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Pregnancy hypertension and its associations with pre-pregnancy depression, anxiety, antidepressants, and anxiolytics

Madhavi Thombre Kulkarni[a,b,*], Claudia Holzman[b], Elizabeth Wasilevich[b], Zhehui Luo[b], Jeanette Scheid[c], Matthew Allswede[a,d]

[a] Department of Obstetrics, Gynecology and Reproductive Biology, College of Human Medicine, Michigan State University, 965 Wilson Road, East Lansing MI-48824, United States
[b] Department of Epidemiology and Biostatistics, College of Human Medicine, Michigan State University, 909 Wilson Road, East Lansing MI-48824, United States
[c] Department of Psychiatry, College of Human Medicine, 909 Wilson Road, Michigan State University, East Lansing MI-48824, United States
[d] Department of Obstetrics and Gynecology, Sparrow Hospital, 1215 East Michigan Avenue, Lansing MI-48912, United States

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ABSTRACT

Introduction: Few studies have examined pre-pregnancy depression/anxiety and antidepressant/anxiolytic medication use in relation to hypertension disorders of pregnancy, i.e. chronic hypertension (CH), pre-eclampsia (PE), and gestational hypertension (GH).

Methods: This nested case-control study uses Blue Cross Blue Shield of Michigan (BCBSM) claims data of women with singleton live birth pregnancies (2010–2014) enrolled from 2 years prior to last menstrual period to ninety days after delivery. All women with ICD-9CM codes for CH, PE, GH, or unspecified hypertension were included as cases; women without hypertension were randomly sampled as controls. Linkage to Michigan birthfiles resulted in a sample of 12,647 women. Using weighted logistic regression, cases and controls were compared for depression and/or anxiety diagnoses (ICD-9CM codes) and anti-depressant and/or anxiolytic prescriptions throughout the study period. Depression and anxiety were defined as primary diagnosis in ≥1 inpatient or ≥2 outpatient visits.

Results: Among women with hypertension disorders of pregnancy, 59% had PE or GH, referred to here as pregnancy hypertension (PH). PH was associated with anti-depressant use prior to LMP only, (aOR = 1.2 95%CI 1.0, 1.5), continued use, (aOR = 1.4 95%CI 1.1, 1.7), and initiation of anxiolytic medication during pregnancy, (aOR = 2.5 95%CI 1.6, 4.2). In this latter group, 96% started medication before PH diagnosis. CH and PH were not associated with depression or anxiety in the absence of anti-depressants/anxiolytics.

Conclusion: While anti-depressants/anxiolytics may be useful indicators in risk stratification for pregnancy hypertension, the same does not appear to be true for depression/anxiety without related medication use.

1. Introduction

Hypertension (HTN) disorders of pregnancy affect 5–10% of pregnancies, and include, chronic hypertension (CH), gestational hypertension (GH), preeclampsia (PE), eclampsia, preeclampsia superimposed on chronic hypertension. These disorders are associated with maternal and neonatal mortality and morbidities [1,2], and later life adverse sequlea [3]. Epidemiological research suggests that risk factors for pregnancy HTN include pre-pregnancy obesity, diabetes, advanced maternal age, and twin pregnancies [4]. Pre-pregnancy maternal depression and anxiety may also be potential risk factors for pregnancy HTN as these conditions confer increased risk of hypertension in men and non-pregnant women [5–7].

Studies investigating associations of pre-pregnancy [8,9] or early pregnancy [10–13] depression and anxiety with hypertension disorders of pregnancy have generated mixed results. Most of these studies investigated preeclampsia only. Their approaches to measuring depression/anxiety varied, typically using symptom screening with cutoff values, and not relying on physician diagnosis [8,9,11–13]. Heterogeneity in, exposure, outcome determination, timing (pre-pregnancy/

Abbreviations: HTN, Hypertension; CH, Chronic Hypertension; PE, Preeclampsia; PH, Pregnancy Hypertension; ICD-9CM, International classification of Diseases, Clinical Modification; NDC, National Drug Codes

* Corresponding author at: Department of Obstetrics, Gynecology and Reproductive Biology, College of Human Medicine, Michigan State University, 965 Wilson road, East Fee Hall, Room A-630, East Lansing MI 48824, United States.
E-mail address: Madhavi.Kulkarni@hc.msu.edu (M. Thombre Kulkarni).

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pregnancy) and conflating of depression and anxiety likely contribute to discordant results across studies. In particular, the independent association of anxiety with pregnancy hypertension is unclear due to simplified anxiety assessment [10] and the small number of study participants with "anxiety only" [8]. In addition, some of the aforementioned studies did not separately consider the impact of antidepressant/anxiolytic medication [10–13]. Studies investigating maternal antidepressant/anxiolytic medication and preeclampsia reported a positive association [8,9,14–19]. While studies with gestational hypertension (GH) produced equivocal results [9,14].

The timing of maternal psychopathology and medication use is a critical question when examining associations with hypertension disorders of pregnancy since many cases of preeclampsia relate to problems of placentation. Information on maternal mental health and related medication use prior to pregnancy may be more relevant for early pregnancy events.

We used medical and pharmacy claims data covering two years prior to pregnancy through ninety days post-delivery. These data provide objective information to study HTN disorders of pregnancy in relation to (1) pre-pregnancy and pregnancy depression and anxiety (combined and separately), and (2) pre-pregnancy and pregnancy antidepressant and anxiolytic medication prescription.

2. Methods

Blue Cross Blue Shield of Michigan (BCBSM) abstracted relevant information from enrolled women who delivered a live birth during the study interval and facilitated confidential linkage with birth certificate (BC) data at the Michigan Department of Health and Human Services (MDHHS). The de-identified, linked dataset was made available for this research study. The Institutional review boards of Michigan State University and Michigan Department of Health and Human services approved this project.

Eligibility criteria included women (age 15–44) with pregnancies ending in live births, as identified by ICD-9CM (International classification of Diseases, Clinical Modification); diagnosis and ICD-9CM procedure codes in any of the diagnostic fields on a claim, between 10 and 1-2010 and 9-30-2014, and who were enrolled in BCBSM medical and pharmacy commercial insurance. Delivery admit date in claims was presumed to be the delivery date. To capture psychopathology and related medication prior to pregnancy we selected a two-year window prior to last menstrual period (LMP) and only women with 75% continuous enrollment in medical and pharmacy claims per year were included, resulting in an eligible sample of 24,281 women, who were linked with their infants in BCBSM.

We designed a nested case control study since limited resources precluded linkage with BC data for all eligible women. We therefore created a sampling scheme by constructing maternal age strata, selecting all women with the outcome of interest (case) and randomly sampling women with no hypertension diagnoses (control) from within age strata. We oversampled unaffected women within two extreme age strata (15–19, 40–44 years), because they were fewer, resulting in a sample of 14,999 women. This sample was linked with BC data yielding a sample of 12,743 women. Post-linkage data cleaning resulted in a final de-identified analytic sample of 12,647 women (Fig. 1).

To assess the impact of this sampling process, we compared characteristics such as delivery timing, antidepressant and anxiolytic prescriptions, and age at delivery between three groups of women: women successfully linked with BC data, women who were not sampled for linkage and women who could not be linked.

Neither gestational age (GA) at delivery nor LMP date is available in claims. Therefore, following the approach of other studies using claims [21], LMP was assigned as 245 days prior to delivery date for preterm births (ICD-9CM codes 644.0, 644.2, and 765.x in any diagnostic field of maternal or infant claims). For women without preterm birth codes we assumed they had a term delivery and assigned 270 days prior to delivery date as the last menstrual period date [21].

3. Exposure

Depression and anxiety were each assessed in two time periods, during two years prior to LMP (*pre-pregnancy*) and LMP to delivery (*pregnancy*). For these analyses, depression or anxiety in a specified time-period was abstracted from medical claims and defined as at least one inpatient or two or more outpatient visits in a facility or professional setting with an ICD-9CM diagnosis code (Appendix A) in the primary diagnosis field. Women with a single depression/anxiety outpatient visit, while not meeting our definition, might be different from women with no such visits. Therefore, we grouped these women separately. All groups were mutually exclusive.

Antidepressant/anxiolytic medication was determined from pharmacy claims using National Drug Codes (NDC). Antidepressant/anxiolytic "use" was grouped as: *pre-pregnancy,* at least one prescription filled within the two years prior to LMP but no prescriptions in pregnancy; *continued use,* at least one prescription filled within two years prior to LMP and at least one prescription filled throughout the pregnancy; and *started in pregnancy,* at least one prescription filled for the first-time during pregnancy.

4. Outcome

ICD-9CM diagnosis codes (Appendix A) from medical claims were used to identify women with hypertension disorders as follows: 1) chronic hypertension (CH), from two years prior to LMP to first twenty weeks of pregnancy; 2) gestational hypertension (GH), 3) preeclampsia (PE) 4) eclampsia, 5) preeclampsia superimposed on chronic hypertension, groups 2–5, from after 20 weeks' gestation to delivery date, and 6) unspecified hypertension (UH), from two years prior to LMP up to delivery date. Codes were included if they were recorded in the primary diagnosis field on an inpatient or outpatient claim in a facility or professional setting. In analyses, groups 2–5 were combined as pregnancy-related hypertension (PH).

5. Covariates

Potentially relevant covariates, i.e., maternal demographics (race/ethnicity, education), pre-pregnancy body mass index (BMI), smoking before and during pregnancy, and parity, were abstracted from BC data, whereas maternal age and diabetes mellitus were abstracted from BCBSM data. We identified covariates as potential confounders (maternal age, race [20], education, parity) based on a priori assumptions of their associations with depression/anxiety, related medications and pregnancy hypertension.

6. Statistical analysis

All analyses use sampling weights to account for the study sampling strategy. Maternal characteristics were compared across a two-level outcome variable, i.e. presence/absence of any HTN disorder and across a four-level outcome variable, i.e. no HTN, CH, PH, and UH using Proc Survey Logistic and Proc Survey Reg procedures in SAS. Exposure variables were created with a focus on timing, the two time periods being prior to LMP and during pregnancy. Operationalization of the exposure is described in detail in Table 1. All variables were modeled separately, first in weighted logistic regression analyses using the two-level hypertension outcome, and then in weighted multinomial logistic regression using the four-level hypertension variable.

Analytic models were repeated after separating PE and GH to look for consistency in results for the PH subtypes. To determine the contributions of women using certain class of medication to our overall results, we first repeated analyses leaving out 23 women who filled only antipsychotic prescriptions, and then excluding 358 women who filled

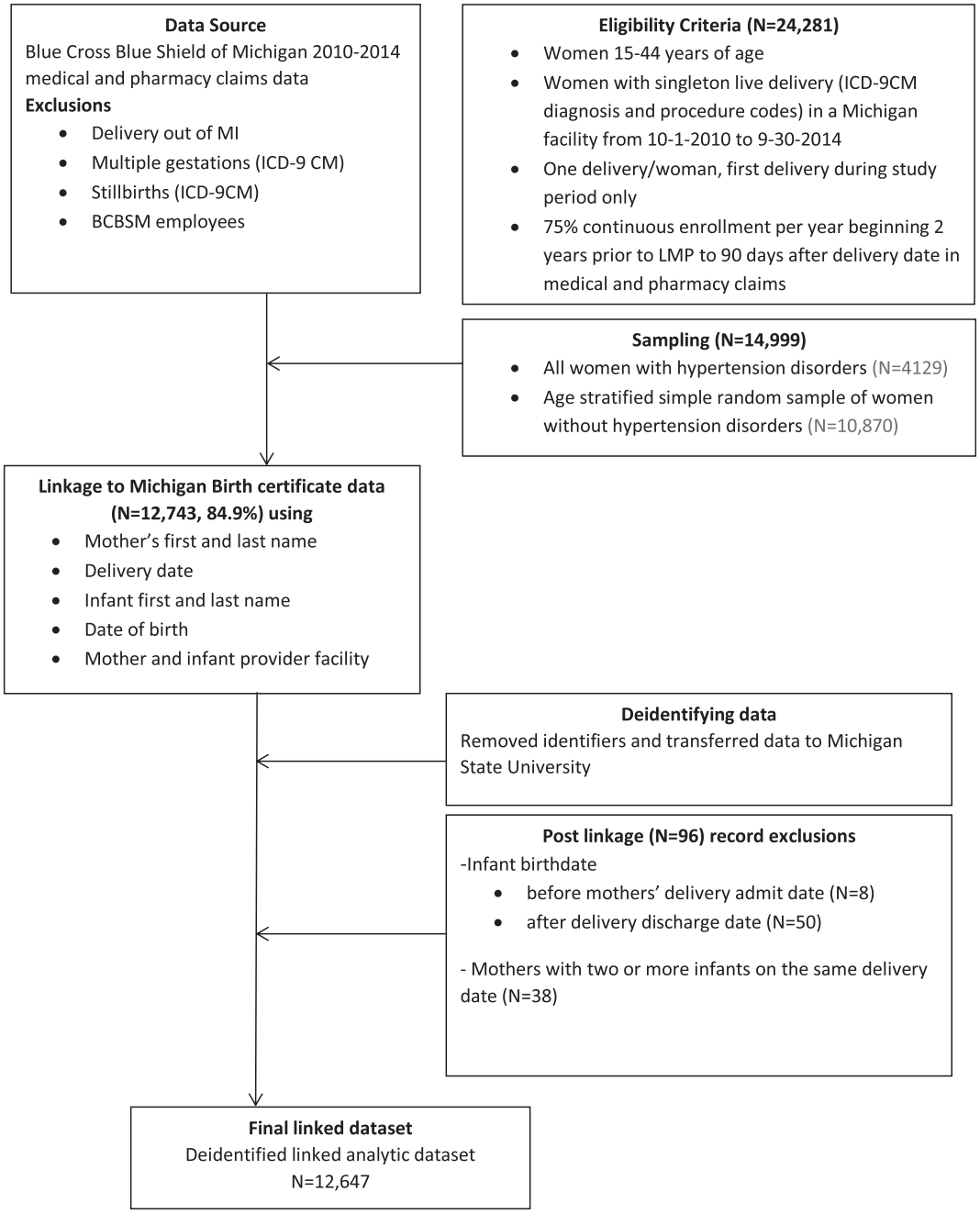

Fig. 1. Flow chart depicting Data Source, Sampling, Linkage and Exclusions.

serotonin and noradrenaline reuptake inhibitors (SNRI) prescriptions during the study period. Timings of exposures and outcomes were based on an estimated LMP. Given this limitation we checked the robustness of our results by excluding women with a LMP date difference between estimated LMP from BCBSM and clinical estimate of GA from BC of more than fifteen days (N = 1311), assuming that GA from BC was a more accurate estimate. All adjusted models included maternal age, race/ethnicity, education and parity along with exposure and outcome. Analyses were conducted with SAS, version 9.4, for windows (SAS Institute, Inc., Cary, North Carolina.

7. Results

All the analyses were weighted for the study sampling scheme. Among women with hypertension disorders of pregnancy, 59% had PE or GH, referred to here as pregnancy hypertension (PH). During the study period from two years prior to LMP to delivery date, 9.7% of all women (N = 1174) had at least one physician visit with a primary diagnosis of depression and 11% (N = 1389) had at least one primary diagnosis of anxiety. Of these women, 5.3% met our definition of depression and 5.7% met the definition of anxiety prior to LMP date. Among 10.6% of women who had a primary diagnosis of depression *or* anxiety, very few women (0.9%) met the definition of depression or anxiety for the first-time during pregnancy. Approximately 11.7% and 10.7% of women filled an antidepressant or anxiolytic prescription respectively prior to LMP only; 6.8% and 1.6% filled antidepressant, anxiolytic prescriptions prior to and during pregnancy; and 1.0% and 0.7% filled antidepressant, anxiolytic prescriptions for the first time in pregnancy.

Demographic and pregnancy characteristics of the 12,647 women are presented by outcome in Table 2. Compared to women with no HTN, a greater percentage of women with CH were African American,

Table 1
Definitions of mutually exclusive variable constructs according to timing of assessment.

Construct by timing	Definition
Depression	
No visits (Reference)	No visits to a physician from two years prior to LMP to delivery date with a primary diagnosis of depression
One depression-related visit in ≥ 1 time point	One outpatient physician visit with a primary diagnosis of depression in one or more time periods, prior to LMP/ during pregnancy
Met depression criteria pre-LMP	At least two outpatient or at least one inpatient physician visits with a primary diagnosis if depression prior to LMP
Met depression criteria for first time in pregnancy	At least two outpatient or at least one inpatient physician visit with a primary diagnosis of depression *after* LMP to delivery date (for the first time in the study period)
Similar variable for Anxiety	
Depression/anxiety overlap variables	
No depression/anxiety (Reference)	No physician visits with a primary diagnosis of either depression or anxiety from two years prior to LMP to delivery date
Depr1visit ≥ 1 time point-no anxiety	One outpatient physician visit with a primary diagnosis of depression in one or more time periods, prior to LMP/ during pregnancy, without any (inpatient or outpatient) diagnosis of anxiety in the same time-period
Depression pre-LMP-no anxiety	At least two outpatient or at least one inpatient physician visits with a primary diagnosis of depression prior to LMP without any physician visits with anxiety diagnosis in the same time-period
Depression in pregnancy-no anxiety	At least two outpatient or at least one inpatient visit with a primary diagnosis of depression during pregnancy, without any physician visits with anxiety diagnosis in the same time-period
No depression-any anxiety	No physician visits with a primary diagnosis of depression, but physician visit(s) with a primary diagnosis of anxiety anytime during study period
Any depression-anxiety-overlap	Presence of any depression and any anxiety diagnosis during study period
Similar six-level anxiety variable with the first four levels without depression	
Antidepressant Medication (National Drug Codes) and depression diagnosis according to timing.	
No anti-depressant-no depression (Reference)	No physician visits with a primary diagnosis of depression and no antidepressant prescription filling from two years prior to LMP to delivery date
Anti-depressant pre-pregnancy	Antidepressant prescription filling from two years prior to LMP to LMP date
Antidepressant continued	Antidepressant prescription filling from two years prior to LMP to LMP date and during pregnancy
Antidepressant pregnancy first time	Antidepressant prescription filling during pregnancy for the first time in the study period to LMP date and during pregnancy
No antidepressant yes depression	Depression diagnosis during study period but no antidepressant prescription

Similarly, for anxiolytic medications and anxiety timing according to diagnosis.

multiparous, and smokers; they also were more likely to have some college and a higher pre-pregnancy BMI. A greater percentage of women with PH were White, primiparous, not married, and smokers; and more likely to have some college and a higher pre-pregnancy BMI.

Weighted analytic models were adjusted for maternal age, race/ethnicity, education and parity (Table 3–5). Unadjusted (Tables S1–S3) and adjusted results were similar. Compared to women with no HTN, those with CH were more likely to have a diagnosis of depression prior to pregnancy (aOR = 1.4; 95%CI 1.0, 1.9), and more likely to have one outpatient visit in one or more time periods with a diagnosis of anxiety (aOR = 1.6; 95%CI 1.2, 2.1). PH was not associated with any of the depression or anxiety measures (Table 2). In models that attempted to

Table 2
Maternal demographic and pregnancy characteristics according to maternal hypertension.[1]

Maternal Characteristics	No HTN N = 9875 N (Wt%)	Any HTN N = 2772 N (Wt%)	Chronic HTN N = 894 N (Wt%)	PH N = 1646 N (Wt%)	Unspecified HTN N = 232 N (Wt%)
Maternal Race[2]					
Caucasian	8905 (89.4)	2488 (89.4)	774 (87.0)	1502 (90.4)	212 (90.7)
African American	386 (4.6)	169 (6.5)	80 (8.9)	79 (5.4)	10 (5.3)
Others	557 (6.0)	109 (4.1)	37 (4.0)	62 (4.1)	10 (4.1)
Maternal Education[3]					
High School Graduate	1227 (15.4)	348 (15.4)	106 (13.5)	223 (17.1)	19 (10.0)
Some college	2531 (27.6)	819 (31.4)	270 (30.8)	487 (31.9)	62 (29.1)
College degree	6096 (57.0)	1599 (53.3)	516 (55.7)	932 (51.0)	151 (61.0)
Current Marital Status[4]					
Never Married	988 (15.7)	305 (16.3)	79 (11.1)	205 (19.3)	21 (13.4)
Currently Married	8749 (83.1)	2414 (82.0)	790 (86.2)	1419 (80.0)	205 (84.1)
divorced/widowed	133 (1.2)	53 (1.7)	25 (2.7)	22 (1.2)	6 (2.4)
Parity					
Primiparous	3882 (43.1)	1291 (49.9)	273 (32.2)	930 (60.2)	88 (39.7)
Multiparous	5993 (56.9)	1481 (50.1)	621 (68.0)	716 (39.8)	144 (60.3)
Maternal Smoking History[5]					
Yes	835 (9.5)	308 (12.3)	104 (12.0)	181 (12.7)	23 (10.5)
No	9013 (90.5)	2458 (87.7)	789 (88.0)	1451 (87.3)	208 (89.5)
	Mean (SE)	***Mean (SE)***	***Mean (SE)***	***Mean (SE)***	***Mean (SE)***
Maternal Pre-pregnancy BMI (kg/m^2)[6]	26.4 (0.06)	30.2 (0.1)	31.3 (0.3)	29.5 (0.2)	29.2 (0.6)
Maternal Age at Delivery	30.2 (0.02)	30.7 (0.03)	32.4 (0.05)	29.8 (0.04)	31.1 (0.09)

Abbreviations: HTN: Hypertension; PH: Pregnancy Hypertension; SE: Standard Error; N: Number of women; Wt%: Weighted percent
[1] Weighted for the Study sampling scheme.
[2] Missing N = 33.
[3] Missing N = 27.
[4] Missing N = 5.
[5] Missing N = 33.
[6] Missing N = 455.

Table 3
Adjusted associations of maternal depression/anxiety diagnosis with maternal hypertension[1].

	No HTN N = 9875 N Wt%	Any HTN N = 2772 N Wt% AOR 95%CI	Chronic HTN N = 894 N Wt% AOR 95%CI	PH N = 1646 N Wt% AOR 95%CI	Unspecified HTN N = 232 N Wt% AOR 95%CI
Depression					
No depression (Ref)	8992 (86.6)	2481 (13.4)	795 (4.0)	1472 (8.2)	214 (1.1)
One depression-related visit in ≥ 1 time point	360 (84.3)	121 (15.7) 1.2 [1.0, 1.5]	39 (4.6) 1.2 [0.9, 1.8]	73 (9.8) 1.2 [0.9,1.6]	9 (1.3) 1.2 [0.6, 2.6]
Met depression criteria Pre-LMP	483 (84.9)	160 (15.1) 1.1 [0.9, 1.4]	58 (5.5) 1.4 [1.0, 1.9]	94 (8.8) 1.0 [0.8, 1.3]	8 (0.8) 0.7 [0.4, 1.7]
Met depression criteria for first time in pregnancy	40 (88.4)	10 (11.6) 0.8 [0.4, 1.7]	2 (2.3) 0.5 [0.1, 2.1]	7 (8.1) 1.0 [0.4, 2.3]	1 (1.1) 1.0 [0.1, 7.2]
Anxiety					
No anxiety (Ref)	8819 (86.6)	2439 (13.4)	733 (4.0)	1460 (8.2)	206 (1.1)
One anxiety related visit ≥ 1 time point	423 (83.7)	150 (16.3) 1.2 [1.0, 1.5]	59 (6.0) **1.6 [1.2, 2.1]** *	79 (8.9) 1.1 [0.8, 1.4]	12 (1.4) 1.3 [0.7, 2.5]
Met anxiety criteria pre-LMP	558 (85.8)	164 (14.2) 1.1 [0.9, 1.3]	55 (4.4) 1.1 [0.8,1.5]	97 (8.9) 1.1 [0.8, 1.4]	12 (0.9) 0.9 [0.5, 1.6]
Met anxiety criteria for the first time in pregnancy	75 (86.9)	19 (13.1) 1.0 [0.6, 1.7]	7 (3.9) 1.1 [0.5, 2.4]	10 (7.4) 0.9 [0.4, 1.8]	2 (1.8) 1.7 [0.4, 7.9]

* p-value < 0.05; [1]Weighted for the Study sampling scheme Adjusted for maternal age, race, education and parity. Abbreviations: HTN: Hypertension; PH: Pregnancy Hypertension; LMP: Last Menstrual Period; N: Number of women; Wt%: Weighted percent; AOR: Adjusted Odds Ratio; CI: Confidence Interval

separate depression and anxiety, CH was associated with the 'pre-LMP depression but no anxiety' group (aOR = 1.8; 95%CI 1.2, 2.5) (Table 4). By contrast, women with CH or PH were not more likely to have primary diagnoses of both depression and anxiety, than their no HTN counterparts.

We considered HTN and its subtypes in relation to antidepressant medication prescriptions, timing of prescriptions, and diagnoses of depression in the absence of medication prescriptions. Women who were not diagnosed with depression and did not fill an antidepressant prescription served as the comparison group. CH and PH were each associated with antidepressant prior to pregnancy only and with continued use into pregnancy (Table 5). Depression diagnosis without antidepressant was not associated with any HTN group.

A similar modeling strategy was repeated focusing on anxiolytics and anxiety. Women with PH were more likely to initiate anxiolytic medication during pregnancy, (aOR = 2.5 95%CI 1.6, 4.2) (Table 5). To rule out reverse causation, we investigated timing of prescription and PH diagnosis. The first anxiolytic prescription date preceded PH diagnosis date in 96% (N = 25/26) of women. Anxiety without an anxiolytic during the study period was not associated with any HTN group.

We separated PE and GH and repeated all above models. Results were similar to the original analyses (data not shown). Exclusions of women who filled only anti-psychotic medications (N = 23) or women who filled SNRI prescriptions (N = 358) or women with discrepant LMP dates (N = 1311) did not alter results significantly.

8. Discussion

This study used medical and pharmacy claims data linked to birth records and found that pregnancy hypertension disorders were associated with depression and anxiety diagnoses in the presence of psychotropic medication use. PH was associated with antidepressant use prior to pregnancy, with continued antidepressant use during pregnancy, and with anxiolytics initiated during pregnancy.

Our finding that CH is positively associated with pre-pregnancy depression/anxiety is consistent with prior studies of non–pregnant populations. In our analyses stratified by psychopathology and medication use, the link of CH with depression/anxiety was confined to those having prescriptions for antidepressant or anxiolytic medications. Longitudinal studies suggest that psychopathologies often precede hypertension [5,6,22,23], though this could vary with the age range of the population studied. Depression/anxiety may lead to hypertension through: 1) dysregulation of the hypothalamic-pituitary-adrenocortical axis (HPA) [24,25], and/or hyperactivity of the sympathetic nervous system. 2) Dysregulation of the autonomic nervous system (ANS), including increased muscle sympathetic nervous system activity [26] and decreased parasympathetic activities, contributing to elevations in blood pressure. 3) Medications used to treat psychopathologies, e.g. tricyclics [27,28]; and other antidepressants such as SSRIs that elicit increased levels of serotonin. Elevated serotonin levels may in turn enhance vasoconstriction of umbilical-placental vessels and can inhibit synthesis of nitricoxide, an important vasodilator [29,30]. and other

Table 4
Adjusted associations of isolated maternal depression/anxiety diagnosis with maternal hypertension[1].

	No HTN N = 9875 N Wt%	Any HTN N = 2772 N Wt% AOR 95%CI	Chronic HTN N = 894 N Wt% AOR 95%CI	PH N = 1646 N Wt% AOR 95%CI	Unspecified HTN N = 232 N Wt% AOR 95%CI
Depression with/without anxiety					
No depression/anxiety (Ref)	8251(86.8)	2247 (13.2)	704 (3.9)	1350 (8.2)	193 (1.1)
Depr1visit ≥ 1 time point-no anxiety	248 (85.1)	80 (14.9) 1.2 [0.9, 1.5]	27 (3.2) 1.3 [0.9, 2.1]	46 (8.8) 1.0 [0.7, 1.5]	7 (1.3) 1.3 [0.6, 2.9]
Depression pre-LMP-no anxiety	298 (83.7)	107 (16.3) 1.2 [1.0, 1.6]	42 (6.5) **1.8 [1.2, 2.5]** *	60 (9.0) 1.1 [0.8, 1.4]	5 (0.8) 0.7 [0.3, 1.6]
Depression in pregnancy-no anxiety	22 (90.4)	5 (10.0) 0.7 [0.3, 1.9]	0 NE	4 (8.0) 1.0 [0.3, 3.0]	1 (2.0) 1.7 [0.2, 12.7]
No depression-any anxiety	741 (84.9)	234 (15.1) 1.1 [1.0, 1.3]	91 (5.5) **1.4 [1.1, 1.8]** *	122 (8.4) 1.0 [0.8, 1.2]	21 (1.2) 1.1 [0.7, 1.8]
Any depression-anxiety-overlap	315 (85.2)	99 (14.8) 1.1 [0.9, 1.5]	30 (4.0) 1.1 [0.7, 1.7]	64 (9.7) 1.1 [0.9, 1.6]	5 (1.0) 1.0 [0.4, 2.7]
Anxiety with/without depression					
No anxiety/depression (Ref)	8251 (86.8)	2247 (13.2)	704 (3.9)	1350 (8.2)	193 (1.1)
Anxiety 1visit ≥1 time point-no depr	308 (84.1)	109 (15.9) 1.2 [1.0, 1.5]	44 (6.1) 1.6 [1.2, 2.2]	55 (8.4) 1.0 [0.7, 1.4]	10 (1.4) 1.3 [0.7, 2.5]
Anxiety-pre-LMP-no depr	383 (85.4)	111 (14.6) 1.1 [0.9, 1.4]	41 (4.9) 1.3 [0.9, 1.8]	60 (8.5) 1.0 [0.8, 1.4]	10 (1.2) 1.0 [0.6, 2.0]
Anxiety in pregnancy-no depr	50 (86.7)	14 (13.3) 1.0 [0.6, 2.0]	6 (5.1) 1.4 [0.6, 3.3]	7 (7.3) 0.9 [0.4, 2.1]	1 (0.8) 0.8 [0.1, 5.6]
No anxiety-any depression	568 (84.5)	192 (15.4) 1.2 [1.0, 1.4]	69 (5.5) 1.5 [1.1, 2.0]	110 (8.9) 1.0 [0.8, 1.3]	13 (1.0) 1.0 [0.5, 1.8]
Any depression-anxiety-overlap	315 (85.2)	99 (14.8) 1.2 [0.9, 1.5]	30 (4.0) 1.1 [0.8, 1.7]	64 (9.7) 1.2 [0.9, 1.6]	5 (1.0) 1.0 [0.4, 2.7]

* p-value < 0.05; [1]Weighted for the Study sampling scheme; Adjusted for maternal age, race, education and parity. Abbreviation: HTN: Hypertension; PH: Pregnancy Hypertension; Depr: Depression, pt.: point; N: Number of women; Wt%: Weighted percent; AOR: Adjusted Odds Ratio; CI: Confidence Interval.

Table 5
Adjusted associations of maternal antidepressant/anxiolytic use and presence of depression/anxiety with Hypertension Disorders in pregnancy.

	No HTN N = 9875 N Wt%	Any HTN N = 2772 N Wt% AOR 95%CI	Chronic HTN N = 894 N Wt% AOR 95%CI	PH N = 1646 N Wt% AOR 95%CI	Unspecified HTN N = 232 N Wt% AOR 95%CI
Antidepressant-depression Status					
No antidepressant-no depression (Ref)	7948 (87.3)	2069 (12.7)	633 (3.7)	1254 (8)	182 (1.1)
Antidepressant pre-pregnancy only	1049 (83)	392 (17.0) **1.4 [1.2, 1.6]** *	141 (5.8) **1.7 [1.4, 2.1]** *	218 (9.8) 1.2 [1.0, 1.5]	33 (1.4) 1.4 [1.0, 2.1]
Antidepressant continued	640 (81.8)	257 (18.2) **1.5 [1.3, 1.8]** *	101 (7.1) **2.0 [1.5, 2.5]** *	142 (10.2) **1.4 [1.1, 1.7]** *	14 (0.9) 0.9 [0.5, 1.6]
Antidepressant-pregnancy first time	86 (87.6)	21 (12.4) 1.0 [0.6, 1.7]	6 (2.8) 0.7 [0.3, 1.8]	15 (9.6) 1.2 [0.7, 2.3]	0 (0.0) NE
No antidepressant-yes depression	152 (90.0)	33 (10.2) 0.7 [0.5, 1.1]	13 (4.0) 1.0 [0.6, 1.7]	17 (5.3) 0.6 [0.4, 1.0]	3 (0.9) 0.8 [0.2, 2.5]
Anxiolytic-anxiety-status					
No anxiolytic-no anxiety (Ref)	8243 (87.1)	2198 (12.9)	675 (3.8)	1331 (8.1)	192 (1.1)
Anxiolytic pre-pregnancy only	1042 (82.8)	383 (17.2) 1.3 [1.1, 1.5]	146 (6.4) 1.7 [1.4, 2.1]	210 (9.5) 1.1 [1.0, 1.3]	27 (1.3) 1.3 [0.8, 2.0]
Anxiolytic continued	151 (81.3)	65 (18.7) 1.4 [1.1, 1.9]	36 (10.1) **2.6 [1.8, 3.8]** *	24 (7.1) 0.9 [0.5, 1.4]	5 (1.4) 1.4 [0.6, 3.5]
Anxiolytic-pregnancy first time	61 (76.6)	32 (23.4) **2.0 [1.3, 3.2]** *	6 (4.6) 1.4 [0.5, 3.4]	26 (18.8) **2.5 [1.6, 4.2]** *	0 (0.0) NE
No anxiolytic-yes anxiety	378 (87.2)	94 (12.8) 1.0 [0.8, 1.3]	31 (3.7) 1.0 [0.7, 1.5]	55 (8.1) 1.0 [0.7, 1.3]	8 (1.1) 1.0 [0.5, 2.1]

* p-value < 0.05; [1]Weighted for the Study sampling scheme; Adjusted for maternal age, race, education, parity. Abbreviation: HTN: Hypertension; PH: Pregnancy Hypertension; N: Number of women; Wt%: Weighted percent; AOR: Adjusted Odds Ratio; CI: Confidence Interval.

unhealthy behaviors, such as poor diet and minimal physical activity [31,32]. Additionally, some have suggested common pathways for both hypertension and depression/anxiety such as inflammation (pro-inflammatory cytokines) and platelet activation [32].

We extended our inquiries into pregnancy because pre-existing chronic conditions and related medication may compromise maternal and infant health. We found no relation between PH and depression/anxiety (pre-pregnancy or during pregnancy) in analyses that did not stratify on medication use. Women with PH were more likely to have a history of antidepressant use either pre-pregnancy only or continuing into pregnancy when compared to women with no HTN. Most studies examining this association report similar results [14–19]. Investigators have struggled to separate potential direct effects of antidepressants from the indication for medication, and its accompanying risk factors (e.g. poor diet, less physical activity, BMI extremes, substance use, social support). This is an area where clinical trials randomizing antidepressant or placebo are ethically challenging, particularly involving pregnant women with severe depression. The effect sizes for the associations between PH and antidepressant were similar for women who discontinued pre-pregnancy or continued prescriptions during pregnancy. This might indicate that any direct effect of antidepressant on PH is not mitigated by discontinuing medication prior to LMP. Alternatively, our findings could support the hypothesis that antidepressant has no direct effect on PH but rather, is a marker for depression severity and/or other factors related to PH. In a set of investigative analyses, inclusion of covariates (diabetes, pre-pregnancy BMI, smoking) that might mediate and/or confound the relation between PH and antidepressant medication did not substantially alter the strength or direction of the results (data not shown).

We also found that women with PH were more likely to have initiated anxiolytic medication in pregnancy without a history of anxiolytic prescriptions in two years prior to the index pregnancy. It is unclear whether anxiolytic use occurred during an etiologically relevant time window in pregnancy, for PH, or if initiation of anxiolytics is a marker of other PH risk factors. To rule out reverse causation in this subgroup of 26 women, we examined the timing of first anxiolytic prescription during pregnancy and noted that it preceded PH diagnosis in nearly all cases. Furthermore, it is unlikely that the results can be explained by women who used SNRI during this time window, since excluding them did not alter the results.

We sampled women who were continuously enrolled in BCBSM for a period of three years and thus this sample may not be generalizable to other populations such as women insured by Medicaid. However, one could argue that low-risk populations provide opportunities to test associations when there is less unmeasured confounding by adverse life circumstances. Since we did not attempt to link all eligible women to BC data we compared these three groups of women (not sent for linkage, unable to be linked, linked) by delivery timing (preterm/term), antidepressant, anxiolytic medication prescription and maternal age at delivery. Linked women and women whose data were not sent for linkage did not differ with the median age at delivery, however a small percentage of women who were unable to be linked (maternal age at delivery was one of the matching variables) had a significantly lower median age at delivery possibly indicating recording errors.

The reliance on ICD-9 codes in claims for assigning exposure and outcome diagnoses has its drawbacks. Claims coding is motivated by reimbursement, and code assignment may vary between providers and by provider expertise (psychiatrist vs general/obstetric practitioner). The prevalence of diagnosis of depression/anxiety during pregnancy-only was low and may reflect the drawback of using only the primary diagnosis field on a claim; as a result, we may increase specificity at the expense of sensitivity for categorizing women with depression/anxiety. Furthermore, we did not have data by provider specialty, and obstetric practitioners might be less likely to code depression/anxiety as the primary diagnosis during a prenatal care visit. Relying on diagnostic codes from the primary diagnostic field only is consistent with most of the literature using claims data for mental health studies and provides diagnostic specificity, indicating the primary reason for that specific visit to the medical practitioner.

Misspecification of LMP could have resulted in misclassification of timing of exposure, (the pre-pregnancy exposure assessment period was two years), particularly in women with hypertension disorders, since these complications are positively associated with preterm delivery. We addressed this concern through a sensitivity analysis that excluded 10% of women with potentially less reliable gestational age estimates and showed results similar to those with all women. Medication exposure was assigned based on filled prescriptions; we cannot be sure that women actually ingested the medication. As is true in any observational study, unmeasured confounding might explain our results.

Strengths of the study included prospectively recorded clinical and pharmacy data with a large sample size, which allowed us to analyze depression and anxiety together and independently. Linkage with birth records provided potential confounders and a check on estimated LMP. Through claims data we were able to separate women with only one outpatient primary claim of depression/anxiety vs. at least two or more outpatient or at least one inpatient visit, and this permitted some measure of diagnostic specificity. By capturing diagnoses and medications prospectively, we avoided recall bias. In addition, we were able to isolate maternal psychopathology and related medication use pre-pregnancy only, from continuation through pregnancy and consider timing in relation to PH diagnoses.

9. Conclusion

In this nested case-control study, we found that primary diagnoses of depression/anxiety are rare in pregnancy among women with no such diagnoses in the previous two years. Studies of women without healthcare insurance prior to pregnancy may miss this point. While anti-depressants/anxiolytics may be useful indicators in risk stratification for pregnancy hypertension, the same does not appear to be true for depression/anxiety without related medication use.

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Contribution to authorship

All authors fulfilled the conditions required for authorship and have approved this submission. MTK and CH conceived the study question and all authors were involved in the study design. MTK and ZL were involved in the statistical analysis while MTK, CH interpreted the results. MTK created the first draft of the manuscript. CH, ZL, MA, BW, JS, made substantial contributions in drafting the article and revising it critically. Furthermore, all authors have given their final approval for this version to be published and agree to be accountable for all aspects of the work.

Ethical approval

This project was approved by the Michigan State University Institutional review board (IRB# 14-554 M, expedited) on November 18-2014 and by Michigan Department of Health and Human services (IRB log # 201402-09-EA) on December 3-2014.

Disclosure of interests

The author declare no conflict of interest.

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Appendix A. ICD9CM diagnosis codes for specified conditions assessed from claim field in a facility or professional setting either during inpatient or outpatient visits, during specified time periods.

Medical Conditions	ICD-9CM Diagnosis codes	Claim Field	Time-period of assessment
Depression	296.x, 300.4, 309.0, 309.1, 311;	Primary diagnostic field	From two years prior to LMP to LMP date; during pregnancy
Anxiety	300.x, 309.x, excluding the ones used in depression diagnosis	Primary diagnostic field	From two years prior to LMP to LMP date; during pregnancy
Chronic Hypertension	401.xx, 403.xx, 404.xx, 405.xx, 642.0x, 642.0x,642.1x,642.2x	Primary diagnostic field	From two years prior to LMP to LMP date; during pregnancy
Transitional (Gestational) Hypertension	642.3x	Primary diagnostic field	Twenty weeks of gestation to delivery date
Preeclampsia	642.4x,642.5x	Primary diagnostic field	Twenty weeks of gestation to delivery date
Eclampsia	642.6x	Primary diagnostic field	Twenty weeks of gestation to delivery date
Preeclampsia superimposed on Chronic Hypertension	642.7x	Primary diagnostic field	Twenty weeks of gestation to delivery date
Unspecified Hypertension	642.9x	Primary diagnostic field	From two years prior to LMP to delivery date

Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2019.03.003.

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