SSRI Use During Pregnancy and Risk of Stillbirth and Neonatal Mortality

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Objective: The authors investigated whether in utero exposure to selective serotonin reuptake inhibitors (SSRIs) increases the risk of stillbirth or neonatal mortality.

Method: The authors conducted a population-based cohort study using the Danish Fertility Database to identify every birth in Denmark between 1995 and 2008. Time of exposure to SSRIs was calculated on the basis of standard treatment dosages and dispensed pack sizes according to the prescription register. Exposure was divided into first-, second-, and third-trimester exposure. Multivariate logistic regression models were used.

Results: The authors identified 920,620 births; the incidence of stillbirths was 0.45%, and the incidence of neonatal mortality was 0.34%. A total of 12,425 offspring were exposed to an SSRI during pregnancy. Stillbirth was not associated with first-trimester SSRI use (adjusted odds ratio=0.77, 95% CI=0.43–1.36), first- and second-trimester use (odds ratio=0.84, 95% CI=0.40–1.77), or first-, second-, and third-trimester use (odds ratio=1.06, 95% CI=0.71–1.58). Neonatal mortality was not associated with SSRI first-trimester use (odds ratio=0.56, 95% CI=0.25–1.24), first- and second-trimester use (odds ratio=0.90, 95% CI=0.37–2.17), or first-, second-, and third-trimester use (odds ratio=1.27, 95% CI=0.82–1.99).

Conclusions: This study found no association between exposure to SSRIs during pregnancy and stillbirth or neonatal mortality.

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The consequences of in utero exposure to selective serotonin reuptake inhibitors (SSRIs) are uncertain. Despite this uncertainty, use of SSRIs during pregnancy has increased in the past 15 years (1–4). Many studies have analyzed the relationship between SSRI exposure and various pregnancy outcomes, including offspring health conditions and malformations, but the data are conflicting. Some of these conditions and malformations are potentially fatal both in utero and during the neonatal period, but information about the risk of stillbirth or neonatal mortality for offspring exposed to SSRIs in utero remains limited. Large cohorts are needed to assess the risk of these rare outcomes.

The Danish Health and Medicines Authority recently issued 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 in these cases were congenital anomalies, persistent pulmonary hypertension, and/or serotonin withdrawal symptoms (5, 6), conditions that have previously been associated with maternal SSRI use during pregnancy (7, 8). Symptoms of discontinuation syndrome lasting up to 28 days after birth have been described in neonates exposed to SSRIs in utero (9).

In this study, we investigated whether in utero exposure to SSRIs during pregnancy is associated with an elevated risk of stillbirth or neonatal mortality.

Method

We identified all pregnant women who gave birth in Denmark between 1995 and 2008 and the subsequent fetal and neonatal survival of their offspring through the Danish Fertility Database. Exposure to any SSRI was estimated using information in the Register of Medicinal Product Statistics.

Study Population

Since 1968, all Danish citizens have been given a unique 10-digit identification number at birth (10), which enables individualized information to be linked across databases. Using the Danish Fertility Database, we identified 974,805 births between 1995 and 2008. We excluded 1,562 records with coding errors, 20 duplicate records, and 52,603 records with missing data (date of birth and duration of pregnancy), leaving us with valid records of 920,620 births (94.4% of all births).

The Danish Fertility Database contains unique identification numbers for the mother, father, and child, along with information on the mother's age and prior births as well as the child's sex, gestational age, and, when applicable, time of death (11). Time of conception is based on ultrasound estimates and date of last menstrual period. We linked these data with information on redeemed prescriptions from the Register of Medicinal Product Statistics, which contains records from 1995 onward of date of redemption, type of drug, quantity dispensed, strength, and other data (12). The international Anatomical Therapeutic Chemical classification system was used to code all SSRIs. Information on smoking was gathered from the National Hospital Register, which contains information on all hospitalizations in the country, including admittance data and discharge diagnoses (13). Data

TABLE 1. Characteristics of Mothers Exposed to an SSRI During Pregnancy or Unexposed[a]

	Exposed (N=12,406)		Unexposed (N=908,214)		
Characteristic	N	%	N	%	p
Education					<0.001
Low	5,395	43.5	310,111	35.4	
Medium	3,394	27.4	285,766	32.6	
High	3,018	24.3	279,619	31.9	
Annual household income					<0.001
<$62,192	5,208	42.0	224,081	24.7	
$62,192–$89,140	2,526	20.4	227,487	25.1	
$89,141–$126,344	2,197	17.7	227,818	25.1	
>$126,344	2,463	19.9	227,551	25.1	
Age (years)					<0.001
<20	358	2.9	26,268	2.9	
21–25	1,985	16.0	146,868	16.2	
26–30	4,045	32.6	349,882	38.5	
31–35	3,976	32.1	280,973	30.9	
>35	2,042	16.5	104,223	11.5	
Parity					<0.001
1	5,457	44.0	394,313	43.4	
2	4,035	32.5	338,752	37.3	
3	1,979	16.0	129,251	14.2	
>3	935	7.5	45,857	5.1	
Smoking (cigarettes/day)[b]					<0.001
0	6,321	67.0	573,601	81.1	
1–10	1,853	19.6	89,428	12.7	
11–20	1,068	11.3	35,646	5.1	
>20	200	2.1	4,736	0.7	

[a] SSRI=selective serotonin reuptake inhibitor.
[b] Information on smoking was available only for 1996–2007; during that period, 10,303 were exposed to an SSRI during pregnancy and 775,825 were unexposed.

on income and education were gathered from Statistics Denmark (http://www.dst.dk/en).

Identification of Exposure

We identified exposure to five SSRIs: fluoxetine, citalopram, paroxetine, sertraline, and escitalopram. Other SSRIs were not included because the number of exposed women was too small (N<50).

We used the Register of Medicinal Product Statistics to identify all SSRI prescriptions filled during the study period. Exposure periods and dosages were estimated by using the date of prescription, the strength, and the number of tablets prescribed. This method for calculating drug treatment periods has been described previously (14). We defined first-trimester exposure as one or more days of exposure between conception and day 84 of pregnancy, first- and second-trimester exposure as exposure throughout the first trimester and between day 85 and day 196 of pregnancy (second trimester), and exposure in all trimesters as exposure throughout the first and second trimesters and between day 197 of pregnancy and birth (third trimester). Women who began treatment during the first (N=186), second (N=84), or third (N=59) trimester were not included in the study because of the low number of cases.

Outcome Measures

Stillbirth was defined as a child showing no signs of life at birth. Fetal deaths that occurred before 2004 were considered stillbirths if death occurred after 28 completed weeks of gestation. After 2004, fetal deaths were recorded as stillbirths if they occurred after 22 completed weeks of gestation. The method by which data on perinatal mortality are recorded has been described previously (15). Neonatal death was defined as death within 28 days of birth.

Statistical Analysis

Data management and all statistical analyses were conducted using SAS, version 9.2 (SAS Institute, Cary, N.C.). Logistic regression models were used to identify a possible statistical association for dichotomous variables. Odds ratios are presented with 95% confidence intervals (CIs). Baseline characteristics are presented as frequencies and percentages. Chi-square tests were used to assess differences in baseline characteristics for categorical variables. The threshold for statistical significance was set at a p value of 0.05. All statistical tests were two-sided.

Mother's age at birth was stratified into five groups: <20, 21–25, 26–30, 31–35, >35 years (0% missing values). Annual gross household income during the year of birth was divided into quartiles (<1% missing values). Education level was divided into three groups (low, medium, and high) according to the highest level of education attained by the end of the birth year; for missing values, we used information from the next calendar year, resulting in 3.6% missing values. Parity was defined as the number of births, including stillbirths, and divided into four classes: 1, 2, 3, and >3 births (<1% missing values). Multivariate analyses in model 1 were adjusted for these variables and for birth year, which was divided into five categories (1995–1997, 1998–2000, 2001–2003, 2004–2006, and 2007–2008). Analyses for stillbirth were additionally adjusted for prior stillbirths. The largest subgroup within each category was used as the reference.

Multivariate analyses in model 2 were adjusted for all variables in model 1 and for smoking. These analyses included all pregnancies between 1996 and 2007; 1995 and 2008 were excluded because information on smoking during pregnancy was not available for those two years. Smoking was divided into four classes according to the number of cigarettes smoked daily: 0, 1–10, 11–20, and >20 (9.3% missing values). We corrected for multiple testing using the Bonferroni method.

Ethics

To ensure that no individuals could be identified, all personal information held in the registers was encrypted and analyzed on computers held by Statistics Denmark. The study was approved by the Danish Data Protection Agency. Retrospective register studies do not require ethical permission in Denmark.

Results

We identified 920,620 pregnancies, of which 12,425 offspring 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. Women who received treatment with an SSRI during pregnancy were more likely to be older, have less education, have a lower income, and smoke more than women who were not exposed during pregnancy (Table 1).

Stillbirth

There were 3,919 stillbirths (0.43% of all births) in our study population: 2,713 (0.41%) between 1995 and 2004 and 1,206 (0.47%) between 2005 and 2008. We identified 75

TABLE 2. Odds Ratios for Stillbirth With Exposure to Different SSRIs During Pregnancy, by Trimester[a]

			Unadjusted		Adjusted (Model 1)[b]		Adjusted (Model 2)[b]			
Exposure	N	%	Odds Ratio	95% CI	Odds Ratio	95% CI	N	%	Odds Ratio	95% CI
Unexposed (N=908,214)	3,844	0.42	1.00	Reference	1.00	Reference	3,344	0.43	1.00	Reference
Any SSRI										
1st trimester (N=3,982)	21	0.53	1.24	0.80–1.90	0.93	0.59–1.47	18	0.51	0.77	0.43–1.36
1st and 2nd trimesters (N=2,065)	12	0.58	1.36	0.77–2.40	1.09	0.62–1.92	10	0.58	0.84	0.40–1.77
All trimesters (N=6,378)	42	0.66	1.55	1.14–2.10	1.19	0.87–1.63	32	0.63	1.06	0.71–1.58
Fluoxetine										
1st trimester (N=894)	7	0.78	1.84	0.87–3.87	1.50	0.71–3.17	7	0.86	1.37	0.56–3.31
1st and 2nd trimesters (N=720)	6	0.83	1.96	0.88–4.37	1.55	0.69–3.48	4	0.64	0.65	0.16–2.63
All trimesters (N=2,434)	16	0.66	1.54	0.94–2.52	1.20	0.72–2.01	12	0.58	0.97	0.50–1.87
Citalopram										
1st trimester (N=2,063)	9	0.44	1.02	0.53–1.96	0.74	0.37–1.49	8	0.44	0.60	0.25–1.45
1st and 2nd trimesters (N=930)	4	0.43	1.00	0.37–2.68	0.77	0.29–2.07	2	0.27	0.26	0.04–1.88
All trimesters (N=1,800)	13	0.72	1.70	0.98–2.93	1.20	0.68–2.12	10	0.78	1.44	0.74–2.79
Escitalopram										
1st trimester (N=541)	2	0.37	0.87	0.22–3.47	0.62	0.16–2.50	0	0.00		
1st and 2nd trimesters (N=198)	1	0.51	1.20	0.17–8.43	0.82	0.11–5.85	1	0.70	1.29	0.18–9.28
All trimesters (N=212)	1	0.47	1.11	0.16–7.87	0.79	0.11–5.65	0	0.00		
Paroxetine										
1st trimester (N=568)	3	0.53	1.24	0.40–3.84	0.78	0.19–3.12	3	0.56	0.94	0.23–3.78
1st and 2nd trimesters (N=329)	3	0.91	2.15	0.69–6.68	1.88	0.60–5.90	3	0.99	2.28	0.73–7.17
All trimesters (N=734)	4	0.54	1.28	0.48–3.41	1.16	0.43–3.12	4	0.59	0.66	0.17–2.67
Sertraline										
1st trimester (N=773)	5	0.65	1.52	0.63–3.66	1.36	0.56–3.28	5	0.71	1.05	0.34–3.28
1st and 2nd trimesters (N=442)	1	0.23	0.53	0.08–3.75	0.42	0.06–3.00	1	0.27	0.54	0.08–3.87
All trimesters (N=1,654)	9	0.54	1.27	0.66–2.45	1.02	0.53–1.96	7	0.55	1.02	0.46–2.29

[a] SSRI=selective serotonin reuptake inhibitor.
[b] Adjusted for maternal age, household income, education level, parity, birth year, and prior stillbirths; model 2 is additionally adjusted for smoking. The cohort in model 2 comprises all births between 1996 and 2007 (N=786,128).

(0.60%) stillbirths among women exposed to an SSRI during pregnancy (Table 2); 21 (0.53%) with first-trimester exposure, 12 (0.58%) with first- and second-trimester exposure, and 42 (0.66%) with exposure in all trimesters (Table 2).

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 (odds ratio=1.55, 95% CI=1.14–2.10) compared with unexposed pregnancies. Adjusting our model rendered this association nonsignificant (odds ratio$_{\text{model 1}}$=1.19, 95% CI=0.87–1.63; odds ratio$_{\text{model 2}}$=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 (Table 2).

Neonatal Mortality

There were 3,138 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 (Table 3): eight (0.20%) with first-trimester exposure, nine (0.44%) with first- and second-trimester exposure, and 30 (0.47%) with exposure in all trimesters (Table 3).

We found no association between SSRI exposure and neonatal mortality (first-trimester exposure: odds ratio$_{\text{model 2}}$=0.56, 95% CI=0.25–1.24; first- and second-trimester exposure: odds ratio$_{\text{model 2}}$=0.90, 95% CI=0.37–2.17; exposure in all trimesters: odds ratio$_{\text{model 2}}$=1.27, 95% CI=0.82–1.99) (Table 3).

Stratifying exposure to different SSRIs revealed an association between three-trimester exposure to citalopram and neonatal mortality (unadjusted odds ratio=2.50; 95% CI=1.50–4.16; adjusted odds ratio$_{\text{model 1}}$=2.13, 95% CI=1.25–3.62; adjusted odds ratio$_{\text{model 2}}$=2.49, 95% CI=1.33–4.65). Estimates for the remaining SSRIs and trimesters were not statistically significant (Table 3).

Exposure to Two SSRIs

We identified 1,629 pregnancies with exposure to two different SSRIs simultaneously. Among these pregnancies were seven that resulted in stillbirths and five that resulted in neonatal deaths. The most frequently used combinations during pregnancy were fluoxetine and citalopram (N=537) and fluoxetine and sertraline (N=439). Treatment with two SSRIs during pregnancy was not associated with stillbirth (adjusted odds ratio$_{\text{model 1}}$=0.81, 95% CI=0.38–1.70; odds ratio$_{\text{model 2}}$=0.47, 95% CI=0.15–1.48),

TABLE 3. Odds Ratios for Neonatal Mortality With Exposure to Different SSRIs During Pregnancy, by Trimester[a]

			Unadjusted		Adjusted (Model 1)[b]		Adjusted (Model 2)[b]			
Exposure	N	%	Odds Ratio	95% CI	Odds Ratio	95% CI	N	%	Odds Ratio	95% CI
Unexposed (N=908,214)	3,091	0.34	1.00	Reference	1.00	Reference	2,656	0.34	1.00	Reference
Any SSRI										
1st trimester (N=3,982)	8	0.20	0.60	0.30–1.20	0.54	0.27–1.08	6	0.17	0.56	0.25–1.24
1st and 2nd trimesters (N=2,065)	9	0.44	1.30	0.68–2.51	1.18	0.61–2.27	5	0.29	0.90	0.37–2.17
All trimesters (N=6,378)	30	0.47	1.41	0.98–2.02	1.14	0.77–1.68	26	0.51	1.27	0.82–1.99
Fluoxetine										
1st trimester (N=894)	3	0.34	1.00	0.32–3.11	0.88	0.28–2.73	3	0.37	1.18	0.38–3.67
1st and 2nd trimesters (N=720)	4	0.56	1.66	0.62–4.44	1.49	0.56–4.00	4	0.64	1.98	0.74–5.31
All trimesters (N=2,434)	7	0.29	0.86	0.41–1.80	0.58	0.24–1.40	6	0.29	0.63	0.24–1.69
Citalopram										
1st trimester (N=2,063)	5	0.24	0.72	0.30–1.74	0.66	0.27–1.59	4	0.22	0.71	0.27–1.91
1st and 2nd trimesters (N=930)	5	0.54	1.61	0.67–3.87	1.44	0.60–3.47	2	0.27	0.83	0.21–3.32
All trimesters (N=1,800)	15	0.83	2.50	1.50–4.16	2.13	1.25–3.62	12	0.94	2.49	1.33–4.65
Escitalopram										
1st trimester (N=541)	1	0.18	0.56	0.08–3.91	0.50	0.07–3.57	1	0.28	0.86	0.12–6.12
1st and 2nd trimesters (N=198)	0	0.00					0	0.00		
All trimesters (N=212)	1	0.47	1.41	0.20–10.04	1.27	0.18–9.08	1	0.65	2.07	0.29–14.85
Paroxetine										
1st trimester (N=568)	0	0.00					0	0.00		
1st and 2nd trimesters (N=329)	2	0.61	1.82	0.45–7.30	1.66	0.41–6.66	2	0.66	2.08	0.52–8.40
All trimesters (N=734)	4	0.54	1.63	0.61–4.35	1.56	0.58–4.17	4	0.59	1.95	0.73–5.23
Sertraline										
1st trimester (N=773)	3	0.39	1.16	0.37–3.60	1.07	0.34–3.33	2	0.29	0.98	0.24–3.92
1st and 2nd trimesters (N=442)	2	0.45	1.35	0.34–5.42	1.23	0.31–4.94	1	0.27	0.82	0.12–5.85
All trimesters (N=1,654)	3	0.18	0.54	0.17–1.67	0.34	0.08–1.35	3	0.23	0.26	0.04–1.81

[a] SSRI=selective serotonin reuptake inhibitor.
[b] Adjusted for maternal age, household income, education level, parity, and birth year; model 2 is additionally adjusted for smoking. The cohort in model 2 comprises all births between 1996 and 2007 (N=786,128).

nor was it associated with neonatal mortality (adjusted odds ratio$_{\text{model 1}}$=0.86, 95% CI=0.36–2.08; odds ratio$_{\text{model 2}}$=1.21, 95% CI=0.50–2.93).

Discussion

We performed a retrospective nationwide cohort study analyzing the association between exposure to an SSRI during pregnancy and stillbirth and neonatal mortality. We found no association between exposure to an SSRI during the three trimesters and these outcomes.

The main limitations of our study are the observational design and the possibility that SSRI treatment periods were overestimated, since we cannot adjust for any lack of adherence. A possible overestimation of treatment periods could bias our estimates toward unity and mask a possible association. However, adherence to antidepressant treatment during pregnancy in Denmark has been estimated to be 80% (16). In addition, exposure to SSRIs is based on information on prescriptions redeemed and paid for at the pharmacy, which increases the probability of exposure. Information was recorded prospectively, which eliminates recall bias.

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 Register of Medicinal Product Statistics (17). The Danish Fertility Database contains records of more than 99% of all births in the study period (11). Thus, our study includes nearly all women who gave birth in Denmark between 1995 and 2008. This minimizes confounding due to race, education level, and other socioeconomic factors.

We were not able to adjust for potential confounding by indication because we did not have data on treatment indication. As previously shown, confounding by indication is an important potential limitation in studies concerning antidepressant exposure during pregnancy (18). Other potential confounders not included in our databases were the degree of depression, maternal weight (which has been associated with early neonatal mortality [19]), alcohol intake, and cause of death for stillbirths. We did not adjust for comedication.

Our findings are in accordance with those of a previous study from Sweden of a cohort of 860,215 pregnancies, in which, as a secondary finding, the authors reported no elevation in rates of intrauterine or infant mortality among

women who filled an SSRI prescription during pregnancy (8). Several other studies have reported no elevation in risk of perinatal mortality, but these studies considered substantially fewer exposed pregnancies (20–25).

A case-control study by Wen et al. (26) found an elevated risk of fetal death (odds ratio=2.23, 95% CI=1.01–4.93) and infant death (odds ratio=1.96, 95% CI=0.97–3.94) among 972 women who redeemed an SSRI prescription in the year before delivery. Note that the confidence limits in that study almost encompassed a value of neutrality. In contrast to the Wen et al. study, we used a large nationwide cohort including all births and all redeemed prescriptions 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 (Table 2).

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 5-HT receptor, their mechanisms of action are not equivalent in terms of pharmacodynamics and pharmacokinetics (27).

Causes of perinatal mortality for SSRI exposure during specific trimesters could include birth defects (first trimester) (7, 8, 28), intrauterine growth restriction (second trimester) (29, 30), and persistent pulmonary hypertension and serotonin withdrawal symptoms (third trimester) (8, 31). We identified no elevated risk for offspring exposed to an SSRI during the individual trimesters.

On the other hand, we found an association between three-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. After correction for multiple testing, the association was no longer statistically significant. Furthermore, we did not find this association for the remaining SSRIs, which further suggests that it is a chance finding.

We consider it likely that women receiving treatment with an SSRI are more closely monitored during pregnancy and are therefore less likely to have perinatal complications with fatal consequences. A Canadian study found that women exposed to an antidepressant during pregnancy had a 30% higher rate of utilization of ultrasounds in pregnancy (32), although that finding may not be applicable to Danish women. However, if this assumption is correct, our results may reflect the consequence of closer monitoring of women in treatment, which may overshadow a possible negative effect of SSRIs.

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