharmacoepidemiol Drug Saf* 2007;**16**(10):1086-1094.

(27) Oberlander TF, Warburton W, Misri S, et al. Major congenital malformations following prenatal exposure to serotonin reuptake inhibitors and benzodiazepines using population-based health data. *Birth Defects Res B Dev Reprod Toxicol* 2008;**83**(1):68-76.

(28) Simon GE, Cunningham ML, Davis RL. Outcomes of Prenatal Antidepressant Exposure. *Am J Psychiatry* 2002;**159**(12):2055-2061.

(29) Wen SW, Yang Q, Garner P, et al. Selective serotonin reuptake inhibitors and adverse pregnancy outcomes. *Am J Obstet Gynecol* 2006;**194**(4):961-966.

(30) Ericson A, Kallen B, Wiholm B. Delivery outcome after the use of antidepressants in early pregnancy. *Eur J Clin Pharmacol* 1999;**55**(7):503-508.

(31) Kallen B, Otterblad Olausson P. Antidepressant drugs during pregnancy and infant congenital heart defect. *Reproductive Toxicology* 2006;**21**(3):221-222.

(32) Lennestal RM, Kallen BM. Delivery Outcome in Relation to Maternal Use of Some Recently Introduced Antidepressants. [Article]. *Journal of Clinical Psychopharmacology* 2007;**27**(6):607-613.

(33) Pedersen CB, Gotzsche H, Moller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull* 2006;**53**(4):441-449.

(34) Knudsen LB, Olsen J. The Danish Medical Birth Registry. *Dan Med Bull* 1998;**45**(3):320-323.

(35) Sorensen HT, Hansen I, Ejlersen E, et al. Identification of patients treated with strong analgesics: an assessment of two Danish information systems with respect to epidemiological research. *J Med Syst* 1996;**20**(1):57-65.

(36) Gaist D, Sorensen HT, Hallas J. The Danish prescription registries. *Dan Med Bull* 1997;**44**(4):445-448.

(37) Statistics Denmark. Containing detailed statistical information on the Danish Society. Available at: http://www.dst.dk/en. Accessed March, 2012.

(38) Andersen TF, Madsen M, Jorgensen J, et al. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999;**46**(3):263-268.

(39) European Surveillance of Congenital Anomalies. EUROCAT Guide 1.3 and reference documents. Newtownabbey Co Antrim: University of Ulster; 2005.Available at: http://www.eurocat-network.eu/content/EUROCAT-Guide-1.3.pdf. Accessed March 2012.

(40) Fosbol EL, Gislason GH, Jacobsen S, et al. The pattern of use of non-steroidal anti-inflammatory drugs (NSAIDs) from 1997 to 2005: a nationwide study on 4.6 million people. *Pharmacoepidemiol Drug Saf* 2008;**17**(8):822-833.

(41) von Elm E, Altman DG, Egger M, et al.The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007;**370**(9596):1453-1457.

(42) Kornum JB, Nielsen RB, Pedersen L, et al. Use of selective serotonin-reuptake inhibitors during early pregnancy and risk of congenital malformations: updated analysis. *Clin Epidemiol* 2010;**2**:29-36.

(43) Bar-Oz B, Einarson T, Einarson A, et al. Paroxetine and congenital malformations: meta-Analysis and consideration of potential confounding factors. *Clin Ther* 2007;**29**(5):918-926.

(44) de Jong van den Berg LT, Feenstra N, Sorensen HT, et al.. Improvement of drug exposure data in a registration of congenital anomalies. Pilot-study: pharmacist and mother as sources for drug exposure data during pregnancy. EuroMAP Group. Europen Medicine and Pregnancy Group. *Teratology* 1999;**60**(1):33-36.

(45) Olesen C, Sondergaard C, Thrane N, et al. Do pregnant women report use of dispensed medications? *Epidemiology* 2001;**12**(5):497-501.

Supplement A. Odds Ratios (OR) and 95% confidence intervals (95% CI) for the incidence and risk of congenital malformations among women exposed to individual SSRIs vs. women with no exposure

	SSRI (n=4183)		Citalopram (n=1606)		Escitalopram (n=293)		Fluoxetine (n=928)		Paroxetine (n=568)		Sertraline (n=817)	
Congenital malformations	**N (%)**	**OR (95% CI)[a]**	**N (%)**	**OR (95% CI)[a]**	**N (%)**	**OR (95% CI)[a]**	**N (%)**	**OR (95% CI)[a]**	**N (%)**	**OR (95% CI)[a]**	**N (%)**	**OR (95% CI)[a]**
Major	208 (4.97)	1.33 (1.16-1.53)	89 (5.54)	89 (5.54-1.51)	8 (2.73)	0.69 (0.34-1.4)	41 (4.42)	1.18 (0.86-1.61)	26 (4.58)	1.25 (0.84-1.85)	44 (5.39)	1.41 (1.03-1.92)
Of the nervous system	7 (0.17)	1.13 (0.54-2.39)	2 (0.12)	2 (0.12-0.84)	1 (0.34)	2.25 (0.32-16.05)	2 (0.22)	1.44 (0.36-5.79)	1 (0.18)	1.19 (0.17-8.45)	1 (0.12)	0.85 (0.12-6.07)
Neural Tube Defects	1 (0.02)	0.73 (0.1-5.21)	-	-	0 (0)	-	1 (0.11)	3.22 (0.45-23.03)	0 (0)	-	0 (0)	-
Of the eye	7 (0.17)	1.43 (0.68-3.01)	5 (0.31)	5 (0.31-2.62)	0 (0)	-	1 (0.11)	0.93 (0.13-6.63)	0 (0)	-	1 (0.12)	1.05 (0.15-7.45)
Of the ear, face and neck	2 (0.05)	2.36 (0.58-9.61)	0 (0)	-	0 (0)	-	0 (0)	-	1 (0.18)	8.32 (1.16-59.81)	1 (0.12)	6.13 (0.85-44.05)
Of the heart	77 (1.84)	2.01 (1.6-2.53)	28 (1.74)	28 (1.74-1.91)	3 (1.02)	1.06 (0.34-3.3)	17 (1.83)	2.05 (1.27-3.31)	8 (1.41)	1.54 (0.77-3.1)	21 (2.57)	2.73 (1.75-4.26)
Septal defects	49 (1.17)	2.04 (1.53-2.72)	17 (1.06)	17 (1.06-1.86)	2 (0.68)	1.12 (0.28-4.51)	9 (0.97)	1.73 (0.89-3.33)	6 (1.06)	1.89 (0.85-4.23)	15 (1.84)	3.09 (1.82-5.25)
Ventricular septal defects	21 (0.5)	1.62 (1.05-2.5)	7 (0.44)	7 (0.44-1.41)	0 (0)	0 (0-0)	3 (0.32)	1.03 (0.33-3.2)	2 (0.35)	1.13 (0.28-4.54)	9 (1.1)	3.6 (1.86-6.96)
Atrial septal defects	34 (0.81)	2.6 (1.84-3.68)	12 (0.75)	12 (0.75-2.41)	1 (0.34)	1.01 (0.14-7.23)	7 (0.75)	2.53 (1.2-5.32)	6 (1.06)	3.51 (1.57-7.87)	8 (0.98)	2.85 (1.35-5.99)
Atrioventricular septal	2 (0.05)	1.25 (0.31-5.02)	0 (0)	-	1 (0.34)	8.71 (1.21-62.64)	0 (0)	-	0 (0)	-	1 (0.12)	3.22 (0.45-23.03)
Of the respiratory system	7 (0.17)	1.41 (0.67-2.98)	2 (0.12)	2 (0.12-1.03)	1 (0.34)	2.66 (0.37-19.02)	1 (0.11)	0.94 (0.13-6.67)	1 (0.18)	1.52 (0.21-10.8)	2 (0.24)	2.09 (0.52-8.38)
Oro-facial clefts	6 (0.14)	1.02 (0.46-2.27)	4 (0.25)	4 (0.25-1.8)	0 (0)	-	1 (0.11)	0.76 (0.11-5.4)	0 (0)	0 (0-0)	1 (0.12)	0.88 (0.12-6.24)
Of the digestive system	13 (0.31)	1.8 (1.04-3.12)	7 (0.44)	7 (0.44-2.5)	0 (0)	-	2 (0.22)	1.25 (0.31-5)	2 (0.35)	2.09 (0.52-8.39)	2 (0.24)	1.43 (0.36-5.74)
Abdominal wall defects	1 (0.02)	1.04 (0.14-7.44)	1 (0.06)	1 (0.06-2.54)	0 (0)	-	0 (0)	-	0 (0)	-	0 (0)	-
Of the internal urinary system	11 (0.26)	0.84 (0.45-1.57)	9 (0.56)	9 (0.56-2.02)	0 (0)	-	0 (0)	-	0 (0)	-	2 (0.24)	0.44 (0.06-3.11)
Of the external genital organs	19 (0.45)	1.55 (0.99-2.44)	8 (0.5)	8 (0.5-1.7)	1 (0.34)	1.08 (0.15-7.67)	3 (0.32)	1.09 (0.35-3.38)	6 (1.06)	3.83 (1.71-8.57)	1 (0.12)	0.41 (0.06-2.93)
Of the limbs	53 (1.27)	0.93 (0.71-1.23)	24 (1.49)	24 (1.49-1.13)	1 (0.34)	0.25 (0.04-1.75)	10 (1.08)	0.76 (0.41-1.42)	7 (1.23)	0.91 (0.43-1.92)	11 (1.35)	1 (0.55-1.81)
Of the musculoskeletal system	8 (0.19)	1.29 (0.64-2.59)	3 (0.19)	3 (0.19-1.25)	1 (0.34)	2.18 (0.31-15.57)	2 (0.22)	1.46 (0.36-5.85)	1 (0.18)	1.2 (0.17-8.55)	1 (0.12)	0.83 (0.12-5.9)
Chromosomal abnormalities	7 (0.17)	1.57 (0.74-3.31)	1 (0.06)	1 (0.06-0.59)	0 (0)	-	1 (0.11)	0.97 (0.14-6.92)	3 (0.53)	4.65 (1.49-14.53)	2 (0.24)	2.35 (0.59-9.45)

Other malformations	9 (0.22)	1.36 (0.68-2.74)	4 (0.25)	4 (0.25-1.32)	0 (0)	-	4 (0.43)	3.08 (1.15-8.23)	0 (0)	-	1 (0.12)	0.88 (0.12-6.28)
And teratogenic syndromes	2 (0.05)	2.78 (0.67-11.6)	1 (0.06)	1 (0.06-3.58)	0 (0)	-	0 (0)	-	0 (0)	-	1 (0.12)	10.13 (1.36-75.44)
Genetic syndromes	1 (0.02)	0.39 (0.06-2.78)	0 (0)	-	0 (0)	-	1 (0.11)	1.79 (0.25-12.76)	0 (0)	-	0 (0)	-

Incidence is presented as number of cases (N) with percentages (%). Estimates of multivariable logistic regressions are presented as Odds Ratios (OR) with 95% confidence intervals (95% CI) [a]Multivariable logistic regressions are adjusted for mother's age, parity, income, education, smoking and year of conception.

Supplement B. Risk of congenital malformations among women exposed to an SSRI vs. women with no exposure further adjusted for co-medication.

	Exposed to any SSRI				No exposure
	First trimester N=4183		Paused during pregnancy N=806		N=843 797
Outcome	N (%)	OR (96% CI)	N (%)	OR (96% CI)	N (%)
Major malformations	208 (4.97)	1.32 (1.14-1.52)	36 (4.47)	1.27 (0.91-1.77)	29703 (3.52)
Congenital malformations of the heart	77 (1.84)	1.98 (1.57-2.49)	13 (1.61)	1.84 (1.06-3.19)	7755 (0.92)
Septal defects	49 (1.17)	2.00 (1.50-2.67)	11 (1.36)	2.54 (1.40-4.62)	4826 (0.57)
Ventricular septal defects	21 (0.50)	1.58 (1.02-2.44)	9 (1.12)	3.71 (1.92-7.17)	2803 (0.33)
Atrial septal defects	34 (0.81)	2.54 (1.79-3.60)	6 (0.74)	2.60 (1.16-5.81)	2490 (0.30)
Congenital malformations of the digestive system	13 (0.31)	1.74 (1.00-3.02)	1 (0.12)	0.74 (0.10-5.29)	1545 (0.18)
Congenital malformations of the internal urinary system	11 (0.26)	0.86 (0.46-1.60)	-	-	2333 (0.28)
Congenital malformations of the external genital organs	19 (0.45)	1.53 (0.97-2.41)	2 (0.25)	0.89 (0.22-3.57)	2504 (0.30)
Congenital malformations of the limbs	53 (1.27)	0.93 (0.71-1.22)	14 (1.74)	1.36 (0.80-2.31)	11785 (1.40)

Estimates are presented as Odds Ratios (OR) with 95% confidence intervals (95% CI). Multivariable logistic regressions are adjusted for mother's age, parity, income, education, smoking, year of conception and co-medication with psycholeptics and antidiabetics.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-8*
Bias	9	Describe any efforts to address potential sources of bias	7,8
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7,8
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9,10
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	9,10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-16
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14-16
Discussion			
Key results	18	Summarise key results with reference to study objectives	16,17
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-21
Generalisability	21	Discuss the generalisability (external validity) of the study results	21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Exposure to selective serotonin reuptake inhibitors and the risk of congenital malformations: a nation-wide cohort study

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EXPOSURE TO SELECTIVE SEROTONINE REUPTAKE INHIBITORS AND THE RISK OF CONGENITAL MALFORMATIONS: A NATION-WIDE COHORT-STUDY

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ABSTRACT

Objectives

To analyse the relation between selective serotonine reuptake inhibitor (SSRI) use and major congenital malformations, with focus on malformations of the heart.

Design

Register based retrospective nation-wide cohort study, using the Danish Medical Birth Registry.

Setting

Denmark

Participants

Pregnant women in Denmark between 1997 and 2009 and their offspring.

Primary outcome measures

For each SSRI odds ratios for major congenital malformations were estimated using multivariable logistic regression models for women exposed to an SSRI during the first trimester and for women with paused exposure during pregnancy.

Results

We identified 848 786 pregnancies; 4183 were exposed to an SSRI throughout the first trimester, and 806 pregnancies paused exposure during pregnancy. Risks of congenital malformations of the heart were similar for pregnancies exposed to an SSRI throughout the first trimester; adjusted OR 2.01 (95% CI 1.60-2.53) and for pregnancies with paused SSRI treatment during pregnancy; adjusted OR 1.85 (95% CI 1.07-3.20). P-value for difference: 0.94. We found similar increased

risks of specific congenital malformations of the heart for the individual SSRIs. Furthermore, we found no association with dosage.

Conclusions

The apparent association between SSRI use and congenital malformations of the heart may be confounded by indications. The moderate absolute risk increase combined with uncertainty for causality still requires the risk versus benefit to be evaluated in each individual case.

ARTICLE SUMMARY

Article focus

- Relation between SSRIs and congenital malformations
- Focus on malformations of the heart
- Focus on women with paused treatment during pregnancy

Key messages

- Risks of congenital malformations of the heart are increased for infants whose mothers were exposed to an SSRI during the first trimester.
- Risks of congenital malformations of the heart are not different for pregnancies exposed during the first trimester as for pregnancies with paused treatment during pregnancy.
- The found risk increases are moderate in absolute terms.

Strengths and limitations of this study

- Observational study – no causal relations.
- Nation-wide study, including all live births in the study period.
- Register based study - no recall bias.

ARTICLE

Introduction

Depression is common during pregnancy and up to 15% of pregnant women suffer from depression or depressive symptoms.[1;2] The most used pharmacological treatment for pregnant women is selective serotonine reuptake inhibitors (SSRIs).[3-6] Treatment with SSRIs during pregnancy in Denmark has doubled over a short span of time with 1.4% of pregnancies treated in 2004 compared to 2.4% in 2007. This rapid increase has also been observed in other countries where the proportion of pregnant women treated with an SSRI is reported to be even higher than in Denmark.[4-8] Several studies have analysed the consequences of this treatment on pregnancy outcomes, and indicated an increased risk of congenital malformations[9;10], and more notably heart defects.[11-21] However, the data are conflicting[11;13;16-18;22-32] and studies including up to a million pregnancies indicate little risk of congenital malformations[11,16;18;30;31]. None of these studies have successfully managed to differentiate between the consequences of the drugs themselves and the underlying disease. Given the uncertainty of safety and the common use, we performed a nationwide study of the relation between SSRI use and congenital malformations with focus on congenital heart defects, and comparison with paused use during pregnancy to account for special characteristics of women using antidepressants.

Materials and methods

Through the Danish Medical Birth Registry we identified all pregnancies in Denmark between 1997 and 2009. Their drug redemptions were identified using the Register of Medicinal Product Statistics. We calculated the associations between exposure to SSRIs and congenital malformations using multivariable logistic regression adjusted for maternal characteristics.

Study Population

At birth, all Danish citizens are given a unique permanent identification number [33], which enables personalized information to be linked across databases.. Using The Danish Medical Birth Registry we identified 854,008 births between 1997 and 2009. We excluded 5,222 records with missing data on date of birth and pregnancy length. The final cohort consisted of 848,786 pregnancies (99.4 % of all pregnancies). The Danish Medical Birth Registry includes data on all births in Denmark since 1973[34] and the following information is contained: unique identification numbers of mother and child as well recorded time of gestation, which is based on last menstrual period and ultrasound estimates. We obtained medical treatment from the Danish Register of Medicinal Product Statistics, which, since 1995, has recorded drugs dispensed from Danish pharmacies. Registration is close to perfect due to partial reimbursement by health-care authorities. [35] For this reason, direct importing by patients is nearly non-existent. The register contains type of drug (International Anatomical Therapeutic Coding (ATC)), date of redemption, quantity dispensed and strength.[36] Information on smoking was gathered from the Danish Medical Birth Registry. Individual information on household income and highest attained level of education was gathered from Statistics Denmark.[37]

Outcome Measures

Congenital malformations were identified through the Danish National Hospital Register.[38] We identified children with congenital malformation within one year of birth and the corresponding grouping according to the European Surveillance of Congenital Anomalies (EUROCAT) classification system guide 1.3.[39]

Identification of Exposure

Exposure to the following SSRIs (ATC codes) was identified in the present study: fluoxetine (N06AB03), citalopram (N06AB04), paroxetine (N06AB05), sertraline (N06AB06), and escitalopram (N06AB10). Other SSRIs were not included because of low incidence of use (n<50).

SSRI prescriptions redeemed during the study period were identified through the Register of Medicinal Product Statistics. Using the date of prescription, strength and number of tablets prescribed we performed an estimation of exposure periods and dosages of the individual SSRIs. We calculated dosage as the average of up to seven prescriptions based on the standard dose of the individual antidepressant. Calculation of drug exposure periods using this method has been described previously.[40]

We identified all pregnancies exposed to an SSRI during the first trimester with a continuous exposure before pregnancy by defining it as exposure between at least one month before conception and day 84 of pregnancy (last day of the first trimester). Women changing exposure to another SSRI during the first trimester were not included in the study (n=646). In order to address a possible confounding by indication we compared our cohort exposed during the first trimester with a control cohort comprised of women with paused exposure during pregnancy. We defined women with paused exposure as exposure to an SSRI three to twelve months before conception and one to twelve months after giving birth, but with no exposure to an SSRI between three months before conception to one month after giving birth. In addition, they had to be exposed to the same individual SSRI before and after pregnancy to ensure comparability with women exposed during the first trimester.

We divided the study population into pregnancies exposed to high or low SSRI dose based on the recommended daily dose values of the individual SSRIs during pregnancy. Doses over the following cut-off values were considered as high doses; 20 mg for citalopram, 10 mg for escitalopram, 20 mg for fluoxetine, 20 mg for paroxetine and 50 mg for sertraline.

Statistical Analysis

Baseline characteristics were compared with chi-square tests for chategorical variables. Risks of malformations were examined with linear logistic regression models. In multiavariable analyses we included the mother's age divided into 5 categories: <20, 20-25, 25-30, 30-35, >35 years (0% missing values). Annual gross household income was divided into quartiles (<1% missing values). The highest obtained level of education attained was divided into three groups: low, medium and high, resulting in 4.3% missing values. The number of prior births (parity), including stillbirths, was divided into four classes: 1, 2, 3 and >3 births (<1% missing values). Year of conception was divided into 5 categories (1995-97, 1998-2000, 2001-03, 2004-06, and 2007-09). Smoking was divided into five categories according to the number of daily cigarette: 0, 1-10, 11-20, >20 and unknown (<1% missing values). Body mass index (BMI) was divided into 5 group (<21, 21-25, 26-30, >30). Information on BMI was only available from January 1st 2004, and includes 7% missing values in the period 2004-2009. (Table 1) Records with missing values in the above mentioned categories were not included in the multivariable analyses.

Ethics

The present study has been approved by The Danish Data Protection Agency (No. 2008-41-2517). Retrospective register studies do not require ethical permission in Denmark. Our findings are reported according to strengthening the reporting of observational studies in epidemiology (STROBE).[41]

Results

We identified 4183 pregnancies exposed to an SSRI throughout the first trimester, 806 pregnancies with paused exposure, and 843 797 pregnancies not exposed to an SSRI. 83% of pregnancies exposed to an SSRI throughout the first trimester went on to redeem a prescription of an SSRI during the third trimester. Table 1 shows the basic characteristics for women exposed and to an SSRI, and for unexposed women. Table 2 presents the association between exposure to SSRIs and major congenital malformation with more than 10 cases, and specific septal congenital defects of the heart. For information on risks associated with the remaining congenital malformations please refer to supplement A.

Table 1. Maternal characteristics of women exposed to an SSRI and unexposed

	Exposed to SSRIs			Unexposed	
Characteristic	**First trimester N=4 183**	**Paused during pregnancy N=806**		**N=843 797**	
	N (%)	**N (%)**	**p-value[a]**	**N (%)**	**p-value[a]**
Education			<0.01		<0.001
short	1731 (41.38)	372 (46.15)		280447 (33.24)	
medium	1119 (26.75)	225 (27.92)		254194 (30.13)	
long	1262 (30.17)	193 (23.95)		272380 (32.28)	
Missing values	71 (1.70)	16 (1.99)		36776 (4.36)	
Annual household income			0.12		<0.001
less than $ 58 335	1320 (31.56)	264 (32.75)		210290 (24.92)	
$ 58 335 - $ 93 656	1101 (26.32)	222 (27.54)		212110 (25.14)	
$ 93 656 - $ 119 082	906 (21.66)	185 (22.95)		211436 (25.06)	
$ 119 082 or greater	856 (20.46)	135 (16.75)		207247 (24.56)	
Missing values	0 (-)	0 (-)		2714 (0.32)	
Age (years)			<0.001		<0.001
<20	70 (1.67)	20 (2.48)		23324 (2.76)	
21-25	555 (13.27)	122 (15.14)		129059 (15.30)	
26-30	1364 (32.61)	269 (33.37)		318664 (37.77)	
31-35	1423 (34.02)	295 (36.60)		268959 (31.87)	
>35	771 (18.43)	100 (12.41)		102791 (12.18)	

Missing values	0 (-)	0 (-)		0 (-)	
Parity			<0.001		<0.001
1	1983 (47.41)	282 (34.99)		368168 (43.63)	
2	1320 (31.56)	310 (38.46)		308992 (36.62)	
>2	833 (19.91)	208 (25.81)		162030 (19.20)	
Missing values	47 (1.12)	6 (0.74)		4607 (0.55)	
Daily cigarettes			0.53		<0.001
0	2810 (67.18)	532 (66)		660888 (78.32)	
1-10	1049 (25.08)	211 (26.18)		128269 (15.2)	
11-20	66 (1.58)	11 (1.36)		5294 (0.63)	
>20	138 (3.30)	34 (4.22)		20967 (2.48)	
No information	118 (2.82)	18 (2.23)		27580 (3.27)	
Missing values	2 (0.05)	0 (-)		799 (0.09)	
Pre-pregnancy BMI[b]			0.89		<0.001
<21	391 (12.23)	66 (12.60)		53500 (13.95)	
21-25	1393 (43.59)	233 (44.47)		186428 (48.62)	
26-30	705 (22.06)	117 (22.33)		74673 (19.48)	
>30	493 (15.43)	74 (14.12)		41652 (10.86)	
Missing values	214 (6.70)	35 (6.68)		27161 (7.08)	

Data indicate number of pregnancies (N) and percentage (%). [a]Chi square tests were used to assess the overall p value for the group comparison with pregnancies exposed to an SSRI during the first trimester. [b]BMI=body mass index. Information on pre-pregnancy BMI was only available for women giving birth after 1. January 2004. Thus this cohort comprises 387 142 pregnancies

1

Table 2. Risk of congenital malformations among women exposed to an SSRI vs. women with no exposure

	Exposed to any SSRI					No exposure
	First trimester N=4183		Paused during pregnancy N=806			N=843 797
Outcome	N (%)	OR (956% CI)	N (%)	OR (965% CI)	p-value[a]	N (%)
Major malformations	208 (4.97)	1.33 (1.16-1.53)	36 (4.47)	1.27 (0.91-1.78)	0.90	29703 (3.52)
Congenital malformations of the heart	77 (1.84)	2.01 (1.60-2.53)	13 (1.61)	1.85 (1.07-3.20)	0.94	7755 (0.92)
Septal defects	49 (1.17)	2.04 (1.53-2.72)	11 (1.36)	2.56 (1.41-4.64)	0.35	4826 (0.57)
Ventricular septal defects	21 (0.50)	1.62 (1.05-2.50)	9 (1.12)	3.74 (1.93-7.23)	0.97	2803 (0.33)
Atrial septal defects	34 (0.81)	2.60 (1.84-3.68)	6 (0.74)	2.61 (1.17-5.84)	0.74	2490 (0.30)
Congenital malformations of the digestive system	13 (0.31)	1.80 (1.04-3.12)	1 (0.12)	0.75 (0.11-5.35)	0.59	1545 (0.18)
Congenital malformations of the internal urinary system	11 (0.26)	0.84 (0.45-1.57)	-	-	-	2333 (0.28)
Congenital malformations of the external genital organs	19 (0.45)	1.55 (0.99-2.44)	2 (0.25)	0.89 (0.22-3.59)	0.46	2504 (0.30)
Congenital malformations of the limbs	53 (1.27)	0.93 (0.71-1.23)	14 (1.74)	1.37 (0.80-2.32)	0.18	11785 (1.40)

Estimates are presented as Odds Ratios (OR) with 95% confidence intervals (95% CI) [a]P-value for comparison of odds ratios between pregnancies exposed throughout the first trimester and pregnancies with paused exposure during pregnancy. [b]Multivariable logistic regressions are adjusted for mother's age, parity, income, education, smoking and year of conception.

First trimester exposure to any SSRI vs. no exposure

The rate of major congenital malformations among pregnancies exposed to any SSRI throughout the first trimester was 50 per 1000 pregnancies, compared to 35 pr 1000 unexposed pregnancies (Figure 1). We found an association between SSRI exposure and major congenital malformations; adjusted OR=1.33 (95% CI, 1.16-1.53) (table 2).

When analysing the association between exposure to any SSRI and the different major malformations according to the EUROCAT classification we found a statistically significant association between exposure to an SSRI and congenital malformations of the heart; adjusted OR=2.01 (95% CI, 1.60-2.53), and congenital malformations of the digestive system; adjusted OR=1.80 (95% CI, 1.04-3.12), but not the remaining major congenital malformations (table 2).

Paused exposure vs. unexposed

The rate of major congenital malformations among pregnancies with paused exposure during pregnancy was 45 per 1000 pregnancies (Figure 1). The risk of any major malformation for women with paused exposure to an SSRI during pregnancy was; adjusted OR=1.27 (95% CI, 0.91-1.78) compared to unexposed pregnancies. When estimating the risk of specific major congenital malformations we found that paused exposure was associated with congenital malformations of the heart; adjusted OR 1.85 (95% CI, 1.07-3.20) (table 2). We performed additional analyses increasing the drug-free period before pregnancy to six and nine months and found similar estimates as for the group pausing exposure three months before conception (supplement C),.

Figure 1.Rates per 1000 pregnancies of major congenital malformations for infants exposed to selective serotonine reuptake inhibitors in utero

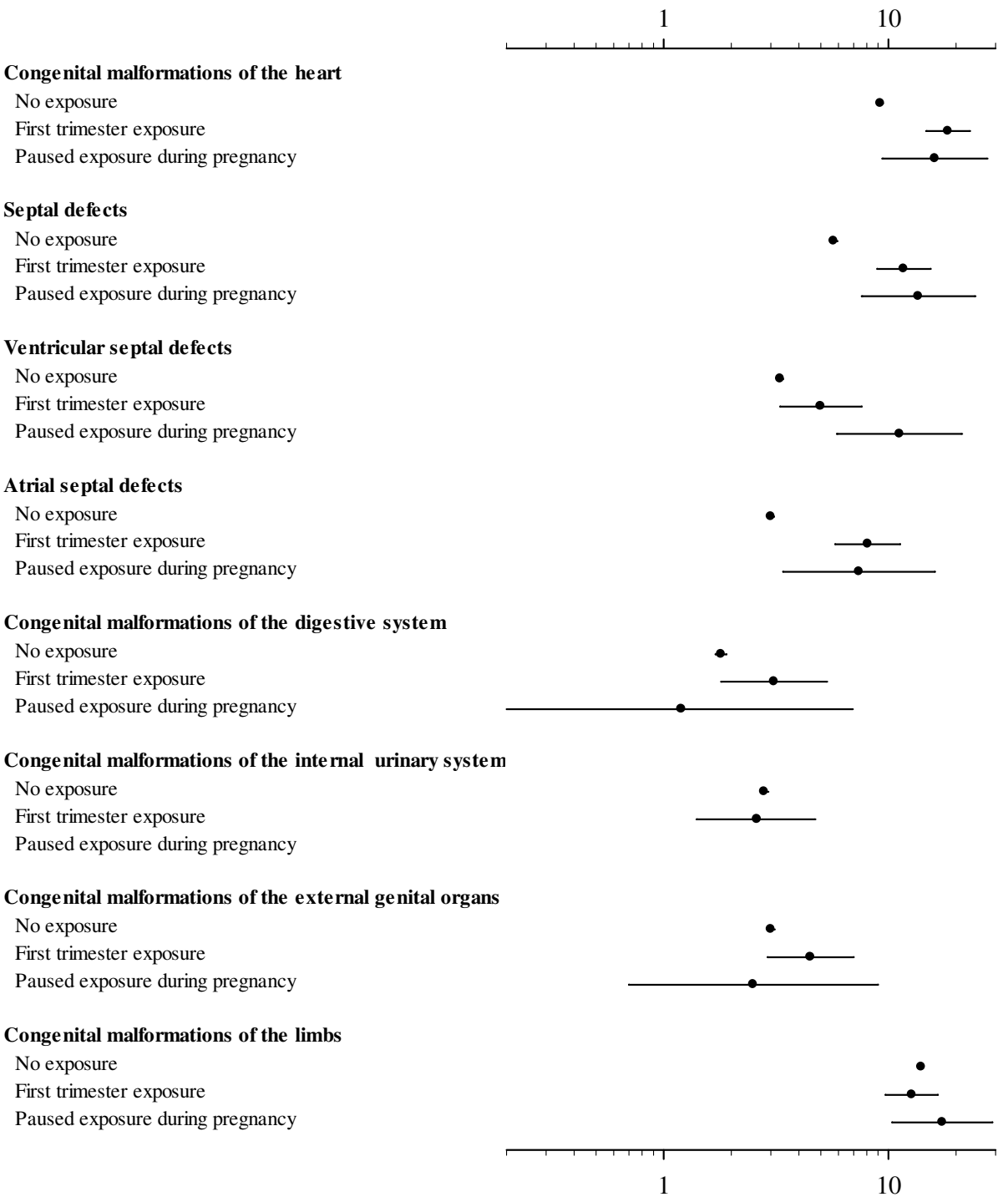

Figure shows number of infants diagnosed with a major malformation per 1000 births. Rates are shown with 95 % confidence intervals.

Other Analyses

Exposure to individual SSRIs

We found a significant association between major congenital malformations and exposure to citalopram; adjusted OR=1.51 (95% CI, 1.21-1.87), and sertraline; adjusted OR=1.41 (95% CI, 1.03-1.92). Furthermore, we found an association between congenital malformations of the heart and exposure to citalopram; adjusted OR=1.91 (95% CI, 1.31-2.77), fluoxetine; adjusted OR=2.05 (95% CI, 1.27-3.31), and sertraline; adjusted OR=2.73 (95% CI, 1.75-4.26). Associations for the remaining major congenital malformations are presented in supplement A.

Specific heart defects

We performed a sub analysis of the specific congenital septal defects of the heart and their association with exposure to SSRIs and found an association between exposure to any SSRI and septal heart defects; adjusted OR=2.04 (95% CI, 1.53-2.72) (table 2).Specifically, ventricular septal defects and atrial septal defects were associated with an increased risk. Increased risk of congenital septal defects was also found for pregnancies with paused exposure; adjusted OR=2.56 (95% CI, 1.41-4.64) (table 2).

For the individual SSRIs we found an association between exposure to all SSRIs, except for escitalopram, and atrial septal defects. Ventricular septal defects was only associated with exposure to sertraline; adjusted OR=3.60 (95% CI, 1.86-6.96), and not the remaining individual SSRIs (supplement A).

Other congenital defects

Studies have reported a possible association between exposure to an SSRI during pregnancy and omphalocele, anencephaly and craniosynostosis.[9;10] We found an association for exposure to an SSRI in the first trimester and craniosynostosis (n=9); adjusted OR=1.94 (95% CI, 1.00-3.76), but not for omphalocele or anencephaly. For pregnancies with paused exposure, the association with craniosynostosis (n=3) was; adjusted OR=3.64 (95% CI, 1.17-11.34).

Dosage

We found an adjusted odds ratio for major malformations: OR 1.39 (95% CI, 1.14-1.68) for low dose exposure and 1.27 (95% CI, 1.03-1.56) for high dose exposure (p for difference=0.29).

For the individual major malformations we found similar associations for pregnancies exposed to low dose and pregnancies exposed to high dose, as for the whole cohort (Table 3). Analysing the effect of dose as a continuous variable yielded no dose-response association.

Table 3. Odds Ratios (OR) and 95% confidence intervals (95% CI) for association between congenital malformations among women exposed to low and high doses SSRI during pregnancy.

Outcome	Low dose SSRI (n=2588)		High dose SSRI (n=1603)		
	N (%)	OR (95% CI)[a]	N (%)	OR (95% CI)[a]	p-value[b]
Major malformations	121 (4.68)	1.26 (1.05-1.51)	87 (5.43)	1.44 (1.15-1.79)	0.29
Congenital malformations of the heart	44 (1.70)	1.83 (1.35-2.48)	33 (2.06)	2.26 (1.60-3.19)	0.41
Congenital malformations of the digestive system	8 (0.31)	1.78 (0.89-3.58)	5 (0.31)	1.80 (0.75-4.35)	0.99
Congenital malformations of the internal urinary system	6 (0.23)	0.82 (0.37-1.83)	5 (0.31)	0.88 (0.33-2.34)	0.63
Congenital malformations of the external genital organs	10 (0.39)	1.32 (0.71-2.46)	9 (0.56)	1.91 (0.99-3.68)	0.42

Congenital malformations of the limbs	33 (1.28)	0.94 (0.67-1.33)	20 (1.25)	0.91 (0.59-1.42)	0.93

[a]Multivariable logistic regressions are adjusted for mother's age, parity, income, education, smoking and year of conception. [b]P-value for comparison of odds ratios between pregnancies exposed to low dose SSRI and high dose SSRI.

Additional adjustments

In order to identify possible unaccounted confounders we performed additional multivariable analyses including co-medication (psycholeptics; ATC code A05, and antidiebetics; ATC code A10) as independent variables in our model. The results showed no considerable change in the estimates or their level of significance compared to our primary analysis (Supplement B).

When including body mass index (BMI) as an independent variable in our multivariable model we found the same statistically significant associations for exposure to any SSRI or individual SSRIs, and the specific congenital malformations as our multivariable model not adjusted for BMI. Information on BMI was only available for pregnancies after January 1st 2004, which reduced our cohort to 3196 pregnancies exposed to an SSRI and 383 946 with no exposure.

Non-SSRI antidepressants

The association between congenital malformations and exposure to non-SSRI antidepressants: tricyclic antidepressants (ATC N06AA, n=223) and other antidepressants (ATC N06AX, n=831) was; adjusted OR=1.04 (95% CI, 0.53-2.03) and; adjusted OR=0.70 (95% CI, 0.47-1.05), respectively. The associations with congenital malformations of the heart were; adjusted OR=1.33 (95% CI, 0.42-4.15) for tricyclic antidepressants and adjusted OR=0.99 (95% CI 0.51-1.91) for other antidepressants.

Discussion

We performed a retrospective nation-wide cohort study analysing the association between redemption of an SSRI during pregnancy and major congenital malformations. We found an association between exposure to an SSRI during the first trimester and major congenital malformations. More specifically; congenital malformations of the heart (ventricular septal defects and atrial septal defects) and congenital malformations of the digestive system. Furthermore, we found an association between women with paused SSRI exposure during pregnancy and congenital malformations of the heart. Based on findings described in the published literature we will centre the following discussion on major congenital malformations and congenital malformations of the heart for pregnancies exposed to SSRIs.

Our study's results are in accordance with two earlier Danish studies[20;42] based on cohorts comprising only part of the entire nation. A third Danish nation-wide study by Pedersen et al found an increased estimate for major congenital malformations and congenital malformations of the heart, though not statistically significant, in the studied period 1996-2004.[17] The number of exposed women in their study was 1370, compared to ours 4183, which could explain why our estimates reached statistical significance. The study concludes that there is a class effect of SSRIs on heart defects.

Several studies have not found an association between exposure to any SSRI and major malformations overall.[11;13;16;18;22-32] We find that some of these study are not comparable to ours because most of them are case-control studies, and with cohorts much smaller than ours.[13;22-29;31] Five of the studies are though similar to ours; based on nation-

wide cohorts and national registers, and cohort-sizes comparable to ours. Four are based on Swedish data and are successive updates [16;18;30;31], and one on Finnish data.[11]

The latest update of Swedish data found an increased risk of cardiovascular congenital malformations for pregnancies exposed to paroxetine, but not for the remaining individual SSRIs, or SSRI as a group.[18] Information on SSRI exposure was partly based on antenatal interviews which could, although unlikely, give rise to recall bias. Furthermore, their analyses were adjusted for BMI. Adjusting our multivariable analysis for BMI had little effect the estimates.

The Finnish study found an increased risk of ventricular septal defects for pregnancies exposed to fluoxetine, but not for the remaining individual SSRIs, or SSRI as a group.[11] The study is completely based on national registers, like our study. Exposure was though defined as redemption of at least one prescription between one month before pregnancy and the end of the first trimester. This could underestimate the number of exposed women if prescriptions for an SSRI were redeemed just before and after this chosen period. This could indicate continuous exposure during the first trimester and push estimates towards unity, and, in theory, explain the lack of association with major congenital malformations, and specifically atrial septal defects.

None of the above mentioned studies assessed the risk of congenital malformations for women with paused exposure during pregnancy and thereby addressing the possibility of confounding by indication. Furthermore, neither the Swedish nor the Finnish studies adjusted their analyses for socioeconomic factors which in our study are unevenly distributed between our exposed and unexposed population. However, additional adjusted analyses not including socioeconomic factors yielded estimates and confidence intervals that

did not differ from our fully adjusted analysis (data not shown). Importantly, we believe there are sociodemographic differences between the populations included in these Scandinavian studies compared to ours. Although Denmark resembles both Sweden and Finland, differences in culture and health care policies could account for the discrepancies in our results. Discrepancies between published studies could also be due to the low number of cases, where each case can have a significant effect on the estimate.

Congenital malformations of the heart have been associated with exposure to SSRIs in some studies [10-12;15-18;27;31;42], in contrast to studies not identifying this association.[9;13;19;26] Our analyses showed an increased risk of congenital heart defects for the individual SSRIs. Risks of atrial septal defects were furthermore associated with exposure to all individual SSRIs, except for escitalopram. The lack of statistical significance with escitalopram exposure could be due to low statistical power. We found the same increased risks for heart defects for those with paused exposure during pregnancy, which strengthens the assumption of confounding by indication.

Although statistically significant, the increased risks associated with SSRI exposure are small in absolute terms. For example, the populations' background risk of atrial septal defects is 0.26 %, and even if we estimate a two-fold risk increase associated with exposure to any SSRI the risk of giving birth to a child with this congenital malformation would be approximately 5 cases for every 1000 births (Figure 1).

Strengths and limitations

The main weakness is the observational design. We had access to important covariates but it cannot be excluded that unaccounted confounder explain the results. Our study could furthermore be affected by a possible detection bias. Pregnant women exposed to

SSRIs are reported to have increased rates of observed malformations, due to increased rates of ultrasound examinations compared to women not treated with SSRIs.[43] In contrast, detection of a malformation during an ultrasound examination could lead to pregnancy termination, and thereby decreased rates of malformations among the SSRI exposed. On the other hand, infants of women redeeming prescriptions for SSRIs undergo, in the first year of life, approximately twice as many echocardiograms compared with infants of unexposed women.[43] More frequent echocardiograms could increase the risk of heart defect detection and give rise to information bias (diagnostic suspicion bias). This bias could partly explain our findings. On the other hand, more frequent echocardiograms could indicate a more severe symptomatology among the exposed children due to an unaccounted factor.

Importantly, information on indication for elective termination of pregnancies was not available in our databases. If pregnant women exposed to an SSRI had a higher rate of provoked abortions due to severe malformations it could mask a possible teratogenic effect of the drugs.

There is a possibility that we have overestimated SSRI treatment periods, since we cannot adjust for lack of compliance, or the patients' intention of commencing a treatment shortly after drug redemption. However, it has been estimated that the majority of redeemed prescriptions by pregnant women are taken[44], and compliance in Denmark has been estimated to be 80% for antidepressant treatment during pregnancy.[45] Furthermore, an overestimation of treatment periods would bias our estimates towards unity. We performed additional analyses defining exposure as redemption of 2 SSRI prescriptions during pregnancy. The results of these analyses, which are not presented, yielded the same statistically significant association as our primary analyses. Furthermore, we cannot rule out that women defined as

pausing their treatment three months before conception were misclassified and had treatment periods reaching into pregnancy. We addressed this issue by increasing the wash-out period before pregnancy and estimating risks for women pausing treatment six and nine months before conception. The results showed similar estimates as for women pausing exposure three months before pregnancy (supplement C).

A main strength is the complete national design including nearly all births in Denmark and the mothers' drug redemptions in the study period. The Register of Medicinal Product Statistics includes approximately 97.5% of all redeemed prescriptions.[35] Danish pharmacies are, by law, required to register all redeemed prescriptions as part of the national health care reimbursement scheme. All prescriptions have been redeemed and paid for, which increases the probability of exposure. Recall bias is eliminated since information was recorded prospectively and not based on questionnaires or interviews. Furthermore, to our knowledge, this is the first study to address a possible confounding by indication by assessing risks associated with paused exposure to SSRIs during pregnancy.

Conclusion

Our study shows with high confidence a relation between exposure to an SSRI during the first trimester and risk of congenital malformations of the heart. In addition, we found a nearly identical risk for women who used an SSRI before and after pregnancy but discontinued use during pregnancy. We find both associations strong enough to conclude that risks related to SSRI use during the first trimester are a result of an unaccounted confounder associated to the redemption of an SSRI prescription. This was sustained by the lack of relation between dose and risk. A possible explanation could be information bias, because children of women redeeming an SSRI are more likely to undergo an echocardiogram during

the first year of life. However, based on our study's design we cannot rule out an actual causal relation between redemption of an SSRI and congenital malformations. We found no relation with non-SSRI antidepressants, which may indicate a particular risk with SSRIs, but which may also be explained by lack of power.

We therefore conclude that the apparent association between SSRI use and congenital malformations of the heart may be confounded by indications. The moderate absolute risk increase combined with uncertainty for causality still requires the risk versus benefit to be evaluated in each individual case.

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Competing interests

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Reference List

(1) Bennett HA, Einarson A, Taddio A, et al. Prevalence of depression during pregnancy: systematic review. *Obstet Gynecol* 2004;**103**(4):698-709.

(2) Chatillon O, Even C. [Antepartum depression: Prevalence, diagnosis and treatment.]. *Encephale* 2010;**36**(6):443-451.

(3) Ververs T, Kaasenbrood H, Visser G, et al. Prevalence and patterns of antidepressant drug use during pregnancy. *Eur J Clin Pharmacol* 2006;**62**(10):863-870.

(4) Cooper WO, Willy ME, Pont SJ, et al. Increasing use of antidepressants in pregnancy. *Am J Obstet Gynecol* 2007;**196**(6):544-545.

(5) Andrade SE, Raebel MA, Brown J, et al. Use of antidepressant medications during pregnancy: a multisite study. *Am J Obstet Gynecol* 2008;**198**(2):194-195.

(6) Alwan S, Reefhuis J, Rasmussen SA, et al. Prevention Study TNBD. Patterns of Antidepressant Medication Use Among Pregnant Women in a United States Population. *J Clin Pharmacol* 2011;**51**(2):264-70.

(7) Bakker MK, Kolling P, van den Berg PB, et al. Increase in use of selective serotonin reuptake inhibitors in pregnancy during the last decade, a population-based cohort study from the Netherlands. *Br J Clin Pharmacol* 2008;**65**(4):600-606.

(8) Wichman CL, Fothergill A, Moore KM, et al. Recent trends in selective serotonin reuptake inhibitor use in pregnancy. *J Clin Psychopharmacol* 2008;**28**(6):714-716.

(9) Alwan S, Reefhuis J, Rasmussen SA, et al. Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. *N Engl J Med* 2007;**356**(26):2684-2692.

(10) Louik C, Lin AE, Werler MM, et al. First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. *N Engl J Med* 2007;**356**(26):2675-2683.

(11) Malm H, Artama M, Gissler M, et al. Selective serotonin reuptake inhibitors and risk for major congenital anomalies. *Obstet Gynecol* 2011;**118**(1):111-120.

(12) Bakker MK, Kerstjens-Frederikse WS, Buys CH, et al. First-trimester use of paroxetine and congenital heart defects: a population-based case-control study. *Birth Defects Res A Clin Mol Teratol* 2010;**88**(2):94-100.

(13) Berard A, Ramos E, Rey E, et al. First trimester exposure to paroxetine and risk of cardiac malformations in infants: the importance of dosage. *Birth Defects Res B Dev Reprod Toxicol* 2007;**80**(1):18-27.

(14) Cole JA, Ephross SA, Cosmatos IS, et al. Paroxetine in the first trimester and the prevalence of congenital malformations. *Pharmacoepidemiol Drug Saf* 2007;**16**(10):1075-1085.

(15) Diav-Citrin O, Shechtman S, Weinbaum D, et al. Paroxetine and fluoxetine in pregnancy: a prospective, multicentre, controlled, observational study. *Br J Clin Pharmacol* 2008;**66**(5):695-705.

(16) Kallen BA, Otterblad OP. Maternal use of selective serotonin re-uptake inhibitors in early pregnancy and infant congenital malformations. *Birth Defects Res A Clin Mol Teratol* 2007;**79**(4):301-308.

(17) Pedersen LH, Henriksen TB, Vestergaard M, et al. Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study. *BMJ* 2009;**339**:b3569.

(18) Reis M, Kallen B. Delivery outcome after maternal use of antidepressant drugs in pregnancy: an update using Swedish data. *Psychol Med* 2010 Oct;**40**(10):1723-33

(19) Wichman CL, Moore KM, Lang TR, et al. Congenital Heart Disease Associated With Selective Serotonin Reuptake Inhibitor Use During Pregnancy. *Mayo Clinic Proceedings* 2009;**84**(1):23-27.

(20) Wogelius P, Norgaard M, Gislum M, et al. Maternal use of selective serotonin reuptake inhibitors and risk of congenital malformations. *Epidemiology* 2006;**17**(6):701-704.

(21) Wurst KE, Poole C, Ephross SA, et al. First trimester paroxetine use and the prevalence of congenital, specifically cardiac, defects: a meta-analysis of epidemiological studies. *Birth Defects Res A Clin Mol Teratol* 2010;**88**(3):159-170.

(22) Malm H, Klaukka T, Neuvonen PJ. Risks associated with selective serotonin reuptake inhibitors in pregnancy. *Obstet Gynecol* 2005;**106**(6):1289-1296.

(23) Kulin NA, Pastuszak A, Sage SR, et al. Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors: a prospective controlled multicenter study. *JAMA* 1998;**279**(8):609-610.

(24) Ramos E, St-Andre M, Rey E, et al. Duration of antidepressant use during pregnancy and risk of major congenital malformations. *The British Journal of Psychiatry* 2008;**192**(5):344-350.

(25) Einarson A, Choi J, Einarson TR, et al. Incidence of major malformations in infants following antidepressant exposure in pregnancy: results of a large prospective cohort study. *Can J Psychiatry* 2009;**54**(4):242-246.

(26) Davis RL, Rubanowice D, McPhillips H, et al. Risks of congenital malformations and perinatal events among infants exposed to antidepressant medications during pregnancy. *Pharmacoepidemiol Drug Saf* 2007;**16**(10):1086-1094.

(27) Oberlander TF, Warburton W, Misri S, et al. Major congenital malformations following prenatal exposure to serotonin reuptake inhibitors and benzodiazepines using population-based health data. *Birth Defects Res B Dev Reprod Toxicol* 2008;**83**(1):68-76.

(28) Simon GE, Cunningham ML, Davis RL. Outcomes of Prenatal Antidepressant Exposure. *Am J Psychiatry* 2002;**159**(12):2055-2061.

(29) Wen SW, Yang Q, Garner P, et al. Selective serotonin reuptake inhibitors and adverse pregnancy outcomes. *Am J Obstet Gynecol* 2006;**194**(4):961-966.

(30) Ericson A, Kallen B, Wiholm B. Delivery outcome after the use of antidepressants in early pregnancy. *Eur J Clin Pharmacol* 1999;**55**(7):503-508.

(31) Kallen B, Otterblad Olausson P. Antidepressant drugs during pregnancy and infant congenital heart defect. *Reproductive Toxicology* 2006;**21**(3):221-222.

(32) Lennestal RM, Kallen BM. Delivery Outcome in Relation to Maternal Use of Some Recently Introduced Antidepressants. [Article]. *Journal of Clinical Psychopharmacology* 2007;**27**(6):607-613.

(33) Pedersen CB, Gotzsche H, Moller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull* 2006;**53**(4):441-449.

(34) Knudsen LB, Olsen J. The Danish Medical Birth Registry. *Dan Med Bull* 1998;**45**(3):320-323.

(35) Sorensen HT, Hansen I, Ejlersen E, et al. Identification of patients treated with strong analgesics: an assessment of two Danish information systems with respect to epidemiological research. *J Med Syst* 1996;**20**(1):57-65.

(36) Gaist D, Sorensen HT, Hallas J. The Danish prescription registries. *Dan Med Bull* 1997;**44**(4):445-448.

(37) Statistics Denmark. Containing detailed statistical information on the Danish Society. Available at: http://www.dst.dk/en. Accessed March, 2012.

(38) Andersen TF, Madsen M, Jorgensen J, et al. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999;**46**(3):263-268.

(39) European Surveillance of Congenital Anomalies. EUROCAT Guide 1.3 and reference documents. Newtownabbey Co Antrim: University of Ulster; 2005.Available at: http://www.eurocat-network.eu/content/EUROCAT-Guide-1.3.pdf. Accessed March 2012.

(40) Fosbol EL, Gislason GH, Jacobsen S, et al. The pattern of use of non-steroidal anti-inflammatory drugs (NSAIDs) from 1997 to 2005: a nationwide study on 4.6 million people. *Pharmacoepidemiol Drug Saf* 2008;**17**(8):822-833.

(41) von Elm E, Altman DG, Egger M, et al.The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007;**370**(9596):1453-1457.

(42) Kornum JB, Nielsen RB, Pedersen L, et al. Use of selective serotonin-reuptake inhibitors during early pregnancy and risk of congenital malformations: updated analysis. *Clin Epidemiol* 2010;**2**:29-36.

(43) Bar-Oz B, Einarson T, Einarson A, et al. Paroxetine and congenital malformations: meta-Analysis and consideration of potential confounding factors. *Clin Ther* 2007;**29**(5):918-926.

(44) de Jong van den Berg LT, Feenstra N, Sorensen HT, et al.. Improvement of drug exposure data in a registration of congenital anomalies. Pilot-study: pharmacist and mother as sources for drug exposure data during pregnancy. EuroMAP Group. Europen Medicine and Pregnancy Group. *Teratology* 1999;**60**(1):33-36.

(45) Olesen C, Sondergaard C, Thrane N, et al. Do pregnant women report use of dispensed medications? *Epidemiology* 2001;**12**(5):497-501.

Supplement A. Odds Ratios (OR) and 95% confidence intervals (95% CI) for the incidence and risk of congenital malformations among women exposed to individual SSRIs vs. women with no exposure

	SSRI (n=4183)		Citalopram (n=1606)		Escitalopram (n=293)		Fluoxetine (n=928)		Paroxetine (n=568)		Sertraline (n=817)	
Congenital malformations	**N (%)**	**OR (95% CI)[a]**	**N (%)**	**OR (95% CI)[a]**	**N (%)**	**OR (95% CI)[a]**	**N (%)**	**OR (95% CI)[a]**	**N (%)**	**OR (95% CI)[a]**	**N (%)**	**OR (95% CI)[a]**
Major	208 (4.97)	1.33 (1.16-1.53)	89 (5.54)	89 (5.54-1.51)	8 (2.73)	0.69 (0.34-1.4)	41 (4.42)	1.18 (0.86-1.61)	26 (4.58)	1.25 (0.84-1.85)	44 (5.39)	1.41 (1.03-1.92)
Of the nervous system	7 (0.17)	1.13 (0.54-2.39)	2 (0.12)	2 (0.12-0.84)	1 (0.34)	2.25 (0.32-16.05)	2 (0.22)	1.44 (0.36-5.79)	1 (0.18)	1.19 (0.17-8.45)	1 (0.12)	0.85 (0.12-6.07)
Neural Tube Defects	1 (0.02)	0.73 (0.1-5.21)	-	-	0 (0)	-	1 (0.11)	3.22 (0.45-23.03)	0 (0)	-	0 (0)	-
Of the eye	7 (0.17)	1.43 (0.68-3.01)	5 (0.31)	5 (0.31-2.62)	0 (0)	-	1 (0.11)	0.93 (0.13-6.63)	0 (0)	-	1 (0.12)	1.05 (0.15-7.45)
Of the ear, face and neck	2 (0.05)	2.36 (0.58-9.61)	0 (0)	-	0 (0)	-	0 (0)	-	1 (0.18)	8.32 (1.16-59.81)	1 (0.12)	6.13 (0.85-44.05)
Of the heart	77 (1.84)	2.01 (1.6-2.53)	28 (1.74)	28 (1.74-1.91)	3 (1.02)	1.06 (0.34-3.3)	17 (1.83)	2.05 (1.27-3.31)	8 (1.41)	1.54 (0.77-3.1)	21 (2.57)	2.73 (1.75-4.26)
Septal defects	49 (1.17)	2.04 (1.53-2.72)	17 (1.06)	17 (1.06-1.86)	2 (0.68)	1.12 (0.28-4.51)	9 (0.97)	1.73 (0.89-3.33)	6 (1.06)	1.89 (0.85-4.23)	15 (1.84)	3.09 (1.82-5.25)
Ventricular septal defects	21 (0.5)	1.62 (1.05-2.5)	7 (0.44)	7 (0.44-1.41)	0 (0)	0 (0-0)	3 (0.32)	1.03 (0.33-3.2)	2 (0.35)	1.13 (0.28-4.54)	9 (1.1)	3.6 (1.86-6.96)
Atrial septal defects	34 (0.81)	2.6 (1.84-3.68)	12 (0.75)	12 (0.75-2.41)	1 (0.34)	1.01 (0.14-7.23)	7 (0.75)	2.53 (1.2-5.32)	6 (1.06)	3.51 (1.57-7.87)	8 (0.98)	2.85 (1.35-5.99)
Atrioventricular septal	2 (0.05)	1.25 (0.31-5.02)	0 (0)	-	1 (0.34)	8.71 (1.21-62.64)	0 (0)	-	0 (0)	-	1 (0.12)	3.22 (0.45-23.03)
Of the respiratory system	7 (0.17)	1.41 (0.67-2.98)	2 (0.12)	2 (0.12-1.03)	1 (0.34)	2.66 (0.37-19.02)	1 (0.11)	0.94 (0.13-6.67)	1 (0.18)	1.52 (0.21-10.8)	2 (0.24)	2.09 (0.52-8.38)
Oro-facial clefts	6 (0.14)	1.02 (0.46-2.27)	4 (0.25)	4 (0.25-1.8)	0 (0)	-	1 (0.11)	0.76 (0.11-5.4)	0 (0)	0 (0-0)	1 (0.12)	0.88 (0.12-6.24)
Of the digestive system	13 (0.31)	1.8 (1.04-3.12)	7 (0.44)	7 (0.44-2.5)	0 (0)	-	2 (0.22)	1.25 (0.31-5)	2 (0.35)	2.09 (0.52-8.39)	2 (0.24)	1.43 (0.36-5.74)
Abdominal wall defects	1 (0.02)	1.04 (0.14-7.44)	1 (0.06)	1 (0.06-2.54)	0 (0)	-	0 (0)	-	0 (0)	-	0 (0)	-
Of the internal urinary system	11 (0.26)	0.84 (0.45-1.57)	9 (0.56)	9 (0.56-2.02)	0 (0)	-	0 (0)	-	0 (0)	-	2 (0.24)	0.44 (0.06-3.11)
Of the external genital organs	19 (0.45)	1.55 (0.99-2.44)	8 (0.5)	8 (0.5-1.7)	1 (0.34)	1.08 (0.15-7.67)	3 (0.32)	1.09 (0.35-3.38)	6 (1.06)	3.83 (1.71-8.57)	1 (0.12)	0.41 (0.06-2.93)
Of the limbs	53 (1.27)	0.93 (0.71-1.23)	24 (1.49)	24 (1.49-1.13)	1 (0.34)	0.25 (0.04-1.75)	10 (1.08)	0.76 (0.41-1.42)	7 (1.23)	0.91 (0.43-1.92)	11 (1.35)	1 (0.55-1.81)
Of the musculoskeletal system	8 (0.19)	1.29 (0.64-2.59)	3 (0.19)	3 (0.19-1.25)	1 (0.34)	2.18 (0.31-15.57)	2 (0.22)	1.46 (0.36-5.85)	1 (0.18)	1.2 (0.17-8.55)	1 (0.12)	0.83 (0.12-5.9)
Chromosomal abnormalities	7 (0.17)	1.57 (0.74-3.31)	1 (0.06)	1 (0.06-0.59)	0 (0)	-	1 (0.11)	0.97 (0.14-6.92)	3 (0.53)	4.65 (1.49-14.53)	2 (0.24)	2.35 (0.59-9.45)

Other malformations	9 (0.22)	1.36 (0.68-2.74)	4 (0.25)	4 (0.25-1.32)	0 (0)	-	4 (0.43)	3.08 (1.15-8.23)	0 (0)	-	1 (0.12)	0.88 (0.12-6.28)
And teratogenic syndromes	2 (0.05)	2.78 (0.67-11.6)	1 (0.06)	1 (0.06-3.58)	0 (0)	-	0 (0)	-	0 (0)	-	1 (0.12)	10.13 (1.36-75.44)
Genetic syndromes	1 (0.02)	0.39 (0.06-2.78)	0 (0)	-	0 (0)	-	1 (0.11)	1.79 (0.25-12.76)	0 (0)	-	0 (0)	-

Incidence is presented as number of cases (N) with percentages (%). Estimates of multivariable logistic regressions are presented as Odds Ratios (OR) with 95% confidence intervals (95% CI) [a]Multivariable logistic regressions are adjusted for mother's age, parity, income, education, smoking and year of conception.

Supplement B. Risk of congenital malformations among women exposed to an SSRI vs. women with no exposure further adjusted for co-medication.

	Exposed to any SSRI				No exposure
	First trimester N=4183		Paused during pregnancy N=806		N=843 797
Outcome	N (%)	OR (96% CI)	N (%)	OR (96% CI)	N (%)
Major malformations	208 (4.97)	1.32 (1.14-1.52)	36 (4.47)	1.27 (0.91-1.77)	29703 (3.52)
Congenital malformations of the heart	77 (1.84)	1.98 (1.57-2.49)	13 (1.61)	1.84 (1.06-3.19)	7755 (0.92)
Septal defects	49 (1.17)	2.00 (1.50-2.67)	11 (1.36)	2.54 (1.40-4.62)	4826 (0.57)
Ventricular septal defects	21 (0.50)	1.58 (1.02-2.44)	9 (1.12)	3.71 (1.92-7.17)	2803 (0.33)
Atrial septal defects	34 (0.81)	2.54 (1.79-3.60)	6 (0.74)	2.60 (1.16-5.81)	2490 (0.30)
Congenital malformations of the digestive system	13 (0.31)	1.74 (1.00-3.02)	1 (0.12)	0.74 (0.10-5.29)	1545 (0.18)
Congenital malformations of the internal urinary system	11 (0.26)	0.86 (0.46-1.60)	-	-	2333 (0.28)
Congenital malformations of the external genital organs	19 (0.45)	1.53 (0.97-2.41)	2 (0.25)	0.89 (0.22-3.57)	2504 (0.30)
Congenital malformations of the limbs	53 (1.27)	0.93 (0.71-1.22)	14 (1.74)	1.36 (0.80-2.31)	11785 (1.40)

Estimates are presented as Odds Ratios (OR) with 95% confidence intervals (95% CI). Multivariable logistic regressions are adjusted for mother's age, parity, income, education, smoking, year of conception and co-medication with psycholeptics and antidiabetics.

Supplement C. Adjusted odds Ratios (OR) and 95% confidence intervals (95% CI) for association between congenital malformations among women pausing SSRI treatment three, six or nine months before pregnancy

	Three months (n=806)		Six months (n=681)		Nine months (n=441)	
Outcome	**N (%)**	**OR (95% CI)**	**N (%)**	**OR (95% CI)**	**N (%)**	**OR (95% CI)**
Major malformations	36 (4.47)	1.27 (0.91-1.78)	29 (4.26)	1.21 (0.83-1.75)	19 (4.31)	1.22 (0.77-1.93)
Congenital malformations of the heart	13 (1.61)	1.85 (1.07-3.20)	12 (1.76)	2.02 (1.14-3.57)	8 (1.81)	2.07 (1.03-4.17)
Septal defects	11 (1.36)	2.56 (1.41-4.64)	10 (1.47)	2.73 (1.46-5.09)	6 (1.36)	2.52 (1.12-5.64)
Ventricular septum defects	9 (1.12)	3.74 (1.93-7.23)	8 (1.17)	3.90 (1.94-7.85)	4 (0.91)	3.00 (1.12-8.04)
Atrial septum defects	6 (0.74)	2.61 (1.17-5.84)	5 (0.73)	2.55 (1.05-6.14)	3 (0.68)	2.35 (0.75-7.31)
Congenital malformations of the digestive system	1 (0.12)	0.75 (0.11-5.35)	1 (0.15)	0.90 (0.13-6.41)	1 (0.23)	1.41 (0.2-10.01)
Congenital malformations of the internal urinary system	-	-	-	-	-	-
Congenital malformations of the external genital organs	2 (0.25)	0.89 (0.22-3.59)	-	-	-	-
Congenital malformations of the limbs	14 (1.74)	1.37 (0.80-2.32)	11 (1.62)	1.26 (0.70-2.30)	7 (1.59)	1.23 (0.58-2.60)

Estimates are presented as Odds Ratios (OR) with 95% confidence intervals (95% CI). Multivariable logistic regressions are adjusted for mother's age, parity, income, education, smoking and year of conception.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-8*
Bias	9	Describe any efforts to address potential sources of bias	7,8
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7,8
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9,10
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	9,10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-16
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14-16
Discussion			
Key results	18	Summarise key results with reference to study objectives	16,17
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-21
Generalisability	21	Discuss the generalisability (external validity) of the study results	21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.