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ORIGINAL RESEARCH

Antidepressant medication use, depression, and the risk of preeclampsia

Lyndsay Ammon Avalos, Hong Chen, and De-Kun Li*

Kaiser Permanente Northern California, Division of Research, Oakland, California, USA

Objective. To assess the effects of depression and antidepressant medication use during pregnancy on the risk of preeclampsia.

Methods. We conducted a retrospective, population-based cohort study that linked automated clinical and pharmacy databases including comprehensive electronic medical records of 21,589 pregnant Kaiser Permanente Northern California members between 2010 and 2012.

Results. The overall risk of preeclampsia was 4.5%. The timing of antidepressant medication exposure was an important factor. A significant increase in the risk of preeclampsia emerged for women with a depression diagnosis who took antidepressant medications during the second trimester compared to women with untreated depression (adjusted relative risk [aRR]: 1.6, 95% CI: 1.06, 2.39) and to women without depression (aRR: 1.70, 95% CI: 1.30, 2.23). Similar associations existed for women who took antidepressant medications, but without depression. In contrast, depressed women with psychotherapy showed no increased risk of preeclampsia compared to women with untreated depression or no depression. There was also a statistically significant relationship between the duration of antidepressant medication use and preeclampsia. The observed association appeared stronger for selective serotonin reuptake inhibitor (SSRI) use, although a nonsignificant trend was also noted for use of norepinephrine-dopamine reuptake inhibitors (NDRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).

Conclusion. Study findings suggest that antidepressant use during pregnancy may increase the risk of preeclampsia, especially use during the second trimester.

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Key words: Antidepressants, class of antidepressant, depression, preeclampsia, pregnancy outcomes.

Introduction

Antidepressant medications are used by up to 13% of pregnant women,[1,2] with the trend suggesting a steady increase in their use during pregnancy.[1] To date, most of the research evaluating antidepressant use during pregnancy has concentrated on outcomes of the fetus, but recent research has begun to focus on the impact they may have on maternal health. Preeclampsia is one specific outcome that has garnered attention, given the increased risk noted among women with depression.[3–8] Preeclampsia is the most severe form of hypertensive disorders during pregnancy, affects 2–5% of pregnant women,[9–13] and it can have serious consequences on maternal and fetal health.

Toh *et al*[5] were one of the first investigators to explore the association of antidepressants with preeclampsia; they documented a nearly 400% increase in the risk of preeclampsia for women continuing selective serotonin reuptake inhibitors (SSRIs) after their first trimester. Since this study, 3 others have reported an elevated risk of preeclampsia associated with antidepressant medications, although of a much smaller magnitude of risk (adjusted relative risks ranging between 1.2 and 3.4).[6–8] Two of these 4 investigations reported a significant increase in the risk of preeclampsia with serotonin-norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs), but not with SSRIs.[6,7]

* Address for correspondence: Lyndsay Ammon Avalos, Kaiser Permanente Northern California, Division of Research, 2000 Broadway, Oakland, CA 94612, USA.
(Email: Lyndsay.A.Avalos@kp.org)

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However, some of the studies were limited in their generalizability (eg, a lack of diversity[6,8] and a special population, ie, Medicaid recipients[7]). One study relied on self-reported depression and antidepressant medication use, which are subject to recall error or bias.[5] Most did not take into account potential confounding factors, such as pre-pregnancy body mass index (BMI),[7] smoking,[6,7] diabetes,[8] chronic hypertension,[8] other mental health conditions,[5,8] or other indications for antidepressant medication use.[5,8] The sample sizes of one study limited the ability to assess exposure to non-SSRI antidepressant medications.[5] Finally, others failed to control for confounding by depression severity.[5,8]

To further examine the effect of depression and antidepressant use on the risk of preeclampsia, we conducted a large, population-based, retrospective cohort study based on information from a racially/ethnically diverse population of 21,589 pregnant Kaiser Permanente Northern California members between 2010 and 2012. We build on previous research by including 2 additional cohorts of women to address the issue of confounding: (1) women without depression but taking antidepressant medications for another indication and (2) women with depression and receiving psychotherapy. The inclusion of this second cohort attempts to address the issue of confounding by severity (ie, depression severity), with the assumption that women who chose psychotherapy have a similar disease severity to those treated with antidepressants.

Methods

Data sources

This study was conducted among the Kaiser Permanente Northern California (KPNC) member population of pregnant women. In 2009, KPNC implemented a universal peripartum depression screening program. Pregnant women entering prenatal care are screened for depression at their first prenatal visit using the Patient Health Questionnaire (PHQ-9). These data, along with diagnoses of depression and preeclampsia, health services utilization such as psychotherapy, dispenses of prescription drugs, and birth delivery data, are available through KPNC's well-established automated clinical and pharmacy databases. This study was approved by the Kaiser Permanente Northern California Institutional Review Board.

Study population

We conducted a population-based, retrospective cohort study of pregnant KPNC women aged 18 or older who gave birth between January 1, 2010, and December 31, 2012. Women who were screened for depression in early pregnancy, had a depression diagnosis, or were taking antidepressant medications during early pregnancy were included. We excluded women with multifetal gestations. Women with a history of hypertension were also excluded, as they were considered to have chronic hypertension. To avoid non-independent observations, only the first pregnancy was included for women with more than one pregnancy during the time period.

Exposure

Depression

Depression during pregnancy was defined as either (1) a clinical depression diagnosis between 6 months prior to the woman's last menstrual period (LMP) and 20 completed weeks of gestation or (2) a PHQ-9 score ≥10 in the first 20 weeks of pregnancy. The PHQ-9 has been validated as an instrument for screening for depression in obstetric patients with high sensitivity (>88%) and specificity (>88%) for scores ≥10.[14–18] It has been adopted by clinicians and researchers for screening in populations including pregnant and postpartum women,[19–24] and is considered the dimensional depression measure in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-V) classification manual.[25]

The first date of the LMP was determined based on gestational age recorded in the KPNC clinical databases in combination with the calendar date at delivery (last menstrual period = date at delivery − gestational age at delivery). To avoid potential reverse causation, we set the exposure window to end immediately before preeclampsia can be diagnosed (20 weeks gestation). Depression diagnoses were defined as *International Classification of Diseases*, Ninth Revision (ICD-9) codes 296.20–296.25, 296.30–296.35, 298.0, 300.4, 309.0, 309.1, 311, 648.4x.

Antidepressant medication exposure

Women exposed to antidepressant medications during pregnancy were identified through linkage to information on dates of drug dispensation and days of supply from the pharmacy database. Please see the Appendix for a list of antidepressant medications identified. Antidepressant use during pregnancy was defined as having at least one pharmacy dispensing record for the time period between the first day of the woman's last menstrual period (LMP) and 20 completed weeks of gestation.

The timing of antidepressant medication exposure was categorized as (1) first trimester only exposure or (2) any second trimester exposure. First trimester only exposure included exposure to antidepressant medications in the first trimester (LMP through 12 weeks gestation) but not during the second trimester (13–20 weeks gestation). Any second trimester exposure was defined as antidepressant medication exposure between 13 weeks and 20 weeks gestation.

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Duration of antidepressant use was categorized into three categories (1–60 days, 61–120 days, or 121–140 days) and started from either the first day of their LMP (if they started prior to pregnancy) or the actual start date (if after the LMP) and ending at 20 completed weeks of gestation or the actual end date (if before 20 weeks of gestation). The total duration of exposure could not exceed 140 days (20 weeks of gestation).

The class of antidepressant medication was categorized in 2 ways for each class of medication: (1) any use or (2) use of only that class. Six classes of antidepressants were assessed: tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), norepinephrine-dopamine reuptake inhibitors (NDRIs), serotonin antagonist and reuptake inhibitors (SARIs), and any other classes of antidepressant medications (other class).

Psychotherapy

Psychotherapy visits between LMP and 20 weeks gestation were ascertained from utilization databases.

Exposure cohorts

Five cohorts were established based on a combination of depression, antidepressant medication use, and psychotherapy. The first 2 cohorts included women exposed to antidepressant medications during pregnancy: (1) antidepressant use with a depression diagnosis or positive PHQ-9 score and (2) antidepressant use without depression or positive PHQ-9 score. Two additional cohorts included women with depression not treated pharmacologically: (1) depression and psychotherapy and (2) untreated depression. The final cohort consisted of women without depression, or not having used any antidepressant medications or received psychotherapy (between LMP and delivery).

Preeclampsia outcome

Preeclampsia was defined as any of the following ICD-9 codes occurring after 20 weeks gestation: 642.4, 642.5, 642.6, or 642.7.

Covariates

The following potential confounders were considered: maternal age, race/ethnicity, marital status, parity, alcohol use and smoking (between LMP and 20 weeks gestation), pre-pregnancy body mass index (BMI) (underweight, normal, overweight/obese), pre-existing or gestational diabetes, a dichotomous variable for other indications for antidepressant medication use for six months prior to LMP through 20 weeks gestation (anxiety, migraines, sleep disorders, chronic musculoskeletal pain, peripheral neuropathic pain, fibromyalgia, rheumatoid arthritis, inflammatory bowel disease, or gastrointestinal ulcers),[21] and a dichotomous variable for other mental health disorders (6 months prior to LMP to 20 weeks gestation).

Data analysis

Characteristics of the 5 exposure cohorts were compared using χ^2 tests. Logistic regression models were conducted comparing the 5 exposure cohorts to assess the risk of preeclampsia associated with antidepressant medication use and depression during pregnancy. Additional logistic regression models were conducted to assess the impact of timing of antidepressant medication exposure, duration of use, and class of antidepressant.

Logistic regression produces an adjusted odds ratio that approximates the relative risk when the disease outcome is rare. Given that the prevalence of preeclampsia is less than 10%, we report the odds ratios as relative risks in this study.

Results

Overall the study included 21,589 women. Of these women, 1,732 (8%) had depression and were treated with antidepressant medications; 149 (<1%) did not have depression but took antidepressant medications during pregnancy; 1,961 (9%) had depression and received psychotherapy; 1,345 (6%) had untreated depression, and 16,402 (76%) did not have depression and did not take any antidepressant medications or receive psychotherapy for depression. Women taking antidepressant medications who had depression were more likely to be identified by a *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) diagnosis (n = 1696, 98%) compared to women with depression who received psychotherapy (n = 49, 49%) and untreated depression (n = 198, 15%). Of the 149 women taking antidepressants without depression, 32 (21%) had an anxiety diagnosis, 71 (48%) had another non-mental health indication, and 46 (31%) did not have any indication listed. Comparisons of the characteristics of the five cohorts are listed in Table 1.

The overall risk of preeclampsia in our study was 4.5%, and ranged from 2.7% for women taking antidepressant medications without depression to 6.9% for women taking antidepressant medications who did have depression.

Exposure to antidepressant medication during pregnancy and the risk of preeclampsia

After adjusting for all covariates, compared to women without depression, women who took antidepressant medications and had depression had nearly a 40%

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TABLE 1. Demographic characteristics, behavioral factors, health, and mental health diagnoses by exposure cohort for 21,598 pregnant women in Kaiser Permanente Northern California 2010–2012

	No depression	Untreated depression	Depression and psychotherapy	Antidepressant use and depression	Antidepressant use and no depression	
	16,402	1,345	1,961	1,732	149	
Total N	n (%)	n (%)	n (%)	n (%)	n (%)	p-value
Age						
18–20	479 (3)	67 (5)	208 (10.6)	80 (5)	3 (2)	<0.0001
21–25	2,256 (14)	207 (15)	383 (19.5)	239 (13.8)	20 (13)	
26–30	5,543 (34)	429 (32)	533 (27)	495 (28.6)	50 (34)	
31–35	5,413 (33)	422 (31)	540 (28)	570 (32.9)	44 (30)	
36–40	2,318 (14)	196 (15)	252 (12.9)	275 (16)	29 (20)	
>40	393 (2)	24 (2)	45 (2)	73 (4)	3 (2)	
Race/ethnicity						
White	5,873 (36)	292 (22)	588 (30)	1,013 (56)	86 (58)	<0.0001
Black	667 (4)	93 (7)	198 (10)	122 (7)	11 (7)	
Hispanic	3,844 (23)	349 (26)	610 (31)	402 (23)	35 (24)	
Asian	5,447 (33)	539 (40)	498 (25)	135 (7.8)	13 (9)	
Others/unknown	571 (4)	72 (5)	67 (3)	60 (4)	4 (2.7)	
Marital status						
Married/partner	14,048 (86)	1,074 (80)	1,245 (64)	1,181 (68)	122 (82)	<0.0001
Divorce/separated	138 (<1)	15 (1)	55 (3)	91 (5)	2 (1)	
Never married	2,178 (13)	253 (19)	652 (33)	456 (26)	24 (16)	
Pre-pregnancy BMI						
<18.5	469 (3)	38 (3)	64 (3)	32 (2)	4 (3)	<0.0001
18.5– <25.0	8,054 (54)	680 (54)	886 (48)	685 (40)	69 (47)	
25.0 +	6,326 (43)	545 (43)	915 (49)	980 (58)	74 (50)	
Parity						
0	7,874 (48)	613 (46)	996 (51)	775 (45)	74 (50)	<0.0001
1	5,347 (33)	422 (31)	586 (30)	517 (30)	48 (32)	
2 +	3,015 (18)	297 (22)	355 (18)	423 (24)	25 (17)	
Smoking status						
No	16,150 (99)	1,301 (97)	1,606 (82)	1,402 (81)	123 (83)	<0.0001
Yes	252 (2)	44 (3)	355 (18)	330 (19)	26 (17)	
Alcohol use						
No	15,583 (95)	1,281 (95)	1,453 (74)	1,330 (77)	114 (77)	<0.0001
Yes	819 (5)	64 (5)	508 (26)	402 (23)	35 (24)	
Diabetes (gestational or pre-existing)						
No	13,963 (85)	1,107 (82)	1,699 (87)	1,464 (85)	127 (85)	0.0066
Yes	2,439 (15)	238 (18)	262 (13)	268 (15)	22 (15)	
Other mental health diseases						
No	16,190 (99)	1,307 (97)	1,646 (84)	1,161 (67)	132 (89)	<0.0001
Yes	212 (1)	38 (3)	315 (16)	571 (33)	17 (11)	
Other indications for antidepressant medications						
No	13,653 (83)	1,032 (77)	1,200 (61)	532 (31)	46 (31)	<0.0001
Yes	2,749 (17)	313 (23)	761 (39)	1,200 (69)	103 (69)	
Method of depression identification						
DSM-IV	NA	198 (15)	966 (49)	1,696 (98)	NA	0.0024
PHQ-9 ≥10	NA	1,147 (85)	995 (51)	36 (2)	NA	

The numbers in each individual category may not sum to the total number because of missing data.

increase in the risk of preeclampsia (95% CI: 1.06, 1.76) (Table 2), while women who took antidepressant medications and did not have depression had a non-significant decreased risk of preeclampsia (aRR: 0.5, 95% CI: 0.19, 1.44). When the timing of antidepressant medication exposure was considered, the results for the 2 antidepressant cohorts mirrored each other. Among antidepressant users with depression, antidepressant medication exposure in the second trimester was significantly associated with a 70% increase in the risk of preeclampsia compared to women without depression. There were no significant differences in the risk of preeclampsia associated with first trimester only exposure when compared to women without depression. Among the antidepressant users without depression, a nonsignificant increased risk of preeclampsia emerged for second trimester exposure when compared to women without depression (aRR: 1.34, 95% CI: 0.5, 3.8).

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TABLE 2. The relative risk of preelampsia for women with untreated depression, depression, and receiving psychotherapy; antidepressant exposure and no depression; antidepressant exposure and depression; and timing of antidepressant exposure, among 21,589 pregnant women in Kaiser Permanente Northern California, 2010–2012

	Total n	Preeclampsia n (%)	cRR[a]	95% CI	aRR[b,c]	95% CI	cRR	95% CI
Antidepressant exposure and depression	1,732	120 (6.9)	1.62	1.33–1.98	1.37	1.06–1.76	1.71	1.24–2.37
First trimester user only	580	25 (4.3)	0.98	0.65–1.48	0.76	0.49–1.19	1.04	0.64–1.68
Second trimester user ever	1,152	95 (8.2)	1.96	1.57–2.45	1.7	1.30–2.23	2.07	1.47–2.91
Antidepressant exposure and no depression	149	4 (2.7)	0.6	0.22–1.63	0.53	0.19–1.44	0.64	0.23–1.78
First trimester user only	91	0 (0)	–	–	–	–	–	–
Second trimester user ever	58	4 (6.9)	1.62	0.58–4.47	1.34	0.48–3.79	1.71	0.60–4.87
Depression and psychotherapy	1,961	83 (4.2)	0.96	0.76–1.22	0.8	0.61–1.04	1.02	0.72–1.44
Untreated depression	1,345	56 (4.2)	0.95	0.72–1.25	0.95	0.71–1.27	Ref	Ref
No depression	16,402	719 (4.4)	Ref	Ref	Ref	Ref		
	aRR[c]	95% CI	cRR	95% CI	aRR[c]	95% CI		
Antidepressant exposure and depression	1.29	0.87– –1.92	1.68	1.26– –2.25	1.63	1.17–2.28		
First trimester user only	0.74	0.43– –1.27	1.02	0.65– –1.61	0.94	0.57–1.54		
Second trimester user ever	1.6	1.06–2.41	2.03	1.50– –2.76	2.05	1.44–2.91		
Antidepressant exposure and no depression	0.49	0.17–1.42	0.62	0.23– –1.73	0.61	0.22–1.71		
First trimester user only	–	–	–	–	–	–		
Second trimester user ever	1.29	0.44–3.79	1.68	0.59– –4.74	1.56	0.54–4.55		
Depression and psychotherapy	0.83	0.57–1.22	Ref	Ref	Ref	Ref		
Untreated depression	Ref	Ref						
No depression								

[a]cRR = crude relative risk.
[b]aRR = adjusted relative risk.
[c]Adjusted for pre-pregnancy BMI, maternal age, race/ethnicity, marital status, parity, alcohol use, smoking, diabetes, other indications for antidepressant medications, other mental health diagnoses.

None of the women in this cohort who were exposed to antidepressant medications during the first trimester only had preeclampsia.

Similar patterns to those described above emerged when the women in the 2 antidepressant medication cohorts were compared to women with depression who received psychotherapy and women with untreated depression.

Depression with psychotherapy and the risk of preeclampsia

There was no increased risk of preeclampsia for women with depression receiving psychotherapy compared to women without depression (aRR: 0.8: 95% CI: 0.6, 1.04) or women with untreated depression (aRR: 0.8, 95% CI: 0.6, 1.2).

Untreated depression and the risk of preeclampsia

The risk of preeclampsia for women with untreated depression did not differ from women without depression (aRR: 0.95, 95% CI: 0.7, 1.3) (Table 2).

Sensitivity analyses

We assessed the sensitivity of our results to our definition of depression by replicating all analyses in Table 2 and excluding all women identified with depression using the PHQ-9. Similar trends appeared for all relationships (results not shown). Additionally, we assessed the prevalence of preeclampsia by indication for antidepressant medication use in the cohort without depression: 3% ($n = 1$) for women with an anxiety diagnosis, 1% ($n = 1$) for women with another indication, and 4% ($n = 2$) for women without an indication.

Duration of exposure to antidepressant medications

We found a significant relationship with duration of use (test for trend $p = 0.01$); increased duration of use appeared to be associated with a greater risk of preeclampsia (Table 3).

Class of antidepressant medication

SSRIs ($n = 1{,}499$, 80% of the women who took antidepressant medications) were the most prevalent antidepressant medication used in our population (Table 4). NDRIs were the second most prevalent ($n = 236$, 13%) followed by TCAs ($n = 154$, 8%). When compared to women without depression, the adjusted relative risk of preeclampsia for exposure to SSRI medications was 1.3 (95% CI: 1.0, 1.8 for exposure to only SSRIs), suggesting a borderline increased risk. We found a 40% increase in the

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TABLE 3. The relative risk of preeclampsia by the duration of antidepressant medication exposure during pregnancy (for all women exposed to antidepressant medication regardless of depression status) compared to women without depression

	Total N	Preeclampsia n (%)	cRR[a]	95% CI	aRR[b,c]	95% CI
No depression	16,402	719 (4.4)	Ref	Ref	Ref	Ref
≤60 days	739	42 (5.7)	1.31	0.95–1.81	1.05	0.72–1.53
>60–120 days	791	56 (7.1)	1.66	1.25–2.20	1.38	0.99–1.93
>120 days	351	26 (7.4)	1.75	1.16–2.62	1.47	0.94–2.29

Test of trend: p-value = 0.0114.

[a]cRR = crude relative risk.

[b]aRR = adjusted relative risk.

[c]Adjusted for pre-pregnancy BMI, maternal age, race/ethnicity, marital status, parity, alcohol use, smoking, diabetes, other indications for antidepressant medications, other mental health diagnoses.

TABLE 4. The relative risk of preeclampsia for women taking antidepressants during pregnancy, by class of antidepressant medication

	Total N	Preeclampsia n (%)	cRR[a]	95% CI	aRR[b,c]	95% CI
No depression	16402	719 (4.4)	Ref	Ref	Ref	Ref
TCA exposure						
TCA/TCA plus other antidepressant	154	6 (3.9)	0.88	0.39– –2.01	0.78	0.33–1.82
TCA only	116	2 (1.7)	0.38	0.10– –1.55	0.35	0.09–1.47
SSRI exposure						
SSRI only/SSRI plus other antidepressant	1499	106 (7.1)	1.66	1.34– –2.05	1.4	1.06–1.85
SSRI only	1262	87 (6.9)	1.62	1.28– –2.03	1.34	1.00–1.81
SNRI exposure						
SNRI/SNRI plus other antidepressant	113	8 (7.1)	1.66	0.81– –3.42	1.45	0.66–3.22
SNRI only	72	5 (6.9)	1.63	0.65– –4.05	1.49	0.57–3.90
NDRI exposure						
NDRI/NDRI plus other antidepressant	236	18 (7.6)	1.8	1.11– –2.93	1.56	0.90–2.69
NDRI only	118	8 (6.8)	1.59	0.77– –3.26	1.23	0.57–2.67
SARI exposure						
SARI/SARI plus other antidepressant	144	9 (6.3)	1.45	0.74– –2.87	1.18	0.56–2.50
SARI only	35	1 (2.9)	0.64	0.09– –4.69	0.55	0.07–4.09
Other class exposure						
Other class/other class plus other antidepressant	27	1 (3.7)	0.84	0.11– –6.19	1.03	0.13–7.98
Other class only	11	0	–	–	–	–

[a]cRR = crude relative risk.

[b]aRR = adjusted relative risk.

[c]Adjusted for pre-pregnancy BMI, maternal age, race/ethnicity, marital status, parity, alcohol use, smoking, diabetes, other indications for antidepressant medications, other mental health diagnoses.

risk of preeclampsia related to any exposure to SSRI medications (95% CI: 1.06–1.85). There also may be an increased risk of preeclampsia associated with use of other antidepressants, but the statistical significance of our findings was limited by small sample sizes and the low frequency of our primary outcome (ie, preeclampsia).

Discussion

Our findings suggest that antidepressant medication use during the second trimester (13 to 20 weeks) may increase the risk of preeclampsia. Timing of exposure emerged as an important factor in the relationship between antidepressant medication use and preeclampsia. We acknowledge that the results were not statistically significant for women without depression exposed to antidepressants during the second trimester. These findings were based on small numbers but nonetheless highlight a similar trend.

The class of antidepressant medication use may also be important. In our investigation, SSRIs were the only class of antidepressant medication in which a statistically significant relationship emerged, but other classes, specifically SNRIs and NDRIs, should be further examined for a possible increased risk of preeclampsia as well.

The relationship between duration of antidepressant exposure and preeclampsia that we report here supports findings from other studies which have found a greater risk of preeclampsia among women who took antidepressant medications for a longer duration.[5–7] In addition, other studies have also documented that timing of

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antidepressant exposure may be an important factor, with second trimester exposure resulting in the highest risk of preeclampsia.[5,6]

From a biological perspective, it is plausible that there would be a relationship between antidepressant medications and preeclampsia. SSRIs, SNRIs, and TCAs are the 3 main classes of antidepressants prescribed to treat depression. They are also known as monoamine neurotransmitter reuptake inhibitors, as they are designed to target the pathways of the 3 main neurotransmitters involved in depression (serotonin, norepinephrine, and dopamine). Monoamine neurotransmitter reuptake inhibitors constrain the reuptake of serotonin, norepinephrine, and dopamine, and thus may change the extracellular concentrations of these 3 neurotransmitters. One potential mechanism through which antidepressants may impact the risk of preeclampsia may be through the type and amount of monoamine neurotransmitter reuptake inhibition.[5,6,27] Research from both human *in vitro* models and animal models suggests that extracellular levels of serotonin and norepinephrine in the placenta may be involved in inducing vasoconstriction.[28–31] In *in vitro* human models, serotonin has been documented to increase placental chorionic vein and umbilical artery vasoconstriction.[28,29] Rat models have identified norepinephrine as a vasoconstrictor in uterine vascular beds.[30] In addition, a decrease in uterine artery blood flow and fetal oxygenation has been found in pregnant sheep infused with fluoxetine, an SSRI.[31] SSRIs have also been noted to inhibit synthesis of nitric oxide, a vasodilator that may play a role in vascular tone and reactivity.[32–34] Likely due to their noradrenergic effects, SNRIs can cause elevated diastolic blood pressure.[35] Further supporting a biological mechanism for the relationship between antidepressant medication exposure and preeclampsia, increased serum levels of both serotonin and norepinephrine have been found in women with preeclampsia.[36–38]

We attempted to control for confounding by depression severity or indication. First, we included a comparison group of women with depression in psychotherapy as a cohort of women who may have a similar level of depression severity to those taking antidepressant medications. Psychotherapy is a safe alternative to antidepressant medications that pregnant women may be more likely to utilize, given the potential adverse fetal and neonatal outcomes associated with antidepressant medications.[39–41] In our study, women with depression receiving psychotherapy did not have an increased risk of preeclampsia compared to either women with untreated depression or women without depression. Yet, women exposed to antidepressant medications in the second trimester had an increased risk of preeclampsia when compared to women with depression receiving psychotherapy, though no difference was found with first trimester antidepressant exposure. It could be argued that women who receive antidepressant medications during pregnancy may have more severe illness than women receiving psychotherapy. This is a possibility that we cannot assess in this study. An additional limitation found with this particular comparison may be the relatively liberal definition of receiving psychotherapy, namely, that subjects needed only 1 visit (or more) to qualify.

We attempted to address the issue of confounding by indication by including a cohort of women without depression who were taking antidepressant medications for various indications. There are several indications listed by the FDA[26] for which antidepressant medications may be prescribed. We did not find the risk of preeclampsia for this cohort of women to be statistically significantly increased compared to women without depression and not taking antidepressants. Thus, we cannot rule out the possibility that the increased risk of preeclampsia that emerged in our study was due to the underlying depression.

Misclassification of depression is a possibility, as our definition included women with a positive PHQ-9 screen or a depression diagnosis. However, our results were replicated when we included women identified with depression only by DSM-IV diagnoses. Misclassification of exposure to antidepressant medication is also possible. We ascertained data on antidepressant prescriptions and dispensing; however, we are limited in our ability to assess actual use. Any misclassification of antidepressant medication use would likely be non-differential and would bias the results toward the null.

Women who remain on antidepressant medications during pregnancy may have other risk factors that would increase their risk for preeclampsia. Attempts were made to address many of these potential factors in both our study design and analyses. First, we restricted the sample to women without pre-existing hypertension or multifetal gestations. Second, we controlled for several factors known to be associated with both antidepressant use and preeclampsia, such as pre-pregnancy body mass index (BMI), diabetes, race/ethnicity, and smoking. Our findings persisted despite these restrictions and adjustments. For any other potential unmeasured confounder to influence our results, it would have to be prevalent in our study population and strongly associated with both antidepressant medication exposure and preeclampsia.[42]

We did not control for multiple comparisons. However, given that the findings that emerged for the various comparisons related to depression, antidepressant exposure, and preeclampsia were all in the same direction and of similar magnitude, these results are not likely due to chance.

Conclusion

In conclusion, an increased risk of preeclampsia was associated with antidepressant use during the second trimester (13 to 20 weeks) of gestation in comparison to

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women who were not depressed or receiving medication. We did not find a significantly increased risk for preeclampsia among women who received antidepressants without a depression diagnosis, or those who received psychotherapy for their depression. The results of this study suggest that clinicians may wish to consider increased monitoring for preeclampsia of women taking antidepressant medications in the second trimester.

Disclosures

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Appendix

APPENDIX. Antidepressant medications by class

TCA	Amitriptyline
	Clomipramine
	Desipramine
	Nortriptyline
	Doxepin
	Imipramine
	Protriptyline
	Trimipramine
SSRI	Citalopram
	Escitalopram
	Fluoxetine
	Fluvoxamine
	Paroxetine
	Sertraline
SNRI	Descenlafaxine
	Duloxetine
	Milnacipran
	Venlafaxine
SARI	Trazodone
NDRI	Bupropion
Other class	
NRIs	Atomoxetine
TeCAs	Mirtazapine
ANTI_H2	Nefazodone
MAOIs	Phenelzine
	Tranylcypromine
ANGO_H1A	Vilazodone

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