*Original Research*

# Exposure to Selective Serotonin Reuptake Inhibitors in Early Pregnancy and the Risk of Miscarriage

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**OBJECTIVE:** To investigate whether exposure to selective serotonin reuptake inhibitors (SSRIs) in early pregnancy is associated with miscarriage.

**METHODS:** This was a nationwide cohort study identifying all registered pregnancies in Denmark from 1997 to 2010. All births were identified using the Medical Birth Registry, and all records of induced abortion or miscarriage were gathered from the National Hospital Register. Data on SSRI use were gathered from the National Prescription Register. Cox proportional hazard regression models were used to calculate the hazard of miscarriage in women exposed to an SSRI in early pregnancy and the hazard of miscarriage in women discontinuing treatment before pregnancy.

**RESULTS:** We identified 1,279,840 pregnancies (911,569 births, 142,093 miscarriages, 226,178 induced abortions). Of the 22,884 exposed to an SSRI during the first 35 days of pregnancy, 12.6% (2,883) ended in miscarriage compared with 11.1% among unexposed. The adjusted hazard ratio of having a miscarriage after exposure to an SSRI was 1.27 (95% confidence interval [CI] 1.22–1.33) compared with unexposed. Women discontinuing SSRI treatment 3–12 months before pregnancy also had an increased hazard ratio of having a miscarriage compared to unexposed (1.24, 95% CI 1.18–1.30).

**CONCLUSION:** Women exposed to SSRIs during early pregnancy were at increased risk of miscarriage as were women discontinuing SSRI treatment before pregnancy, and these risks were similar. Therefore, treatment with SSRIs during pregnancy should not be discontinued as a result of fear of miscarriage.

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It is estimated that up to 15% of all women are affected with depressive symptoms during pregnancy.[1,2] Untreated depression has previously been associated with preeclampsia, preterm delivery, low birth weight, and miscarriage.[3–5] Since Bassiouni and Rafei showed that women who experienced miscarriage had a higher concentration of serotonin in the blood compared with women giving birth, there has been a great concern regarding treatment with selective serotonin reuptake inhibitors (SSRIs).[6] In Denmark the number of women being treated with SSRIs during pregnancy has increased 16-fold from 1997 to 2010[7] and in the United States up to 13% of pregnant women are treated with an SSRI in the first trimester.

Several studies have investigated the risk of miscarriage in association with SSRI exposure, but the results are contradictory and none of the studies have successfully managed to differentiate between the consequences of the drugs and the underlying disease.[8–14] A recent Danish study showed a clear association between use of SSRIs during pregnancy and spontaneous abortions.[15] They did not, however, compare their results with women discontinuing exposure during pregnancy. We have previously shown that it is important to include this group of women as comparison when analyzing outcomes related to SSRI intake during pregnancy to account for possible confounding by indication.[16]

Therefore, we conducted a nationwide cohort study to evaluate whether the use of SSRIs during the early part of pregnancy was associated with miscarriage compared with discontinuation of SSRIs 3–12 months before pregnancy.

## MATERIALS AND METHODS

We identified all (1,289,523) registered pregnancies in Denmark between 1997 and 2010.

Using the National Hospital Register[17] we identified all registered cases of miscarriage (O021 and O03 according to the International Classification of Diseases, 10th Danish Revision) and induced abortion (International Classification of Diseases, 10th Danish Revision codes O04, O05 and O06). All live births in the study period were identified through the Danish Medical Birth Registry.[18] We excluded 9,683 records (0.8%) as a result of coding errors.

The National Hospital Register contains information on all hospitalizations in the country, including admittance data and discharge diagnosis.[17] It holds more than 99% of all discharge records from all Danish hospitals.[19] Since 1997, information on gestational length has been added to the diagnoses of induced abortion and miscarriage. The diagnosis of miscarriage has been found to have a positive predictive value of 99% and more than 99% of all discharge diagnoses have been registered in the National Hospital Register.[19,20] All diagnoses are given by the attending physician.

The Danish Medical Birth Registry consist of individual-level data on the mother and father, including a unique identification number, age, previous births and abortions as well as birth weight and length, death and cause of death, sex, and gestational age of the offspring. The time of conception is based on ultrasonograms or information on the date of the last menstrual period. More than 99.5% of all births in Denmark since 1978 are registered in the Danish Medical Birth Registry.[21]

Information on use of prescription medication was collected from the National Prescription Register (the Register of Medicinal Product Statistics).[22,23] The register contains individual-level data on all prescribed drugs dispensed at all pharmacies in Denmark since 1995. Pharmacies are required to register all prescriptions, and this activity is coupled with the reimbursement of expenses from the state, which ensures highly accurate prescription data. Completeness has previously been estimated to be 98%.[24] The register has no information concerning over-the-counter drugs or indication of treatment.

Exposure was defined as dispensing of a prescription of fluoxetine (Anatomical Therapeutic Chemical Classification N06AB03), citalopram (N06AB04), paroxetine (N06AB05), sertraline (N06AB06), or escitalopram (N06AB10). The remaining SSRIs were not included in the study because of low prevalence (less than 50).

We estimated exposure periods and dosages based on the date of prescription, strength, and number of tablets prescribed. The averages of up to seven prior prescriptions based on the standard doses of the individual antidepressants were used to calculate dosages. This method of estimating drug exposure periods during pregnancy has previously been used and is described elsewhere.[16]

To identify all pregnancies exposed to an SSRI during the first trimester with a continuous exposure before pregnancy, we defined exposure as continuous exposure as at least the first 35 days of pregnancy. We did not allow for a change in type of SSRI during this period.

To analyze the importance of dose, the study population was divided into pregnancies exposed to high or low SSRI dose. Based on the recommended daily dose values of the individual SSRIs, doses over the following cutoff 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.

We used Cox proportional hazard regression models with exposure to an SSRI within minimum the first 35 days and time from conception to miscarriage as outcome to estimate the hazard of miscarriage. Time to birth or induced abortion was considered as censoring variables. Prescriptions redeemed after miscarriage or censoring were not included in the analyses.

A priori, an unadjusted model was planned in addition to a model adjusted for maternal age (five categories: younger than 20, 20–24, 25–29, 30–34, and 35 years or older), number of previous miscarriages (four categories: zero, one, two, three or more miscarriages), income (categorized as quartiles), year of outcome or censoring (three categories: 1997–2001, 2002–2006, and 2007–2010), and educational length (four categories: 0–143 months, 144–155 months, 156–179 months, and 180 months or greater).

To investigate whether any association between exposure to SSRIs and miscarriage was the result of confounding by indication, we investigated the hazard of miscarriage for women exposed to SSRIs 3–12 months, 6–12 months, and 9–12 months before pregnancy but not after these periods or during pregnancy.

Data on maternal age, previous registered miscarriages, and income had less than 1% missing values. Information on educational length had 3.4% missing data. Hazard ratios are presented with 95% confidence intervals (CIs). For all analyses, a two-sided $P$ value of $<.05$ was considered statistically

significant. All data management and analyses were performed using SAS 9.2.

In Denmark, the Act on Processing of Personal Data does not require ethical permission or obtained consent for anonymized retrospective register studies. The Danish Data Protection Agency approved the study (no. 2008-41-2517).

We report our findings according to Strengthening The Reporting of OBservational studies in Epidemiology (STROBE).[25]

## RESULTS

We identified 1,279,840 registered pregnancies in the study period of whom 911,569 (71.2%) ended up in live births, 226,178 (17.7%) in induced abortions, and 142,093 (11.1%) in miscarriages. We identified 22,884 (1.8%) women exposed to an SSRI during the first 35 days of pregnancy. Women exposed to an SSRI were more likely to be older ($P<.001$), have a lower educational length ($P<.001$), lower income ($P<.001$), and have experienced more previous miscarriages compared with unexposed women ($P<.001$) (Table 1).

We found 139,210 (11.1%) miscarriages among women not exposed to an SSRI during pregnancy and 2,883 (12.6%) among pregnancies exposed to an SSRI during the first 35 days of pregnancy. The unadjusted hazard of having a miscarriage for pregnancies exposed to an SSRI during the first trimester was 1.31 (95% CI 1.27–1.36) and the adjusted hazard 1.27 (95% CI 1.22–1.33) (Table 2). The hazard of miscarriage for the specific SSRIs can be seen in Table 2.

We identified 14,016 (1.8%) women discontinuing SSRI treatment 3–12 months before conception of whom 1,936 (13.8%) experienced a miscarriage compared with 140,157 (11.1%) among the unexposed women. The unadjusted hazard of having a miscarriage for pregnancies discontinuing SSRI treatment before conception is 1.38 (95% CI 1.32–1.44) and adjusted 1.24 (95% CI 1.18–1.30) (Table 2). The hazard of miscarriage for the specific SSRIs can be seen in Table 2 and Figure 1. The hazard of having a miscarriage for women discontinuing SSRI treatment 6–12 or 9–12 months before conception was similar (Fig. 2). There were no difference in the hazard of miscarriage between women exposed to an SSRI during early pregnancy and women discontinuing treatment 3–12 months before pregnancy ($P$ value for difference=.47), 6–12 months before pregnancy

**Table 1. Basic Characteristics**

| | Women Exposed to SSRIs During the First 35 Days of Pregnancy | Women Not Exposed to SSRIs During the First 35 Days of Pregnancy | | Women Exposed to SSRIs 3–12 Months Before but Not During or 3 Months Before Pregnancy | |
|---|---|---|---|---|---|
| Characteristic | n=22,884 | n=1,256,956 | P* | n=14,016 | P* |
| Age (y) | | | <.001 | | <.001 |
| Younger than 20 | 776 (3.4) | 52,905 (4.2) | | 555 (4.0) | |
| 20–24 | 3,356 (14.7) | 167,223 (13.3) | | 2,611 (18.6) | |
| 25–29 | 5,890 (25.7) | 385,371 (30.7) | | 3,897 (27.8) | |
| 30–34 | 7,002 (30.6) | 408,671 (32.5) | | 3,970 (28.3) | |
| Older than 35 | 5,860 (25.6) | 242,786 (19.3) | | 2,983 (21.3) | |
| Educational length (mo) | | | <.001 | | <.001 |
| 0–143 | 9,521 (42.4) | 349,301 (28.9) | | 6,461 (47.2) | |
| 144–155 | 3,694 (16.5) | 193,998 (16.1) | | 2,106 (15.4) | |
| 156–179 | 4,551 (20.3) | 335,111 (27.7) | | 2,674 (19.5) | |
| 180 or more | 4,691 (20.9) | 329,673 (27.3) | | 2,461 (18.0) | |
| Income | | | <.001 | | <.001 |
| Lowest quartile | 8,707 (38.7) | 305,040 (24.8) | | 5,338 (40.7) | |
| Low quartile | 5,557 (24.7) | 308,190 (25.0) | | 3,346 (25.5) | |
| Medium quartile | 4,364 (19.4) | 309,386 (25.1) | | 2,457 (18.7) | |
| High quartile | 3,851 (17.1) | 309,899 (25.1) | | 1,982 (15.1) | |
| No. of previous miscarriages | | | <.001 | | .002 |
| 0 | 19,278 (84.2) | 1,079,944 (85.7) | | 11,593 (82.7) | |
| 1 | 2,934 (12.8) | 149,541 (11.9) | | 1,959 (14.0) | |
| 2 | 518 (2.3) | 24,606 (2.0) | | 355 (2.5) | |
| 3 or more | 154 (0.7) | 5,865 (0.5) | | 109 (0.8) | |

SSRI, selective serotonin reuptake inhibitor.
Data are n (%) unless otherwise specified.
* Likelihood ratio $\chi^2$ tests were used to assess the overall $P$ value for the group comparison with pregnancies exposed to an SSRI during the early pregnancy.

**Table 2. Hazard Ratio of Miscarriage After Exposure to Selective Serotonin Reuptake Inhibitors During and Before Pregnancy**

| Exposure | Adjusted* HR of Miscarriage in Women Exposed During the First 35 Days of Pregnancy Compared With Those Unexposed | Adjusted* HR of Miscarriage in Women Discontinuing Treatment 3–12 Months Before Pregnancy Compared With Those Unexposed | *P* |
|---|---|---|---|
| Any SSRI | 1.27 (1.22–1.33), 22,884 | 1.24 (1.18–1.30), 14,016 | .47 |
| Citalopram | 1.29 (1.21–1.37), 9,927 | 1.26 (1.17–1.35), 6,857 | .94 |
| Escitalopram | 1.25 (1.09–1.42), 2,377 | 1.33 (1.17–1.51), 1,839 | .13 |
| Fluoxetine | 1.10 (1.01–1.21), 4,111 | 1.17 (1.03–1.33), 1,738 | .69 |
| Paroxetine | 1.27 (1.14–1.42), 2,739 | 1.20 (1.05–1.37), 1,469 | .59 |
| Sertraline | 1.45 (1.33–1.58), 4,453 | 1.20 (1.08–1.34), 2,755 | .13 |

HR, hazard ratio; CI, confidence interval; SSRIs, selective serotonin reuptake inhibitors.
Data are HR (95% confidence interval), n unless otherwise specified.
* Adjusted for year of outcome or censoring, maternal age, educational length, income, and the number of previous miscarriage.

(*P* value for difference=.59), and 9–12 months before pregnancy (*P* value for difference=.99).

We analyzed a possible dose–response relation to investigate whether women exposed to a high daily dose of SSRIs were more likely to experience a miscarriage compared directly with women exposed to a low daily dose of SSRI. Women exposed to a low daily dose of SSRI had an adjusted hazard of 1.00 (95% CI 0.91–1.09) of having a miscarriage compared with women exposed to a high dose of SSRI (Table 3).

Furthermore, we did not find any increased hazard of miscarriage in women exposed to more than one SSRI during the first 35 days of pregnancy compared with women exposed to only one SSRI (hazard ratio [HR] 1.12, 95% CI 0.90–1.39).

To identify other confounders, we analyzed the hazard of miscarriage in women exposed to an SSRI before (discontinued use) and during pregnancy and adjusted the model further for antipsychotics (Anatomical Therapeutic Chemical Classification N05A), anxiolytics (N05B), thyroid preparations (H03A), antithyroid preparations (H03B) and drugs used in diabetes (A10) (Table 4). The HR did not differ from the original model (HR 1.25; 95% CI 1.20–1.30 for discontinued exposure and HR 1.27; 95% CI 1.21–1.34 for exposure during pregnancy).

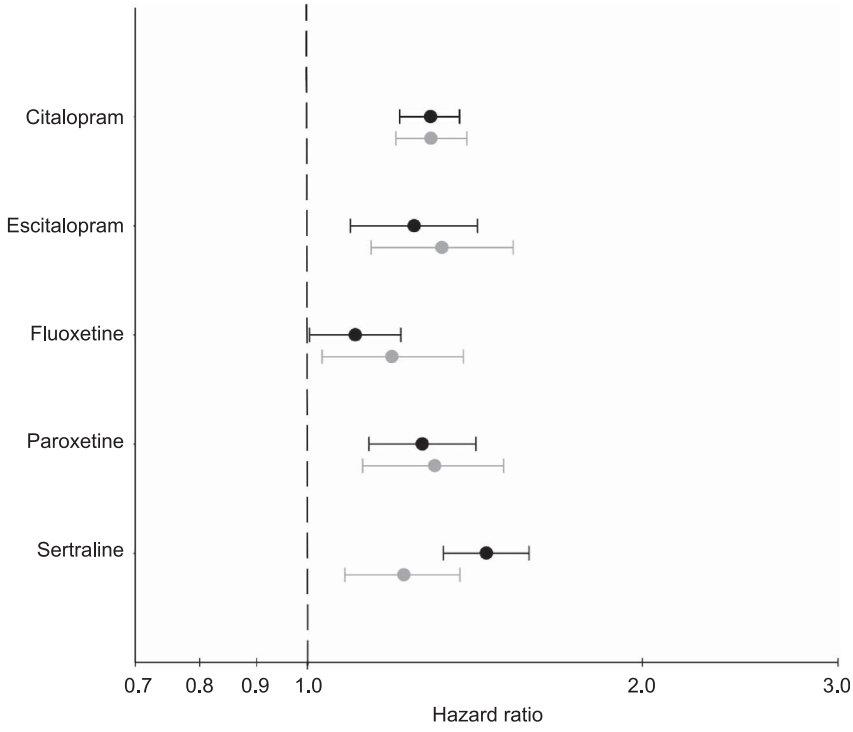


**Fig. 1.** Hazard of miscarriage in women exposed to a selective serotonin reuptake inhibitor (SSRI). The black line represents the hazard ratio of miscarriage in women exposed during the first 35 days of pregnancy compared to unexposed women. The gray line represents the hazard ratio of miscarriage in women discontinuing SSRI treatment 3–12 months prior to pregnancy compared to unexposed women. Hazard ratios are adjusted for year of outcome or censoring, maternal age, educational length, income, and the number of previous miscarriages.

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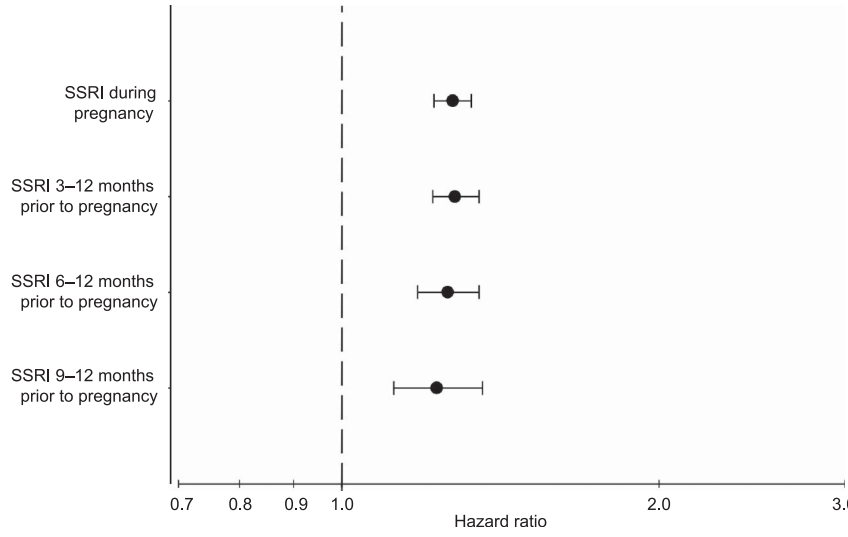


**Fig. 2.** The hazard of miscarriage in women exposed to selective serotonin reuptake inhibitors (SSRI) in different periods before and during pregnancy. Hazard ratios are adjusted for year of outcome or censoring, maternal age, educational length, income, and the number of previous miscarriages.

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To test the robustness of our method of identifying exposed women (based on an algorithm described in the "Methods" section), we also analyzed the hazard of having a miscarriage when redeeming a prescription for an SSRI during the first 35 days of pregnancy and in the period of 3–12 months before pregnancy start and not 3 months before and during pregnancy. The hazard of having a miscarriage when redeeming a prescription of an SSRI during the first 35 days of pregnancy was 1.24 (95% CI 1.18–1.31) and 1.30 (95% CI 1.19–1.43) in women exposed 3–12 months before pregnancy start and not 3 months before and during pregnancy.

## DISCUSSION

In the present study we found that women exposed to an SSRI during the early part of pregnancy had an increased risk of experiencing a miscarriage compared with unexposed.

**Table 3. Hazard Ratio of Miscarriage in Women Exposed to Selective Serotonin Reuptake Inhibitors During Pregnancy, Dose–Response**

| Exposure | HR (95% CI) |
|---|---|
| SSRI low compared with high (mg) | 1.00 (0.91–1.09) |
| Citalopram low (20 or less) compared with high (greater than 20) | 1.08 (0.94–1.23) |
| Escitalopram low (10 or less) compared with high (greater than 10) | 0.99 (0.76–1.31) |
| Fluoxetine low (20 or less) compared with high (greater than 20) | 0.83 (0.68–1.02) |
| Paroxetine low (20 or less) compared with high (greater than 20) | 1.03 (0.80–1.32) |
| Sertraline low (50 or less) compared with high (greater than 50) | 0.95 (0.79–1.14) |

HR, hazard ratio; CI, confidence interval; SSRI, selective serotonin reuptake inhibitor.

However, we also found that women discontinuing SSRI treatment in the time periods of 3–12 months, 6–12 months, and 9–12 months before pregnancy had essentially the same risk of having a miscarriage as women exposed during pregnancy suggesting that there is no causal relationship between SSRIs and miscarriage. The increased risk of miscarriage in our study may be explained by the underlying illness or lifestyle factors such as alcohol use,[26] smoking,[27] or poor compliance to folic acid supplementation during pregnancy.[28] It has previously been shown that mood disorders, smoking, and alcohol use co-occur[29] and women with depression may be less compliant with folic acid supplementation before and during pregnancy. This approach has previously been used to analyze the association between SSRI use and heart defects. Just like in the present study, we found that women exposed to SSRIs during pregnancy had the same increased risk of having offspring with heart defects compared with women pausing SSRI treatment during pregnancy.[16] This strengthens the possibility that the associations seen with exposure to SSRIs could be the result of confounding by indication.

Furthermore, we did not find any increased hazard in women exposed to high-dose SSRI compared with low-dose SSRI nor did we find an increased hazard in women exposed to more than one SSRI. This further suggests no causal relationship between SSRIs and miscarriage.

The study has some limitations that are important to consider. Although a physician prescribed an SSRI, the prescription was redeemed, and the drug was collected at the pharmacy and paid for, we do not

**Table 4. Comedication During First Part of Pregnancy**

| Medication | Women Exposed to SSRIs Within the First 35 Days of Pregnancy (n=22,884) | Women Not Exposed to SSRIs Within the First 35 Days of Pregnancy (n=1,256,956) | *P* | Women Exposed to SSRIs 3–12 Months Before but Not During or 3 Months Before Pregnancy (n=14,016) | *P* |
|---|---|---|---|---|---|
| Antipsychotics | 781 (3.4) | 1,535 (0.1) | <.001 | 189 (1.4) | <.001 |
| Anxiolytics | 1,096 (4.8) | 3,523 (0.3) | <.001 | 287 (2.1) | <.001 |
| Thyroid preparations | 136 (0.6) | 3,391 (0.3) | <.001 | 44 (0.4) | .04 |
| Antithyroid preparations | 31 (0.1) | 955 (0.1) | .001 | 11 (0.1) | .12 |
| Antidiabetics | 172 (0.8) | 5,680 (0.5) | <.001 | 100 (0.7) | .68 |

SSRI, selective serotonin reuptake inhibitor.
Data are n (%) unless otherwise specified.

have any information on whether the drug was actually taken. Furthermore, we might have overestimated the SSRI treatment periods because it is not possible to adjust for lack of adherence or a person's intention of commencing a treatment shortly after redemption of a prescription. However, the majority of redeemed prescriptions by pregnant women are taken and compliance to treatment with antidepressive drugs among Danish pregnant women has been estimated to be 80%.[30,31] A register-based method to analyze the risk of miscarriage, like in present study, cannot identify the earliest miscarriages unrecognized by the women because they are not recorded in the registers. If SSRIs specifically is associated with these early miscarriages, a register-based method would underestimate the risk of SSRIs. If women experience a miscarriage without contacting a hospital, the number of registered miscarriages would be underestimated. This underreporting has been estimated to 25% and is probably the result of miscarriages early in pregnancy.[32] If women exposed to SSRIs during or before pregnancy were more likely to report a miscarriage than unexposed, this could explain the increased hazard observed in the study.

We cannot completely rule out that women classified as discontinuing SSRI treatment 3–12 months before pregnancy were misclassified and their treatment periods actually reached into pregnancy. We addressed this by analyzing the risk of miscarriage in women discontinuing SSRI treatment 6–12 months and 9–12 months before pregnancy. These analyses gave similar results.

We conclude that the increased hazard found both for women exposed to SSRIs in early pregnancy and for women discontinuing SSRIs is most likely confounded by factors associated with the redemption of an SSRI prescription. Because the risk of miscarriage is elevated in both groups compared with an unexposed population, there is likely no benefit in discontinuing SSRI use before pregnancy to decrease one's chances of miscarriage.

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