Exposure to antidepressants during pregnancy - prevalences and outcomes

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This review has been accepted as a thesis together with three previously published papers by University of Copenhagen on 6th September 2013 and defended on 28th November 2013

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Dan Med J 2014;61(9): B4916

1. PREFACE

The PhD thesis is the result of studies performed during my fellowship at the Laboratory of Clinical Pharmacology Q7642 at Rigshospitalet, a remote function of the Department of Clinical Pharmacology, Bispebjerg Hospital, Copenhagen, between 2010 and 2013.

The thesis is based on three studies:

I

Jimenez-Solem E, Andersen JT, Petersen M, Broedbaek K, Andersen NL, Torp-Pedersen C, Poulsen HE. (2013) **Prevalence of antidepressant use during pregnancy in Denmark, a nation-wide cohort study.** PLoS ONE 8(4): e63034. doi:10.1371/journal.pone.0063034

II

Jimenez-Solem E, Andersen JT, Petersen M, Broedbaek K, Jensen JK, Afzal S, Gislason GH, Torp-Pedersen C, Poulsen HE. **Exposure to selective serotonin reuptake inhibitors and the risk of congenital malformations: a nationwide cohort study**. BMJ Open 2012;2:e001148. doi:10.1136/bmjopen-2012-001148

III

Jimenez-Solem E, Andersen JT, Petersen M, Broedbaek K, Lander AR, Afzal S, Torp-Pedersen C, Poulsen HE. **SSRI Use During Pregnancy and Risk of Stillbirth and Neonatal Mortality.** Am J Psychiatry. 2013 Jan 30. doi: 10.1176/appi.ajp. 2012.1108125

2. ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical Classification System
BMI	Body Mass Index (kg/m^2)
CI	Confidence Interval
ICD-10	International Classification of Diseases, version 10
OR	Odds Ratio
SSRI	Selective Serotonin Reuptake Inhibitor
TCA	Tricyclic Antidepressant

3. INTRODUCTION

It is estimated that approximately 20 % of women of childbearing age (25-45 years),[1, 2] and up to 15 % of pregnant women suffer from depressive symptoms.[3, 4] Untreated depression can have serious consequences for the mother, the newly born and their family. Depression during pregnancy is associated with preterm delivery, low birth weight, epidural analgesia, caesarean section, intensive ward admission, and disturbances in the child's neurocognitive and socioemotional development.[4-8] Untreated depression during pregnancy is associated with a 6-fold risk increase of postpartum depression.[4, 9]

Treatment of depression during pregnancy is a challenge, where careful risk-benefit analyses have to be made for each individual patient. Mild depression is not usually treated with antidepressants, while major depression is treated pharmacologically. The most commonly prescribed pharmacological treatment against depression during pregnancy is selective serotonin reuptake inhibitors (SSRIs).[10-13] 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.[11-15] It is important to know the prevalence of prenatal exposure to antidepressants in order to estimate its potential public health consequences. Therefore, we set out to quantify the percentage of pregnant women in treatment with antidepressants in Denmark. We assessed temporal trends over the years 1997-2010, and use in relation to pregnancy. Additionally, we looked at maternal characteristics associated with antidepressant exposure. [I]

Several studies have analysed the consequences of this treatment on pregnancy outcomes, and indicated an increased risk of congenital malformations[16, 17], and more notably heart defects.[18-28] However, the data are conflicting[18, 20, 23-25, 29-39] and studies including up to a million pregnancies indicate little risk of congenital

Table 1:

		Study		
Register	**Information included in register**	**I Use of antidepressants**	**II Risk of congenital malformations**	**III Risk of stillbirth and neonatal mortality**
Medical Birth Register [49]	*Mothers´ age, parity, BMI and smoking. Offspring's time of gestation and conception.*	Identification of study population: All pregnancies 1997-2010 N=920 639	Identification of study population: All pregnancies 1997-2009 N= 848 786	-
The Danish Fertility Database [50-52]	*Mothers´ age and parity, Offspring's gestational age and time of death.*	-	-	Identification of study population: All pregnancies 1995-2008 N= 920 620
The Danish National Hospital Register [53]	*All admission dates, discharge dates and diagnoses.*	Identification of hospitalization dates to calculate exposure periods.	Identification of hospitalization dates to calculate exposure periods. Diagnoses of congenital malformations	Identification of hospitalization dates to calculate exposure periods. Diagnoses of smoking.
The Danish National Prescription Register [54, 55]	*Records of all redeemed prescriptions at community pharmacies; date, type, strength and quantity.*	Identification of antidepressant exposure periods.	Identification of antidepressant exposure periods.	Identification of SSRI exposure periods.
Register of Income Statistics [48]	*Annual income statistics for anyone who is economically active in Denmark.*	Household income at birth year		
Register of Education and Training Statistics [48]	*Annually updated information on highest obtained level of education for all residents in Denmark.*	Highest obtained educational level of the mother		

Overview of information sources used to construct the individual study populations included in each study of the thesis [I, II, III]

malformations[18,23, 25, 37, 38]. On the other hand, studies show a clear association between SSRI use and persistent pulmonary hypertension of the newborn.[40] 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 widespread use, we performed a nationwide study of the relation between use of antidepressants 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. [II]

Some of these conditions and malformations are potentially fatal both *in utero* and during the neonatal period, but information on the risk of stillbirth or neonatal mortality for children exposed to SSRIs *in utero* is still limited.[41, 42] Large cohorts are needed to assess the risk of these rare outcomes. Until now only one large cohort-study has dealt with this issue and found no increased risk of perinatal mortality. [41]

The Danish Medicines Agency issued in 2011 a warning about a possible association between *in utero* exposure to SSRIs and perinatal mortality. The concerns were based on several case reports of perinatal death after *in utero* exposure to SSRIs. The etiologies of these cases were congenital anomalies, persistent pulmonary hypertension and/or serotonin withdrawal symptoms [43, 44]. These conditions have previously been associated with maternal SSRI use during pregnancy [23, 39]. Symptoms of discontinuation syndrome have been described in neonates exposed to SSRIs *in utero* for up to 28 days after birth.[45] We therefore investigated whether *in utero* exposure to SSRIs during pregnancy is associated with an increased risk of stillbirth or neonatal mortality. [III]

4. MATERIALS AND METHODS

Data from Danish nationwide health registers are the bases of the present PhD thesis. At birth, all Danish citizens are given a unique permanent identification number[46, 47] that enables personalized information to be linked across databases, and places Denmark at the pinnacle of register-based research. Table 1 shows the information gathered from each register to construct the study population for each study included in the thesis. For detailed description of methods and materials, please consult the individual studies. [I, II, III]

IDENTFICATION OF ANTIDEPRESSANT PHARMACOTHERAPY

To estimate exposure prevalence we calculated dosages for each individual in the cohort, based on the dispense date of each prescription, strength and number of tablets prescribed. Detailed description of how exposure periods were calculated is described in Study I. [I]

STATISTICS

Data management and all statistical analyses were performed using SAS, version 9.2 (SAS Institute, Cary, N.C.). The threshold for statistical significance was set at a p value of 0.05. All statistical tests were two-sided. Odds ratios are presented with 95 % confidence intervals.

ETHICS

All personal information held in the registers was encrypted and analyzed on computers held by Statistics Denmark.[48] In Denmark The Act on Processing of Personal Data does not require ethical permission or obtained written informed consent for anonymised retrospective register studies. The present study has been approved by The Danish Data Protection Agency (No. 2008-41-2517).

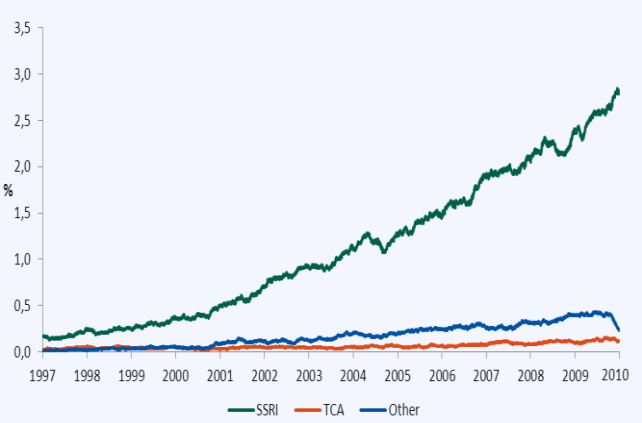
5. RESULTS

The main results are presented in the following, with focus on results considered in the discussion. For a more detailed presentation of the results, please consult the individual studies. [I, II, III]

PREVALENCE OF ANTIDEPRESSANT USE DURING PREGNANCY IN DENMARK [I]

We identified 19 740 pregnancies (2.2 %) exposed to an antidepressant at some point during pregnancy. These women were characterized by being older, having more prior pregnancies, having lower annual household income, having a shorter educational career, smoking more and having a higher BMI than unexposed women. Most were exposed to an SSRI (n=16 928), followed by other antidepressants (n=3 135) and TCAs (n=1 297).

Figure 1:



Point prevalence of pregnant women in treatment with an antidepressant between 1997 and 2010 based on estimated treatment periods. SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressants; AD, antidepressant.

Exposure between 1997 and 2010

Between January 1997 and January 2010, the percentage of pregnant women exposed to an antidepressant increased from 0.2 % in early 1997 to 3.2 % in December 2009 (figure 1). The biggest increase was seen for SSRIs, where citalopram and sertraline were the preferred SSRIs at the end of the period. In contrast, use of fluoxetine has been decreasing since 2007 (figure 2). The prevalence of exposure to TCAs remained steady since 1997 at an average of 0.03 % of pregnancies (figure 1). Amitriptyline and nortriptyline represented over 70 % of TCA exposure. Exposure to other antidepressants increased in the study period reaching a maximum peak point prevalence of 0.4 % of pregnant women in August 2009 (figure 1). Venlafaxine was the preferred antidepressant of its class.

Figure 2

Point prevalence of pregnant women in treatment with an SSRI based on estimated treatment periods.

Exposure in relation to pregnancy

At the time of conception, 16 962 (1.9 %) of all pregnancies were exposed to an antidepressant, of these, 51 % were still exposed at the time of delivery. The greatest decrease in antidepressant exposure is consistent with the period of pregnancy recognition (first trimester) (figure 3). 1 694 (0.2 %) pre-pregnancy treatment naïve women commenced treatment with an antidepressant at some point during pregnancy. Within the first twelve months after delivery 11 151 (1.2 %) commenced treatment among women who had never been in treatment with an antidepressant before the time of delivery.

This pattern of exposure from 6 months before to 12 months after pregnancy was similar for the individual antidepressants, except for fluoxetine (figure 4). For fluoxetine, we saw a rise in prevalence after conception followed by a slight decrease until delivery.

Figure 3:

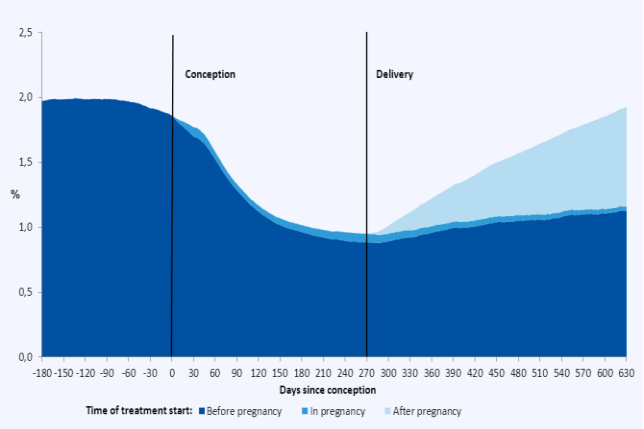
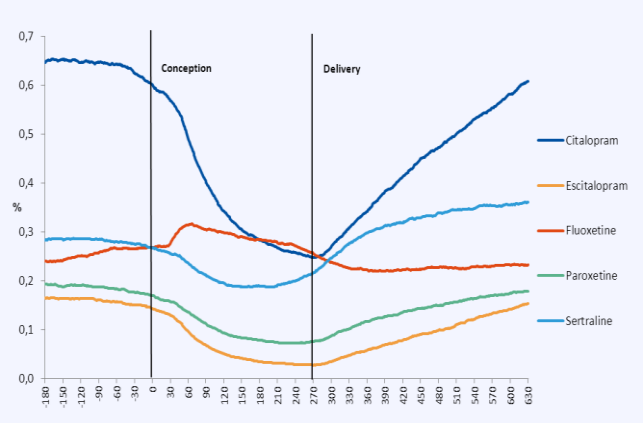


*Figure 3 Percentage of pregnant women in treatment with an antidepressant for each day from 180 days before conception to 630 days after conception (approximately 1 year after mean time of delivery). The figure is divided into three areas of different color indicating the period of treatment start; before (**dark blue**), during (**blue**) or after pregnancy (**light blue**).*

Figure 4:



Percentage of pregnant women in treatment with a specific SSRI for each day from 180 days before conception to 630 days after conception (approximately 1 year after mean time of delivery).

Antidepressant switch during pregnancy

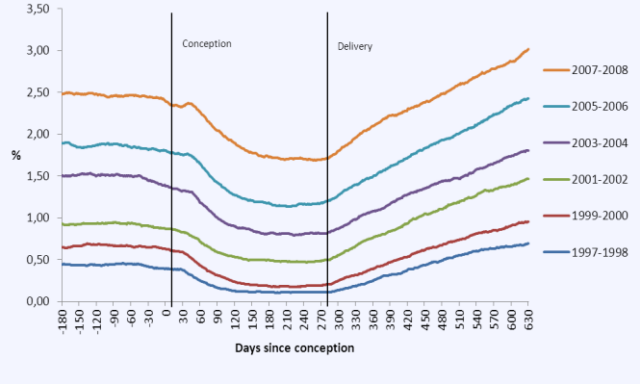
While 43.3 % (n=8 552) stopped antidepressant treatment during pregnancy, 11.3 % (n=2 224) of pregnant women switched to a different antidepressant. Among those who switched treatment, the preferred new antidepressant was fluoxetine (41.7 %) followed by citalopram (20.5 %) and sertraline (19.1 %).

Exposure in relation to pregnancy, 1997-2009.

Figure 5 shows changes in antidepressant exposure patterns in relation to pregnancy between 1997 and 2008. The same pattern can be seen for the analysed periods, with an absolute increase in exposure over time. However, the rate of antidepressant discontinuation has decreased over the years reaching 12 % in 2009 (figure 6). In contrast, the relative increase in exposure preva-

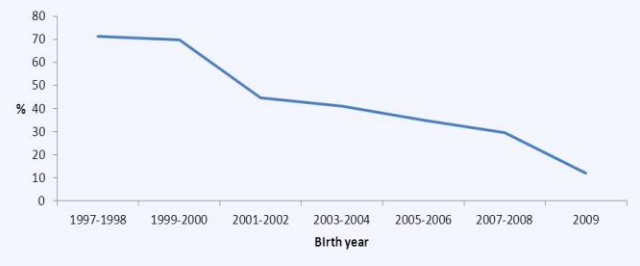
lence seen within one year after delivery has fallen from 7-fold increase in 1997-1998 to a 2-fold increase in 2007-2008 (figure 5).

Figure 5:



Percentage of pregnant women in treatment with an antidepressant for each day from 180 days before conception to 630 days after conception (approximately 1 year after mean time of delivery) according to birth year. 2009 is not included due to lack of data for the year after delivery.

Figure 6:



Percentage of women discontinuing treatment with an antidepressant during pregnancy according to birth year.

EXPOSURE TO SSRIS AND THE RISK OF CONGENITAL MALFORMATIONS [II]

We identified 4 183 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 2 presents the association between exposure to SSRIs and major congenital malformations and specific septal congenital defects of the heart.

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 per 1000 unexposed pregnancies. 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 with congenital malformations of the heart, and congenital malformations of the digestive system, 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. 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 (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.

Table 2:

	Exposed to any SSRI					No exposure
	First trimester N=4183		Paused during pregnancy N=806			N=843 797
Outcome	N (%)	OR (95 % CI)	N (%)	OR (95 % 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	29 703 (3.52)
Heart	77 (1.84)	2.01 (1.60-2.53)	13 (1.61)	1.85 (1.07-3.20)	0.94	7 755 (0.92)
Septal defects	49 (1.17)	2.04 (1.53-2.72)	11 (1.36)	2.56 (1.41-4.64)	0.35	4 826 (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	2 803 (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	2 490 (0.30)
Digestive system	13 (0.31)	1.80 (1.04-3.12)	1 (0.12)	0.75 (0.11-5.35)	0.59	1 545 (0.18)
Internal urinary system	11 (0.26)	0.84 (0.45-1.57)	-	-	-	2 333 (0.28)
External genital organs	19 (0.45)	1.55 (0.99-2.44)	2 (0.25)	0.89 (0.22-3.59)	0.46	2 504 (0.30)
Limbs	53 (1.27)	0.93 (0.71-1.23)	14 (1.74)	1.37 (0.80-2.32)	0.18	11 785 (1.40)

Table 2 Risk of major congenital malformations. 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] Multivariate logistic regressions are adjusted for mother's age, parity, income, education, smoking and year of conception.

Other Analyses

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).

Dosage

We found an adjusted odds ratio for major malformations: OR 1.26 (95 % CI, 1.05-1.51) for low dose exposure and 1.44 (95 % CI, 1.15-1.79) for high dose exposure (p for difference=0.29).

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.

EXPOSURE TO SSRIS AND THE RISK OF STILLBIRTH AND NEONATAL MORTALITY [III]
The cohort of these analyses consists of 920 620 pregnancies, of which 12 425 were exposed to an SSRI: 3 982 with first-trimester exposure, 2 065 with first and second-trimester exposure, and 6 378 with exposure in all trimesters.

Risk of stillbirth
We identified 75 (0.60 %) stillbirths among women exposed to an SSRI during pregnancy compared to 3 938 stillbirths (0.43 % of all births) among unexposed women. In unadjusted analyses, exposure to an SSRI in all trimesters (but not for first-trimester or first- and second-trimester exposure) was significantly associated with stillbirth (OR=1.55, 95 % CI=1.14–2.10) compared with unexposed pregnancies. Adjusting our model rendered this association non-significant (OR=1.06, 95 %CI=0.71–1.58). When stratifying for different SSRIs, we did not find an increased risk of stillbirth with exposure in any trimester. [III]

Neonatal Mortality
There were 3 091 neonatal deaths (0.34 %) between 1995 and 2008 in our study population. We identified 47 (0.38 %) neonatal deaths among women exposed to an SSRI during pregnancy.
We found no association between exposure to an SSRI in any trimester and neonatal mortality. Stratifying exposure to different SSRIs revealed an association between three-trimester exposure to citalopram and neonatal mortality: adjusted OR=2.49 (95 % CI, 1.33-4.65). Estimates for the remaining SSRIs and trimesters were not statistically significant. [III]

6. DISCUSSION
In order to assess whether antidepressants increase the risk of severe negative birth outcomes we performed a retrospective nation-wide cohort study analyzing the association between exposure to antidepressants during pregnancy and stillbirth, neonatal mortality and major congenital malformations. Furthermore we analyzed exposure patterns to antidepressants in relation to pregnancy. The overall hypothesis that antidepressants are associated with severe negative birth outcomes is not supported by our findings.
In the following, we discuss each study´s results, and their relation to previously published literature.

PREVALENCE OF ANTIDEPRESSANT USE DURING PREGNANCY [I]
Consequences of the use of antidepressants in relation to pregnancy is associated with great uncertainty. By ascertaining the possible relations between antidepressants and severe pregnancy outcomes we have given mothers and physicians better tools to decrease this uncertainty. In spite of the insecurity related to these drugs, the numerous publications and the extensive negative media coverage we find a pronounced increase (16-fold) in their use during pregnancy over time. In comparison, use of drugs in Denmark increased 67 % between 1997 and 2007[56], and use of antidepressants in the general population increased 87 % between 1999 and 2011.[57] The increase in use seen among pregnant women is larger than the general population trend and therefore probably not solely due to the general increase of drug use in Denmark. The same is applicable for the increase in exposure over the years seen in the period of lactation (figure 5).
We found an increase in prevalence of exposure during the study period from 0.2 % to 3.2 %. Furthermore we described a decrease in exposure to antidepressants related to the time of pregnancy recognition, and a steep increase in exposure among pre-pregnancy treatment-naïve after delivery.

Exposure rates, 1997-2010
The increase in prevalence over the years is comparable to studies from other countries, although our estimates are considerably lower.[10, 12, 14, 15, 58, 59] Two studies from the USA describe prevalences of 7.6 % in 2005[12] and 13.3 % in 2003.[58] Two studies from The Netherlands reported prevalences of 2 % between 2000 and 2003 and 3 % in 2004.[14] The first three studies were based on health insurance records and the fourth on data from a Dutch region. One study from the UK estimated a prevalence of 3.3 % in 2006, based on data from general practices.[59] None of the mentioned studies were based on nation-wide cohorts as the present study. Differences in prevalence could be accounted for by study methodology, and sociodemographic differences.
The increasing exposure to antidepressant during pregnancy until 2010 was mainly due to redemption of SSRIs, where citalopram was the most frequently used SSRI in 2009. Use of paroxetine has stagnated since 2004, and accounted for only 5.3 % of SSRI use in 2008 (figure 2), and could be due to reports published in 2005 by the FDA associating paroxetine with heart defects.[60] Use of TCAs and other antidepressants increased at a more moderate rate between 1997 and 2010.
One possible reason for the increase in antidepressant use over the last 13 years is the widening of usage and therapeutic indications for antidepressants to include anxiety disorders, premenstrual syndrome, posttraumatic stress disorders, migraine prophylaxis, pain and eating disorders.[61] We hypothesize that a second reason could be a more liberal prescription of antidepressants during pregnancy. We find a decrease in the rate of antidepressant discontinuation during pregnancy in the study period (figure 6), which may support our hypothesis. In spite of many studies reporting increased risks of congenital malformations associated with antidepressants, the absolute risk increases are low. On the other hand, in spite of doctor recommendation, only 35 % of pregnant women reported to be willing to take antidepressants during pregnancy in an American study.[62] Thirdly, it has been suggested that influence by the pharmaceutical industry could play a role in the increased use of antidepressants during pregnancy.[63]
Increased rates of exposure to some newer antidepressants (e.g. escitalopram) will open for the possibility of safety studies on these drugs and their possible association with less frequent pregnancy outcomes (e.g. specific congenital malformations and persistent pulmonary hypertension of the new-born).

Exposure in relation to pregnancy
Overall, at the time of pregnancy recognition we see a considerable decrease in prevalence of antidepressant exposure, and an increase after delivery (figure 3).

Approximately half of all pregnancies discontinued treatment during pregnancy, which is in accordance with previously published literature.[13, 14, 59, 64-66] However, we describe a change in this pattern, from 71 % of pregnant women discontinuing antidepressant treatment during pregnancy in 1997 to 12 % in 2009 (figure 6).

In our study, this decrease was not found for fluoxetine, for which the prevalence increased. This could indicate a switch in treatment to fluoxetine when pregnancy is detected, which is in accordance with recommendations from The Danish Society of Obstetrics and Gynecology (DSOG). DSOG recommends the use of fluoxetine or sertraline during pregnancy[67] which could explain why exposure to sertraline decreased only 26.5 % during pregnancy in contrast to citalopram (60.7 %), escitalopram (81.4 %) and paroxetine (56.0 %). During the first year after pregnancy (period of lactation) we see the steepest increase in use for citalopram (figure 4), which is not in accordance with DSOGs guidelines for treatment during lactation. During lactation DSOG recommends the use sertraline or paroxetine.[67]

During pregnancy, only 1694 (0.19 %) treatment-naïve women commenced use of an antidepressant. This could indicate physicians and women's reluctance towards starting treatment during pregnancy, unless symptoms are severe. It is of note that most of these women continued treatment at least one year after delivery (figure 3).

Pregnancy does not seem to protect against the risk of depression relapse.[68] Discontinuation of antidepressant treatment during pregnancy is associated with a 5-fold increase in the risk of relapse of depression during pregnancy compared to women who maintained their medication[69] and is estimated to create a substantial economic burden on society due to added use of the health care system by mother and child.[70] The cause of discontinuation could be fear of harm to the foetus or physicians' recommendations.[71] Elevated teratogenic risk perception has been correlated with depressive symptomatology during pregnancy.[72] In our study, 27 % of women discontinuing treatment during pregnancy resumed treatment within one year after delivery. This could indicate a low rate of relapse in our Danish cohort comprising antidepressant users without information on depression severity. On the other hand, only 1.3 % of treatment-naïve women commenced antidepressant treatment during the first year after delivery.

RISK OF CONGENITAL MALFORMATIONS [II]

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[27, 73] 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.[24] The number of exposed women in their study was 1 370, compared to ours 4 183. Their study had therefore less power, which could explain why our estimates reached statistical significance. The study concluded 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.[18, 20, 23, 25, 29-39] We find that some of these studies are not comparable to ours because most of them are case-control studies, and with cohorts much smaller than ours.[20, 29-36, 38] 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 [23, 25, 37, 38], and one on Finnish data.[18]

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.[25] 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 multivariate analysis for BMI had little effect on 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.[18] 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 bias 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 [17-19, 22-25, 34, 38, 73], in contrast to studies not identifying this association.[16, 20, 26, 33] 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 0.30 %, 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 congen-

ital malformation would be approximately 6 cases for every 1000 births.

To account for a possible overestimation of exposure periods we performed additional analyses defining exposure as redemption of two 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. [II]

RISK OF STILLBIRTH AND NEONATAL MORTALITY [III]

We found no association between exposure to an SSRI during the three trimesters and stillbirth and neonatal mortality.

Our findings are in accordance with those of a previous study from Sweden of a cohort of 860 215 pregnancies, which reported, as a secondary finding, no increased rates of intrauterine or infant mortality among women redeeming an SSRI prescription during pregnancy.[39] Several other studies have reported no increased risk of perinatal mortality, but these considered substantially fewer exposed pregnancies.[19, 29, 30, 33, 74, 75]

A case-control study by Wen et al. found an increased risk of fetal death (OR=2.23, 95 % CI=1.01-4.93), and infant death (OR=1.96, 95 % CI=0.97-3.94), in a small study of 972 women who redeemed an SSRI prescription in the year before delivery.[36] It is of note that the confidence limits of this latter study almost encompassed a value of neutrality. In contrast to the study by Wen *et al*., we used a large nationwide cohort including all births and all redeemed prescription in the study period. Furthermore, the adjustment variables used by Wen et al. are not comparable to ours. In our study, inclusion of covariates had a major impact on the results. [III]

A recent publication by Stephansson et al analyzed the risk of stillbirth and infant mortality in a cohort including all Nordic countries.[41] Their cohort comprised over 1.6 million pregnancies and was based on nation-wide register data. In comparison to our analyses, they included comorbidity (psychiatric disease, diabetes and hypertension) in their adjusted models, and we included socioeconomic factors (income and education). In spite of these methodological differences the results and conclusions are the same as ours; there is no increased risk of stillbirth or neonatal mortality for SSRI exposed. They do not present adjusted analyses for the individual SSRIs.

No previous study has examined the risk of stillbirth or neonatal mortality stratified for exposure to different SSRIs and trimesters. Although SSRIs have the same primary effect and act on the same 5HT-receptor, their mechanisms of action are not equivalent in terms of pharmacodynamics and pharmacokinetics.[76]

Causes of perinatal mortality for SSRI exposed during specific trimesters could include birth defects (first trimester),[23, 24, 39] intrauterine growth restriction (second trimester),[77, 78] and persistent pulmonary hypertension and serotonin withdrawal symptoms (third trimester).[39, 79] We identified no elevated risk for offspring exposed to an SSRI during the individual trimesters.

On the other hand, we found an association between third-trimester exposure to citalopram and neonatal mortality. We cannot rule out that this might be a chance finding or be due to confounding by indication. Upon correcting our results for multiple testing, using the Bonferroni method, the association ceases to be statistically significant (p=0.08). Furthermore, we did not find this association for the remaining SSRIs, which further suggests that this is a chance finding if SSRIs´ pharmacodynamics are comparable.

STRENGTHS AND LIMITATIONS

We had no information on compliance or the women's intention of commencing a treatment shortly after redemption of an antidepressant. This could lead to an overestimation of treatment periods. However, a Dutch study estimated that the majority of pregnant women redeeming a prescription take their medication.[80] A small Danish study estimated that compliance in Denmark is 80 % for antidepressant treatment during pregnancy.[81]

We did not have information on women discontinuing their treatment to commence treatment with herbal medications against depression (e.g. St John's Wort). A possible overestimation of treatment periods could bias our estimates towards unity and mask a possible association. However, exposure to antidepressants is based on information on prescriptions redeemed and paid for at the pharmacy, which thereby increases the probability of exposure. Information is recorded prospectively and not based on questionnaires or interviews, which eliminates recall bias. Data gathered from the registries include information on drug-names and quantities redeemed. This information is difficult to obtain through questionnaires or interviews of women who have to remember use of medications over a long period of time. [82-85]

We had access to important covariates but it cannot be excluded that unaccounted confounders 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.[86] This study was performed in Canada, and it may not be applicable to Danish women. However, if this assumption is correct, our results might reflect the consequence of closer monitoring of women in treatment, which may overshadow a possible negative effect of the SSRIs. 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.[86] 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. However, more frequent echocardiograms could indicate a more severe symptomatology among the exposed children due to an unaccounted factor.

Importantly, information on drug use for women experiencing a spontaneous or provoked abortion was not included in our analyses, and exposure rates during pregnancy could differ from those reported in our study. If pregnant women exposed to an antidepressant had a higher rate of provoked abortions due to severe malformations it could mask a possible teratogenic effect of the drugs.

The main strength of our studies is the completeness of the registries, including nearly all births in Denmark and the mothers' drug redemptions in the study period. The national Danish registers cover the entire nation and are considered valid. As part of the national health care reimbursement scheme, Danish pharmacies are required by law to register all redeemed prescriptions. Approximately 97.5 % of all redeemed prescriptions are noted in the

The Danish National Prescription Register.[87] The Danish Fertility Database contains records of more than 99 % of all births in the study period.[88] Thus, our study includes nearly all women giving birth in Denmark between 1995 and 2010. This minimizes confounding due to race, educational level, and other socioeconomic factors.

We were not able to fully adjust for potential confounding by indication due to the absence of data on treatment indication. Other potential confounders not included in our databases were the degree of depression, alcohol intake and cause of death for stillbirths.

To our knowledge, this is the first study to address a possible confounding by indication by assessing risks of congenital malformations associated with paused exposure to SSRIs during pregnancy. The congenital malformation diagnoses derived from the Danish National Patient Register have been validated and their quality found acceptable for epidemiological research.[89]

7. CONCLUSIONS

PREVALENCE OF EXPOSURE

Although the overall prevalence of antidepressant use through the last 13 years has increased, half of all pregnant women discontinue their use during pregnancy, probably due to uncertainty of the safety of antidepressants. However, this tendency has changed over time and in 2009 only one out of every eight women discontinued treatment. Based on these findings it seems important for women of childbearing age and physicians to have information of high standards to help them in treatment decisions during pregnancy.

RISK OF CONGENITAL MALFORMATIONS

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.

RISK OF STILLBIRTH AND NEONATAL MORTALITY

Our analyses show no association between exposure to SSRIs during pregnancy and stillbirth or neonatal mortality, apart from a statistically significant association between third-trimester exposure to citalopram and neonatal mortality. We believe this may be a chance finding arising from multiple testing or a result of confounding by indication. This finding needs to be verified in an independent cohort.

8. PERSPECTIVES

Ever since N. M. Gregg demonstrated that rubella caused congenital cataract in 1941 it has been known that agents circulating in the mother´s bloodstream could cross placenta and cause foetal harm.[90] This belief was strengthened in 1961 when W. G. McBride published a letter in The Lancet reporting a substantial risk of congenital malformations associated with intake of thalidomide during early pregnancy.[91] The establishment of thalidomide´s teratogenicity led to drugs being guilty until proven innocent if used during pregnancy. This has led to a variety of drugs being labelled as teratogenic (e.g. mycophenolate, isotretionin and warfarin), but also to a substantial number of women being undertreated for serious illnesses during pregnancy.

It is challenging to prove causality between in utero exposure to a drug and foetal harm. Before a drug is introduced to the marked, studies on teratogenicity have been performed on at least two mammalian species, but results can seldom be directly translated to pregnant women. Randomised controlled trials are not performed on pregnant women, and we are left with epidemiological cohort studies as the best alternative. In order to asses risks of rare outcomes, such as stillbirth or atrial septal defects, very large cohorts are needed which, for practical reasons, excludes randomised controlled trials. The ability to conduct large cohort studies has improved considerably through the past two decades with the development of prescription drug, birth and patient registries. Denmark is in the pinnacle of pharmacoepidemiological research due to their nation-wide registers. The size of the cohorts in these registries enables analyses of rare outcomes, such as specific heart defects, stillbirths or neonatal deaths which we analysed in the present study.

Our overall conclusion is that antidepressants are not associated with increased risks of serious outcomes. However, due to the observational design of our study we cannot rule out a possible causal relation.

The main question still remains though; should pregnant women be treated with antidepressants? The answer is that treatment has to be based on an individual assessment of each woman analysing possible risks versus possible benefit. Due to beliefs of antidepressants being guilty of negative fetal outcomes, a considerable number of pregnant women have discontinued treatment of much-needed antidepressants resulting in increased risks of worsening of symptoms and hospitalization. We believe that the present study brings us one step closer to a verdict of not guilty for the SSRIs. Based on our findings, reports have recently emerged suggesting that SSRIs should be acquitted from being major teratogenic agents.[92, 93]

Further studies are needed to completely dismiss SSRIs, and other antidepressants, from causing fetal harm. The importance of such studies is enhanced by the increasing exposure to antidepressants seen in our Danish study and believed to be even more prominent in other countries, such as the USA. It is crucial for physicians and women of childbearing age to have the best possible information to help them in treatment decisions during pregnancy.

9. SUMMARY

Pharmacological treatment during pregnancy has been a huge challenge since the establishment of thalidomide´s teratogenicity in the early sixties. Analyses of possible risks associated with drug intake during pregnancy are not possible by performing randomized trials, and interspecies extrapolation is challenging. The best available method is through epidemiological studies.

Key messages

- 16-fold increase in the use of antidepressants between 1997 and 2010. Half of all pregnant women discontinue treatment during pregnancy.
- No increased risk of congenital malformations of the heart for children exposed to an SSRI during the first trimester.
- No increased risk of stillbirth or neonatal mortality for children exposed to an SSRI *in utero*.

During the past decade use of antidepressants during pregnancy has been associated with negative birth outcomes, such as congenital malformations. In spite of a considerable number of studies on the subject, the data are still conflicting. The main challenge is how to discern between the effects of the drug and the effect of the depression itself.

We approached this dire problem conducting a nation-wide register based study analyzing the relation between use of antidepressants during pregnancy and the risk of congenital malformations and perinatal mortality. We performed our analysis with focus on women pausing treatment before pregnancy to account for special characteristics associated with women redeeming a prescription for an antidepressant. Furthermore, we report prevalences of antidepressant use, in Denmark, in relation to pregnancy and over time, between 1997 and 2010.

We found that use of antidepressants during pregnancy has increased from 0.2 % in 1997 to 3.2 % in 2010. This considerable increase is mostly due to exposure to selective serotonin reuptake inhibitors (SSRIs). In addition, at the time of pregnancy recognition we saw a halving in prevalence of antidepressant exposure and a steep increase after delivery.

Our analyses showed an association between being in treatment with an SSRI and congenital malformations. However, this increased risk was also found for women pausing treatment before pregnancy. We conclude that the apparent risk associated with use of SSRIs during pregnancy is not related to the drug exposure, but to unknown characteristics associated with mothers redeeming a prescription for an antidepressant. We found no increased risk of stillbirths or neonatal mortality among off-spring exposed in utero to an antidepressant in any of the three trimesters.

The overall conclusion is that antidepressants are not associated with increased risks of congenital malformations and perinatal mortality. However, we cannot rule out a possible causal relation, and treatment must therefore be based on an individual assessment of each woman analysing possible risks versus possible benefit.

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