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Selective serotonin reuptake inhibitor use and risk of gestational hypertension

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Abstract

Objective—To assess the effects of selective serotonin reuptake inhibitor (SSRI) use on risks of gestational hypertension (GHT) and preeclampsia.

Method—We used data from 5,731 women with non-malformed infants and no underlying hypertension who participated in the Slone Epidemiology Center Birth Defects Study in 1998–2007. GHT was defined as incident hypertension diagnosed after the 20th week of pregnancy with and without proteinuria (i.e., with and without preeclampsia). We compared the risks of GHT and preeclampsia between users and non-users of SSRIs during pregnancy. Relative risks (RR) and 95% confidence intervals (CI) were estimated by Cox proportional hazard models, adjusting for pre-pregnancy sociodemographic, reproductive, and medical factors.

Results—GHT was present in 9.0% of the 5,532 non-users and 19.1% of the 199 SSRI users; among users, GHT was present in 13.1% of the 107 women who used SSRIs only in the first trimester and in 26.1% of the 92 who continued SSRIs beyond the first trimester. For preeclampsia, the incidence was 2.4% among non-users, 3.7% among women who were exposed only in the first trimester and 15.2% among those who continued SSRIs beyond the first trimester. Compared with non-users, the adjusted RR of preeclampsia was 1.4 (95% CI: 0.5, 3.8) for women who discontinued and 4.9 (95% CI: 2.7, 8.8) for those who continued SSRIs.

Conclusion—Whether a causal factor or not, SSRI exposure late in pregnancy might identify women at increased risk for GHT and preeclampsia. Further investigation is required to separate the effects of SSRIs from those of underlying mood disorders.

Keywords

antidepressive agents; gestational hypertension; preeclampsia; selective serotonin reuptake inhibitors; epidemiology

Introduction

Studies suggest that 12–25% of all pregnant women display some signs of depression (1,2) and 3–13% of pregnant women are treated with antidepressants (3,4). The most commonly used

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antidepressants among pregnant women are the selective serotonin reuptake inhibitors (SSRIs) (3,4). Antidepressants can control mood effectively and reduce the risks of serious consequences associated with untreated depression for both the mother and her offspring (5, 6). However, use of antidepressants during pregnancy could be potentially associated with adverse effects to the fetus. While findings have not been consistent for some outcomes (7-12), first trimester exposure to certain SSRIs has been associated with certain specific birth defects (13-16), and SSRI use late in pregnancy has been associated with pulmonary hypertension of the newborn (17), prematurity (18-21), low birth weight (20,21), small for gestational age (22), and various other neonatal complications (18-20,23).

Very few studies have focused on the potential medical and obstetrical adverse effects of antidepressants for the mothers themselves. A leading cause of morbidity and mortality in pregnancy is preeclampsia, clinically recognized by gestational hypertension (GHT) and proteinuria (24,25). It has been suggested that psychological conditions such as stress (26) and anxiety and depression (27,28) may trigger the pathogenic vascular processes that lead to this condition. Serotonin may play an important role in the etiology of preeclampsia through its vascular and hemostatic effects (29), and SSRIs have been shown to affect circulating serotonin levels (30). The few studies that suggested an elevated risk of preeclampsia among pregnant women with depression did not assess the potential independent effect of medications (27, 28). If this association is real, it would still be unclear whether it is due to biologic or behavioral factors intrinsic to women with mood disorders, to medications used to treat the disorder, or a combination of both.

Women treated with medications for depression who are pregnant or planning a pregnancy, and their doctors, often struggle with the decision about treatment options, and a critical clinical question is whether to continue or discontinue antidepressants during pregnancy. In this study, we investigated the risk of GHT and preeclampsia associated with continuing and discontinuing these antidepressants beyond the first trimester. To our knowledge, this is the first study to examine this question.

Methods

Study population

We used data from the Slone Epidemiology Center Birth Defects Study (BDS), a multi-center case-control surveillance program of birth defects in relation to environmental exposures (particularly medications) (13,17). More than 35,000 mothers of babies with and without birth defects from the greater metropolitan areas of Philadelphia, San Diego, and Toronto, as well as selected regions in Iowa, Massachusetts and New York State, have been interviewed since 1976. Study subjects are identified through review of admissions and discharges at major birth hospitals and pediatric referral hospitals and clinics, logbooks in perinatal intensive care units, through weekly telephone contact with collaborators at newborn nurseries in community hospitals, and through collaborations with state birth defects registries. Since 1998, the study has also included a random sample of Massachusetts births. The mothers of non-malformed infants are recruited independently from any exposure and therefore provide an estimate of the distribution of exposures (including use of medications) in the study population. Institutional Review Board approval was obtained from each of the participating institutions and mothers provide informed consent before participation.

Inclusion and exclusion criteria

We restricted our analyses to a retrospective cohort of women who gave birth to non-malformed liveborns between 1998 and 2007 and were ascertained at either the hospital-based centers or through the Massachusetts birth registry (N=5,912). Women with elective terminations,

miscarriages, or stillbirths were not included, because most are not at risk of the outcomes of interest, which occurred after 20 weeks of gestation.

Exposure ascertainment and definitions

Within six months of delivery, trained study nurses unaware of study hypotheses conduct a 45-60 minute telephone interview of the study mothers. The interview collects information on demographic, reproductive, and medical factors, as well as cigarette smoking, alcohol consumption, occupational exposures, and dietary intake. It also uses a series of increasingly detailed questions to collect information on medications (prescription, over-the-counter, vitamins/minerals, and herbal products) used anytime from two months prior to conception through the pregnancy (31). Standardized questions prompt with a list of indications and specific conditions (e.g., “depression”) and specific drugs (e.g., “Prozac (fluoxetine)”). When possible, reported medications are verified by asking the subject to read information from the medication container. Identification of timing of drug exposure is facilitated by use of a 12-month calendar covering periods before and after pregnancy; special dates (e.g., last menstrual period (LMP), holidays) are marked to help enhance recall. Data are collected on starting and stopping dates, duration, frequency, indication, form, and number of pills per day. The interview also elicits information on LMP, whether based on maternal recall or ultrasound exam; LMP allows estimation of the due date, approximate conception date, and gestational age at birth.

We identified women who were receiving SSRIs two months before pregnancy and then categorized them into those who stopped their treatment before the end of the first trimester and those who continued to use their medications after the first trimester. Since very few women initiate SSRIs during pregnancy (N=36), assessing the effect of starting treatment during pregnancy would be less clinically relevant and statistically underpowered, and these women were not analyzed separately (no cases of preeclampsia were observed in these women). Use of non-SSRI antidepressants was classified in a similar manner.

Outcome ascertainment and definition

We specifically asked women if a health care provider had diagnosed “high blood pressure” or “toxemia or preeclampsia” during their pregnancy, the dates when the condition started and ended, and whether they had used medications to treat the conditions. Given the potential misclassification of pregnancy-induced hypertension with and without preeclampsia, we combined the two diagnoses in our main analyses. Thus, *gestational hypertension* (GHT) was defined as incident hypertension during pregnancy with and without proteinuria (i.e., with and without *preeclampsia/toxemia*). To exclude underlying hypertension as a potential source of both confounding and outcome misclassification bias, we restricted the definition of GHT to that first diagnosed after the 20th week of pregnancy; as a result, we excluded 145 women with an early diagnosis of hypertension from all the analyses. For each woman with GHT, the onset date was defined as the gestational month when GHT was first diagnosed.

Statistical Analysis

We considered our study a retrospective cohort design. Using as the reference group women with no SSRI use throughout pregnancy, we estimated the relative risk of GHT for those who stopped their SSRIs before the end of the first trimester and those who continued treatment beyond the first trimester. Characteristics of the latter two groups were compared by chi-square analyses and Fisher's exact tests.

Relative risks (RR) and 95 percent confidence intervals (95% CI) were estimated for each outcome using Cox proportional hazard models with time measured in days since the 20th week of gestation. We considered the following potential confounders: region, birth year, maternal

age, race/ethnicity, education, family income, gravidity, number of fetuses, pre-pregnancy body mass index (BMI; kg/m²), age at menarche, diabetes mellitus, infertility treatment, cigarette smoking, coffee and alcohol intake, and use of illicit drugs or other psychotherapeutic medications during pregnancy (24,32-36). We retained in the models those factors associated with the outcome in our population (even if the association was not statistically significant), as well as use of non-SSRI antidepressants. We repeated our analyses separately for preeclampsia and GHT without preeclampsia.

We conducted a number of secondary analyses. Because of the different heritability, clinical manifestations, and prognosis of early- and late-onset GHT, we distinguished these conditions according to timing of onset (33,34,37,38). GHT was considered early-onset when it began between 20 and 32 weeks after the LMP and late-onset afterwards. We analyzed primigravidae separately from multigravidae as well as smokers separately from non-smokers, and restricted our analysis to singleton births (39). Effect measure modification on a multiplicative scale was formally tested by the Wald test comparing whether two stratum-specific RRs were equivalent. We verified the proportional hazards assumptions by including in the models an interaction term for time to event and SSRI use.

Results

Of the 5,731 women without pre-gestational hypertension, 538 (9.4%) reported being diagnosed with GHT and among these 538 women, 153 (28.4%) developed preeclampsia (2.7% of all subjects). A total of 199 (3.5%) women were using SSRIs two months before conception (191 used these medications for mood disorders); 107 of them discontinued SSRIs before the first trimester (i.e., “discontinuers”), and 92 remained on the medications beyond the first trimester of pregnancy (i.e., “continuers”) (Figure 1). Most women maintained their exposure status during the later trimesters: 12 (11.0%) of the discontinuers restarted their treatment and 6 (6.5%) of the continuers stopped taking SSRIs.

Maternal characteristics by SSRI use status are shown in Table 1. SSRI discontinuers and continuers did not differ substantially in their baseline characteristics. The risk of GHT and/or preeclampsia was associated with region, younger maternal age, White race, lower family income, younger age at menarche, cigarette smoking, diabetes mellitus, higher pre-pregnancy BMI, multiple gestations (twins or more), primigravidae, and history of fertility treatment (data not shown). These variables were included in our final models.

Sixty-eight women were using non-SSRI antidepressants two months before pregnancy (16 used serotonin/norepinephrine reuptake inhibitors, SNRIs); 13 of them (19.1%; 3 used SNRIs) developed GHT and 4 (5.9%; 1 used SNRIs) developed preeclampsia. Compared with non-users, the adjusted RR for women who used non-SSRI antidepressants immediately before or during pregnancy was 1.58 (95% CI: 0.90-2.80) for GHT and 1.55 (95% CI: 0.55-4.38) for preeclampsia. Due to small numbers, non-SSRI antidepressant use was not analyzed further, except as a potential confounder.

Figure 2 shows the cumulative incidence of GHT and preeclampsia by SSRI exposure status. SSRI users had a higher risk of GHT, compared with women not exposed to SSRIs; the risk was greater for continuers than for discontinuers (Table 2). The increased risk observed among continuers appeared to be largely attributable to preeclampsia, although there was also a suggestion of elevated risk for GHT without preeclampsia. The results were similar when we compared discontinuers who did not restart their treatment with continuers who did not stop using SSRIs during later trimesters. RRs did not vary greatly by gravidity or smoking status; restricting our analyses to singleton births, or using women exposed to SSRIs only (and not to

non-SSRI antidepressants concomitantly) did not materially change the results (data not shown). We did not have the power to evaluate specific SSRIs.

There were 146 and 35 early-onset GHT and preeclampsia cases, respectively. The RRs for continuers and discontinuers were similar for early- and late-onset GHT compared with non-users. However, comparing continuers with non-users, the RR of early-onset preeclampsia was 16.4 (95% CI: 6.2, 43.7; based on 6 cases among continuers), and the RR of late-onset preeclampsia was 3.5 (95% CI: 1.6, 7.5; 8 cases among continuers). There was no indication of violation of the proportional hazards assumption in any analyses.

Discussion

We found that peri-conceptional SSRI use was associated with a higher risk of GHT, and particularly preeclampsia. Further, the risk of preeclampsia was greater among women who continued treatment after the first trimester (15.2%), compared with both non-users (2.4%) and those who discontinued SSRIs (3.7%). Our findings may have at least four interpretations: 1) SSRIs cause these outcomes; 2) underlying mood disorders are associated with an increased risk for these outcomes; 3) methodological limitations create a spurious association between SSRIs and these outcomes; and 4) a combination of the above.

Causal effect of SSRIs

In our study, SSRI use exclusively in early pregnancy, when placentation occurs, was not associated with a higher risk of preeclampsia. Thus, if real, the effect of SSRIs on preeclampsia might not be mediated via placentation but rather through hypertension or vascular effects later in pregnancy. Serotonin may play a role in the pathophysiology of preeclampsia through its effects on hemostasis and vascular tone in uteroplacental tissues (29,40,41). In addition, SSRIs inhibit synthesis of nitric oxide, a vasodilator that appears to play a role in vascular tone and reactivity both *in utero* and during postnatal life (42-44). The more recently introduced SNRIs can cause elevations of diastolic blood pressure, probably due to their noradrenergic effects (45), but we did not have sufficient numbers of exposed women to examine the outcomes associated with these medications.

Confounding by depression or other mood disorders

The association between SSRIs and preeclampsia might stem from the underlying mood disorders (e.g., depression, anxiety), which could reflect both the indication for treatment and the ultimate cause of preeclampsia, or it could represent a marker for a higher risk (e.g. linked genetic predisposition for the two conditions). For example, depression or anxiety could induce vasoconstriction and uterine artery resistance through an altered excretion of vasoactive hormones and other neuroendocrine transmitters (5). In a Finnish study, anxiety and depression during pregnancy were associated with a three-fold increased risk for preeclampsia (27), and a similar association was found in a recent case-control study (28). However, these studies did not examine the effects of these conditions independent of treatment. In our study, the greater incidence of GHT and preeclampsia found among users of non-SSRI antidepressants compared to non-users suggests that women who need antidepressive agents might be at an increased risk for these outcomes, and that the increased risk might not be related to the SSRIs themselves.

Unfortunately, we were not able to compare SSRI users with non-users among women with depression since we did not identify mood disorders in study participants who did not report drug treatment. The small number of outcomes among women receiving non-SSRI antidepressants (e.g., SNRIs, tricyclic antidepressants) limited our ability to examine the effect of SSRIs compared to these medications. However, while it might appear that such comparisons would be ideal to adjust for confounding by the underlying condition, depression

severity and other potential risk factors for preeclampsia among women with depression may differ between users and non-users of specific antidepressants. For example, it has been observed that among pregnant women with a diagnosis of depression, those receiving SSRIs have clinical indicators suggesting a more severe depression than non-users (22).

Therefore, in addition to comparing antidepressant users with non-users, we compared those who discontinued to those who continued SSRI use after the first trimester. Although the two groups did not differ in most baseline variables (Table 1), these women might differ in other unmeasured characteristics that could potentially explain our findings. In particular, we did not have a measure of depression severity for women who discontinued or continued SSRI use. Those continuing SSRIs might have better control of their symptoms than those who discontinued their treatment, or they might have a more severe condition that requires pharmacologic treatment. Thus, the higher risk of preeclampsia associated with continuation of treatment after the first trimester might simply reflect a more severe mood disorder. In the absence of treatment randomization, comparing these two groups might reduce, but not eliminate, the possibility of confounding by depression severity.

Confounding by other factors

Characteristics such as high pre-pregnancy BMI are positively associated with both SSRI use and preeclampsia (46). Failure to adjust for these confounders could overestimate the risks associated with these drugs; in our analyses, estimates adjusted for these confounders did not differ substantially from the unadjusted estimates. Other important socioeconomic and lifestyle factors, such as family income and maternal education level, were also considered, but did not appear to be major confounders in our study population. For an unmeasured confounder to have an appreciable impact, it would have to be reasonably prevalent and must be strongly associated with both SSRI use during pregnancy and risk of GHT.

Information bias

A potential weakness of this study lies in the outcome information, which was based on self-report because we did not have routine access to obstetric notes in mothers' medical records. Thus, under- and over-reporting of events, misclassification of the exact date of onset, and cross-classification of preeclampsia and transient hypertension in pregnancy, are possible. Under-diagnosis is unlikely since over 99% of the women in our population had had prenatal care, where screening for GHT and proteinuria is standard practice. Information errors are likely to have been minimized by use of a carefully designed questionnaire, with specific questions on hypertension onset and preeclampsia as diagnosed by a health care provider, and administered within six months of delivery by trained nurses.

Further, the data offer evidence of the general validity of the outcome classification: First, the reported incidence of GHT (12.6%) among primiparous women, and the overall incidence of preeclampsia (2.7%) in our population are similar to those in population-based studies (47, 48). Second, the frequency and effect of other known risk factors (e.g., gravidity, number of fetuses, and maternal weight) are similar to those consistently reported in the literature (24, 32-36). Other previously suggested risk factors, such as advanced maternal age, were not associated with a higher frequency of GHT in our study, most likely because we excluded women with pre-gestational hypertension (i.e., these factors were associated with hypertension diagnosed before 20 weeks of gestation). Our failure to find the previously suggested protective effect of smoking (49) might be due to various factors, including differences among characteristics of smokers over time and methodological factors.

In addition, if reported outcomes were misclassified similarly for users and non-users of SSRIs, the effect would be to bias our results towards a null effect of SSRIs. Of greater concern would

be differential misclassification of outcome among SSRI users and non-users: For example, if women on chronic treatments such as antidepressant therapy were diagnosed with GHT or preeclampsia more readily, this situation would indeed tend to bias the association between SSRIs and GHT/preeclampsia towards an increased risk among users, and for continuers vs. discontinuers. However, while more intensive monitoring and diagnosis would likely produce stronger associations for GHT, an event that may be variably detected, they would be less likely to do so for preeclampsia, which is a clinically significant event that is difficult to miss.

Studies using medication prescribing or dispensing data might not capture actual use and time of use during pregnancy, leading to potential misclassification of exposure (50). Our study collected information on medications actually taken by the mother, and timing of use was systematically collected. Although any data based on maternal recall might be subject to misclassification, we do not believe recall bias was a major concern in our study since SSRIs are used on a regular basis and for nontrivial reasons and the study interviewers specifically probed for use of antidepressants and were unaware of the study hypothesis. While underreporting of antidepressant use is possible since women might be reluctant to disclose such information, it is reassuring that the prevalence of SSRI use in our study was consistent with that reported by prospective studies (4,22). Further, if women with the study outcomes were less likely to report their SSRI use, such underreporting would lead to an underestimation of the true risk.

SSRI, preeclampsia, and prematurity/fetal growth restriction

Several (18-22), but not all (8-12) studies have suggested that SSRIs may be associated with a greater risk of prematurity and/or fetal growth restriction. Since preeclampsia is a known risk factor for these outcomes (51), it is possible that the suggested associations between SSRIs and prematurity or fetal growth restriction are mediated through an elevated risk of preeclampsia among SSRI users.

Conclusion

The benefits of treating depression in pregnancy (52) and the risk of relapse associated with treatment discontinuation (6) are well described, and this study can only inform the risk component of the risk-benefit assessment. Our data suggest that SSRI exposure in pregnancy might identify women at increased risk for GHT and preeclampsia. Continuation of SSRI treatment beyond the first trimester might be associated with a higher risk than discontinuation of SSRIs soon after pregnancy awareness. However, we were unable to disentangle whether the risk is attributable to the drugs or to the underlying mood disorder, or a combination of both. In addition, we were limited by potential differential misclassification of the outcomes. Thus, future efforts, including well-designed and powered prospective cohort studies, are needed to confirm or refute these findings. Independent of a causal link or mechanism, if these findings are confirmed, women exposed to SSRIs during pregnancy should be carefully monitored for the occurrence of GHT and preeclampsia.

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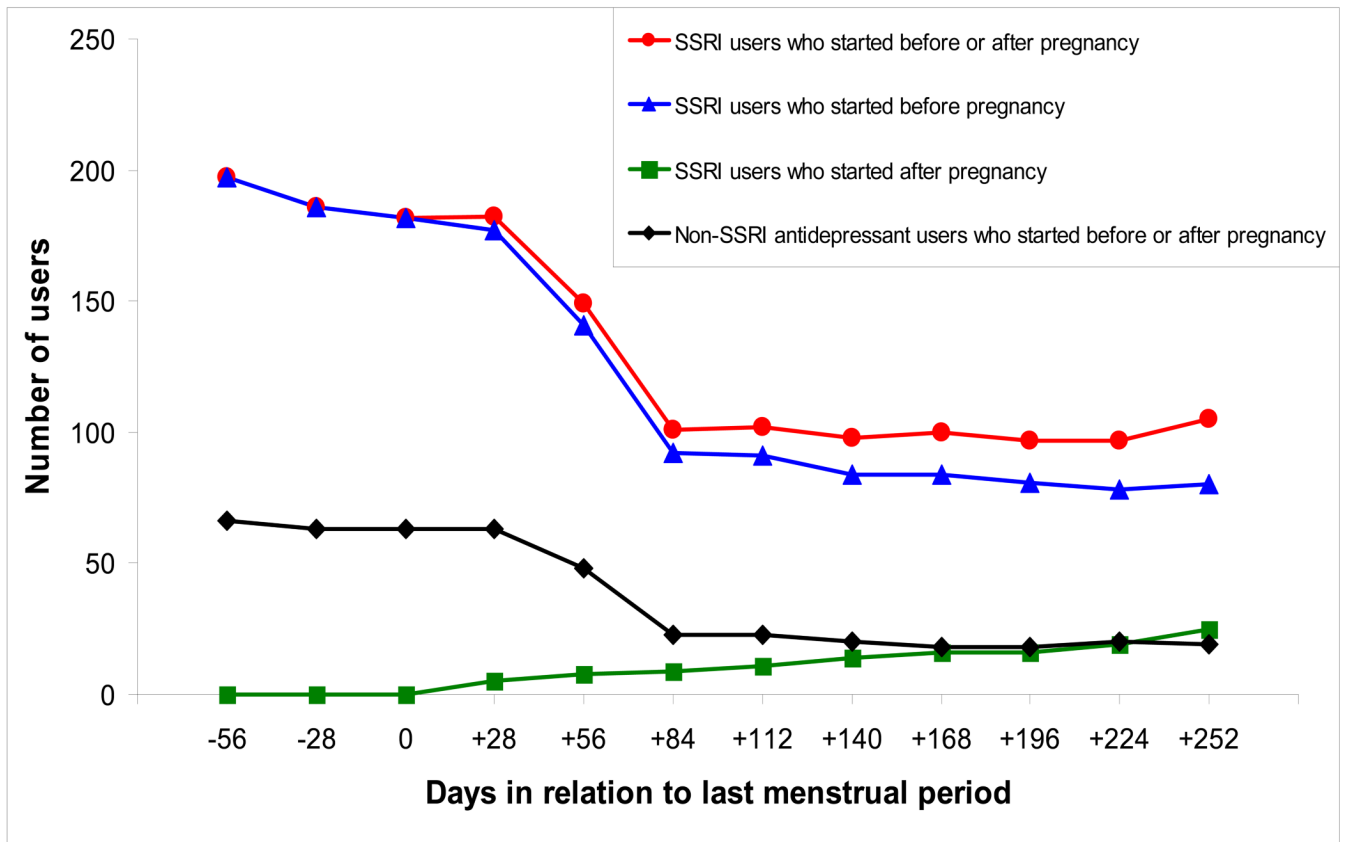
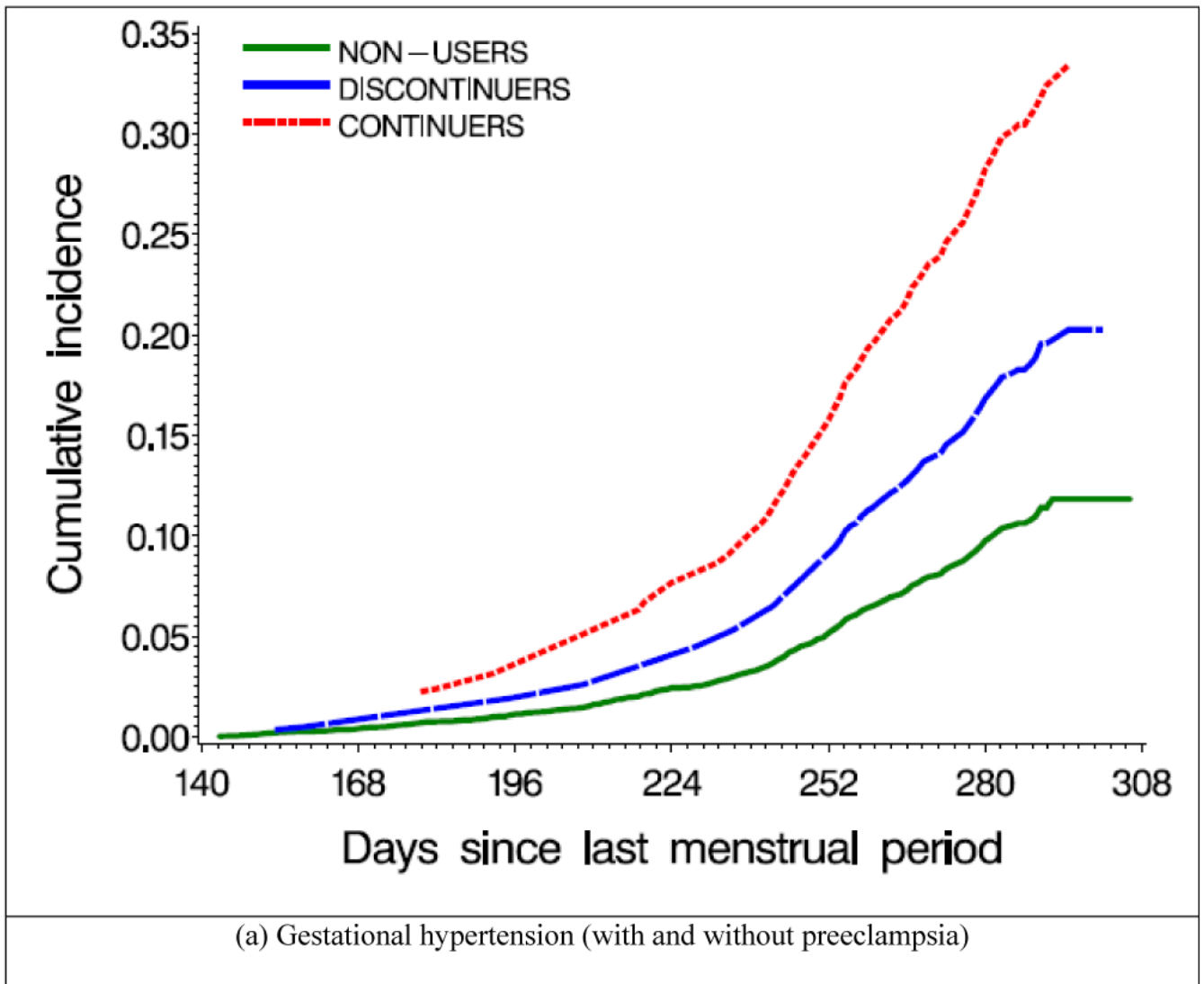


Figure 1. Antidepressant use in relation to the last menstrual period, Slone Epidemiology Center Birth Defects Study, 1998-2007 *
 * SSRI: selective serotonin reuptake inhibitor. Non-SSRI antidepressants include tricyclic antidepressants, serotonin/norepinephrine reuptake inhibitors, and other antidepressant



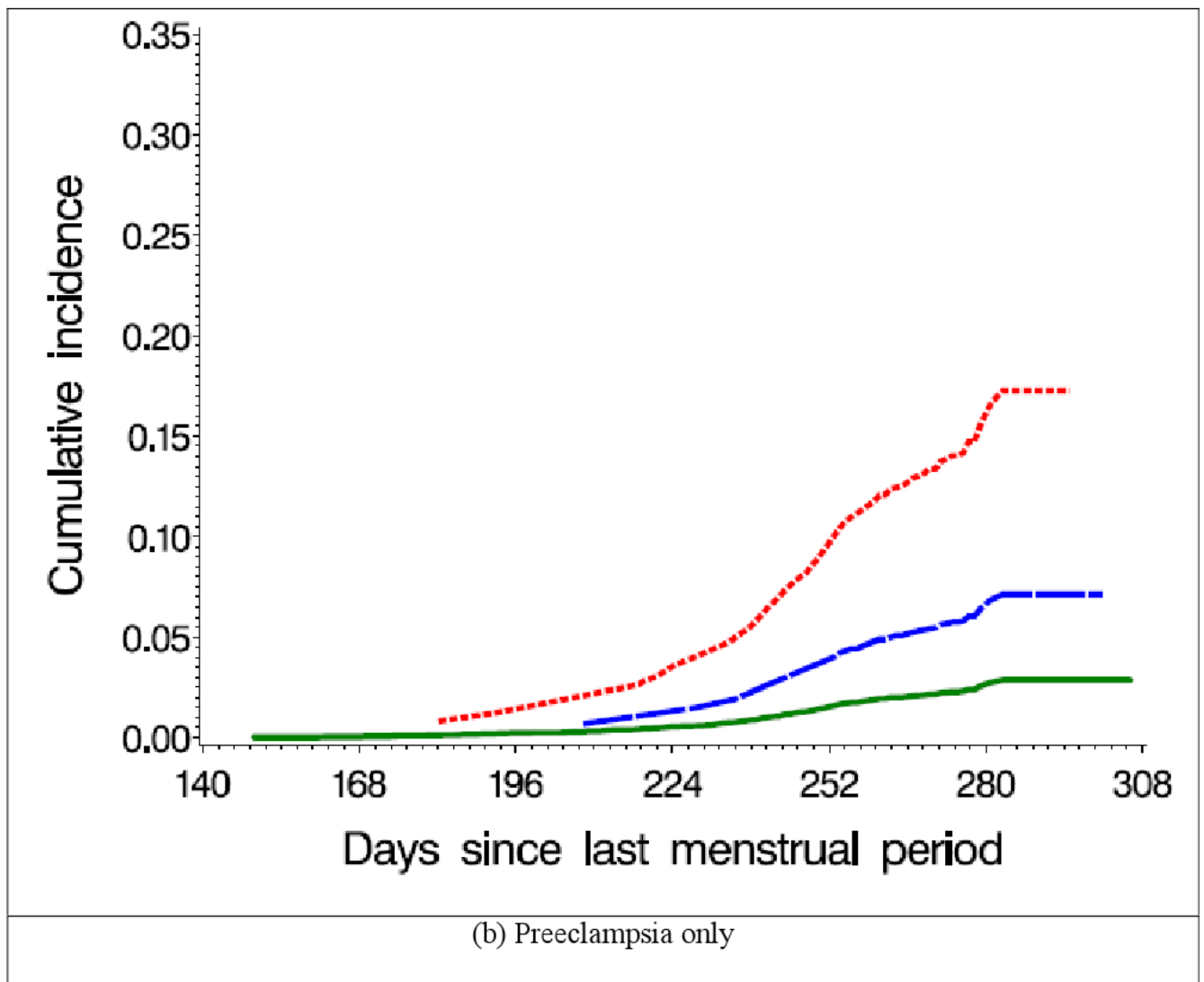


Figure 2.

Cumulative incidence of gestational hypertension and preeclampsia by selective serotonin reuptake inhibitor (SSRI) use, Slone Epidemiology Center Birth Defects Study, 1998-2007 *

* Non-users (N=5,532) were women who were not exposed to SSRIs from two months before pregnancy through delivery; Discontinuers (N=107) were women who used SSRIs two months before pregnancy, but stopped taking them by the end of the first trimester; Continuers (N=92) were women who used SSRIs two months before pregnancy, and continued to use them after the first trimester

Table 1
Maternal characteristics by selective serotonin reuptake inhibitor (SSRI) use status, Slone Epidemiology Center Birth Defects Study, 1998-2007 *

Characteristics	Non-users (N=5,532) †	Discontinuers (N=107) ‡	Continuers (N=92) ‡	p-value (discontinuers vs. continuers) ‡
Maternal age (years)				
< 25	1,047 (18.9)	23 (21.5)	16 (17.4)	0.56
25-29	1,284 (23.2)	29 (27.1)	18 (19.6)	
30-34	1,979 (35.8)	27 (25.2)	26 (28.3)	
≥ 35	1,196 (21.6)	27 (25.2)	31 (33.7)	
Maternal race/ethnicity				
Caucasian	3,994 (72.2)	86 (80.4)	82 (89.1)	0.13
Hispanic	739 (13.4)	8 (7.5)	6 (6.5)	
African American	380 (6.9)	8 (7.5)	4 (4.4)	
Other	417 (7.5)	5 (4.7)	0 (0.0)	
Maternal education (years)				
≤ 12	1,470 (26.6)	33 (30.9)	25 (27.2)	0.81
13-15	1,320 (23.9)	29 (27.1)	28 (30.4)	
> 15	2,739 (49.5)	45 (42.1)	39 (42.4)	
Married or living with baby's father	4,969 (89.8)	90 (84.1)	83 (90.2)	0.21
Family income				
< 45,000 US dollars per year	1,498 (27.1)	34 (31.8)	29 (31.5)	0.84
≥ 45,000 US dollars per year	3,577 (64.7)	65 (60.8)	58 (63.0)	
Diabetes mellitus	262 (4.7)	6 (5.6)	5 (5.4)	1.00
Age at menarche				
< 12	983 (17.8)	16 (15.0)	20 (21.7)	0.36
≥ 12	4,343 (78.5)	89 (83.2)	69 (75.0)	
Fertility treatment	375 (6.8)	5 (4.7)	10 (10.9)	0.11
Number of fetuses				
Single	5,376 (97.2)	106 (99.1)	87 (94.6)	0.10
Two or more	156 (2.8)	1 (1.0)	5 (5.4)	
Gravidity				
Primigravidae	1,718 (31.1)	35 (32.7)	24 (26.1)	0.07

Characteristics	Non-users (N=5,532) [†]	Discontinuers (N=107) [‡]	Continuers (N=92) [‡]	p-value (discontinuers vs. continuers) [‡]
Multigravidae, first liveborn	449 (8.1)	6 (5.6)	15 (16.3)	
Multiparous, last pregnancy ≤ 3 years	2,054 (37.1)	30 (28.0)	31 (33.7)	
Multiparous, last pregnancy > 3 years	1,294 (23.4)	35 (32.7)	22 (23.9)	
Illicit drug use	100 (1.8)	3 (2.8)	4 (4.4)	0.71
Non-SSRI antidepressant use	53 (1.0)	6 (5.6)	9 (9.8)	0.29
Other psychotherapeutic drug use	33 (0.6)	7 (6.5)	3 (3.3)	0.35
Pre-pregnancy body mass index[§]				
< 18.5	260 (4.7)	11 (10.3)	5 (5.4)	0.54
18.5 - 25.0	3,510 (63.5)	60 (56.1)	50 (54.4)	
25.1 - 30.0	1,085 (19.6)	19 (17.8)	21 (22.8)	
> 30.0	583 (10.5)	17 (15.9)	16 (17.4)	
Smoking during pregnancy				
Never smoked	3,297 (59.6)	45 (42.1)	43 (46.7)	0.76
Past smoker	1,355 (24.5)	27 (25.2)	23 (25.0)	
Smoked < 10/day during pregnancy	426 (7.7)	17 (15.9)	10 (10.9)	
Smoked ≥ 10/day during pregnancy	454 (8.2)	18 (16.8)	16 (17.4)	
Alcohol intake during pregnancy				
Never drank	2,535 (45.8)	45 (42.1)	38 (41.3)	0.85
Past drinker	2,823 (51.0)	57 (53.3)	48 (52.2)	
Drank during pregnancy	174 (3.2)	5 (4.7)	6 (6.5)	
Coffee drinking during pregnancy				
Never drank	2,725 (49.3)	50 (46.7)	27 (29.4)	0.04
Past drinker	2,050 (37.1)	44 (41.1)	49 (53.3)	
Drank during pregnancy	757 (13.7)	13 (12.2)	16 (17.4)	

* Numbers might not add up due to missing data. Numbers in parentheses represent proportions of all women in each category; independent categories were created for women with missing values

[†] Non-users were women who were not exposed to SSRIs from two months before pregnancy through delivery; Discontinuers were women who used SSRIs before pregnancy, but stopped taking them after first trimester; Continuers were women who used SSRIs before pregnancy, and continued to use them after first trimester

[‡] Based on chi-square test, except for binary variables, which were based on Fisher's exact test (two-tailed)

[§]Body mass index was calculated by $\text{weight}/(\text{height})^2$, kg/m^2

Table 2
Risks of gestational hypertension with and without pre-eclampsia according to selective serotonin reuptake inhibitor (SSRI) exposure status, Slone Epidemiology Center Birth Defects Study, 1998-2007 *

Perinatal outcomes	Number of cases (%)	Crude relative risk (95% confidence interval)	Adjusted relative risk † (95% confidence interval)
Any gestational hypertension			
Pre-pregnancy SSRI use			
Non-users	500 (9.0)	Reference	Reference
Users	38 (19.1)	2.29 (1.64, 3.18)	1.90 (1.35, 2.67)
Discontinuers	14 (13.1)	1.44 (0.85, 2.45)	1.33 (0.78, 2.27)
Continuers	24 (26.1)	3.47 (2.30, 5.23)	2.49 (1.62, 3.83)
Preeclampsia			
Pre-pregnancy SSRI use			
Non-users	135 (2.4)	Reference	Reference
Users	18 (9.0)	3.91 (2.39, 6.39)	3.16 (1.89, 5.29)
Discontinuers	4 (3.7)	1.51 (0.56, 4.08)	1.37 (0.50, 3.76)
Continuers	14 (15.2)	7.16 (4.13, 12.43)	4.86 (2.70, 8.76)
Gestational hypertension without preeclampsia			
Pre-pregnancy SSRI use			
Non-users	365 (6.6)	Reference	Reference
Users	20 (10.0)	1.61 (1.03, 2.53)	1.36 (0.85, 2.15)
Discontinuers	10 (9.4)	1.41 (0.75, 2.64)	1.30 (0.69, 2.46)
Continuers	10 (10.9)	1.88 (1.00, 3.53)	1.41 (0.74, 2.69)

* Non-users (N=5,532) were women who were not exposed to SSRIs from two months before pregnancy through delivery; Discontinuers (N=107) were women who used SSRIs two months before pregnancy, but stopped taking them by the end of the first trimester; Continuers (N=92) were women who used SSRIs two months before pregnancy, and continued to use them after the first trimester

† Adjusted for region, maternal age, race/ethnicity, marital status, family income, age at menarche, diabetes mellitus, cigarette smoking, pre-pregnancy body mass index, use of non-SSRI antidepressants, number of fetuses, gravidity, and history of fertility treatment. See Table 1 for all potential confounders considered