DEPRESSION, ANXIETY, ANTIDEPRESSANT, ANXIOLYTIC MEDICATIONS AND THIER ASSOCIATIONS WITH MATERNAL HYPERTENSION

By

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ABSTRACT

DEPRESSION, ANXIETY, ANTIDEPRESSANT, ANXIOLYTIC MEDICATIONS AND THEIR ASSOCIATION WITH MATERNAL HYPERTENSION

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Our goal is to better understand maternal depression, anxiety and related medications in relation to risk of maternal hypertension (HTN) disorders, i.e. chronic hypertension (CH), Gestational hypertension (GH), and preeclampsia (PE). We first systematically reviewed relevant literature by searching electronic databases PubMed and EMBASE from inception to May 2017. Observational studies were included if they were published in the English language and assessed the association of pre-pregnancy and/or pregnancy depression, anxiety, or antidepressant medication use with maternal HTN disorders. A total of 29 studies meeting these criteria were critiqued and findings summarized. Reports of pre-pregnancy depression/anxiety and chronic hypertension (CH) were few and results were inconsistent. Most failed to find a compelling link between pre-pregnancy depression/anxiety and GH or PE. Pregnancy depression /anxiety was associated with PE in some studies but not others. A majority of studies reported higher rates of PE and GH among women taking antidepressants.. It is unresolved whether the increased risk for PE and GH represents a direct effect of medication or the severity of the disorder marked by pregnancy medication use.

We next conducted our own study to further explore maternal mental health in relation to HTN disorders of pregnancy. Working with Blue Cross Blue Shield of Michigan (BCBSM) we examined medical and pharmacy claims data of women who met our study eligibility criteria, i.e. singleton pregnancy ending in live birth between

October-1-2010 and September-30-2014,15-44 years of age at delivery, and 75% continuous enrollment in medical and pharmacy claims for 2 years prior to last menstrual period (LMP). These data were then linked with birth certificate data to obtain an analytic sample of 12,647 women. We used International Classification of diseases ninth revision Clinical modification (ICD-9CM) to assess depression, anxiety, and HTN disorders of pregnancy from medical claims, and National Drug Codes (NDC) to get antidepressant and anxiolytic medication prescription data from pharmacy claims.

In our analytic sample the majority of HTN disorders were pregnancy hypertension (PH) which includes PE and GH. Approximately 10.6% of all women had a depression or anxiety diagnosis (defined as ≥ 1 inpatient or ≥ 2 outpatient visits) in the study period; only 0.9% first met the diagnostic criteria for depression during pregnancy CH was positively associated with antidepressant and anxiolytic medication use prior to and during pregnancy. PH was associated with: 1) antidepressant use prior to pregnancy only; 2) antidepressant use prior to and during pregnancy; and 3) initiation of anxiolytic medication during pregnancy. CH and PH were not associated with depression or anxiety among non-users of medications.

Our observations reinforce the importance of pre-pregnancy mental health and related medication assessment; this information may help in risk stratification for HTN disorders of pregnancy, plans for greater surveillance during prenatal care and development of prevention strategies. Clearly, the benefits of controlling maternal depression symptoms must be weighed against any excess risk posed by medication.

To my father and mother for inspiring me
to pursue my dreams

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KEY TO ABBREVIATIONS

HTN	Hypertension
BP	Blood Pressure
Depr	Depression
Anx	Anxiety
BMI	Body Mass Index
SES	Socio-economic status
DM	Diabetes Mellitus
CH	Chronic Hypertension
GH	Gestational Hypertension
PE	Preeclampsia
Wt.%	Weighted percentage
CI	Confidence Interval\
aOR	Adjusted Odds Ratio
OR	Odds Ratio
CI	Confidence Interval
pt.	Point

CHAPTER 1

BACKGROUND LITERATURE AND AIMS

A young woman well accomplished in her thirties had just married and was pregnant. She had suffered from depression and anxiety for most of her adult life with symptoms coming and going and therapy sessions weaved into her schedule. Antidepressant medications managed her symptoms and she had tried a couple of different medications until one that worked well for her. She always wanted to be a mother and was thrilled with her pregnancy, however taking medications for her depression and anxiety during pregnancy was worrisome and she obsessed about the possible effects it would have on her unborn child. She knew that stopping her mediations was probably not advisable but she reasoned that with the doctor's offer to closely monitor her during her medication discontinued phase she was seriously thinking about discontinuing her medications at least until the birth of her child. Stop or continue? The dilemma did not help with her anxiety, would she be okay with psychotherapy during pregnancy? Could she take a lower dose of medication? Should she try some other forms of therapy, with close monitoring from her physician?

For all of recorded history of mankind, man has believed in a spiritual plane of existence which somehow interacts with our physical plane of existence. A common belief is that souls, spirits, demons exist and can invade and cause illness especially mental illness. A common form of eliminating these evil spirits has been some form of ritual invocation or exorcism. The view that supernatural forces can cause and cure illness stretches back to furthest antiquity.[1] Exorcism is one form of supernatural healing. Since the ancient Babylonians and Egyptians (circa 3000 B.C.E.) the mentally

abnormal have been treated with techniques like the laying on of hands, music and herbs, and a ritual of exorcism. In fact, spiritual and religious practices such as exorcism, faith healing, prayer, charms, amulets, and similar methods have been the most common treatments for mental illness throughout human history. "Between the years 200 and 1700, almost all mental disorders were understood in terms of demonic possession"[2], and even today "spirit possession is the most common explanation of problems throughout the world".[3] The Greek word "psyche" means mind or soul, and is the root of the words psychology and psychiatry, which means the study of the psyche and the treatment of the psyche, respectively.[4]

1.1 Anxiety Disorders

The origin of the word anxiety is thought to be Latin or French and the root is from Latin word “anxius” or “anxietas”. Anxiety disorders have been distinctly defined according to the (Diagnostic and Statistical manual) DSM-IV diagnostic criteria.[5] They are conditions which involve more than temporary fear. In general, for a person to be diagnosed with an anxiety disorder, the fear or anxiety must be out of proportion to the situation or age inappropriate, and hinder one’s ability to function normally.[5] Anxiety disorders may be roughly grouped as: (1) those characterized primarily by acute fear (e.g., phobias) and (2) those associated with lower level, but chronic, anxiety and apprehension (with the clearest example being generalized anxiety disorder).[6] Anxiety disorders include generalized anxiety disorder, panic disorder, with agoraphobia, agoraphobia without history of panic disorder, specific phobia, social phobia, obsessive-compulsive disorder, posttraumatic stress disorders.[15] Anxiety disorders are characterized by prominent

symptoms of anxiety that are not proportional to the circumstances and persist in a subject for the majority of at least six months prior to diagnosis.

Recent epidemiological research has shown that anxiety disorders collectively, are the most common set of psychiatric disorders. In the United Sates approximately 30% of women in the age group of 15-54 are diagnosed with lifetime anxiety while the one year prevalence is 22.6% .[7] Estimates of current anxiety prevalence range between 0.9% and 28.3% and past-year prevalence between 2.4% and 29.8% from data originating from 44 countries.[8] Different definitions of anxiety disorders account for the wide variation in prevalence of these conditions. The peak age for onset of anxiety disorders in women appears to be in mid to late 20's .[9] Anxiety disorders in the perinatal period have received relatively less research attention even as some findings indicate that symptoms of anxiety are common during the pregnancy and postpartum period[10, 11] and maternal symptoms of anxiety during pregnancy are associated with adverse fetal and developmental consequences[12]. In a population-based community sample of pregnant women, in the first trimester (gestation week 8–12) anxiety symptoms were assessed using the Hospital Anxiety Depression Scale (HADS-A). The prevalence of anxiety symptoms (HADS-A scores ≥8 during pregnancy) was 15.6 % in early pregnancy.[13]

Anxiety has been assessed in the pregnancy literature using Spielberger's State Trait Anxiety Inventory (STAI), to assess the levels of state and trait anxiety[14]. State anxiety is defined as the transient emotional condition characterized by subjective feelings of tension and apprehension, generally fluctuating over time. Trait anxiety refers to the relatively stable anxiety proneness, indicating the individual's tendency to respond to situations perceived as threatening. Retest reliability is high for trait anxiety ($r > .70$)

and, as expected, lower for state anxiety. Diagnosis codes using the International classification of diseases ninth revision Clinical Modification (ICD-9CM), tenth, or eighth revision depending on the time of the study have been used. Typically large databases like the hospital discharge data from Nationwide Inpatient sample or electronic medical records databases, or claims data have used ICD-9 classification to identify anxiety disorders. The main limitation of the larger databases is the non-systematic nature of assessment of subjects, which could be dependent on the provider expertise. One potential advantage with these data are that they are documented prospectively (they may be motivated by reimbursement) without knowledge of the outcome, although they may be assessed retrospectively. Smaller studies lack sample sizes for complete anxiety assessment. Clinician administered diagnostic instruments are the gold standards however they are time consuming and staff-intensive to administer. Patient rated screens are easier to use but may have lower sensitivity and specificity. Furthermore study design could influence the patient recall of these symptoms contingent on the knowledge of the outcome. A large prospective study with adequate power (sample size) and prolong pre-pregnancy period would be necessary to adequately address the link between anxiety disorders and pregnancy hypertension.

1.2 Depression Disorders

Depression has been assessed in the perinatal period to encompass major, minor depression, mood disorders, and symptoms of depression assessed by various screens. Major and minor depression and mood disorders have been clearly defined by DSM-IV criteria. Estimates of the prevalence of depression vary widely, studies assessing major depression have estimated a point prevalence of 3.1% to 4.9% at

various times during the pregnancy. Prevalence of either major or minor depression during pregnancy ranged from 8.5% to 11%, while incidence estimates for major or minor depression hovered around 14.5% during pregnancy.[15] Prevalence rates of depression symptoms by pregnancy trimester were 7.4% (2.2, 12.6) 12.8% (10.7, 14.8) 12.0% (7.4, 16.7) for the first, second and third trimester respectively.[17] Depression scales used to identify symptoms of depression include the Beck Depression Inventory (BDI), Edinburgh Postnatal Depression Scale (EPDS) Center for Epidemiologic Depression Scale (CES-D) and structured clinical interviews. Structured interviews found lower rate than the BDI but not the EPDS.[16] Maternal depression has been associated with placental corticotrophin releasing hormone (CRH) which is predominantly secreted in the latter half of pregnancy and may influence placental function and uterine blood flow, thus possibly contributing to adverse maternal and fetal outcomes such as preterm delivery and low birth weight.[17, 18]

1.3 Antidepressant Medications

Antidepressant medication use is controversial as is any medication use in pregnancy. However untreated depression may carry maternal and fetal health risks. Women who discontinue their antidepressants before pregnancy have a 68% risk of becoming depressed, 50% by the first trimester, and 90% by the second trimester.[20,21] Einarson et al found that 70.3% women who discontinued their medication had adverse effects and one third became suicidal.[22] Roca et al reported that 57% of women who discontinued their medications had to restart them, 48% of these in the first trimester.[23] An estimated of 3 to 13% of women with depression use medication to manage their condition, the most common type of medication being selective serotonin reuptake inhibitors (SSRI).[19]

Antidepressants can control mood effectively and reduce the risk of serious consequences associated with untreated depression.[22,24]

1.4 Hypertension Disorders of Pregnancy

Hypertension (HTN) disorders of pregnancy have been classified by the National High Blood Pressure Education program (NHBPEP) working group on high blood pressure in pregnancy into four categories:[25] 1) Chronic hypertension (CH,1-5% of pregnancies) 2) gestational hypertension (GH, 6-7% of pregnancies; may also be called transient hypertension of pregnancy) 3) preeclampsia/eclampsia (PE, 5-7% of pregnancies), 4) Preeclampsia superimposed on chronic hypertension (20-25% of chronic hypertension pregnancies). Hypertensive disorders complicate about 5-10% of pregnancies[3] and, along with hemorrhage and infection, are responsible for a large proportion of maternal morbidity and mortality, particularly in developing countries. Secular increases in chronic hypertension, gestational hypertension and preeclampsia have occurred as a result of changing maternal characteristics such as diabetes, obesity, maternal age and multiple gestations. The etiology of hypertension disorders of pregnancy is multifactorial and several demographic (maternal age, race/ethnicity) anthropometric (Body Mass Index (BMI)) and obstetric (parity, previous history of preeclampsia, multifetal gestations) factors have been implicated[11]. Pre-existing medical conditions such as diabetes mellitus and renal disease are also risk factors for hypertensive disorders of pregnancy. Depression and anxiety may be two other conditions to consider given that in men and non-pregnant populations such associations have been studied and observed. [26-28]

1.5 Depression, Anxiety, Antidepressant Medications and Hypertension Disorders of Pregnancy

Table 1 summarizes the studies linking depression/anxiety prior to and during pregnancy to maternal hypertension. About 29 studies have assessed the link between depression, anxiety, related medication and hypertension disorders of pregnancy. Most studies are published after 2012 perhaps reflecting interest in the topics but also the rise in antidepressant use during pregnancy. Since these studies are present over a long span of time it is important to note that the terminologies have changed over time and definitions/criteria for diagnosis have evolved (e.g. criteria for preeclampsia). This change in definition is likely to increase PE rates marginally as confirmed by a study from Finland.[29] More than one third of the 29 studies have reported on PE as the outcome. Depression, anxiety assessment is heterogeneous and hence difficult to compare various results. To add to the complexity of comparing results over many studies, most of the studies have conflated depression, anxiety, and not quantified the overlap between the two conditions. Investigations addressing the association of antidepressant medication use with hypertension disorders have tried to control for confounding by depression severity by adjusting for depression and assessing the risk of PE among depressed women. Most of the studies report an increased risk for PE with antidepressant medication use prior to and during pregnancy. Certain antidepressants (tricyclics) were associated with increased risk for PE.

Table 1 Summary of studies investigating the association of pre-pregnancy and pregnancy depression/anxiety with hypertension disorders of pregnancy

No.	First Author, Year, location of study, gestation status	Study Design, Number of participants, data source	Depression/Anxiety Measurement, timing with respect to index pregnancy	Antidepressant measurement, timing with respect to index pregnancy	Hypertension type measurement/timing with respect to index pregnancy	Control variables	Results
1.	Crandon [30], 1978, Australia	Cross-sectional, N=146, clinical setting?	Anxiety using the Anxiety self-analysis form in the third trimester.	Not assessed	Any persisting diastolic blood pressure of 90mm of Hg or more after the 24th week without prior hypertension.	Not mentioned	Incidence of PE was significantly higher in highly anxious women.
2	Kurki et al [31] ,2000, Finland, Singletons	Prospective, N=623, Maternity clinics Helsinki	Beck Depression Inventory(BDI), Anxiety question; not clear when both were administered	No assessed	PE, from medical records, not clear how it was assessed, after 20 weeks.	Age, smoking, alcohol, marital status, ses, bacterial vaginosis	Positive; Depression with PE, Anxiety with PE
3	Sikkema et al [32] 2001, Netherlands, singletons	Nested case referent, 2 control groups , Cases N=9, Matched Controls N=9, Controls N=233	State –Trait Anxiety Inventory (STAI) administered at 1718 weeks and 27-28 weeks gestation	Not assessed	PE, Diastolic BP ≥90mm Hg, on two consecutive occasions at least 4 hours apart and presence of proteinuria in late pregnancy		STAI scores did not differ between cases and controls

Table 1 (cont'd)							
4	Andersson et al [33] 2004, N.Sweden	Cross-sectional, N=1495, Obstetric clinics in Northern Sweden	Primary Care evaluation of Mental Disorders in second trimester (after 18-20 week ultrasound)	Not assessed	Hypertensive disorder including PE from medical records after delivery no timing of measurement specified	Maternal age, parity, marital status, socioeconomic status, smoking habits, parity, BMI in first trimester, history of chronic disease, miscarriage, infertility treatment	Null association of depression and anxiety with hypertensive disorders including PE
5.	Qiu et al [34], 2007, Peru	Case control; Case (PE)=339 Control (no PIH or PE) = 337	Patient Health Questionaire-9 (PHQ-9) at delivery	Not assessed	PE hypertension (≥140/90mm of Hg)with proteinuria after 20 weeks on two occasions four hours apart	Mat age, prepregnancy BMI, parity	PE associated with moderate and moderate to severe depression
6	Vollebregt et al [35], 2007, Amsterdam, singleton	Pregnant women seeking Antenatal care in Amsterdam	Dutch version of Center for Epidemiological Studies Depression Scale (CES-D) and State –Trait Anxiety Inventory (STAI)	Did not ask about antidepressant use	GH,PE(after 20 wks), CH (before 20 wks) Self-report 3-5 months after delivery, verified by medical records for PE/ GH.	BMI, CH, DM, Pregnancy smoking, previous miscarriage /abortion/hemorrhage Model 2 = 1+ age, ethnicity, education, marriage/cohabitation	Neither anxiety nor depression associated with PE or GH

Table 1 (cont'd)							
7	Toh et al [36], 2009, multiple gestations, multicenter USA, Canada, Slone Epidemiology Center Birth defects Study	Retrospective cohort, N=5912 Major birth hospitals	Not assessed	Post-delivery telephone interview selfreported, SSRI discontinued,(2 months prior to pregnancy before end of first trimester), continued after first trimester	Self-reported after delivery, diagnosis after 20 wks.	Region, maternal age, race, marital status, family income, age at menarche, diabetes mellitus, cigarette smoking, pre-pregnancy BMI, treatment with non SSRI antidepressants, number of fetuses, gravidity, history of fertility.	The risk for gestational hypertension was higher for women treated with SSRI, risk was greater for women who continued treatment
8	Qui et al [37] , 2009, Seattle	Prospective, N= 2601	Medical records, and self-reported depression or anxiety before pregnancy and in first 20 weeks	Medication use during pregnancy from medical records	Clinic and medical records after 20 weeks gestation.	Age, race, ethnicity, prepregnancy BMI	Pre-pregnancy mood or anxiety not associated with PE, pregnancy mood or anxiety, medication use associated with PE.

Table 1 (cont'd)							
9	Reis et al [38] 2010, Sweden	Retrospective cohort, N= 14,821, Swedish Medical Birth register	Not assessed	Self-report at first prenatal visit and information from antenatal care	From antenatal records	Delivery year, maternal age, parity, smoking, BMI	CH and PE are associated with early and later antidepressant use.
10	Bansil et al [39], 2010, US	Crosssectional, N= 32,156,438, Nation-wide inpatient sample	ICD-9 diagnosis of depression, anxiety at delivery	Not assessed	Preeclampsia or hypertension ICD-9 diagnosis codes at the time of delivery admission	Maternal age, insurance status, hospital characteristics	Women at delivery with a depression diagnosis were more likely to have PE
11	Cripe et al [40] 2011, Seattle,	Prospective, N= 3432	Medical records, and self-reported depression or anxiety before pregnancy and in first 20 weeks	Not analyzed	Clinic and medical records	Age, race, ethnicity, marital status, parity, smoking status, chronic hypertension, pre-existing diabetes mellitus, prepregnancy BMI	Mood with PH (PE +PIH) null Mood with PIH null Mood with PE positive

Table 1 (cont'd)							
12	Katon et al [42], 2012, University of Washington, Obstetrics clinic	Prospective N= 2398, women at the University of Washington, Obstetrics clinic	Patient Health Questionaire-9 (PHQ-9) in second or third trimester	Self-reported	ICD-9 diagnosis codes from medical records for Pre-existing hypertension, pregnancy induced hypertension, and preeclampsia/eclampsia	Maternal age, marital status, ethnicity, education, employment, chronic conditions, current cigarette smoking, prior pregnancy, gestational week at depression screener, prior pregnancy complications.	Pre-existing hypertension associated with major depression or antidepressant use. Both preexisting and superimposed PE associated with any depression or antidepressant use
13	Kharaghani et al [41], 2011, Iran	Case (156) Control (156), matched on maternal age, weight, height, from antepartum, labor and delivery and emergency wards	Patient Health Questionnaire-9 (PHQ), at delivery.	Not measured	PE, Systolic BP ≥ 140mm of Hg, DBP≥ 90mm of Hg, after 20 weeks gestation, two consecutive separate assessments at least 6 hours apart with proteinuria	Prepregnancy BMI	PE cases score >=15 (moderate to severe depression)

Table 1 (cont'd)							
14	DeVera et al [43] , 2012, Canada	Nested Case (1216)-control (1:10), Quebec pregnancy registry built by linkage of provincial medical, pharmaceutical, hospital, and birth databases	Used ICD 9diagnosis codes for depression and anxiety, adjusted for these conditions	Prescription drug file, at least one prescription filled between first day of gestation and earliest date of diagnosis of pregnancyinduced hypertension	ICD-9 diagnosis codes for PIH included PE,GH or eclampsia after 20 weeks gestation	Maternal age, residence, social assistance, depression, anxiety, DM, CVD, asthma, antidepressant , other medication use in the year pre-pregnancy, NSAIDs, visited psychiatrists, inpatient emergency visits	Antidepressants (SSRI's) during pregnancy were associated with increased risk of PIH
15	Kim et al [46], 2013, Pennsylvania , Singleton, live birth	Retrospective cohort, N=261 pregnant African- Am	EPDS at initial prenatal visit, cutoff 10	Self-reported	Medical records PE (hypertension and proteinuria)	Maternal age, parity	EPDS>= 10 associated with PE

Table 1 (cont'd)							
16	Palmsten et al [44] ,2012, British Columbia	Cohort of women having live births, N= 69,448, and with ICD-9 diagnosis code for depression in the year prior to the last menstrual period and until 20 completed gestation weeks, province wide health care utilization databases	ICD-9 diagnosis codes, during the year prior to last menstrual period up to 20 weeks of gestation	At least one pharmacy dispensing record for an SSRI,SNRI,TCA, or other antidepressant during estimated gestational weeks 10-20	Inpatient or outpatient ICD-9 or ICD10 diagnosis codes for preeclampsia, between gestational week 20 and 1 month after delivery.	Adjusted variables in 4 models, delivery year, age, DM, multifetal , obesity, primiparity, physician visits, number of depression claims, psychiatrist visits, mental health hospitalizations, benzodiazepines, anticonvulsants, antipsychotics.	Continuation of antidepressants during pregnancy is linked with high risk for PE. During weeks 10-20 TCA monotherapy has the highest risk for PE, followed by SNRI and then by SSRI

Table 1 (cont'd)							
17	Palmsten et al [45], 2013, US	Cohort women with delivery related ICD9diagnosis, procedure codes and with depression diagnosis codes. N=100,942, Medicaid data.	ICD-9 diagnosis codes between LMP and 225 days gestation	Antidepressant dispensing from 90 to 225 gestational days.	Preeclampsia, ICD-9 diagnosis codes after 20 weeks gestation	Delivery year, maternal age, race diabetes, multiparity, multiple gestation, number of outpatient and inpatient depression, pain related diagnoses, mental, sleep disorders, number of anti-convulsant, benzodiazepine, prescriptions and outpatient visits.	SNRIs and Tricyclics were associated with higher risk of PE than SSRI
18	Pavlov et al [47], 2014, Soroka Medical center Israel, singletons	Retrospective study, N=256,312, perinatal database, medical charts at the medical center	Anxiety from medical charts, recorded at admission for delivery from referral data (antenatal?)	Not assessed	Hypertensive disorders from perinatal database reported by obstetrician at delivery	Maternal age, ethnicity, smoking, induction of labor, DM, PPROM, Preterm labor	In adjusted results anxiety was not associated with

Table 1 (cont'd)							
19	Winkel et al [48] 2015, Germany	Prospective longitudinal N=283,gynecological outpatient settings	Composite International Diagnostic Interview (CIDI-V) lifetime version, during first/ second trimester of pregnancy	Not assessed	Arterial hypertension during pregnancy BP≥ 140/90mmof Hg, from "Mutterpass" medial records book in pregnancy	Maternal age, parity, smoking, occupation, household income, education	Presence of lifetime comorbid depression and anxiety disorder associated with significantly higher systolic and diastolic BP.
20	Thombre et al [49] , 2015, MI, singletons	Cohort, N=1371, 52 prenatal clinics in 5 Michigan communities	Pre-pregnancy depression self-reported. Pregnancy depression symptoms assessed by CES-D at 16-27weeks,cutoff 16	Self –reported in pregnancy	From medical records, CH before 20 weeks, DBP≥90mmHg and SBP≥140mmHg or use of antihypertensive medication, gestational HTN after 20 weeks elevated BP, PE =GH + proteinuria	Maternal age, race, smoking history, parity, Medicaid insurance status prepregnancy BMI.	Pre-pregnancy depression associated with CH, and preterm PE. Antidepressant medication use in pregnancy was associated with CH.
21	Franco et al [58],2015, Brazil	Cross sectional N= 105, prenatal care	Anxiety measured in third month using State Anxiety Inventory. Depression not mentioned.	No assessed	Gestational arterial hypertension in third trimester	Race, obesity, anxiety, depression	Depression and anxiety are linked with HTN in 3rd trimester

Table 1 (cont'd)							
22	Avalos et al [50], 2015, US, singletons	Retrospective cohort N=21,589 One (first during study period) pregnancy /woman, Kaiser Permanente California	PHQ, depression diagnosis ICD-9 diagnosis codes in early pregnancy	Antidepressant medication from pharmacy data, LMP to 20weeks gestation at least one pharmacy dispensing for specified time period Psychotherapy between LMP and 20 weeks	Preeclampsia ICD-9 diagnosis codes after 20 weeks gestation	Pre-pregnancy BMI, maternal age, race/ethnicity, marital status, parity, alcohol use, smoking, diabetes, other indications for antidepressant medications, other mental health diagnoses	Antidepressant use during pregnancy may increase risk of PE
23	Sion et al [53], 2016, Israel, singletons	Cohort, N= 256,312, University medical center	Depression diagnosis prior to pregnancy on patients charts	Not assessed	Perinatal databases after delivery	Not mentioned	Prepregnancy depression associated with CH
24	Kang et al [54], 2016,China, singletons	Crosssectional , N=467,Gynecology and obstetrics hospital	Anxiety measured by self-rating anxiety scale, at 38 weeks gestation	Not assessed	Pregnancy induced hypertension self-reported at 38 weeks gestation	Area, household income, maternal age	Anxiety was associated with pregnancy induced HTN

Table 1 (cont'd)							
25	Malm et al [51], 2015, Finland, singletons	Prospective birth cohort N= 556,775, National register data	Hospital discharge register ICD-8,9,10, impatient diagnosis in somatic and psychiatric hospitals	Drug reimbursement register, three groups women who used SSRIs during pregnancy, women who had psychiatric diagnosis related to SSRI but did not use the SSRI, no psychiatric diagnosis and no SSRI use	From medical birth register, hypertension of pregnancy/ preeclampsia	Infant gender, birth period, mat age at delivery, residence, marital status, parity, smoking, socioeconomic status, purchase of anxiolytics, sedativehypnotics, antiepileptic, DM, other chronic diseases	Increase risk of hypertension/preeclampsia after exposure to SSRI at least during second and/or third trimester
26	Suzuki et al [52],2015, Japan, singleton	Cross sectional, Maternity hospital	Depression/anxiety diagnosed prior to or during early pregnancy by psychiatrists	Not mentioned how they assessed it	PIH BP≥140/90mmof Hg on two occasions at least 6 hours apart, not mentioned when in pregnancy it was measured		PIH associated with anxiety, and self-interruption of medication but not depressive disorders.

Table 1 (cont'd)							
27	De Ocampo et al [55] 2016, US, Canada, singletons	MotherToBaby cohort n=3471,	Not assessed	Self-report at intake and then every 3 months until delivery and once after delivery. Timing of antidepressant <20 wks ;>20wks Class of anti-depressant SSRI, SNRI, other alone, >=2 drug classes.	Self-reported and medical records for PE(GH+ proteinuria after 20 weeks gestation) and GH(BP ≥ 140/90mmof Hg two or more occasions after 20 weeks gestation)	Maternal race, age, prepregnancy BMI, gravidity, ethnicity, parity, diabetes, asthma, autoimmune disease status, cigarettes smoked per day, cohort study, enrollment year	Women who continued to use anti-depressants during pregnancy are at increased risk for PE and GH.
28	Cetin et al [56], 2017,Turkey	Cross sectional, N=152, Obstetric center	Hospital Anxiety and Depression Scale after delivery	Not assessed	PE if gestational hypertension and proteinuria present after 20 weeks gestation self-reported at delivery	Not mentioned	Depression correlated with PE.

Table 1 (cont'd)							
29	Newport et al [57] 2016,US, live singletons	Case cohort, N=686, Emory Women's Mental Health program (referred for mental health)	Structured clinical interview for DSMIV-TR Axis I Disorders , depressive and anxiety symptoms assessment using the Hamilton rating Scales for depression and anxiety and the Beck Depression Inventory, timing of assessment not mentioned	Prospective weekly documentation of medication exposure across gestation	Hypertensive disorders of pregnancy (PE, GH, Eclampsia, HELLP syndrome) abstracted from obstetrical records after 20 weeks of gestation. GH =two BP measurements equal to or exceeding 140/90mm of HG. PE= GH+ proteinuria.	Nulliparity, obesity, advanced maternal age, African American race, lifetime histories of panic disorder	Adjusted models suggested that hypertensive disorders of pregnancy were associated with SNRI after 20th week of gestation

1.5.1 Biological Plausibility

The association of depression, anxiety symptoms and hypertension is biologically plausible and explained by the dysregulation of the hypothalamic-pituitary adrenal axis, changes in the autonomic nervous system and unhealthy lifestyles. Depression is associated with dysfunction of hypothalamic pituitary adrenal (HPA) axis, hypersecretion of cortisol and inactivation of the negative feedback system.[59] Dysfunction of the HPA axis in depressed subjects is accompanied by dysfunction in the sympathetic nervous system. Norepinephrine and dopamine have both been implicated in the pathophysiology of depression.[60] It is also possible that a third common variable like exogenous stressors may influence both mood and hypertension disorders. Stressors such as marital conflicts, health problems, and work overload have been demonstrated to be associated with both unipolar and bipolar depression.[61] Furthermore it has been suggested that chronic stressors which do not favor the development of adaptation (coping) are likely to be associated with depressive symptoms.[62] Many animal models of stress induced hypertension have been developed and used to demonstrate that environmental stressors are involved in the pathogenesis of hypertension.[60] Some other third variables that could affect both hypertension and depression include unhealthy lifestyles (e.g. unhealthy dietary patterns, smoking, excessive alcohol use), childhood maltreatment,[63-66] and personality traits like neuroticism, introversion. Depressive symptoms are also associated with unhealthy lifestyles in hypertensive subjects with the metabolic syndrome.[67] Certain antidepressant medications have also been associated with hypertension.[68,69] and can act through changing sympathetic and parasympathetic activity.[70] Serotonin, and norepinephrine induce uterine, placental and umbilical vasoconstriction in in vitro studies.[71-76] Very few studies have studied the association

between hypertension and incidence of depression, these studies usually are done in older populations.[77] Pharmacological treatment of hypertension directly or through side effects has been demonstrated to lead to depression, anxiety.[78]

1.6 Methodological limitations and gaps in current literature

1) Cross-sectional and case control studies have assessed the exposure after the outcome, hence possibly biasing the results.
2) In studies with modest effect sizes using administrative data cofounder adjustments are inadequate
3) Given the recurrent nature of psychopathology assessing history of depression, anxiety prior to pregnancy is essential since risk for hypertension disorders might vary depending on whether the psychopathology is new onset in pregnancy or present pre-pregnancy. Very few studies have queried history of depression, anxiety or medication use.
4) Depression, anxiety diagnosis/symptoms have been assessed at varying time points during the pregnancy, and depression and anxiety have been conflated and the overlap not quantified, hence creating ambiguity about the timing and nature of exposure.
5) Anxiolytic medications were not assessed.

Larger studies with prospective and objective exposure and outcome assessment are needed since psychopathology related medication use in pregnancy is relatively rare and the outcomes (hypertension disorders of pregnancy) are rare.

To address these gaps the project was envisioned to include Blue Cross Blue Shield (BCBSM) of Michigan medical and pharmacy claims data linked with birth certificate

data. The project was approved by the Michigan State University (MSU) Institutional review board (IRB) and the Michigan Department of Health and Human Services IRB.

1.7 Study Aims

1) To conduct a systematic review of the literature evaluating the association of pre-pregnancy, pregnancy depression, anxiety, related medication use with hypertension disorders of pregnancy.
2) To investigate the association of pre pregnancy, pregnancy depression, anxiety diagnosis in women with hypertension disorders of pregnancy compared to women without HTN disorders of pregnancy.
3) To investigate the association of antidepressant, anxiolytic medication use prior to and during pregnancy in women with hypertension disorders of pregnancy compared to women without hypertension disorders of pregnancy.

CHAPTER 2

MATERNAL DEPRESSION/ANXIETY, ANTI-DEPRESSANT, ANXIOLYTIC MEDICATION AND ITS ASSOCIATION WITH PREGNANCY HYPERTENSION: A SYSTEMATIC REVIEW

2.1 Introduction

Hypertension (HTN) disorders of pregnancy have been classified by the National High Blood Pressure Education program (NHBPEP) working group on high blood pressure in pregnancy into four categories[25, 79]: Chronic hypertension (1-5% of pregnancies) Gestational hypertension (6-7% of pregnancies; may also be called transient hypertension of pregnancy) preeclampsia/eclampsia (5-7% of pregnancies), Preeclampsia superimposed on chronic hypertension (20-25% of chronic hypertension pregnancies). Hypertensive disorders complicate about 5-10% of pregnancies[80] and, along with hemorrhage and infection, are responsible for a large proportion of maternal morbidity and mortality, particularly in developing countries. A systematic review[81] by the World Health Organization (WHO) identified hypertension as the single leading cause of maternal mortality in industrialized countries, accounting for 16% of maternal deaths. In Africa and Asia hypertensive disorders accounted for 9% of maternal deaths whereas in Latin America and the Caribbean hypertensive disorders were responsible for more than 25% of maternal deaths[81] . In the US 8.4% of pregnancy-related maternal deaths are due to hypertensive disorders of pregnancy.[82] Terminologies worldwide may differ for example pregnancy induced hypertension (PIH) has in the past been used as a synonym for preeclampsia in North America whereas it refers to gestational

hypertension without proteinuria in the United Kingdom and chronic hypertension has been termed as pre-existing hypertension in Canada.

In the United States new guidelines for diagnosis and management of hypertension disorders of pregnancy were proposed by the American College of Obstetrician and Gynecologists (ACOG) in 2013. Chronic hypertension is defined as hypertension (BP≥140/90mmof Hg) that is present and observable before pregnancy or that is diagnosed before 20 weeks of gestation. Hypertension that is diagnosed for the first time during pregnancy and does not resolve postpartum is also classified as chronic hypertension. Gestational hypertension (may also be called transient hypertension of pregnancy) is characterized most often by new onset elevations of BP after 20 weeks of gestation often near term with no proteinuria. Preeclampsia/eclampsia is defined as a syndrome which includes the development of hypertension (persistent systolic BP ≥140mmof Hg or a diastolic BP ≥90mm of Hg) after 20 weeks of gestation in a woman with previously normal blood pressure. Although often accompanied by new onset proteinuria (excretion of 300mg or more of protein in a 24 hour urine collection), PE can be diagnosed in the absence of proteinuria if any of the following develops for the first time; thrombocytopenia (platelet count less than 100,000/microliter), renal insufficiency (serum creatinine concentration greater than 1.1mg/dL, or a doubling of the serum creatinine concentration in the absence of other renal disease), impaired liver function (elevated blood concentrations of liver transaminases to twice the normal concentration), pulmonary edema, cerebral or visual symptoms. Preeclampsia superimposed on chronic hypertension (20-25% of chronic hypertension pregnancies) is defined as the presence of diagnostic features of preeclampsia in women with history of

hypertension prior to gestation or during the first 20 weeks of gestation. In recognition of the syndromic nature of PE the task force has eliminated the dependence of the diagnosis of PE on proteinuria. New diagnosis criteria introduced in 2013 are likely to show a marginal increase in the number of women diagnosed with PE. Results from the Finnish preeclampsia consortium cohort Study[29] reported a small increase (n=12) in the number of PE cases identified from 2008-2011 using the 2013 (n=1459) ACOG criteria versus the 2002 (n=1447) ACOG criteria.

Secular increases in chronic hypertension, gestational hypertension and preeclampsia have occurred[83] as a result of changing maternal characteristics such as diabetes[84,85], obesity[84,85], maternal age[87] and multiple gestations[87]. The etiology of hypertension disorders of pregnancy is multifactorial and several demographic (maternal age, race/ethnicity) anthropometric (Body Mass Index (BMI)) and obstetric (parity, previous history of preeclampsia, multifetal gestations) factors have been implicated[88]. Pre-existing medical conditions such as diabetes mellitus and renal disease are also risk factors for hypertensive disorders of pregnancy.

Depression and anxiety may be two other conditions to consider given that in men and non-pregnant populations such associations have been studied and observed. [26-28] Estimates for one year prevalence of major depressive disorder in adult women have ranged from 7% in Taiwan[106] and Australia, [107] 9% in Canada, [108] Sao Paulo, Brazil. [109] In the United States lifetime and 12 month prevalence for major depressive disorder in women aged 15-54 was reported to be 12.3% and 12.9% respectively in nationally representative sample.[7] Similarly lifetime and twelve month prevalence for any anxiety disorders were 30.5% and 22.6% respectively.[7] Point prevalence of depression in

pregnancy ranges from 7.4% to 11% in the first trimester, 8.5% to 13% in the second trimester, and 8.5% to 12.0% in the third trimester.[16,110] An estimated 15.6% of women had anxiety symptoms in early pregnancy[13] while 8.5% to 18.4% of pregnant women were depressed during their pregnancy,[15, 110] however estimates of depression diagnosed for the first time during pregnancy were significantly lower, 14.5% during pregnancy, 2.7% between first and second trimester, and 2.2% between second and third trimester.[110] Risk of depression in pregnancy increases with history of depression prior to pregnancy[111-115] and this period can represent a time of increased susceptibility for relapse of depression. Women with history of depression prior to gestation are at an increased risk for recurrence of depression during pregnancy especially if they discontinue their medications during pregnancy.[21] Furthermore if women with depression during pregnancy are untreated 50% will experience a postpartum exacerbation, which can confer a risk of attempted suicide of up to 15%.[116]

The association of depression, anxiety symptoms and hypertension is biologically plausible and explanations include unhealthy lifestyle, [63, 126] changes in the autonomic nervous system, [127] and dysregulation of the hypothalamic-pituitary-adrenal axis.[128] Depression is associated with dysfunction of hypothalamic pituitary adrenal (HPA) axis, hypersecretion of cortisol and inactivation of the negative feedback system.[59] More recent evidence also suggests hyperactivity of corticotrophin releasing hormone (CRH).Some investigators have identified elevated concentrations of CRH in the cerebrospinal fluid of depressed subjects. [117,118] Furthermore when this hormone is administered intra-cerebroventricularly to rats or monkeys it induces several depression-like symptoms including decreased food intake and sexual activity, disturbed sleep,

altered motor behavior and impaired learning.[119-121] Dysfunction of the HPA axis in depressed subjects is accompanied by dysfunction in the sympathetic nervous system. Norepinephrine and dopamine have both been implicated in the pathophysiology of depression.[60] Researchers have demonstrated an elevation of norepinephrine in the vascular and extravascular compartments in depressed subjects relative to controls.[122] Interactions between the HPA axis and the sympathetic nervous system may be involved in the risk of adverse cardiovascular events in depression.

CRH has been demonstrated to act within the brain to stimulate sympathetic outflow.[123] In addition norepinephrine and epinephrine acting on cardiac β-adrenergic receptors increases heart rate and contractility. Elevated heart rate is associated with factors such as hypertension, increased body mass index, and increased blood glucose. It is possible that depression is associated with HPA dysregulation and elevated sympathetic activity which in turn may lead to cardiovascular dysregulation. It is also possible that a third common variable like exogenous stressors may influence both mood and hypertension disorders. In animal models environmental stress can lead to altered neurochemical function such as changes in utilization and synthesis of norepinephrine, changes in dopamine activity and enhanced synthesis of serotonin.[124,125] In humans stressors such as marital conflicts, health problems, and work overload have been shown to be associated with both unipolar and bipolar depression.[61] Furthermore it has been suggested that chronic stressors which do not favor the development of adaptation (coping) are likely to be associated with depressive symptoms.[62] Many animal models of stress induced hypertension have been

developed and used to demonstrate that environmental stressors are involved in the pathogenesis of hypertension.[130]

Some other third variables that could affect both hypertension and depression include unhealthy lifestyles (e.g. unhealthy dietary patterns, smoking, excessive alcohol use), childhood maltreatment, [64-67] and personality traits like neuroticism, introversion. Depressive symptoms are also associated with unhealthy lifestyles in hypertensive subjects with the metabolic syndrome.[63]

The time order of depression, anxiety and hypertension is unclear in cross sectional studies however in certain longitudinal studies[26-28] depression, anxiety precedes hypertension though this could vary with the age range of the population studied. Certain antidepressant medications have also been associated with hypertension.[68, 69] and can act through changing sympathetic and parasympathetic activity. Serotonin reuptake inhibitors (SSRI) serotonin norepinephrine reuptake inhibitors (SNRI) and tricyclics inhibit serotonin transporters or both serotonin and nor epinephrine transporters and augment extracellular concentrations of these monoamines.[70] Serotonin, and norepinephrine induce uterine, placental and umbilical vasoconstriction in in vitro studies.[71-76] Very few studies have studied the association between hypertension and incidence of depression, these studies usually are done in older populations.[129] Pharmacological treatment of hypertension directly or through side effects could also lead to depression, anxiety.[78]

In women of reproductive age the link between psychopathology and related medication use during pregnancy and prior to pregnancy with pregnancy hypertension has been studied with mixed results.

The aim of the present article is to systematically review studies investigating the link between maternal depression and /or anxiety prior to and/or during pregnancy, and maternal anti-depressant medication use prior to and/or during pregnancy with hypertension disorders in pregnancy. The included studies of pre-pregnancy, pregnancy depression/anxiety and hypertension disorders of pregnancy are summarized in six outcome sections depending on the outcomes reported by individual studies Association of maternal pre-pregnancy/pregnancy depression/anxiety with, i) chronic hypertension ii) gestational hypertension iii) preeclampsia. iv) pregnancy induced hypertension v) hypertension disorders of pregnancy vi) hypertension in pregnancy. We also reviewed studies investigating the association of anti-depressant medication use with HTN disorders of pregnancy and summarized their results by the same above mentioned outcomes sections.

2.2 Methods

2.2.1 Search Strategy

In the current review article we initially searched the two electronic databases, PubMed and EMBASE, from inception to May 2017 using the following keywords in various combinations, depression or anxiety or anti-depressant use; preeclampsia or pregnancy hypertension or gestational hypertension or maternal hypertension or obstetric complications. Each broad item listed above was combined with “and” or “or”. This search was carried out from December 2016 to May 2017. In addition, manual search of bibliographies of the relevant articles (procured from the initial search) were examined to obtain any pertinent publications missed in the first search.

2.2.2 Eligibility Criteria

We considered articles for inclusion if they, i) were full text articles in English ii) employed observational designs (case control or cohort, retrospective cohort, crosssectional) iii) were focused on pregnant women iv) compared the risk of any or all of the outcomes (see list below) in the exposed/non exposed group, our exposures of interest were depression, anxiety (screen, diagnosis, self-report, medical records) during pregnancy and/or prior to pregnancy; antidepressant/ anxiolytic medication prescriptions/use during and prior to pregnancy. Outcomes assessed were PIH (e.g.: pregnancy induced hypertension = preeclampsia, and gestational hypertension): chronic hypertension, gestational hypertension, preeclampsia, preeclampsia superimposed on chronic hypertension, eclampsia, maternal hypertension. These outcomes were assessed either by medical records, ICD-8/9/10 diagnosis codes or by self-report.

We excluded studies that were in a language other than English and then examined titles and abstracts of all records to identify studies for full text review. These full text articles were then reviewed and those that did not meet the eligibility criteria were excluded. We also examined the bibliographies of designated articles to look for additional manuscripts we may have missed in the initial search. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed.[89]

2.2.3 Data Extraction

We extracted the following information from all the studies that met the inclusion criteria; study author and year of publication, study design, place and population, inclusion and exclusion criteria, definition of exposure and outcome, and time period of assessment (of exposure and outcome) with respect to the index pregnancy, confounding variables

considered in the analysis, and unadjusted and adjusted ratio measures of effect (relative risks, odds ratios) with 95% confidence interval.

2.2.4 Data Synthesis

Figure 1 provides a flow chart of the process used to determine studies eligible for inclusion. We summarized descriptive characteristics (first author, year of publication, study location, study design, study population, number of participants, singleton, multifetal pregnancy and study period) of the 29 eligible studies in Table 1. We summarized details about exposure, outcome assessment method and timing with respect to the index pregnancy and results in Table 2.

2.3 Results

Bibliographic database searches identified 2116 titles and abstracts distilling to 1267 unique records. Of these 1213 were excluded because 1173 were not relevant to our review (i.e. did not include both exposure and outcome of interest) 24 were reviews, 8 were letters, 6 were studies in languages other than English, and 2 were meta-analyses. We examined the full text for the remaining 54 articles of which 25 were excluded for reasons listed in Figure 7. The excluded conference abstracts (N=12) were not listed as published articles in either of the bibliographic databases assessed. The other studies[90-100] were excluded because they did not assess the specific exposure or outcome or the association of exposure and outcome pertinent to our review. One study was excluded because the exposure was compared among women with PE (severe vs mild) [101] (Figure 7). We included a total of 29 studies, 11 of which were published prior to 2012 [30-40] and the remainder [41-58] between 2012 to November 2016 (Table 2).

Of the 29 studies we included, 13 studies used data from the United States and Canada [36,37,39,40,37-42,49,50,55,57] two each from Finland, [31,51] Netherlands, [32,35] Sweden [33,38] and Israel,[47,53] and one each from Germany,[48] Brazil,[58] Japan,[52] China,[54] Iran,[41] Peru,[34] Australia,[30] and Turkey [56] (Table 2). There were eighteen cohort studies (10 from the US and Canada [36,37,40,42,44-46,49,50,55]) four case-control studies (one each from Peru,[34] Iran,[41] Japan,[52] Turkey[56]) four crosssectional studies (Australia,[30] US,[39] China,[44] Brazil [58]) two nested case-control studies (Canada,[43] Netherlands [32]) and one case-cohort study (US [57]). The studies included pregnant women from either outpatient antenatal care clinics, established pregnancy cohorts, or hospitals at the time of delivery. The earlier studies' inclusion criteria required nulliparity [31, 32, 35,] while later studies included multiparous women; some studies captured multiple births per woman during the study period. Fifteen of the 29 studies recorded singleton gestations while the others either did not specify or included multiple gestations. Study sample sizes ranged from 105 to 32,256,438 women.

Figure 1. ***PRISMA Diagram***

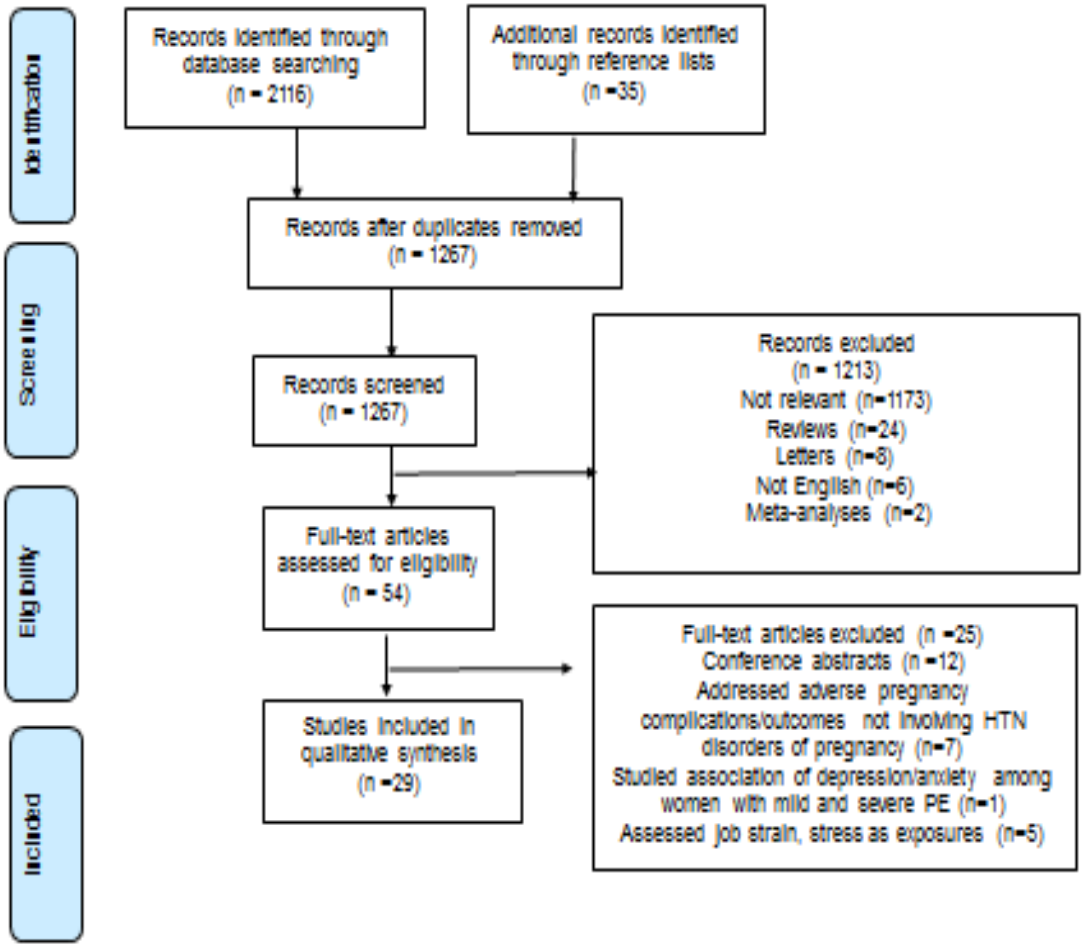


Table 2 Characteristics of Studies included in the review

First AuthorYear	Location of Study	Study Design	Study population	Number of	Singletons	Study period
Crandon-1978	Australia	Cross-sectional	Women in third trimester of pregnancy antenatal care	146	NR	NR
Kurki et al-2000[26]	Finland	Prospective Cohort	Women from maternity clinics in Helsinki	623	Yes	NR
Sikemma et al 2001[27]	Netherlands	Nested Case control	Women with preeclampsia, 2 matched control groups	250	Yes	NR
Andersson et al 2004[28]	Sweden	Cohort	Pregnant women in second trimester from obstetric clinics in N. Sweden	1495	No	10- 2-2000 to 10-1-2001
Qui et al 2007[29]	Peru	Case Control	Women with PE and normotensive controls attending prenatal care at two study hospitals in Lima	676	NR	5-2004 to 10-2005
Vollebregt et al2007[30]	Amsterdam	Cohort	Pregnant women from ongoing Study seeking antenatal care approached by their Obstetricians	3679	Yes	1-2003 to 3-2004

Table 2 (cont'd)						
Toh et al2009[31]	US and Canada	Retrospective Cohort	Participants of ongoing birth defect study[2] (only non- malformed live born infants were included)	5731	Yes	1998-2007
Qui et al 2009[32]	US	Cohort	Participants from a prospective study recruited before completion of 20 weeks gestation.	2601	No	1996-2004
Reis et al2010[33]	Sweden	Cohort	Data from Swedish Medical Birth register sourced from pregnant women in the free prenatal care system	14,821	No	7-1-1995-2007
Bansil et al2010[34]	US	Cross-sectional	Delivery hospitalizations among pregnant women from the Nationwide Inpatient Sample	32,256,438	No	1998 to 2005
Cripe et al2011[35]	US	Cohort	Participants from a prospective study recruited before completion of 20 weeks gestation.	3272	Yes	1996-2008

Table 2 (cont'd)						
Kharaghani et al-2011[36]	Iran	Case-Control	Women with preeclampsia and controls without history of PE admitted in study hospitals	312	No	12-2009-to 12-2010
Katon et al2012[37]	US	Cohort	Linked records of women receiving prenatal care at a University based Obstetrics clinic who delivered at University hospital	2398	No	1- 2004 to 1-2009
DeVera et al2012[38]	Canada	Nested Case control	Women with PIH with no history of pre-gestational HTN from Quebec pregnancy registry and continuously insured by Quebec's prescription drug insurance plan for at least 12 months before and during pregnancy controls matched by gestational age 1:10	13,376	No	1-1997 to 12-2013

Table 2 (cont'd)						
Palmsten et al2012[39]	Canada	Retrospective Cohort	Pregnancies ending in live births, women had continuous health enrollment from 1 year pre-LMP to 2 months after delivery, and had depression ICD9/10 diagnosis codes from 1 year prior to LMP to 20 weeks of gestation from healthcare utilization databases	69,448	No	1997 to 2006
Palmsten et al2013[40]	US	Retrospective Cohort	Women with delivery related diagnosis and procedures were identified from Medicaid data	100,942	No	2000-2007
Kim et al2013[41]	US	Retrospective Cohort	Pregnant women, initial prenatal visit and who delivered at Study Hospital	254	Yes	11-2008 to 04-2009

Table 2 (cont'd)						
Pavlov et al-2014[42]	Israel	Retrospective Cohort	Pregnant women delivering at a Study center	256,312	Yes	1989 to 2010
Winkel et al2015[43]	Germany	Longitudinal prospective cohort	Women recruited from Obstetric outpatient setting in early pregnancy to forth month postpartum, followed up in two month intervals and then one year later	283	Yes	1-2009 to 6-2010
Thombre et al2015[44]	US	Prospective cohort	Pregnant women from 52 prenatal clinics recruited at 16-27weeks gestation from five Michigan communities	1371	Yes	1998 to 2004
Franco et al2015[53]	Brazil	Cross-sectional	3rd trimester pregnant women from prenatal care who delivered in Study hospital	105	No	9-2013 to 8-2014

Table 2 (cont'd)						
Avalos et al2015[45]	US	Retrospective Cohort	Pregnant Kaiser Permanente members with electronic medical pharmacy records	21,589	Yes	1-1-2010 to 12-31-2012
Sion et al2015[48]	Israel	Retrospective Cohort	Pregnant women delivering at a Study medical center	256,312	Yes	1989 to 2010
Malm et al 2015[46]	Finland	Population Prospective birth cohort	Pregnant women with live births identified from National Birth	56,775	Yes	1-1-1996 to 12-31-2010
Suzuki et al2015[47]	Japan	Case Control	Obstetric records of deliveries ≥ 22 weeks in Study hospital	9461	Yes	2009-2012
Kang et al2016[49]	China	Cross-sectional	Pregnant women at least 38 weeks gestation	467	Yes	1-2015 to 3-2015

Table 2 (cont'd)						
DeOcampo et al-2016[50]	US and Canada	Cohort	Pregnant women enrolled at most 20 weeks gestation and later delivered a live singleton infant, MotherToBaby pregnancy Study	3471	Yes	1-1-2004 to 6-30-2014
Cetin et al2017[51]	Turkey	Case Control	Pregnant women who delivered at the study obstetric center	130	No	Not mentioned
Newport et al 2017[52]	US	Case cohort analyses	Pregnant women enrolled at most 16 weeks gestation and later delivered a live infant	686	Yes	1-1998 5-2012

Measures of exposure and outcome varied across studies (Table 3). Four studies evaluated associations between pre-pregnancy and pregnancy depression/anxiety/antidepressant medication use with chronic hypertension[33,37,38,49] as the outcome, eighteen assessed preeclampsia as the outcome,[30-32,34,35,37-41,4446,49,50,53,55,56] four studies assessed gestational hypertension,[35,36,49,55] five assessed pregnancy induced hypertension (PIH),[33,40,42,43,54] three assessed hypertensive disorder of pregnancy (HDP),[47,52,57,] two measured arterial hypertension (AHtn),[48,58] and one hypertension of pregnancy.[51] Some of the included studies assessed more than one type of hypertension disorder as the outcome. Below we grouped studies by the subtypes of maternal hypertension (CH, PE, GH, PE+GH), by the psychopathologies measured (depression, anxiety, depression + anxiety), by medications used to treat psychopathology, and by the timing of the latter two, i.e. pre-pregnancy, during pregnancy. Within the groups we discuss the studies and their results.

Table 3 Exposure and outcome characteristics of included studies

First Author - Year of publication	Exposure	Ascertainment of exposure	Timing of of exposure	Outcome subjects	Ascertainment of outcome	Timing of of outcome	CH	Last Menstrual Period	Results
Crandon 1978	Anxiety symptoms	Anxiety Analysis form	Third Trimester	PE[a]	Any persisting diastolic blood pressure of 90mm of Hg or more	After 24th week	Not Assessed	NM	Positive
Kurki et al 2000	Depression symptoms	Beck Depression Inventory (BDI) Cut off 3	8-17 weeks gestation	PE[a]	From medical records	After 20th week	Excluded	Ultrasound at 16-20 weeks	Positive
	Anxiety symptoms	One question	NM	PE[a]					Positive
Sikemma et al -2001	Anxiety symptoms	State -Trait Anxiety Inventory (STAI)	17-18 weeks and 27-28 weeks	PE[b]		After 33 weeks gestation	Included	NM	Null
Andersson et al -2004	Depression Anxiety symptoms Assessed together	Primary care evaluation of Mental Disorders if positive then clinician evaluation guide administered	18-20 weeks if screen positive 1-2 weeks later	Hypertensive disorder including PE (PIH)	Medical charts		Adjusted	NM	Null

Table 3 (cont'd)									
Qui et al -2007	Depression symptoms	Patient Health Questionnaire (PHQ-9)	At delivery	PE[c]	Identified at study hospitals	After 20 weeks	NM	NM	Positive
Vollebregt et al -2007	Depression symptoms	Dutch version of the Center for Epidemiological Studies Depression (CES-D) Scale	Before 24 weeks gestation	GH[d] PE[e]	Self-reported 3-5 months after delivery	After 20 weeks	Adjusted	NM	Null Null
	Anxiety	State-Trait Anxiety Inventory (STAI)	Before 24 weeks gestation						Null Null
Toh et al -2009	Selective Serotonin Reuptake Inhibitors (SSRI)	Self-report, 6months after delivery	2 mth Pre-LMP to 1st tri pre LMP and 1st tri-delivery	GH[f]	Self-report, 6months after delivery	After 20 weeks	Excluded	NM	Null
				GH[f]					Positive
			2 mth Pre-LMP to 1st tri pre LMP and 1st tri-delivery	GH with PE[g]					Null
				GH with PE[g]					Positive

Table 3 (cont'd)

Qui et al -2009	Mood or Anxiety	Medical records and self-report	Before pregnancy	PE[h]	Clinic and Medical records	After 20 weeks	Excluded	NM	Null
			first 20wks						Positive
	SSRI	Medical records	During pregnancy	PE[h]					Positive
Reis et al -2010	Antidepressants	Self-report Medical records	10-20 weeks	CH, PE	Antenatal records	Not mentioned	Assessed	NM	Positive
			During pregnancy	CH, PE					Positive
Bansil et al -2010	Depression Diagnosis	ICD-9CM diagnosis codes	At delivery	PE	ICD-9CM diagnosis codes	At delivery	NM	NM	Positive
Cripe et al -2011	Mood	Medical records and self-report	Before pregnancy	PIH	Medical records	After 20 weeks	Pregestation excluded	NM	Null
	Mood		and/or first 20wks	PE[h]					Positive
Kharaghani et al-2011	Depression symptoms	Patient Health Questionnaire (PHQ-9)	Second or third trimester	PE[i]	From maternal medical records	At delivery	Excluded	NM	
	severe (≥15)								Positive
	Moderate (10-14) Moderate-								Null
	Mild(5-9);								Null
	<4 ref								

Table 3 (cont'd)

Katon et al-2012	CH	ICD-9 diagnosis codes from medical records	NM	Major or minor Depression	Patient Health Questionnaire (PHQ-9) or use of antidepressant medications by self-report	During pregnancy	Assessed	NM	Positive
	PIH					second or third trimester			Null
				Major Depression or antidepressant use					
DeVera et al -2012	Antidepressant	At least one prescription	Before PIH first diagnosis date during pregnancy	PIH	ICD-9 diagnosis codes for GH,PE, Eclampsia	After 20 weeks	Excluded	Hospital records	Positive
	SSRI	filling		PIH					Positive
	Antidepressant	At least one prescription filling							Null
			Year before pregnancy	PIH					

Table 3 (cont'd)

Palmsten et al -2012		At least one pharmacy dispensing	Gestation weeks 10 to 20		ICD-9/10 diagnosis codes	After 20 weeks to 1 month after delivery	NM	Assigned 280 days	
	SSRI			PE					Positive
	SNRI			PE					Positive
	TCA			PE					Positive
	Antidepressants	At least one pharmacy dispensing	3 mth prior to LMP + At least 1 depression diagnosis (Ref) Gestation weeks 10-24	PE					Positive
Palmsten et al -2013	SSRI, SNRI, TCA	At least one pharmacy dispensing	From 90 to 225 gestational days	PE	ICD-9 diagnosis codes	After 140 days	NM	Derived with PTD codes	Positive
	Other								

Table 3 (cont'd)									
Kim et al -2013	Depression symptoms	Edinburgh Postnatal Depression Scale (EPDS) Cutoff 10	Initial prenatal visit	PE (Hypertension+ proteinuria)	Medical charts	NM	NM	NM	Positive
Pavlov et al -2014	Anxiety	Medical charts obtained at delivery	During pregnancy	Hypertensive Disorders	Perinatal Databases at delivery	At delivery	NM	NM	Null
Winkel et al -2015	Depression	Composite International Diagnostic Interview (CIDIV) Lifetime version Administered during pregnancy	Pre-pregnancy	Arterial Hypertension BP≥ 140/90	Medical record book in pregnancy At least two raised readings	During pregnancy second and third trimester	NM	NM	Null
	Anxiety								Positive
	Comorbid								Positive (Crude)

Table 3 (cont'd)									
Thombre et al -2015	Depression	Self-report	Pre pregnancy	CH[j]	Medical records	Before20 wks	Assessed	Self-report	Positive
	Depression/ Anxiety Symptoms	CES-D cutoff 16	16-27 wks gestation	GH	elevated BP[k]	After 20 wks			Null
				PE	elevated BP+ proteinuria[l]	After 20 wks			Null
Franco et al -2015	Anxiety	STAI-A	3rd gestational month	Arterial Hypertension	Measured	During pregnancy time period not specified	NM	NM	Positive
	Depression	NM	NM						Positive
Avalos et al -2015	Antidepressant	At least one pharmacy dispensing	LMP and first 20 weeks	PE	ICD-9 diagnosis codes	After 20 weeks	NM	LMP=delivery date-GA at delivery	Positive
	SSRI								Positive
	SNRI, NDRI, SARI								

Table 3 (cont'd)									
Sion et al -2015	Depression	Medical charts obtained at delivery	Pre pregnancy	CH	Perinatal Databases at delivery	NM	Assessed	NM	Null
Malm et al -2015	SSRI	Drug purchases From drug reimbursement	30 prior to LMP to end of pregnancy	Hypertension of pregnancy	ICD-8/9/10 diagnosis codes from Medical Birth	During pregnancy	NM	NM	Positive
Suzuki et al -2015	Depression diagnosis Anxiety Diagnosis	By medical records	Before or during early pregnancy	Hypertensive Disorders	By medical records	During pregnancy	Excluded	NM	Null Positive

Table 3 (cont'd)									
Kang et al -2016	Anxiety symptoms	Anxiety Scale cutoff ≥ 50 Self-rating	At least 38 weeks gestation	PIH	Self - reported	At least 38 weeks gestation	NM	NM	Positive
DeOcampo et al-2016	Anti-depressant (>20wks)	self-report	Intake (not> 20wks) and every 3 months until delivery	GH; GH or PE	Self - reported	After 20 weeks	Excluded		Positive
	SSRI			GH					Positive
	SNRI			GH, PE					Positive
Cetin et al -2017	SSRI	Hospital Depression	At delivery	PE (mild, severe)[m]	Self - reported at delivery	After 20 weeks	Excluded	NM	Positive
	SNRI	Anxiety scale							Positive
Newport et al -2017	Antidepressant	From medical records?	After 20 weeks	Hypertensive Disorders of pregnancy	Obstetrical records diagnosed by providers using ACOG diagnostic criteria	After 20 weeks	Excluded	NM	Positive

Table 3 (cont'd)

PE: Preeclampsia, GH: Gestational Hypertension; PIH: pregnancy induced hypertension; HDP:Hypertensive Disorders of Pregnancy; NM:Not mentioned; Wks:Weeks; Antidepr:antidepressant; BP:Blood pressure; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; mth: month; DSM: Diagnostic and Statistical Manual of Mental Disorders; SSRI: Selective Serotonin Reuptake Inhibitor; TCA: Tricyclic; SNRI: Serotonin Norepinephrine Reuptake Inhibitors; ICD: International Classification of Diseases; CM: Clinical Modification; tri:trimester; deliv:delivery; [a] Preeclampsia (PE) Defined as elevated blood pressure ≥ 140/90 mmof Hg and proteinuria (0.3g during 24 hours or more) [b]

Preeclampsia (PE) Defined as diastolic blood pressure ≥ 90 mmof Hg on two consecutive occassions at least 4 hours apart and proteinuria ≥ 300mg /24 hours in a previously normo tensive womanassessed after 33 weeks

[c]Preeclampsia (PE) Defined as sustained blood pressures of 140/90mm of Hg on atleat two occassions at least four hours apart with proteinuria defined as urine protien concentration≥ 30 mg/dl(or 1+ on urine dipstick) in at least tw orandom specimens collected atleast four hours apart [e]

Preeclampsia combination of GH and proteinuria ≥ 0.3 g/24 hours or dipstick ++ [d]

Gestational Hypertension diastolic pressure ≥ 90 mmof Hg in previously normotensive women

[f]Gestational Hypertension was defined as incident hypertension during pregnancy [g]GH with PE was defined as incident hypertension with proteinuria

[h]PE sustained blood pressure of ≥ 140/90 mmof Hg with readings performed ≥ 6hours apart and urine protein concentration of ≥ 30mg/dl or 1+ protein on a urine dipstick on ≥ 2 urine specimens collected ≥ 4 hours apart after 20 weeks gestation

[i]PE sustained blood pressure of ≥ 140/90 mmof Hg with readings performed ≥ 6hours apart and urine protein concentration of ≥ 30mg/dl or 1+ on a urine dipstick after 20 weeks gestation [j]CH elevated BP ≥ 140/90 mmof Hg or use of antihypertensive medication [k]

Elevated Blood pressure(BP) is BP ≥ 140/90 mmof Hg

[l]Proteinuria is urine protein concentration of ≥ 300mg/dl or 1+ protein on a urine dipstick on ≥ 2 urine specimens

[m]PE mild BP ≥ 140/90 mmof Hg and proteinuria ≥ 300mg/24h; Severe PE, BP ≥ 160/110 mmof Hg and proteinuria ≥ 2g/24h after 20 weeks of gestation

2.3.1 Chronic hypertension and pre-pregnancy depression

Thombre et al[49] studied the association of self-reported pre-pregnancy history of depression symptoms with CH and reported a positive association (aOR=3.5 95%CI (1.5, 7.8) while another cohort study from Israel[53] reported a null result (aOR=1.28 95%CI (0.80, 2.04). Of the two studies, one[49] was more racially diverse and had a lower mean maternal age. In both studies the time order of the association was unclear since first diagnosis dates for CH and depression were not available.

2.3.2. Chronic hypertension and pregnancy depression

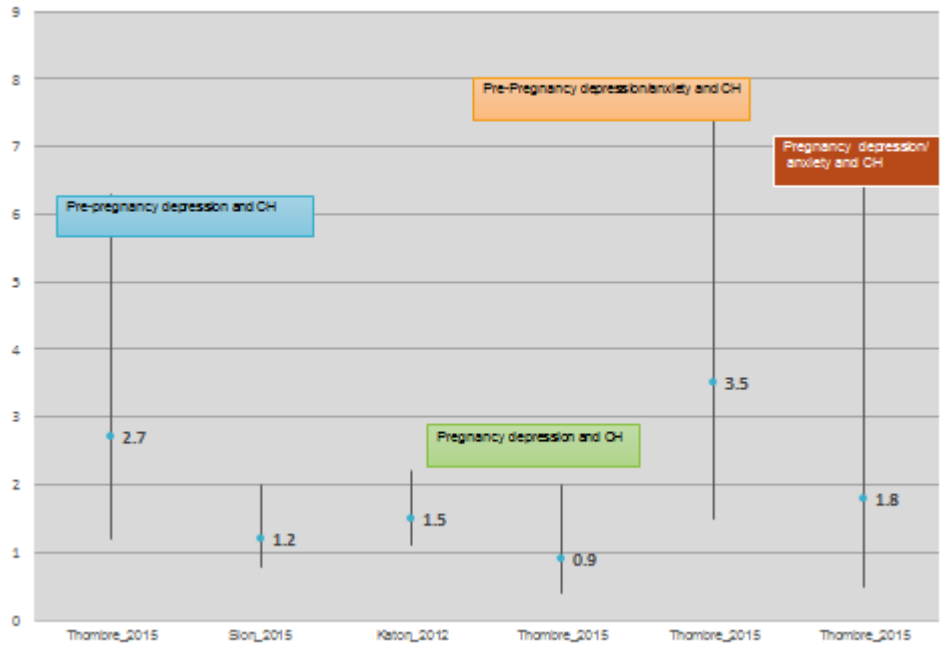
Katon et al [42] reported a positive association between pre-existing hypertension identified by ICD-9 diagnosis codes and any depression during pregnancy (aOR=1.55 95%CI 1.08, 2.23) identified by the Patient Health Questionnaire-9 (PHQ-9) administered at the second or third trimester or self-reported use of antidepressant medication during pregnancy. Thombre et al did not detect an association between CH (from medical records) and pregnancy depression/anxiety symptoms (aOR=0.9 95%CI 0.4, 2.0) assessed by the Center for Epidemiologic Studies Depression (CES-D) scale administered at 16-27 weeks gestation.

2.3.3 Chronic hypertension and antidepressants

Reis et al [38] investigated the association of CH with antidepressant prescription use in early (between weeks 10-12, self-reported) and later (antenatal prescriptions after the week 12) pregnancy from the Swedish Medical Birth Register that contained all births in Sweden in study time frame. CH was linked with antidepressant prescriptions during pregnancy (early and later use) (aOR=1.50 95%CI 1.33, 1.69). Thombre et al [49] reported a borderline significant association between antidepressant use during

pregnancy (abstracted from labor and delivery medical records) and CH (aOR=2.4 95%CI 0.9, 6.4).

Figure 2. Depression/Anxiety with CH



2.3.4 Preeclampsia and pre-pregnancy depression/anxiety

Three studies [37, 49, 53] investigating the link between pre-pregnancy depression/anxiety and preeclampsia reported null results. Two studies[37, 49] measured depression/anxiety symptoms by self-report in the second trimester while one study[53] used physician documented depression diagnosis. All three ascertained information about PE from medical charts.

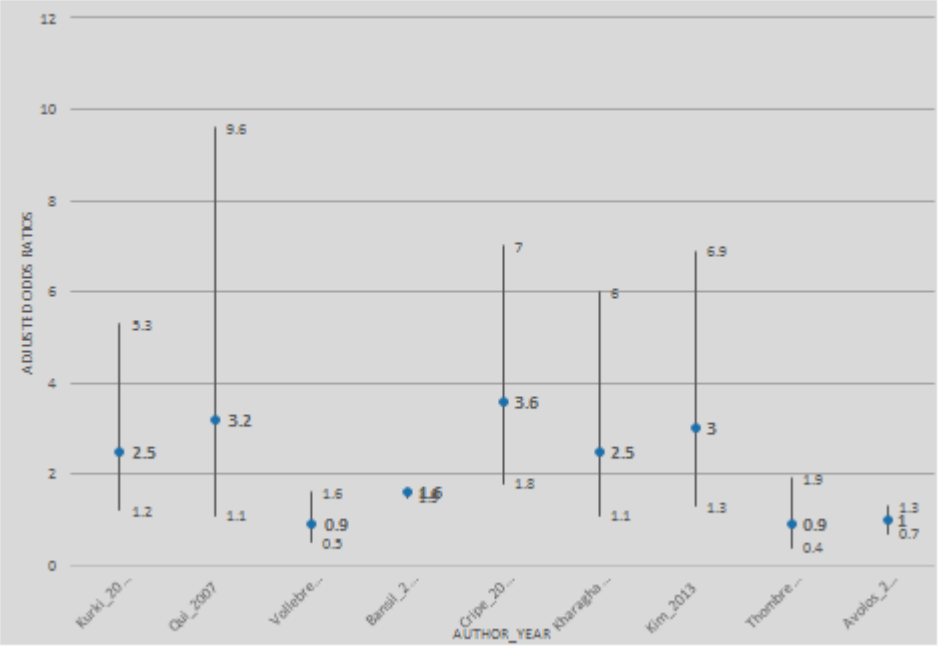
2.3.5 Preeclampsia and pregnancy depression

Seven studies [31,34,35-36,46,56] reported a positive association between pregnancy depression and PE, five [31,34,41,46,56] assessed depression symptoms during pregnancy and timing of assessment ranged from 7 weeks to 27 weeks gestation. Of these five

studies Kharaghani et al [41] (second to third trimester) (aOR= 2.52 95%CI 1.05, 6.02) and Qui_2007 [34] (at delivery) used the same instrument (PHQ-9) and reported similar effect sizes for moderate to severe depression (score of ≥ 15 on the PHQ-9) (aOR= 3.2 95%CI 1.1, 9.6) though the timing of administration of the screen differed. Kurki et al [31] used Beck Depression Inventory (BDI) as a screening tool however the cutoff (3) they used was very low. Kim et al [46] assessed depression symptoms with the Edinburgh Postnatal Depression Scale (EPDS) and found that women with a score of 10 or more were more likely to have PE (aOR=2.95 95%CI 1.26, 6.89); the population was predominantly African American. Cetin et al [56] conducted a case-control study using a hospital anxiety and depression scale administered and completed after delivery. Given the case-control design, there may have been recall bias. Of the two other positive studies, one, Bansil et al, [39] was cross-sectional. They used ICD- 9CM (Clinical Modification) diagnosis codes for identification of depression diagnosis and PE concurrently at the time of delivery. Cripe et al[40] assessed mood and anxiety disorders with self-reported history in combination with medical reports.

Three studies[35, 49, 50] reported a null association between pregnancy depression symptoms and PE. Two of the three [35, 49] assessed depression symptoms using the CES-D scale administered in the second trimester. One study[49] was racially/ethnically diverse with singleton gestations while the other study [35] included predominantly Caucasian, nulliparous women with singleton gestations and the CES-D was administered 3-5 months after delivery. The third null study[50] was based on health insurance claims data with ICD-9 diagnosis codes for depression (between six months prior to pregnancy and through 20 weeks of gestation) and PE.

Figure 3. Pregnancy Depression and Preeclampsia



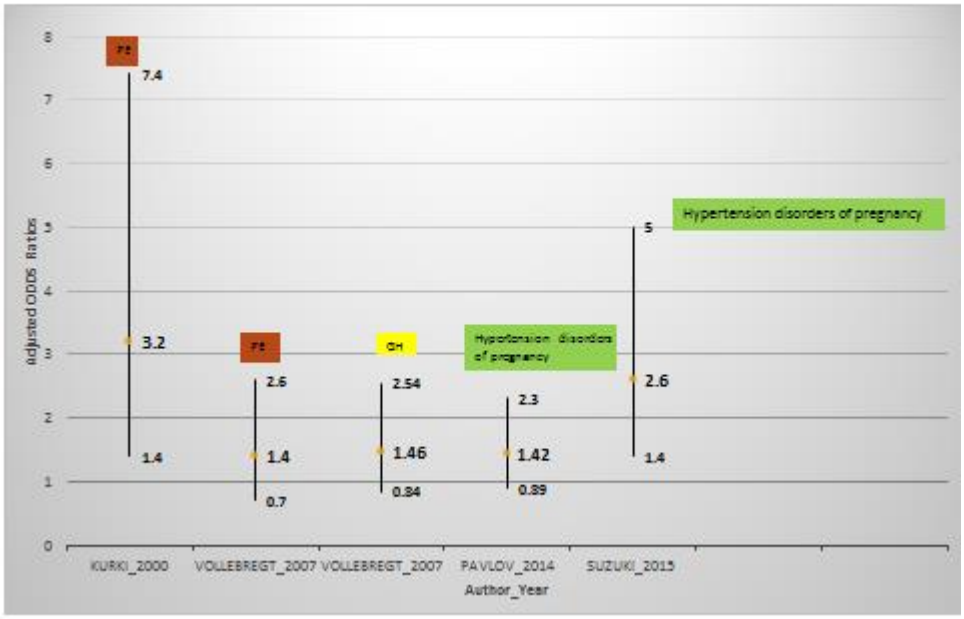
2.3.6 Preeclampsia and pregnancy anxiety

One of the earliest studies[30] to report a positive association between maternal anxiety and PE was in 1978; anxiety was assessed during the third trimester. Kurki et al[31] measured anxiety with one question posed to pregnant women in the first or second trimester and likewise reported a positive association (aOR=3.2 95%CI 1.4, 7.4). In the other positive study by Cetin et al, [56] anxiety was queried after delivery. Vollebregt et al [35] reported a null association between pregnancy anxiety (State Trait Anxiety Inventory) and PE (aOR=1.38 95%CI 0.74, 2.58).

However studies reporting both anxiety and depression association with PE separately have not elaborated on the degree of overlap between the two conditions or the absence of such an overlap. In other words it is not clear how many in the depression group have/have not concurrent anxiety at the same time. Risk for

hypertension might differ depending on the presence of isolated disorder or comorbidity[48].

Figure 4. Pregnancy Anxiety and Hypertension disorders of pregnancy



2.3.7 Preeclampsia or gestational hypertension and antidepressant use

Six[37, 38, 44,45,50,55] of the seven [37,38,44,45,49,50,55] studies have reported positive associations of antidepressant prescriptions in the pre-pregnancy/pregnancy period with PE. Out of these six positive studies most [38,44,45,50] (four) utilized administrative data (Table 1).

Qui et al[37] used data from an ongoing prospective study and reported a positive association between psychotropic medications during pregnancy and PE (aOR=2.38 95%CI (1.13, 5.00). Only one study[49] reported a null association of antidepressant medication use and PE (aOR=0.9 95%CI 0.2, 3.5).

Six studies [38, 43, 44,45,50,55] have assessed whether specific timing of antidepressant prescription with respect to index pregnancy is associated with increased risk for PE. These studies assessed the risk of PE in women taking antidepressant medication from prior to and during early pregnancy (first 10-12 weeks only) and women taking antidepressants prior to and during pregnancy. However pharmacy dispensing data in the years preceding the index pregnancy and during pregnancy varied between studies with maximum data available for a year prior to gestation. In women with depression diagnosis and prescribed antidepressants prior to and during pregnancy Palmsten et al[44] reported an increased risk for PE with continued serotonin norepinephrine reuptake inhibitors (SNRI) (aOR=3.43 95%CI 1.77, 6.65) and Tricyclic antidepressant (TCA) exposure (aOR=3.26 95%CI 1.04, 10.24), while another study[45] utilizing a slightly younger, lower socioeconomic status and less white population reported a lower magnitude of association of continued serotonin reuptake inhibitors (SSRI) (aOR=1.21 95%CI 1.02, 1.45), SNRI (aOR=1.61 95%CI(1.04, 2.47) prescriptions with PE. DeOcampo et al[55] reported increased risk for GH in women who continue taking SSRI during pregnancy (aOR=1.96 95%CI 1.02, 3.76), SNRI (aOR=4.96 95%CI 1.33, 18.56), and no association of SSRI. SNRI medication use with PE. However women taking “other” (not SSRI, SNRI) were at increased risk for PE even if they stopped their antidepressants prior to 20 weeks gestation. They did not specify what the “other” class of antidepressant was or if it was a combination of multiple classes.

Studies have evaluated if women prescribed only one class of (monotherapy) antidepressant or more than one class of antidepressants (polytherapy) are at increased

risk for PE. One study[44] included women with depression used data from the health care utilization databases of British Columbia reported increased risk for PE in women with diagnosed depression and exposed to SNRI monotherapy (aOR=1.95 95%CI(1.25, 3.03), and tricyclic monotherapy (aOR=3.23 95%CI 1.87, 5.59). DeOcampo et al[55] also reported that women who took antidepressants prior to and during pregnancy had an increased risk for PE only if they used two or more antidepressant drug classes (aOR=3.24 95%CI 1.19, 8.81), and singular use of SNRI increased risk for GH (aOR=4.96 95%CI 1.33, 18.56).

However none of these studies have been able to disentangle if the increased risk of PE/GH associated with continued use of antidepressants prior to and during pregnancy represents a direct pharmacological effect or is a marker for underlying severity of the disorder.

Figure 5. Antidepressant use during pregnancy and hypertension disorders of pregnancy

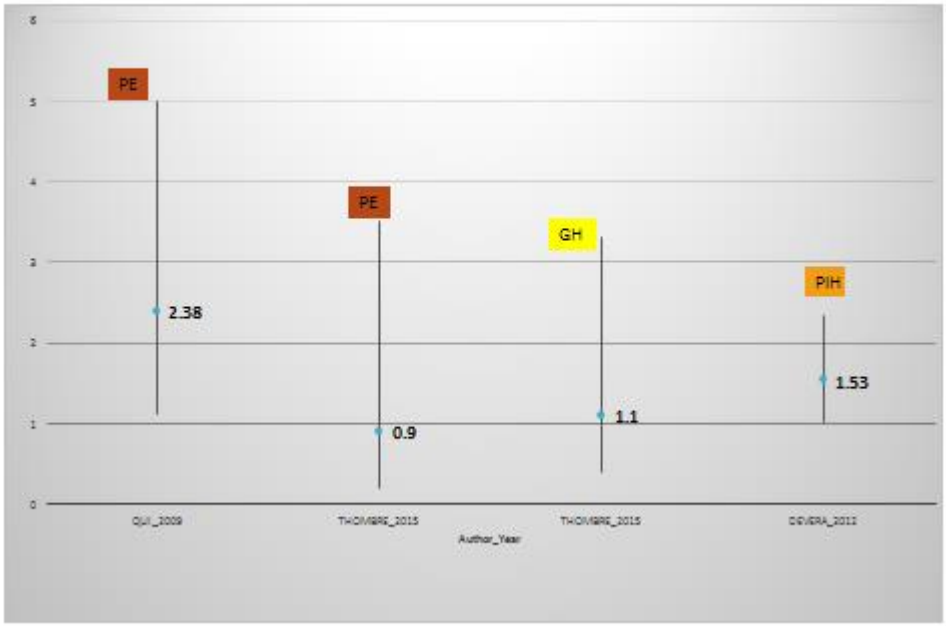


Figure 6. Antidepressant use prior to and during pregnancy and PE/GH

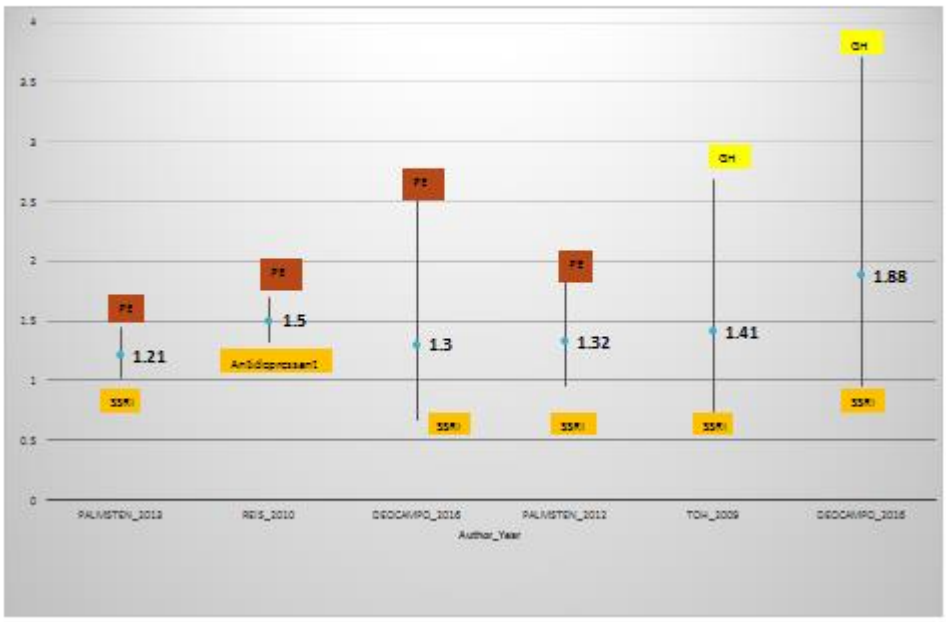
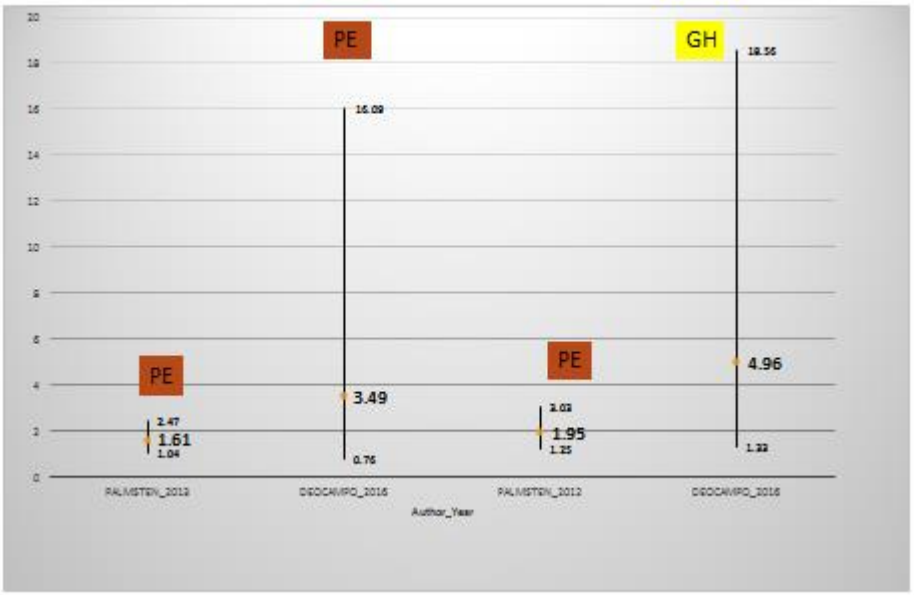


Figure 7. Antidepressant (SNRI) use prior to and during pregnancy and PE/GH



2.3.8 Gestational hypertension and depression

Only two studies[35, 49] have addressed the issue of risk of gestational hypertension with exposure to depression/anxiety symptoms either pre-pregnancy[49] or during pregnancy.[35, 49] Both studies have concluded that depression/anxiety and gestational hypertension were not associated (aOR=1.19 95%CI 0.67, 2.11)[35]; (aOR=0.6 95%CI (0.3, 1.3)[49]. Although these studies rely on self-reported and or screens for exposure data they are prospective in nature (study participants are administered screens, questionnaires before development of outcome) and there is no plausible reason to expect systematic bias (differential with respect with the outcome) in self-reported symptoms.

2.3.9 Gestational hypertension and pregnancy anxiety

Vollebregt et al[35] assessed the association of pregnancy anxiety and GH and reported a null result (aOR=1.46 95%CI (0.84, 2.54)

2.3.10 Pregnancy induced hypertension with pregnancy depression, anxiety

Some investigations [33, 40, 54] have evaluated the association of pregnancy depression, anxiety with gestational hypertension and preeclampsia together or pregnancy induced hypertension after 20 weeks of pregnancy. Two studies reported null associations[33,40] while one study from China[54] investigating PIH and pregnancy anxiety reported a strong association (aOR = 6.17, 2.42, 15.62) However it was a cross-sectional study assessing anxiety at 38 weeks gestation by the self-rating anxiety scale.

2.3.11 Hypertension disorders and pregnancy anxiety

Pavlov et al[47] reported a significant unadjusted association when studying the link between pregnancy anxiety and hypertension disorders of pregnancy, but lost the

statistical significance after adjusting for age, ethnicity, smoking, diabetes mellitus, preterm premature rupture of membranes, preterm labor, and induction of labor.

2.3.12 Hypertension disorders of pregnancy (PE and GH) and antidepressant

Two studies [36, 43] have assessed increased risk of PIH with pregnancy antidepressant use and reported positive results. DeVera et al[43] conducted a matched (index case date and gestational age) case (PIH with and without PE) control study using the Quebec pregnancy registry and reported antidepressant use prior to the diagnosis of PIH to be significantly associated with PIH after adjusting for depression (aOR=1.53 95%CI (1.01, 2.33). Further analyses revealed the association to be carried by singular prescriptions of SSRI (aOR=1.60 95%CI (1.0, 2.55) prior to PIH diagnosis and "other" antidepressant (did not specify class) prescriptions (aOR=3.71 95%CI (1.25, 10.98). Toh et al[36] conducted a timing analyses of antidepressant use with respect to the index pregnancy and reported a significantly increased risk for PIH with SSRI use prior to and during pregnancy (aOR=4.86 95%CI (2.70, 8.76).

2.3.13 Hypertension disorders of pregnancy and antidepressant

Two studies [51, 57] evaluated the exposure to antidepressants during pregnancy and the link with pregnancy hypertension. Newport et al[57] assessed SNRI exposure after pregnancy week twenty and reported significant positive association with hypertensive disorders of pregnancy (aOR=2.57 95%CI (1.34, 4.93). On the other hand Malm et al[51] reported a null association of SSRI exposure during pregnancy and hypertension of pregnancy (aOR=1.10 95%CI (097.04, 1.26) compared to women with psychiatric diagnosis and no medication. The latter analyses was from a population based

prospective birth cohort study while the former study population had a higher mean maternal age and was from a prospective longitudinal study in a tertiary referral center.

2.3.14 Pre-gestation depression/anxiety with hypertension in pregnancy

Two studies [48, 52] evaluated the link between pre-gestation depression/anxiety with hypertension in pregnancy. Winkel et al[48] distinctly evaluated separate groups of women with isolated depression and isolated anxiety and their independent associations with hypertension in pregnancy. These analyses demonstrated an increased risk of hypertension in pregnancy in women with pre-pregnancy anxiety and comorbid depression and anxiety (both assessed pre-pregnancy) but a null association between pre-pregnancy depression and hypertension in pregnancy. Another study[52] examined the association of depression diagnosis (before or early pregnancy) with hypertension in pregnancy and reported a null association. The same study[52] reported an increased risk of hypertension in pregnancy with anxiety diagnosis.

2.3.15 Pregnancy depression/anxiety with hypertension in pregnancy

One study[58] reported a positive association of anxiety (assessed by STAI-A) but a null association with depression and hypertension in pregnancy.

2.4 Discussion

This systematic review of the literature assessing associations of depression/anxiety and antidepressant medication with hypertensive disorders of pregnancy suggests that: 1) there are conflicting reports on an association between pre-pregnancy or pregnancy depression/anxiety and CH; 2) there is little evidence of a link between pre-pregnancy or pregnancy depression/anxiety and GH; 3) pre-pregnancy depression/anxiety does not appear associated with PE, however a majority of studies focused on depression in

pregnancy and PE report a positive association; 4) results from most studies suggest that anti-depressant use, e.g. SSRI, SNRI, TCA prior to and during pregnancy are significantly associated with PE and GH; 5) Monotherapy with SNRI and tricyclic is associated with increased risk for PE; 6) SSRI and TCA polytherapy is associated with PE; 7) It is not clear if continuing antidepressant in pregnancy represents an increased risk because of the medication or the underlying severity of the disorder.

Studies reporting a positive association between pre-pregnancy depression/anxiety and CH are unable to report on the specific time order of the association since first diagnosis dates are unavailable. Given that the prevalence of advanced maternal age[102] and obesity[103] is increasing among childbearing women in the US, chronic hypertension is likely to become a common obstetric condition. Understanding the complex web of CH, antihypertensive medication, depression/anxiety, antidepressants and the time order of their associations should be an important public health objective given that both these conditions and associated medication use[19, 20] have increased in reproductive aged women in recent years. Katon et al[42] reported a positive association between preexisting CH and pregnancy depression symptoms although it is unclear if the association indicates a link between the condition and depression symptoms or the pharmacological link between antihypertensives and depression. Certain antihypertensive medications are suspected to be associated with mood disorders and a recent study investigated the role of monotherapy with various antihypertensive drug classes. This study concluded that beta blockers and calcium antagonists may be associated with increased risk for mood disorders[104].

Studies investigating the association between CH and pregnancy antidepressant prescriptions report a positive association.[38, 49] Women taking antidepressants during pregnancy may be different in terms of severity of disorder and antidepressant use during this time period may reflect severity of the disorder. Moreover these women are more likely to have other health problems, may be more likely to have frequent health care contact and hence more likely to be diagnosed with depression symptoms. Furthermore women with CH are likely to be older[49] likely to report a higher mean prepregnancy body mass index, likely to be taking antihypertensive medications which have been associated with increase in prevalence of mood disorders[104].

All three studies [42, 49, 53] assessing pre-pregnancy depression/anxiety with GH or with PE have reported a null association. Depression/anxiety symptoms during pregnancy and their association with PE have been most widely reported (12 studies). In some studies participants were nulliparous women, depression/anxiety symptoms were assessed using screens that were administered by trained study personnel or insufficiently assessed (anxiety). Study design varied and case control designs might be biased since self-reported depression/anxiety symptoms were assessed at the time of admission for delivery in cases (with PE diagnosis) and controls (without PE diagnosis).[34, 41, 56] One other study was cross-sectional[39] one study[31] used a very low cutoff (3) to assess depression symptoms, and one question to assess anxiety, two analyses were from the same cohort[37, 40] and hence really one result.

Although some studies assessed depression and anxiety separately they did not report on the overlap between the two conditions and the association of the overlap with PE.

Depression and anxiety are comorbid many times and mechanisms of action of association with PE/GH might differ and hence independent association of isolated depression and isolated anxiety along with their overlap with PE/GH should be evaluated.

Depression and anxiety are chronic conditions with periods of remission and relapse and hence history of the conditions is an important factor for a couple of different reasons. Women with new onset depression/anxiety in pregnancy might be different than women with a relapse in pregnancy. Furthermore women with history might not manifest symptoms at the time of assessment due to adequate treatment, however the timing, duration of medication use with respect to the pregnancy might be an important factor to consider in the association with PE or any other hypertensive disorder of pregnancy.

Antidepressant use has been assessed in the following ways. 1) Studies have tried to control confounding by depression by assessing the association of antidepressant medication with PE among the depressed pregnant women[44, 45]. Another study[38] has controlled for depression in their analyses. 2) Studies have tried to assess the associations of monotherapy, polytherapy with HTN disorders. Palmsten[45] et al addressed combinations (polytherapy) across drug classes and concluded that combinations of SSRI and SNRI, SSRI and bupropion, SSRI and other were not associated with increased risk for PE. However SSRI and tricyclic were associated with significantly increased risk for PE (aOR=1.49 95%CI (1.02, 2.16). However they did not address within class (SSRI/SNRI) polytherapy. 3) Six studies have assessed the association of timing of antidepressant use with respect to index pregnancy and its

association with GH/PE, and concluded that continued antidepressant use was associated with increased risk for PE[38, 44, 45, 50] GH[36, 55] PIH[36]. 4) Avolos et al[50] concluded that increased duration (≥ 60-120 days; ≥120 days) of antidepressant use was associated with greater risk of PE. 5) No increased risk for PE was reported by one study[50] which assessed the risk of PE for women with depression and psychotherapy compared to women without depression. 6) Palmsten[45] reported no increased risk for PE with any dose of SSRI or low doses of SNRI, and increased risk for PE with higher doses of SNRIs and any dose of TCAs.

About seven of the eleven studies have assessed the association of antidepressant use with PE, with six reporting positive and one null association. Four positive studies have used large administrative datasets [38,44,45,50,] and hence are able to report on prescription filled but not necessarily ingested. In the absence of clinical trials data, data with significant unmeasured confounding (lacking pertinent covariate information, e.g.: lifestyle factors) might be limiting in terms of drawing meaningful conclusions, especially if the covariates have a strong association with the outcome and are highly prevalent (e.g.; Obesity).

Certain methodological limitations of current studies include:

First due to nature of datasets used LMP determination may not be very accurate and hence may misclassify exposure and outcome. Second depression and anxiety although comorbid many times should be assessed in isolation to tease out independent associations with either or both (comorbid) of the conditions. Third assessment of depression anxiety symptoms by a structured clinical interview and by

trained research personnel during pregnancy along with a supporting history of the conditions may be required to establish a definitive diagnosis of the psychopathology. Using ICD diagnosis codes from different providers might introduce bias depending on provider expertise and access to these experts.

Administrative datasets or electronic databases used to assess antidepressants medication prescription cannot ascertain that woman actually took the prescribed medications and hence are inept in ascertaining medication compliance and drop outs. Some of the administrative datasets lack data about important covariates like lifestyle factors, or anthropometric measurements. Lastly since randomized clinical trials are lacking in this area of research due to ethical considerations, reaching an unbiased and definitive conclusion might be challenging.

2.5 Conclusion

Given that hypertension disorders of pregnancy are rare and depression and anxiety are chronic conditions with remittances and relapses large datasets with relevant exposure outcome and covariate data or large inceptions cohorts of women of reproductive ages and longitudinal follow ups for a substantial period of time is warranted. Furthermore with increasing obesity, maternal age at first delivery and multiple gestations all significant risk factors for hypertension disorders of pregnancy more research about the association of CH with psychopathology is apt. With regards to antidepressant use and lack of clinical trial data alternative psychotherapeutic methods for maternal depression treatment (e.g. cognitive therapy) should be explored and researched. Although the links between anxiety and pregnancy hypertension disorders has been examined the association of anxiolytic medication use with hypertension disorders of pregnancy

needs to be studied. Since untreated depression/anxiety carries significant maternal, fetal, infant risks and should be carefully weighed with benefits of antidepressant therapy.

CHAPTER 3

DEPRESSION, ANXIETY, ANTI-DEPRESSANT, ANXIOLYTIC MEDICATION USE AND THEIR ASSOCIATIONS WITH MATERNAL HYPERTENSION

3.1 Introduction

Hypertension (HTN) disorders of pregnancy affect 5-10% of pregnancies and are classified as chronic hypertension (CH), preeclampsia (PE), eclampsia, preeclampsia superimposed on chronic hypertension and Gestational hypertension (GH).[25,79] These disorders are associated with maternal and neonatal mortality, stillbirths, and a range of maternal and neonatal morbidities such as abruptio placentae, disseminated intravascular coagulation and intrauterine growth restriction.[130-132] Although the risk of dverse outcomes (e.g. very preterm delivery, fetal death) is greater with PE, gestational HTN also is associated with significant maternal and fetal morbidity.[88]

Epidemiological research suggests that pregnancy HTN disorders have a multi factorial etiology. Shared established risk factors include pre-pregnancy obesity and diabetes, advanced maternal age, and twin pregnancies.[88] Maternal depression and anxiety also may be risk factors, as these psychopathologies confer increased risk of hypertension in men and non-pregnant women.[26-28] Explanations for associations between anxiety and depressive symptoms and hypertension include unhealthy lifestyle,[63, 126] changes in the autonomic nervous system,[127] and dysregulation of the hypothalamic-pituitary-adrenal axis.[128]

Studies investigating associations of pre-pregnancy[37, 49] or early pregnancy[31-35, 37, 40-42, 46, 49] depression and anxiety symptoms with any one or all of the HTN disorders of pregnancy have generated mixed results. Heterogeneity in outcome (PE, GH, CH,

maternal hypertension), exposure determination (self-reported recall, symptoms, diagnosis), timing (pre-pregnancy/pregnancy) and conflating of depression and anxiety[33, 37,49,35,40] likely contribute to discordant results. In particular, the independent association of anxiety (pre-pregnancy/ pregnancy) with HTN disorders is unclear due to inadequate anxiety assessment[31] and the small number of study participants with 'anxiety only.'[37] In addition most studies assessing psychopathology symptoms did not evaluate associated medication use.[31,34,33,32,40,41,46]

Medications used to treat maternal psychopathologies, e.g. antidepressant/anxiolytic, might play a mediating role in HTN disorders of pregnancy; it is estimated that 8-9 % of women use antidepressant medications during pregnancy.[1920] Most Studies investigating maternal anti-depressant/anxiolytic medication and PE have reported a positive association.[36,37,43-45,49,50,55] Studies of these medications and gestational hypertension have produced equivocal results.[49,55,36] One challenge is separating direct effects of medication versus medication use as a marker (proxy) of psychopathology severity.

The timing of maternal psychopathology and medication use is a critical question when examining associations with HTN disorders of pregnancy. Physiological changes in pregnancy could elicit maternal symptoms of psychopathology, or for reasons stated above in non-pregnant populations, psychopathology and related medications could lead to hypertension. One pregnancy HTN disorder, PE, is thought to have its origin early in pregnancy at the time of placentation, but symptoms and diagnosis appear later. Information on maternal psychopathology and related medication use prior to pregnancy may be more relevant for early pregnancy events, and shed light on timing

issues. Overall, it must be recognized that depression and anxiety are, most often, chronic conditions with periods of high and low/absent symptomatology. Any relation to HTN disorders of pregnancy might involve physiology underlying chronicity or acute symptomatology or both. While these are complex considerations, a starting point is determining associations between maternal psychopathology, related medication use and HTN disorders of pregnancy, and carefully examining the time order of these associations.

Here we use a unique data source, insurance medical and pharmacy claims data covering two years prior to pregnancy up through 90 days post-delivery. These data provide objective information (not relying on maternal self-report) to study hypertension 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 use.

3.2 Methods

3.2.1 Data Source

Study data are from Blue Cross Blue Shield of Michigan (BCBSM) which internally abstracted relevant information from enrolled women who delivered a live birth during a set time period (described below). BCBSM then facilitated a confidential linkage of abstracted data with birth certificate (BC) data at the Michigan Department of Health and Human Services (MDHHS). This process created a de-identified, linked dataset that was made available for this research study. This Study was approved by the Institutional Review Boards of Michigan State University and MDHHS.

3.2.2 Study Population

Initial eligibility criteria included women with pregnancies ending in live births between October-1-2010 and September-30-2014 who were enrolled in BCBSM medical and pharmacy commercial insurance and between the ages of 15-44 at delivery. (N=123,225). Live births were identified using delivery-related ICD-9CM diagnosis and ICD-9CM procedure codes in any of the diagnostic or procedure fields on claims. Women were excluded if they delivered outside of Michigan, were BCBSM employees or had deliveries with ICD-9CM diagnostic codes indicative of multifetal gestations or stillbirths. Eligible women were linked with relevant infants in BCBSM based on BCBSM contract number, delivery facility, infant date of birth and maternal admit and discharge dates.

To capture psychopathology and related medication use prior to pregnancy we selected a two year window prior to LMP. We reasoned that a longer window might limit our sample size of women continuously enrolled in BCBSM before pregnancy and a shorter window might miss episodes of chronic psychopathology that elicit encounters with medical professionals (claims data). Thus we narrowed our eligibility criteria further to include only women continuously enrolled in BCBSM for at least 75% of the time in each year beginning two years prior to their LMP date through to ninety days after delivery date (n= 24,281 women). Determination of delivery date and LMP is described later in a section below.

Finally, limited resources precluded linkage of BCBSM data with BC data for all 24,281 women. We therefore created a sampling scheme by constructing maternal age strata, selecting all women with the outcome of interest (hypertensive disorders before

and/or during pregnancy based on ICD-9 CM diagnostic codes in BCBSM claims data), and randomly sampling women with no hypertension diagnoses from within age strata. We oversampled unaffected women within two extreme age strata (15-19, 40-44 years), because they are fewer in number. The sampling scheme resulted in a sample size of 14,999 eligible women to be linked with BC data. Later we compared the linked and unlinked women on delivery timing, antidepressant prescriptions and age at delivery.

3.2.3 Data Linkage

The delivery admit date in BCBSM claims data was presumed to be the delivery date, and only the first delivery date during the study period for each woman was used for the BC linkage (only one live birth per woman). BCBSM data and BC data were linked using mother's first and last name, age, delivery date, infant first and last name and date of birth, and mother and infant provider facility. The linkage was 85% successful yielding a sample of 12,743 women. Post-linkage data cleaning resulted in exclusion of records with infant birthdate before mothers' delivery admit date (N=8) or after delivery discharge date (N=50), or mothers with two infants on the same delivery date (N=38). The final de-identified analytic sample included 12,647 women.

3.2.4 Dating of Delivery and LMP

Because eligibility for linkage included BCBSM enrollment beginning two years prior to the LMP date through to ninety days after delivery date, we could not use BC data to determine LMP and had to rely on BCBSM available data. Neither gestational age (GA) of infant at delivery nor LMP date is available in claims data, therefore, following convention of previous studies, 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 data). Absent preterm birth ICD-9CM codes, infants were assumed to be born at term and we used 270 days prior to delivery date to calculate LMP.[133] We compared these LMP dates with LMP dates estimated from BC data obtained after linkage and performed sensitivity analyses (described in analytic section).

3.2.5 Exposure measures

BCBSM data included maternal and infant diagnostic, maternal procedural and pharmacy information from physician services and hospitalizations. Depression and anxiety were each assessed in two time periods, during the two years prior to LMP (*pre-pregnancy*) and LMP to delivery date (*pregnancy*). For these analyses, depression or anxiety in a specified time period was defined as at least one inpatient or two or more outpatient visits in a facility or professional setting with an ICD-9CM diagnosis code (depression: 296.x, 300.4, 309.0, 309.1, 311; anxiety: 300.x, 309.x, excluding the ones used in depression diagnosis) in the primary diagnosis field of a claim. We reasoned that women with a single depression/anxiety outpatient visit, while not meeting our definition for the condition, might be different from women with no such visits. Therefore, in some of our analyses we grouped these women separately. All groups were mutually exclusive.

Anti-depressant/anxiolytic medication prescription was determined from BCBSM pharmacy claims using National Drug Codes (NDC). Anti-depressants included Serotonin Reuptake inhibitors (SSRI), Serotonin and Noradrenaline Reuptake Inhibitors (SNRI), tricyclic, Norepinephrine and Dopamine Reuptake Inhibitors (NDRI) and Noradrenergic and Specific Serotonergic antidepressant (NaSSA), and antipsychotics**.**

Anxiolytics included a wide variety of medications (e.g. Diazepam, Alprazolam and Buspirone among others). Antidepressant/anxiolytic medication '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 *pregnancy initiated,* at least one prescription filled for the first time during pregnancy.

3.2.6 Outcome measures

BCBSM claims data were used to identify women with hypertensive disorders: 1) chronic hypertension (CH), ICD-9CM diagnosis codes 401.xx, 402.xx, 403.xx, 404.xx, 405.xx, 642.0x, 642.1x, 642.2x, from two years prior to LMP to first twenty weeks of pregnancy; 2) gestational hypertension (GH), ICD-9CM for 'transitional hypertension 642.3x; 3) preeclampsia (PE), ICD-9CM 642.4x, 642.5x; 4) eclampsia, ICD-9CM 642. 6x; 5) preeclampsia superimposed on chronic hypertension, ICD-9CM 642.7x from twenty weeks after LMP to the delivery date; and 6) unspecified hypertension (UH), ICD-9CM 642.9x from two years prior to LMP up to delivery date. The above mentioned 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).

3.2.7 Covariates

Information on potentially relevant covariates i.e. maternal demographics (age, race/ethnicity, education, marital status), pre-pregnancy BMI, smoking before and during pregnancy, diabetes mellitus and parity was collected from BCBSM claims

(derived maternal age and diabetes mellitus) and/or linked BC data. Race/ethnicity was grouped as White, Black and other. While all of the above covariates may be confounders, BMI, smoking and diabetes mellitus could play a mediating role as well.

3.2.8 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 disorders and across a four-level outcome variable, i.e. no HTN, CH, PH (includes GH and PE), and UH using chi-square for categorical variables and t-test for continuous variables. In one set of models we created a fourlevel exposure variable for depression with a focus on timing, i.e. no depression (referent), only one visit with depression diagnosis in one or more time periods (the two time periods being pre-LMP, during pregnancy); depression pre-LMP (according to definition described above) and depression diagnosis for the first time during pregnancy (within our study period). The same four-level variable was created for anxiety. The depression and anxiety variables were modeled separately, first in weighted logistic regression analyses using the two-level hypertension outcome, and then in weighted polynomial logistic regression using the four-level hypertension variable.

Recognizing that depression and anxiety are often co-morbid, we attempted to isolate each one in a second set of analyses by creating two new six-level variables, one that detailed depression without anxiety, and the other that detailed anxiety without depression. For the depression variable the six levels were: no depression/no anxiety (referent), depression one visit in one or more time periods and no anxiety, depression

prior to LMP and no anxiety, depression only after LMP and no anxiety, no depression but anxiety anytime during the study period, and both depression and anxiety anytime. We created a similar variable for anxiety, with the first four levels of the six-level variable having no depression. These variables were then compared to the HTN outcomes using the same analytic strategy described above.

A third set of models evaluated anti-depressant and anxiolytic medications; we again focused on timing and separated women with psychopathology diagnosis but no medication use to see if any observed associations were related to medication use but not necessarily psychopathology diagnoses alone. The five-level antidepressants variable included: no depression and no antidepressants (referent), antidepressants used prior to LMP only, antidepressants used prior to LMP and during pregnancy, antidepressants first used after LMP, and depression anytime but no antidepressants. A similar five-level variable was created for anxiolytics. The anti-depressant and anxiolytic variables were modeled separately, first in weighted logistic regression analyses using the two-level hypertension outcome, and then in weighted polynomial logistic regression using the four-level hypertension variable. All adjusted models included maternal age, race/ethnicity, education and parity along with exposure and outcome. Subsequently we added BMI, smoking and diabetes mellitus as additional covariates; interpretations of these latter models required caution because these maternal characteristics might act as confounders and/or mediators. For this reason we report final results unadjusted for these latter three potential mediators. Analyses were conducted with SAS, version 9.4, for windows (SAS Institute, Inc., Cary, North Carolina).

3.2.9 Sensitivity Analyses

Anti-psychotics are prescribed for conditions other than depression/anxiety as well as for depression/anxiety. To determine if the antipsychotics alone explained any observed associations, we repeated analyses after excluding women who filled only anti-psychotic prescriptions during the study period.

We lacked sufficient power to analyze the association of each class of antidepressants with hypertension disorders of pregnancy. In previous literature use of serotonin norepinephrine reuptake inhibitors (SNRI) has been associated with hypertension disorders of pregnancy hence we conducted sensitivity analyses after excluding women who filled these medication prescriptions during the study period.

Our estimated timing of exposures and outcome was based on LMP date, which was derived from the BCBSM data (delivery date and preterm/term distinction). Given this limitation we conducted sensitivity analyses excluding women with LMP date difference (between estimated LMP from BCBSM and clinical estimate of LMP from BC) more than fifteen days (N=1311, about 10%), assuming that the clinical estimate of LMP date from birth certificate data was the gold standard.

3.3 Results

All the analyses were weighted for the Study sampling scheme. The majority of women with hypertension disorders, 59%, had 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 about 5.3**%** met our definition of depression (at least one inpatient or two out-patient visits in a time period) and 5.7**%**

met the definition of anxiety prior to LMP date. Among 10.6% of women who had at least one inpatient or two or more outpatient visits with a primary diagnosis of depression *or* anxiety diagnosis, very few women met the definition of depression or anxiety (0.9%) for the first time during the pregnancy portion of our study period. Approximately 11.7% and 10.7% of women filled an antidepressant, anxiolytic prescription respectively prior to LMP only; 6.8% and

1.6% filled antidepressant, anxiolytic prescriptions prior to and during pregnancy, while 1.0% and 0.7% filled anti-depressant, anxiolytic prescriptions in pregnancy for the first time during the study period.

Demographic and pregnancy characteristics of the 12,647 women are presented by outcome groups, i.e., HTN disorder absence/presence and HTN subtype, in Table 4. Women with HTN disorders were more likely to be African American, primiparous, and smokers, and more likely to have some college but no four year college degree and a higher pre-pregnancy BMI. CH was associated with all of the above, with the exception that a higher percentage was multiparous. Women with PH were more likely to be White, primiparous, not married, smokers, and have some college but no four year college degree and a higher pre-pregnancy BMI.

Table 4 Maternal demographic and pregnancy characteristics according to HTN disorder presence and subtype[1]

Maternal Characteristics	**No HTN**	**Any HTN**	**p-value**	**Chronic HTN**	**Pregnancy HTN**	**Unsp HTN**	**p-value**
	N= 9875	**N=2772**		**N= 894**	**N= 1646**	**N= 232**	
	N (Wt%)	**N (Wt%)**		**N (Wt%)**	**N (Wt%)**	**N (Wt%)**	
Maternal Race[*2]			<0.0001				<0.0001
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]			0.0015				<0.0002
No college	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]			0.118				<0.0001
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)	
divoced/widowed	133 (1.2)	53 (1.7)		25 (2.7)	22 (1.2)	6 (2.4)	
Parity			<0.0001				<0.0001
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]			<0.0001				<0.0007
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)	
MaternalPre-pregnancy BMI (kg/m^2)[6]	***Mean (SE)***	***Mean (SE)***	<0.0001	***Mean (SE)***	***Mean (SE)***	***Mean (SE)***	<0.0001
	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)	<0.0008	32.4 (0.05)	29.8 (0.04)	31.1 (0.09)	0.2933

[1] Weighted for study sampling scheme Missing [*2]N=33, [*3]N=27, [*4]N=5, [*5]N=33, [*6]N=455Abbreviations: HTN: hypertension; SE: Standard Error; PE: Preeclampsia; GH: Gestational hypertension; N= Number of women; Wt.%: Weighted percent

Here we present results from weighted analytic models adjusted for maternal age, race/ethnicity, education and parity (Table 5). Unadjusted results were similar to that of adjusted models and can be found in the Appendix tables 8-10. 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 also more likely to have one visit in one or more time periods with a primary diagnosis of anxiety (aOR=1.6; 95%CI 1.2, 2.1). PH was not associated with any of the depression or anxiety measures. In models that attempted to 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), the 'no depression and any anxiety' group (aOR=1.4; 95%CI 1.1, 1.8), and the 'one visit with a primary diagnosis of anxiety but no depression' group (aOR=1.6; 95%CI 1.2, 2.2) (Table 6). By contrast, women with CH or PH were not more likely to have primary diagnoses of both depression and anxiety than were their 'no HTN' counterparts.

Table 5 Adjusted associations of maternal depression/anxiety diagnosis with hypertension disorders in pregnancy[1]

	No HTN[2]	AnyHTN[3]	Chronic HTN[4]	Pregnancy HTN[5]	Unspecified HTN[6]
	N= 9875	N=2772	N= 894	N= 1646	N= 232
	N Wt%	N Wt% OR 95%CI	N Wt% OR 95%CI	N Wt% OR 95%CI	N Wt% OR 95%CI
No depression	8992 (86.6)	2481(13.4)	795 (4.0)	1472 (8.2)	214 (1.1)
One depr related visit ≥1 timept.	360 (84.3)	121 (15.7) 1.2 [0.9, 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 depr criteria PreLMP	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 depr criteria 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]
No anxiety	8819 (86.6)	2439 (13.4)	733 (4.0)	1460 (8.2)	206 (1.1)
One anx related visit ≥1 timept.	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 anx criteria PreLMP	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 anx criteria 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 < 0.10; * p-value <0.05; [1]Weighted for the Study sampling scheme. Adjusted for maternal age, race, education and parity
Abbreviations: HTN: hypertension; PE: Preeclampsia; GH: Gestational hypertension; LMP: Last Menstrual Period; N= Number of women; Wt. %: Weighted percent; AOR: Adjusted Odds Ratio; CI: Confidence Interval

Table 6 Adjusted associations of maternal depression/anxiety overlap with hypertension disorder subtypes[1].

	No HTN	AnyHTN	Chronic HTN	Pregnancy HTN	Unspecified HTN
	N= 9875	N=2772	N= 894	N= 1646	N= 232
	N Wt%	N Wt% OR 95%CI	N Wt% OR 95%CI	N Wt% OR 95%CI	N Wt% OR 95%CI
No Depression-anxiety	8251 (86.8)	2247 (13.2)	704 (3.9)	1350 (8.2)	193 (1.1)
Depression one visit >=1 time pt-Noanxiety	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 anx	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 anx	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 [0.8, 1.7]	64 (9.7) 1.1 [0.9, 1.6]	5 (1.0) 1.0 [0.4, 2.7]
No Anxiety-depression	8251 (86.8)	2247 (13.2)	704 (3.9)	1350 (8.2)	193 (1.1)
Anxiety one visit >=1 time pt/no depression	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 depression	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 [0.7, 1.4]	10 (1.2) 1.0 [0.6, 2.0]
Anxiety in pergtnancy -no depression	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, 5.5]
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) 1.1[0.8, 1.3]	13 (1.0) 1.0 [0.5, 1.8]
Any Anxiety- depression 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]

[1]Weighted for study sampling scheme; + p-value = 0. 10 * p-value <0.05; Adjusted for maternal age, race, education and parity. Abbreviation: HTN: hypertension; Depr: Depression, pt: point; N= Number of women; Wt.%: Weighted percent; AOR: Adjusted Odds Ratio; CI: Confidence Interval Adjusted for maternal age, race, education and parity

We next considered HTN and its subtypes in relation to anti-depressant 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 anti-depressant prescription during the study period served as the comparison group. In these models CH and PH were each associated with anti-depressant prescription prior to pregnancy only and with continued use into pregnancy; for the latter CH aOR=2.0 (95%CI 1.5, 2.5) and PH aOR=1.4 (95%CI 1.1, 1.7) (Table 3.4). Depression diagnosis without an anti-depressant prescription was not associated with any HTN group.

The same modeling strategy was repeated, this time focusing on anxiolytics and anxiety. Women with CH were more likely to have anxiolytic prescriptions prior to pregnancy only and continued use into pregnancy; for the latter aOR=2.6 (95%CI 1.8, 3.8). PH was associated with initiation of anxiolytic medication during pregnancy, aOR=2.5 (95%CI 1.6, 4.2). To better understand this observation we investigated timing of prescription and PH diagnosis and found that first prescription preceded diagnosis date in 96.1% (N=25/26) of women. Anxiety diagnosis without an anxiolytic prescription during the study period was not associated with any HTN group.

We separated PE and GH and repeated all above models. Despite smaller numbers, results were similar for these two pregnancy-related hypertension groups and supported our decision to combine them into one group, PH. To examine the effect of including anti-psychotic medications in our models of anti-depressants and anxiolytics, we re-analyzed our data after excluding women who filled only an anti-psychotic medication; we found that our results were similar to those in the original analyses.

Results from sensitivity models that removed 10% (N=1311) of women who had discrepant LMP dates, i.e. > 15 day disagreement between BCBS-based estimate and BC data estimate, were similar to those in analyses with all women included (Appendix Table 3.9.1 - 3.9.3). Results from sensitivity analyses excluding women with exclusive antipsychotic prescriptions (N=23) did not alter the results significantly (Appendix Table 3.10.1 - 3.10.3). Another sensitivity analysis excluding women with SNRI prescriptions during the study period (N=358) did not change results significantly (Appendix Table 3.11.1 - 3.11.3).

Table 7 Adjusted associations of maternal anti-depressant /anxiolytic use and presence of depression/anxiety with hypertension disorder subtypes[1]

	No HTN	**Any HTN**	**Chronic HTN**	**Pregnancy HTN**	**Unsp HTN**
	N= 9875	**N=2772**	**N= 894**	**N= 1646**	**N= 232**
	N Wt%	**N Wt% OR 95%CI**	**N Wt% OR 95%CI**	**N Wt% OR 95%CI**	**N Wt% OR 95%CI**
No Anti-depr-No depression	7948 (87.3)	2069 (12.7)	633 (3.7)	1254 (8.0)	182 (1.1)
Anti-deprassant pre-preg	1049 (83.0)	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 [0.9, 2.1]
Anti-depressant 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]
Anti-depressant preg initiated	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 anti-depessantr-Yes Depr	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]
No anxiolytic-no anxiety	8243 (87.1)	2198 (12.9)	675 (3.8)	1331 (8.1)	192 (1.1)
Anxiolytic pre-preg	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 preg initiated	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]

[1]Weighted for study sampling scheme; + p-value = 0. 10 * p-value <0.05; Adjusted for maternal age, race, education and parity.

3.4 Comments

This study uses medical and pharmacy claims data linked to birth certificate data to examine relations among maternal hypertension disorders, depression/anxiety, and psychopathology-related medications. Among the women with hypertension disorders, the majority were pregnancy-related, i.e. gestational hypertension or preeclampsia. We observed that most women with a depression and/or anxiety diagnosis had a documented diagnosis before the onset of pregnancy; this was true for those with or without hypertensive disorders. Similarly few women had their first documented psychopathology-related prescriptions during pregnancy. Women with CH were more likely to receive anti-depressant and/or anxiolytics prescriptions prior to pregnancy only or prior to and during pregnancy. PH was associated with anti-depressant medication prior to pregnancy only or prior to and during pregnancy, and with anxiolytics initiated during pregnancy. We aIso found that maternal hypertension disorders were not associated with depression and/or anxiety diagnoses absent evidence of psychopathology-related medication.

Our results for women with CH are best compared to studies of non-pregnant populations. In cross-sectional studies with non-pregnant participants, hypertension is more common among individuals with depression/anxiety, but the ordering of these two conditions is unclear. [26, 28, 134,135,136,137] Longitudinal studies suggest that psychopathologies most often precede hypertension,[26,28,134,135] though this could vary with the age range of the population studied. Depression/anxiety may lead to hypertension through: 1) altered neuroendocrine functions that include dysregulation of the hypothalamic-pituitary-adrenocortical axis (HPA), [138,139] and/or hyperactivity of the

sympathetic nervous system; 2) medications used to treat psychopathologies, e.g. tricyclics; [68,69] and 3) behaviors such as diet and physical activity.[63,126] Additionally, some have suggested common pathways for both hypertension and depression/anxiety such as inflammation (pro-inflammatory cytokines) and platelet activation.[140] Pharmacological treatment of hypertension, directly or through side effects, could also lead to depression/anxiety.[78]

Our findings related to CH are consistent with those from prior studies of non–pregnant populations i.e. CH is positively associated with pre-pregnancy depression/anxiety. In our analyses stratified by psychopathology and medication use, the link with depression/anxiety was confined to those having prescriptions for antidepressant or anxiolytic medications. We extended our inquiries into pregnancy because pre-existing chronic conditions and medications used to treat these conditions may compromise the health of mother and baby. Only one other pregnancy study, to our knowledge, assessed pre-pregnancy depression/anxiety and CH[49]; this study also reported a positive association.[49] The two studies of CH and depression/anxiety measured during pregnancy produced inconsistent results, one found a positive association,[42] and the other reported no association.[49]

Pregnancy-related hypertension can arise superimposed on CH, though most often this is not the case. The unique timing of PH has prompted investigations into whether depression/anxiety might contribute to PH or be a consequence of underlying pathologies accompanying PH. Of the two studies that considered PE or GH and prepregnancy depression/anxiety one found positive unadjusted association [37] and another reported a negative association.[49] A larger group of studies have examined PH

and depression/anxiety assessed during pregnancy with six reporting a positive association[31,34,37,40,41,46] and five reporting no association.[32,33,35,42,49] Most of these studies investigated PE only. Their approaches to measuring depression/anxiety varied, typically using symptom screening with cutoff values and not relying on physician diagnosis.[31-35, 41,42,46,49] In addition depression and anxiety were not always considered separately [33, 35,37,40,49] or the focus was primarily on either anxiety[32] or depression [34,41,42,46] with only one study assessing the two conditions separately, [31] however anxiety assessment in this study was based on one question. We found no relation between PH and depression/anxiety (pre-pregnancy or during pregnancy) in analyses that did not stratify on medication use. It's worth noting that our pre-pregnancy time period was constrained to two years, we focused only on primary diagnoses in the BCBSM claims, and our population was a relatively low-risk, majority white group of women with BCBSM insurance coverage. The ready access to health care providers may have permitted women with less severe depression to seek mental health care, thereby creating a broad range of symptom severity in our group of women with depression/anxiety diagnoses claims. In addition, claims data are reimbursement driven and may lack diagnostic specificity. Other studies that query pregnant women to assess their depression/anxiety likely include affected women who have and have not sought treatment, and this latter group may have distinct characteristics.

In our analyses stratified by psychopathology and medication use, we found that women with PH were more likely to have a history of anti-depressant prescriptions either pre-LMP only or continuing into pregnancy. The majority of studies examining this association report similar results.[36, 43-45, 50, 55] Attempts to explain these associations have motivated in-vitro studies showing certain anti-depressants can induce uterine,

placental and umbilical vasoconstriction.[72, 141] Vasoconstriction may then lead to uteroplacental underperfusion, ischemia and PH.[141] In-vivo data are sparse regarding the impact of anti-depressants on uterine and umbilical blood flow in pregnant women.[141, 142]

Investigators have struggled to separate potential direct effects of antidepressant medication on pregnancy from the indication for medication, i.e. moderate/severe depression, and all its accompanying risk factors (poor diet, less physical activity, BMI extremes, substance use, social support). This is an area where clinical trials randomizing anti-depressant or placebo are challenging, particularly among pregnant women with severe depression. We observed that the effect sizes for the associations between PH and anti-depressant use were similar for women who discontinued or continued prescriptions during pregnancy. This might suggest that any direct effect of anti-depressant medications on PH risk is not mitigated by discontinuing medication prior to LMP. Alternatively, our findings could support the hypothesis that anti-depressant use has no direct effect on PH but rather is a marker for depression severity and/or other factors related to PH, and that is why discontinuation does not alter the effect size of the association. In a set of investigative analyses, we added covariates, i.e. diabetes, pre-pregnancy BMI, smoking, that might mediate and/or confound the relation between PH and anti-depressant medication use. Inclusion of these covariates 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 the two years

prior to the LMP (study period). It's unclear whether anxiolytic use occurred during an important time window in pregnancy that is etiologically relevant 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 in relation to timing of PH diagnosis. The first BCBS diagnostic claim of PH occurred after the first anxiolytic prescription date in 25 of the 26 women. Furthermore it is unlikely that the results can be explained by SNRI use during this time window since excluding this class of antidepressants frequently used in anxiety treatment did not alter results.

Some of our study limitations merit consideration. We sampled women who were continuously enrolled in BCBSM medical and pharmacy for a period of three years; this sample may not be generalizable to other more high-risk populations. 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 (due to limited resources) we compared women who were not sent for linkage and women who were unable to be linked with women who were linked with BC data (Appendix Table 3.8). We compared women by delivery timing (preterm/term), antidepressant, anxiolytic medication prescription and maternal age at delivery. A small percentage of women were unable to be linked, these women had a significantly lower median age at delivery possibly indicating recording errors in BCBSM data. The reliance on ICD-9 codes in claims data for assigning exposure and outcome diagnoses has its drawbacks, e.g. claims and coding are motivated by reimbursement and code assignment may vary between providers and by

provider expertise (psychiatrist vs obstetric practitioner). Prevalence of diagnosis of depression/anxiety for the first time in the study period during pregnancy was low and may reflect the drawback of using only the primary diagnosis field on a claim. Hence these first time diagnosis percentages for depression/anxiety may reflect an underestimation of the true rates. 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. However 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 using the BCBSM data could have also resulted in misclassification of timing of exposure (prior to LMP/after LMP), particularly in women with hypertension disorders since these complications are positively associated with preterm delivery. We attempted to address this concern through sensitivity analyses that excluded women with an LMP date difference (between assigned LMP and estimated gestational age from birth certificate) of more than 15 days. Results from models with and without these exclusions were comparable and did not alter our conclusions. Medication exposure was assigned based on filled prescriptions; we cannot be sure that women actually used the medication as directed. As is true in any observational study, unmeasured confounding may have played a role in our results.

The strengths of this study include the large sample size with recorded clinical and pharmacy data. Linking claims data with birth certificate data provided additional sources of information to include as potential confounders and a check on estimated

LMP. The BCBSM claims data allowed us 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 (diagnostic definition for this paper), and this permitted some measure of diagnostic specificity during the study period. By capturing diagnoses and medications prospectively, we avoided the problem of recall bias that impacts many studies in this area. In addition we were able to isolate maternal psychopathology and related medications pre-pregnancy only from continuation through pregnancy and consider timing in relation to PH diagnoses.

In conclusion we found that 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. Our observations reinforce the importance of pre-pregnancy mental health assessments. Women with CH or PH were more likely to have used anti-depressants prior to pregnancy only or prior to and during pregnancy. In this study we could not determine if this association is explained by direct effects of medication or if medication is solely an indicator of depression severity and other related risk factors. Clearly, the benefits of controlling maternal depression symptoms must be weighed against any excess risk posed by medication use in the peri-conception or pregnancy periods. In at least one study, discontinuation of anti-depressant medication was associated with depression relapse during pregnancy.[21] Our findings do point to a subgroup of women, those taking anti-depressants, who might be followed more closely for the development of PH. The observed association between initiation of anxiolytics during pregnancy and increased risk of PH merits further investigation.

CHAPTER 4

SUMMARY

The Systematic review of studies from various countries provided inconsistent results regarding associations between maternal depression/anxiety and HTN disorders of pregnancy. In contrast, most studies found that antidepressant use prior to and during pregnancy was related to an increased risk of PE and GH; polytherapy with two different classes of antidepressants carried an increased risk as did number of days of antidepressant prescription. In the absence of randomized controlled trials it is still unclear if these associations reflect direct pharmacological effects of mediation or if medication is a marker for other causal explanations, e.g. depression/anxiety severity, unmeasured lifestyle factors.

Current US trends of older maternal age at pregnancy, higher rates of obesity, and increases in antidepressant use, all of which have been linked to HTN disorders of pregnancy, heighten the importance of investigation into links among these factors. Previous findings of associations between antidepressant medication use prior to and during pregnancy and PH were confirmed in our study using BCBSM claims data. In addition we found links between new onset anxiolytic medication use during pregnancy and PH. CH risk was greater among women with antidepressant use or anxiolytic medication use prior to and during pregnancy. Our finding of the association of anxiolytic medication initiated in pregnancy with PH should be investigated further in studies with more detailed information on indications for prescriptions.

In our study, stratification of women by medication use and depression/anxiety status revealed no association between psychopathology diagnosis and HTN disorders

of pregnancy in the absence of related medication use. While others have reported that maternal pregnancy depression and anxiety symptoms increase the risk of HTN disorders of pregnancy, not all separate out medication use and their measures of depression/anxiety vary considerably. Our criteria for depression, anxiety may be more stringent than some studies which could partially explain why our results differ.

HTN disorders of pregnancy are not common (typically 3-10%) and depression and anxiety are chronic conditions with remittances and relapses. Thus examining the time ordering of these associations and teasing out potential confounding factors will require large cohorts of women of reproductive age and longitudinal follow up for a substantial period of time. In light of recent trends, i.e. increasing obesity, older maternal age at first pregnancy, and multiple gestations, all of which are significant risk factors for HTN disorders of pregnancy, the added risks of mental health disorders and related medications deserve investigation within this growing public health concern.

Risks associated with maternal antidepressant use in the peri-conception and pregnancy periods are mainly inferred from observational studies. The more definitive study design, a randomized clinical trial, presents an ethical dilemma given that untreated depression/anxiety carries significant maternal, fetal, and infant risks. There may be subsets of women who could be randomized to alternative psychotherapeutic methods for maternal depression treatment (e.g. cognitive therapy); this would represent an important next step and results could help providers and women carefully weigh the benefits and risks of antidepressant therapy during pregnancy.

APPENDIX

Table 8 Unadjusted associations of maternal depression/anxiety diagnosis with hypertension disorder subtypes[1].

	No HTN	AnyHTN	Chronic HTN	Pregnancy HTN	Unsp HTN
	N= 9875	N=2772	N= 894	N= 1646	N= 232
	N Wt%	N Wt% OR 95%CI	N Wt% OR 95%CI	N Wt% OR 95%CI	N Wt% OR 95%CI
No depression	8992 (86.6)	2481 (13.4)	795 (4.0)	1472 (8.2)	214 (1.1)
One depr related visit ≥1 timept.	360 (84.3)	121 (15.7) 1.2 [1.0, 1.5]	39 (4.6) 1.2 [0.8, 1.7]	73 (9.8) 1.2 [0.9, 1.6]	9 (1.3) 1.2 [0.6, 2.4]
Met depr criteria PreLMP	483 (84.9)	160 (15.1) 1.1 [0.9, 1.4]	58 (5.5) **1.4 [1.0, 1.9]**+	94 (8.8) 1.1 [0.9, 1.4]	8 (0.8) 0.7 [0.3, 1.6]
Met depr criteria in pregnancy	40 (88.4)	10 (11.6) 0.9 [0.4, 1.7]	2 (2.3) 0.6 [0.1, 2.3]	7 (8.1) 1.0 [0.4, 2.1]	1 (1.1) 1.0 [0.1, 7.4]
No anxiety	8819 (86.6)	2439 (13.4)	733 (4.0)	1460 (8.2)	206 (1.1)
One anx related visit ≥1 timept.	423 (83.7)	150 (16.3) 1.3 [1.0, 1.5]	59 (6.0) **1.5 [1.2, 2.0]***	79 (8.9) 1.2 [0.9, 1.5]	12 (1.4) 1.3 [0.7, 2.4]
Met anx criteria PreLMP	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 [0.9, 1.4]	12 (0.9) 0.9 [0.5, 1.6]
Met anx criteria in pregnancy	75 (86.9)	19 (13.1) 1.0 [0.6, 1.7]	7 (3.9) 1.0 [0.4, 2.1]	10 (7.4) 0.9 [0.4, 1.9]	2 (1.8) 1.7 [0.4, 7.6]

[1] Weighted for study sampling scheme; + p-value = 0.10 * p-value <0.05

Table 9 Unadjusted associations of maternal depression/anxiety overlap with hypertension disorder subtypes[1].

	No HTN	AnyHTN	Chronic HTN	Pregnancy HTN	Unsp HTN
	N= 9875	N=2772	N= 894	N= 1646	N= 232
	N Wt.%	N Wt.% OR 95%CI	N Wt.% OR 95%CI	N Wt.% OR 95%CI	N Wt.% OR 95%CI
No depression-anxiety	8251 (86.8)	2247 (13.2)	704 (3.9)	1350 (8.2)	193 (1.1)
Depr 1 visit ≥1 timept-noanx	248 (85.1)	80 (14.9) 1.2 [0.9, 1.5]	27 (3.2) 1.2 [0.8, 1.9]	46 (8.8) 1.1 [0.8, 1.6]	7 (1.3) 1.2 [0.5, 2.8]
Depr pre-LMP-no anx	298 (83.7)	107 (16.3) 1.3 [1.0, 1.6]	42 (6.5) **1.7 [1.2, 2.5]***	60 (9.0) 1.1 [0.8, 1.5]	5 (0.8) 0.6 [0.3, 1.6]
Depr in preg-no anx	22 (90.4)	5 (10.0) 0.7 [0.3, 1.9]	0 NE	4 (8.0) 0.9 [0.3, 2.8]	1 (2.0) 1.7 [0.2, 12.9]
No depr_any anx	741 (84.9)	234 (15.1) 1.2 [0.9, 1.4]	91 (5.5) **1.4 [1.1, 1.8]***	122 (8.4) 1.0 [0.8, 1.3]	21 (1.2) 1.2 [0.7, 1.8]
Any depr anx overlap	315 (85.2)	99 (14.8) 1.1 [0.9, 1.5]	30 (4.0) 1.0 [0.7, 1.6]	64 (9.7) 1.2 [0.9, 1.6]	5 (1.0) 1.0 [0.4, 2.5]
No anxiety-depression	8251 (86.8)	2247 (13.2)	704 (3.9)	1350 (8.2)	193 (1.1)
Anx 1 visit ≥1 timept-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) 1.1 [0.8, 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) 1.1 [0.8, 1.5]	60 (8.5) 1.1 [0.8, 1.4]	10 (1.2) 1.1 [0.6, 2.1]
Anxiety in perg -no depr	50 (86.7)	14 (13.3) 1.0 [0.5, 1.9]	6 (5.1) 1.3 [0.5, 3.1]	7 (7.3) 0.9 [0.4, 2.1]	1 (0.8) 0.8 [0.1, 5.6]
No anxiety-any depr	568 (84.5)	192 (15.4) 1.2 [1.0, 1.4]	69 (5.5) 1.4 [1.1, 1.9]	110 (8.9) 1.1 [0.9, 1.4]	13 (1.0) 1.0 [0.5, 1.7]
Any anxiety- depr overlap	315 (85.2)	99 (14.8)1.0 [0.6, 1.7]	30 (4.0) 1.0 [0.4, 2.1]	64 (9.7) 0.9 [0.4, 1.9]	5 (1.0) 1.0 [0.4, 2.5]

[1] Weighted for study sampling scheme; + p-value = 0.10 * p-value <0.05

Table 10 Unadjusted associations of maternal anti-depressant /anxiolytic use with and without depression/anxiety status with hypertension disorder subtypes[1].

	No HTN	Any HTN	Chronic HTN	Pregnancy HTN	Unsp HTN
	N= 9875	N=2772	N= 894	N= 1646	N= 232
	N Wt.%	N Wt.% OR 95%CI	N Wt.% OR 95% CI	N Wt.% OR 95%CI	N Wt.% OR 95%CI
No Anti-depr-No depression	7948 (87.3)	2069 (12.7)	633 (3.7)	1254 (8.0)	182 (1.1)
Anti-depressant pre-preg	1049 (83.0)	392 (17.0) **1.4 [1.2, 1.6]***	141 (5.8) **1.7 [1.4, 2.0]***	218 (9.8) **1.3 [1.1, 1.5]+**	33 (1.4) 1.4 [0.9, 2.0]
Anti-depressant continued	640 (81.8)	257 (18.2) **1.5 [1.3, 1.8]***	101 (7.1) 2**.1 [1.6, 2.6]***	142 (10.2) **1.4 [1.1, 1.7]+**	14 (0.9) 0.9 [0.5, 1.6]
Anti-depressant preg initiated	86 (87.6)	21 (12.4) 1.0 [0.6, 1.6]	6 (2.8) 0.8 [0.3, 1.7]	15 (9.6) 1.2 [0.7, 2.2]	0 (0.0) NE
No anti-depressant-Yes Depr	152 (90.0)	33 (10.2) **0.8 [0.5, 1.1]+**	13 (4.0) 1.1 [0.6, 1.9]	17 (5.3) **0.6 [0.4, 1.1]***	3 (0.9) 0.8 [0.3, 2.6]
No anxiolytic-no anxiety	8243 (87.1)	2198 (12.9)	675 (3.8)	1331 (8.1)	192 (1.1)
Anxiolytic pre-pregnancy	1042 (82.8)	383 (17.2) 1.4 [1.2, 1.6]	146 (6.4) 1.8 [1.5, 2.2]	210 (9.5) 1.2 [1.0, 1.5]	27 (1.3) 1.3 [0.8, 2.0
Anxiolytic- continued	151 (81.3)	65 (18.7) 1.5 [1.1, 2.1]	36 (10.1) **2.9 [2.0, 4.2]***	24 (7.1) 0.9 [0.6, 1.5]	5 (1.4) 1.4 [0.6, 3.4]
Anxiolytic preg initiated	61 (76.6)	32 (23.4) **2.1 [1.3, 3.3]***	6 (4.6) 1.4 [0.6, 3.4]	26 (18.8) **2.6 [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, 1.4]	55 (8.1) 1.0 [0.7, 1.4]	8 (1.1) 1.0 [0.5, 2.1]

[1] Weighted for study sampling scheme; + p-value = 0.10 * p-value <0.05

Table 11 Comparing linked and not linked data on delivery timing, antidepressant, and anxiolytic medication filling by timing and maternal age.

Maternal Characteristics	**Linked**	**Not for linkage**	**Could not link**	**pvalue**
	N= 12,705	**N=9280**	**N= 2256**	
	N (Col Wt%)	**N (Col Wt%)**	**N (Col Wt%)**	
Preterm codes on mom or baby claims				<0.0001
No	11867 (93.4)	8829 (93.7)	2114 (95.1)	
Yes	838 (6.6)	451 (6.3)	142 (4.9)	
Antidepressant medicaiton fillings by timing				<0.0001
No antidepressant medicaiton	10250 (80.7)	7520 (81.0)	1687 (74.8)	
Prepregnancy medication	1446 (11.4)	1064 (11.4)	366 (16.2)	
Pre-pregnancy and pregnancy medication	901 (7.1)	614 (6.6)	164 (7.3)	
First time pregnancy medication	108 (0.9)	82 (0.9)	39 (1.7)	
Anxiolytic Medication				<0.0001
No anxiolytic medicaiton	10963 (86.3)	8112 (87.4)	1940 (86.0)	
Prepregnancy medication	1432 (11.3)	982 (10.6)	235 (10.4)	
Pre-pregnancy and pregnancy medication	217 (1.7)	119 (1.3)	61 (2.7)	
First time pregnancy medication	93 (0.7)	67 (0.7)	20 (0.9)	
Maternal age at delivery	***Median (SE)***	***Median (SE)***	***Median (SE)***	<0.0001
	31.0 (0.04)	31.0 (0.05)	22 (0.13)	

Table12 Sensitivity analyses excluding women with LMP date difference greater than or equal to fifteen days (N=1311~10%), unadjusted and adjusted examining the associations of maternal depression/anxiety diagnosis with hypertension disorder subtypes[1]

	No HTN	Any HTN	Chronic HTN	Pregnancy HTN	Unsp HTN
	N= 8817	N=2519	N= 810	N= 1499	N= 210
	N Wt.%	N Wt.% OR 95%CI	N Wt.% OR 95%CI	N Wt.% OR 95%CI	N Wt.% OR 95%CI
No Depression	8028 (86.3)	2261 (13.7)	725 (4.1)	1342 (8.4)	194 (1.1)
One depr related visit ≥1 timept.	323 (84.6)	105 (15.4) 1.1 [0.9,1.5]	31 (4.1) 1.0 [0.7, 1.5]	66 (9.9) 1.2 [0.9, 1.6]	8 (1.3) 1.2 [0.5, 2.5]
Adjusted Odds Ratio		1.2 [0.9,1.5]	1.1 [0.7, 1.6]	1.2 [0.9, 1.6]	1.2 [0.6, 2.7]
Met depression criteria Pre-LMP	433 (84.8)	143 (15.1) 1.1 [0.9,1.4]	52 (5.6) **1.4 [1.0, 1.9]***	84 (8.8) 1.1 [0.8, 1.4]	7 (0.8) 0.7 [0.3, 1.7]
Adjusted Odds Ratio		1.1 [0.9,1.4]	1.4 [1.0, 2.0]*	1.0 [0.8, 1.3]	0.7 [0.3, 1.7]
Met depr criteria in pregnancy	33 (86.5)	10 (13.5) 1.0 [0.5,2.0]	2 (2.7) 0.7 [0.1,2.7]	7 (9.5) 1.1 [0.5, 2.6]	1 (1.3) 1.2 [0.2, 8.6]
Adjusted Odds Ratio		0.9 [0.4,1.8]	0.6 [0.1,2.5]	1.0 [0.4, 2.4]	1.1 [0.2, 8.4]
No Anxiety	7871 (86.3)	2217 (13.7)	699 (4.1)	1331 (8.4)	187 (1.1)
One anx related visit ≥1 timept.	386 (83.6)	139 (16.4) 1.2 [1.0,1.5]	54 (6.0) 1.5 [1.1, 2.0]	74 (9.0) 1.1 [0.8, 1.4]	11 (1.4) 1.3 [0.7, 2.5]
Adjusted Odds Ratio		1.2 [1.0,1.5]	1.5 [1.1, 2.1]	1.1 [0.8, 1.4]	1.3 [0.7, 2.5]
Met anxiety criteria Pre-LMP	494 (85.8)	146 (14.2) 1.0 [0.9,1.3]	51 (4.7) 1.1 [0.8, 1.6]	85 (8.6) 1.0 [0.8, 1.3]	10 (0.9) 0.8 [0.4, 1.5]
Adjusted Odds Ratio		1.1 [0.8,1.2]	1.1 [0.8, 1.5]	1.0 [0.8, 1.3]	0.8 [0.4, 1.5]
Met anx criteria in pregnancy	66 (86.4)	17 (13.6) 1.0 [0.6,1.8]	6 (3.8) 0.9 [0.4, 2.2]	9 (7.7) 0.9 [0.4, 2.0]	2 (2.1) 1.8 [0.4, 8.4]
Adjusted Odds Ratio		1.0 [0.5, 1.8]	1.0 [0.4, 2.4]	0.8 [0.4, 1.8]	1.9 [0.4, 8.6]

[1] Weighted for study sampling scheme; + p-value = 0.10 * p-value <0.05; Adjusted Odds Ratio: adjusted for maternal age, race, education and parity

Table 13 Sensitivity analyses excluding women with LMP date difference greater than or equal to fifteen days (N=1311~10%), unadjusted and adjusted examining the associations of maternal depression/anxiety overlap with hypertension disorder subtypes[1]

	No HTN	**Any HTN**	**Chronic HTN**	**Pregnancy HTN**	**Unsp HTN**
	N= 8817	**N=2519**	**N= 810**	**N= 1499**	**N= 210**
	N Wt.%	**N Wt.% OR 95%CI**	**N Wt.% OR 95%CI**	**N Wt.% OR 95%CI**	**N Wt.% OR 95%CI**
No depression-anxiety	7363 (86.5)	2044 (13.5)	640 (4.0)	1229 (8.4)	175 (1.1)
Depr 1 visit ≥1 timept-noanx	220 (84.9)	71 (15.1) 1.1 [0.9, 1.5]	22 (4.4) 1.1 [0.7, 1.8]	43 (9.3) 1.1 [0.8, 1.6]	6 (1.3) 1.2 [0.5, 2.9]
Adjusted Odds Ratio		1.1 [0.9, 1.5]	1.2 [0.8, 2.0]	1.1 [0.7, 1.6]	1.2 [0.5, 3.0]
Depr pre-LMP-no anx	269 (83.5)	97 (16.5) 1.3 [1.0, 1.6]	37 (6.5) **1.7 [1.2, 2.5]***	55 (9.2) 1.1 [0.8, 1.6]	5 (0.8) 0.7 [0.3, 1.7]
Adjusted Odds Ratio		1.2 [0.9, 1.6]	1.7 [1.2, 2.5]*	1.1 [0.8, 1.5]	0.7 [0.3, 1.7]
Depr in preg-no anx	19 (88.7)	5 (11.3) 0.8 [0.3, 2.2]	0 NE	4 (9.0) 1.1 [0.4, 3.1]	1 (2.2) 1.2 [0.3, 14.5]
Adjusted Odds Ratio		0.6 [0.2, 1.9]	NE	0.8 [0.2, 2.8]	1.1 [0.3, 14.3]
No depr_any anx	665 (84.6)	217 (15.4) 1.2 [1.0, 1.4]	85 (5.7) **1.5 [1.1, 1.9]***	113(8.5) 1.0 [0.8, 1.3]	19 (1.3) 1.1 [0.7, 1.9]
Adjusted Odds Ratio		1.1 [1.0, 1.3]	1.4 [1.1, 1.8]*	1.0 [0.8, 1.2]	1.1 [0.7, 1.8]
Any depr anx overlap	218 (85.7)	85 (14.3) 1.1 [0.8, 1.4]	26 (4.0) 1.0 [0.7, 1.5]	55 (9.3) 1.1 [0.8, 1.5]	4 (1.0) 0.9 [0.3, 2.7]
Adjusted Odds Ratio		1.1 [0.8, 1.4]	1.1 [0.7, 1.6]	1.1 [0.8, 1.5]	1.0 [0.3, 2.8]
No anxiety-depression	7363 (86.5)	2044 (13.5)	640 (4.0)	1229 (8.4)	175 (1.1)
Anx 1 visit ≥1 timept-no depr	278 (83.4)	103 (16.6) 1.3 [1.0, 1.6]	42 (6.4) **1.7 [1.2, 2.3]+**	52 (8.8) 1.1 [0.8, 1.5]	9 (1.4) 1.3 [0.7, 2.6]
Adjusted Odds Ratio		1.2 [1.0, 1.6]	1.7 [1.2, 2.3]+	1.0 [0.7, 1.4]	1.3 [0.6, 2.5]
Anxiety pre-LMP-no depr	345 (85.5)	101 (14.5) 1.1 [0.9, 1.4]	38 (5.1) 1.3 [0.9, 1.8]	54 (8.2) 1.0 [0.7, 1.4]	9 (1.2) 1.1 [0.5, 2.1]
Adjusted Odds Ratio		1.0 [0.8, 1.3]	1.2 [0.9, 1.8]	1.0 [0.7, 1.3]	1.0 [0.5, 2.0]
Anxiety in perg -no depr	42 (85.3)	13 (14.7) 1.1 [0.6, 2.1]	5 (5.0) 1.3 [0.5, 3.3]	7 (8.6) 1.0 [0.4, 2.5]	1 (1.0) 0.9 [0.1, 6.5]
Adjusted Odds Ratio		1.1 [0.6, 2.2]	1.4 [0.5, 3.4]	1.0 [0.4, 2.5]	0.9 [0.1, 6.5]
No anxiety-any depr	508 (84.3)	173 (15.7) 1.2 [1.0, 1.4]	59 (5.4) 1.4 [1.0, 1.9]	102(9.3) 1.1 [0.9, 1.4]	12 (1.1) 1.0 [0.5, 1.8]
Adjusted Odds Ratio		1.2 [1.0, 1.4]	1.4 [1.1, 1.9]	1.1 [0.8, 1.3]	1.0 [0.5, 1.8]
Any anxiety- depr overlap	281 (85.7)	85 (14.3) 1.1 [0.8, 1.4]	26 (4.0) 1.0 [0.7, 1.5]	55 (9.3) 1.1 [0.8, 1.5]	4 (1.0) 0.9 [0.3, 2.7]
Adjusted Odds Ratio		1.1 [0.8, 1.4]	1.1 [0.7, 1.6]	1.1 [0.8, 1.5]	1.0 [0.3, 2.8]

Table 14 Sensitivity analyses excluding women with LMP difference equal to or more than fifteen days (N=1311~10%), unadjusted and adjusted associations of maternal anti-depressant /anxiolytic use and depression/anxiety status with hypertension disorder subtypes[1].

	No HTN	**Any HTN**	**Chronic HTN**	**Pregnancy HTN**	**Unsp HTN**
	N= 8817	**N=2519**	**N= 810**	**N= 1499**	**N= 210**
	N Wt%	**N Wt.% OR 95%CI**	**N Wt.% OR 95%CI**	**N Wt.% OR 95%CI**	**N Wt.% OR 95%CI**
No Anti-depressant-No Depression	7079 (87.0)	1881 (13.0)	576 (3.7)	1441 (8.2)	164 (1.1)
Anti-depressant Pre-Pregnancy	942 (82.7)	356 (17.3) 1.4 [1.2, 1.6]	125 (5.8) 1.6 [1.3, 2.0]	199 (9.9) 1.3 [1.1, 1.5]	32 (1.5) 1.5 [1.0, 2.2]
Adjusted Odds Ratio		1.4 [1.2, 1.6]	1.7 [1.4, 2.1]	1.2 [1.0, 1.5]	1.5 [1.0, 2.3]
Anti-depressant Continued	586 (81.7)	236 (18.3) 1.5 [1.3, 1.8]	93 (7.2) 2**.0 [1.6, 2.6]***	131(10.3) 1.3 [1.1, 1.7]	12 (0.9) 0.8 [0.5, 1.5]
Adjusted Odds Ratio		1.4 [1.3, 1.8]	1.9 [1.5, 2.5]*	1.4 [1.1, 1.7]	0.8 [0.4, 1.5]
Anti-depressant-Pregnancy Initiated	75 (89.9)	16 (10.1) 0.8 [0.4, 1.3]	4 (2.1) 0.6 [0.2, 1.5]	12 (7.9) 0.9 [0.5, 1.8]	0 NE
Adjusted Odds Ratio		0.7 [0.4, 1.3]	0.5 [0.2, 1.5]	0.9 [0.4, 1.8]	NE
No Anti-depressant-Yes depression	135 (89.6)	30 (10.4) 0.8 [0.5, 1.2]	12 (4.1) 1.1 [0.6, 2.0]	16 (5.5) 0.7 [0.4, 1.1]	2 (0.7) 0.6 [0.1, 2.5]
Adjusted Odds Ratio		0.7 [0.5, 1.1]	1.0 [0.5, 1.8]	0.6 [0.4, 1.1]	0.6 [0.1, 3.1]
No Anxiolytic-No Anxiety	7369 (86.8)	1998 (13.2)	608 (3.8)	1215 (8.3)	175 (1.1)
Anxiolytic Pre-Pregnancy	921 (82.1)	355 (17.9) 1.4 [1.3, 1.6]	135 (6.6) **1.9 [1.5, 2.3]**+	195 (9.9) 1.3 [1.1, 1.5]	25 (1.4) 1.3 [0.8, 2.0]
Adjusted Odds Ratio		1.3 [1.2, 1.5]	1.8 [1.5, 2.2]+	1.2 [1.0, 1.4]	1.3 [0.8, 2.0]
Anxiolytic Continued	138 (81.2)	59 (18.8) 1.5 [1.1, 2.1]	35 (10.9) 3.1 [2.1, 4.5]	20 (6.7) 0.9 [0.5, 1.4]	4 (1.3) 1.2 [0.4, 3.3]
Adjusted Odds Ratio		1.4 [1.0, 2.0]	2.8 [1.9, 4.2]	0.8 [0.5, 1.3]	1.2 [0.4, 3.3]
Anxiolytic Pregnancy Initiated	52 (77.3)	26 (22.7) 1.9 [1.2, 3.2]	5 (4.6) 1.4 [0.5, 3.7]	21 (18.1) 2.5 [1.4, 4.2]	0 NE
Adjusted Odds Ratio		1.9 [1.1, 3.1]	1.4 [0.5, 3.9]	2.3 [1.3, 4.0]	
No Anxiolytic-Yes Anxiety	337 (87.5)	81 (12.5) 0.9 [0.7, 1.2]	27 (3.7) 1.0 [0.6, 1.5]	48 (7.9) 0.9 [0.7, 1.3]	6 (1.0) 0.8 [0.4, 2.1]
Adjusted Odds Ratio		0.9 [0.7, 1.2]	1.0 [0.6, 1.5]	1.1 [0.8, 1.3]	0.9 [0.6, 1.3]

Weighted for study sampling scheme; + p-value = 0.10 * p-value <0.05; Adjusted Odds Ratio: adjusted for maternal age, race, education and parity

Table 15 Sensitivity analyses excluding women with exclusive antipsychotic use (N=23), unadjusted and adjusted associations of maternal depression/anxiety diagnosis with hypertension disorder subtypes[1]

	No HTN	**Any HTN**	**Chronic HTN**	**Pregnancy HTN**	**Unsp HTN**
	N= 9856	**N=2768**	**N= 892**	**N= 1644**	**N= 232**
	N Wt%	**N Wt% OR 95%CI**	**N Wt% OR 95%CI**	**N Wt% OR 95%CI**	**N Wt% OR 95%CI**
No Depression	8984 (86.6)	2479 (13.4)	794 (4.1)	1471 (8.2)	214 (1.1)
One depr related visit ≥1 timept.	357 (84.5)	119 (15.5) 1.2 [0.9, 1.5]	38 (4.6) 1.0 [0.8, 1.7]	72 (9.7) 1.2 [0.9, 1.6]	9 (1.3) 1.2 [0.6, 2.5]
Adjusted Odds Ratio		1.2 [1.0, 1.5]	1.2 [0.9, 1.8]	1.2 [0.9, 1.6]	1.3 [0.6, 2.6]
Met depression criteria Pre-LMP	476 (84.7)	160 (15.3) 1.2 [1.0, 1.4]	58 (5.6) **1.4 [1.0, 1.9]***	94 (8.9) 1.1 [0.9, 1.4]	8 (0.8) 0.8 [0.4, 1.7]
Adjusted Odds Ratio		1.2 [0.9, 1.4]	**1.5 [1.1, 2.0]***	1.1 [0.8, 1.3]	0.8 [0.4, 1.7]
Met depr criteria in pregnancy	39 (88.1)	10 (11.9) 0.9 [0.4,1.8]	2 (2.4) 0.6 [0.1, 2.4]	7 (8.3) 1.0 [0.4, 2.3]	1 (1.2) 1.0 [0.1, 7.6]
Adjusted Odds Ratio		0.8 [0.4,1.8]	0.5 [0.4, 2.2]	0.9 [0.4, 2.1]	1.0 [0.1, 7.4]
No Anxiety	8806 (86.8)	2436 (13.4)	771 (4.0)	1459 (8.2)	206 (1.1)
One anx related visit ≥1 timept.	421 (83.8)	149 (16.2) 1.2 [1.0,1.5]	59 (6.0) 1.5 [1.2, 2.1]	78 (8.7) 1.1 [0.8, 1.4]	12 (1.4) 1.3 [0.7, 2.4]
Adjusted Odds Ratio		1.2 [1.0, 1.5]	1.6 [1.2, 2.1]	1.1 [0.8, 1.4]	1.3 [0.7, 2.5]
Met anxiety criteria Pre-LMP	554 (85.7)	164 (14.3) 1.1 [0.9, 1.3]	55 (4.4) 1.1 [0.8, 1.5]	97 (9.0) 1.1 [0.9, 1.4]	12 (1.0) 0.9 [0.5, 1.6]
Adjusted Odds Ratio		1.1 [0.9, 1.3]	1.1 [0.8, 1.5]	1.1 [0.9, 1.4]	0.9 [0.5, 1.6]
Met anx criteria in pregnancy	756 (86.9)	19 (13.1) 1.0 [0.6, 1.7]	7 (3.9) 1.0 [0.4, 2.1]	10 (7.4) 0.9 [0.4, 1.9]	2 (1.8) 1.7 [0.4, 7.6]
Adjusted Odds Ratio		1.0 [0.6, 1.7]	1.1 [0.5, 2.4]	0.9 [0.4, 1.9]	1.7 [0.4, 7.9]

[1]Weighted for study sampling scheme; + p-value = 0.10 * p-value <0.05; Adjusted Odds Ratio: adjusted for maternal age, race, education and parity

Table16 Sensitivity analyses excluding women exclusive antipsychotic use (N=23), unadjusted and adjusted associations of maternal depression/anxiety overlap with hypertension disorder subtypes[1]

	No HTN	**Any HTN**	**Chronic HTN**	**Pregnancy HTN**	**Unsp HTN**
	N= 9856	**N=2768**	**N= 892**	**N= 1644**	**N= 232**
	N Wt%	**N Wt% OR 95%CI**	**N Wt% OR 95%CI**	**N Wt% OR 95%CI**	**N Wt% OR 95%CI**
No depression-anxiety	8245 (86.8)	2245 (13.2)	703 (3.9)	1349 (8.2)	193 (1.1)
Depr 1 visit ≥1 timept-noanx	245 (85.0)	79 (15.0) 1.2 [0.9, 1.5]	26 (4.7) 1.2 [0.8, 1.9]	46 (8.9) 1.1 [0.8, 1.6]	7 (1.3) 1.3 [0.6,2.8]
Adjusted Odds Ratio		1.2 [0.9, 1.5]	1.3 [0.9, 2.0]	1.1 [0.8, 1.5]	1.3 [0.6,3.0]
Depr pre-LMP-no anx	294 (83.5)	107 (16.5) 1.3 [1.0, 1.6]	42 (6.6) **1.8 [1.2, 2.5]***	60 (9.2) 1.2 [0.9, 1.6]	5 (0.7) 0.7 [0.3,1.6]
Adjusted Odds Ratio		1.2 [1.0, 1.6]	1.8 [1.3, 2.6]*	1.1 [0.8, 1.5]	0.7 [0.3,1.6]
Depr in preg-no anx	22 (90.0)	5 (10.0) 0.7 [0.3, 1.9]	0 NE	4 (8.0) 0.9 [0.3, 2.8]	1 (2.0) 1.7 [0.2,12.9]
Adjusted Odds Ratio		0.6 [0.2, 1.7]	NE	0.8 [0.2, 2.5]	1.7 [0.2,12.6]
No depr_any anx	739 (85.0)	234 (15.1) 1.2 [1.0, 1.4]	91 (5.5) **1.0 [1.1, 1.8]***	122 (8.4)1.0 [0.8, 1.3]	21 (1.3) 1.2 [0.7,1.8]
Adjusted Odds Ratio		1.1 [1.0, 1.3]	1.4 [1.1, 1.8]*	1.0 [0.8, 1.3]	1.2 [0.7, 1.8]
Any depr anx overlap	311 (85.3)	98 (14.7) 1.1 [0.9, 1.5]	30 (4.1) 1.1 [0.7, 1.6]	63 (9.5) 1.2 [0.9, 1.6]	5 (1.1) 1.0 [0.4,2.6]
Adjusted Odds Ratio		1.1 [0.9, 1.5]	1.1 [0.8, 1.7]	1.2 [0.9, 1.6]	1.0 [0.4,2.7]
No anxiety-depression	8245 (86.8)	2245 (13.2)	703 (3.9)	1349 (8.2)	1193 (1.1)
Anx 1 visit ≥1 timept-no depr	308 (84.1)	109 (15.9) 1.2 [1.0, 1.6]	44 (6.1) **1.6 [1.2, 2.2]+**	55 (8.4) 1.1 [0.8,1.4]	10 (1.4) 1.3 [0.7,2.5]
Adjusted Odds Ratio		1.2 [1.0, 1.5]	1.6 [1.2, 2.2]+	1.0 [0.7,1.4]	1.3 [0.7, 2.5]
Anxiety pre-LMP-no depr	381 (85.3)	111 (14.7) 1.1 [0.9, 1.4]	41 (5.0) 1.3 [0.9, 1.8]	60 (8.5) 1.1 [0.8,1.4]	10 (1.2) 1.1 [0.6,2.1]
Adjusted Odds Ratio		1.1 [0.9, 1.4]	1.3 [0.9, 1.8]	1.0 [0.8,1.4]	1.1 [0.6,2.0]
Anxiety in perg -no depr	50 (86.7)	14 (13.3) 1.0 [0.5, 1.9]	6 (5.1) 1.3 [0.6, 3.1]	7 (7.3) 0.9 [0.4,2.1]	1 (0.8) 0.8 [0.1,5.6]
Adjusted Odds Ratio		1.0 [0.5, 2.0]	1.4 [0.6, 3.3]	0.9 [0.4,2.1]	0.8 [0.1,5.6]
No anxiety-any depr	561 (84.4)	191 (15.6) 1.2 [1.0, 1.5]	68 (5.5) 1.4 [1.1, 1.9]	110 (9.0)1.1 [0.9,1.4]	13 (1.0) 1.0 [0.5,1.7]
Adjusted Odds Ratio		1.2 [1.0, 1.4]	1.5 [1.1, 2.0]	1.1 [0.8,1.3]	1.0 [0.5,1.8]
Any anxiety- depr overlap	311 (85.3)	98 (14.7) 1.1 [0.9, 1.5]	30 (4.1) 1.1 [0.7, 1.6]	63 (9.5) 1.2 [0.9, 1.6]	5 (1.1) 1.0 [0.4,2.6]
Adjusted Odds Ratio		1.1 [0.9, 1.5]	1.1 [0.8, 1.7]	1.2 [0.9, 1.6]	1.0 [0.4,2.7]

[1] Weighted for study sampling scheme; + p-value = 0.10 * p-value <0.05; Adjusted Odds Ratio: adjusted for maternal age, race, education and parity

Table 17 Sensitivity analyses excluding women with exclusive antipsychotic use (N=23), unadjusted and adjusted associations of maternal anti-depressant /anxiolytic and depression/anxiety status with hypertension disorder subtypes[1].

	No HTN	**Any HTN**	**Chronic HTN**	**Pregnancy HTN**	**Unsp HTN**
	N= 9856	**N=2768**	**N= 892**	**N= 1644**	**N= 232**
	N Wt%	**N Wt% OR 95%CI**	**N Wt% OR 95%CI**	**N Wt% OR 95%CI**	**N Wt% OR 95%CI**
No Anti-depressant-No Depression	7948 (87.3)	2069 (12.7)	633 (3.7)	1254 (8.0)	182 (1.1)
Anti-depressant Pre-Pregnancy	1037 (82.9)	388 (17.1) 1.4 [1.2, 1.6]	139 (5.8) **1.7 [1.4, 2.1]***	216 (9.8) 1.3 [1.1, 1.5]	33 (1.4) 1.4 [0.9, 2.1]
Adjusted Odds Ratio		1.4 [1.2, 1.6]	**1.7 [1.4, 2.1]***	1.2 [1.0, 1.5]	1.5 [1.0, 2.2]
Anti-depressant Continued	635 (81.7)	257 (18.3) 1.5 [1.3, 1.8]+	101 (7.1) **2.1 [1.6, 2.6]***	142 (10.3)1.4 [1.1, 1.7]	14 (0.9) 0.9 [0.5, 1.6]
Adjusted Odds Ratio		1.5 [1.3, 1.8]+	**2.0 [1.6, 2.5]***	1.4 [1.1, 1.7]	0.9 [0.5, 1.6]
Anti-depressant-Pregnancy Initiated	84 (87.2)	21 (12.8) 1.0 [0.6, 1.7]	6 (2.8) 0.8 [0.3, 1.8]	15 (9.9) 1.2 [0.7, 2.3]	0 NE
Adjusted Odds Ratio		1.0 [0.6, 1.7]	0.8 [0.3, 1.8]	1.2 [0.6, 2.3]	NE
No Anti-depressant-Yes depression	152 (89.8)	33 (10.2) 0.8 [0.5, 1.1]	13 (4.0) 1.1 [0.6, 1.9]	17 (5.3) 0.6 [0.4, 1.1]	3 (0.9) 0.8 [0.3, 2.6]
Adjusted Odds Ratio		0.7 [0.5, 1.7]	1.0 [0.5, 1.7]	0.6 [0.4, 1.0]	0.8 [0.2, 2.5]
No Anxiolytic-No Anxiety	8232 (87.1)	2195 (12.9)	608 (3.8)	1329 (8.1)	192 (1.1)
Anxiolytic Pre-Pregnancy	1036 (82.7)	383 (17.3) 1.4 [1.2, 1.6]	146 (6.4) **1.8 [1.5, 2.2]***	210(9.5) 1.2 [1.1, 1.5]	27 (1.3) 1.3 [0.8, 2.0]
Adjusted Odds Ratio		1.3 [1.2, 1.5]	**1.7 [1.4, 2.1]***	1.1 [1.0, 1.4]	1.3 [0.8, 2.0]
Anxiolytic Continued	150 (81.5)	64 (18.5) 1.5 [1.1, 2.1]	35 (9.9) **2.8 [1.9, 4.1]***	24 (7.2) 0.9 [0.6, 1.5]	5 (1.4) 1.4 [0.6, 3.5]
Adjusted Odds Ratio		1.4 [1.0, 1.9]	**2.6 [1.8, 3.8]***	0.9 [0.6, 1.4]	1.4 [0.6, 3.5]
Anxiolytic Pregnancy Initiated	61 (76.6)	32 (23.4) 2.1 [1.3, 3.3]	6 (4.6) 1.4 [0.6, 3.4]	26 (18.8) **2.6 [1.6, 4.3]***	0 NE
Adjusted Odds Ratio		2.0 [1.3, 3.2]	1.4 [0.5, 3.4]	**2.5 [1.5, 4.1]***	
No Anxiolytic-Yes Anxiety	377 (87.1)	94 (12.9) 1.0 [0.8, 1.3]	31 (3.7) 1.0 [0.7, 1.4]	55 (8.1) 1.0 [0.7, 1.4]	8 (1.1) 1.0 [0.5, 2.1]
Adjusted Odds Ratio		1.0 [0.8, 1.3]	1.0 [0.7, 1.5]	1.0 [0.7, 1.3]	1.0 [0.5, 2.2]

[1] Weighted for study sampling scheme; + p-value = 0.10 * p-value <0.05; Adjusted Odds Ratio: adjusted for maternal age, race, education and parity

Table 18 Sensitivity analyses excluding women with SNRI use (N=358), unadjusted and adjusted associations of maternal depression/anxiety diagnosis with hypertension disorder subtypes[1]

	No HTN	AnyHTN	Chronic HTN	Pregnancy HTN	Unspecified HTN
	N= 9629	N=2660	N= 851	N= 1584	N= 225
	N Wt%	N Wt% OR 95%CI	N Wt% OR 95%CI	N Wt% OR 95%CI	N Wt% OR 95%CI
No Depression	8873 (86.7)	2426 (13.3)	775 (4.0)	1442 (8.2)	209 (1.1)
One depression-related visit in≥1 time point	314 (84.1)	107 (15.9) 1.2 [1.0, 1.6]+	32 (4.3) 1.1 [0.8, 1.6]	66 (10.1) **1.2 [1.0, 1.7]***	9 (1.4) 1.3 [0.6, 2.8]
Adjusted Odds Ratio		1.3 [1.0, 1.6]+	1.2 [0.8, 1.8]	1.2 [0.9, 1.7]	1.4 [0.7, 3.0]
Met depression criteria Pre-LMP	406 (86.6)	119 (13.4) 1.0 [0.8, 1.3]	42 (4.8) **1.2 [0.9, 1.7]***	71 (7.8) 1.0 [0.7, 1.3]	6 (0.8) 0.7 [0.3, 1.7]
Adjusted Odds Ratio		1.0 [0.8, 1.2]	**1.3 [0.9, 1.8]***	0.9 [0.7, 1.2]	0.7 [0.4, 1.8]
Met depr criteria for the first time in pregnancy	36 (89.5)	8 (10.5) 0.8 [0.4, 1.7]	2 (2.6) 0.6 [0.2, 2.6]	5 (6.6) 0.8 [0.3, 2.0]	1 (1.1) 1.1 [0.2, 8.3]
Adjusted Odds Ratio		0.6 [0.3, 1.4]	0.5 [0.1, 2.3]	0.7 [0.2, 1.8]	1.1 [0.1, 8.1]
No Anxiety	8679 (86.8)	2366 (13.2)	744 (4.0)	1420 (8.2)	202 (1.1)
One anxiety-related visit ≥1 time point	384 (84.0)	132 (15.9) 1.2 [1.0, 1.5]	52 (5.8) 1.5 [1.1, 2.1]+	69 (8.7) 1.1 [0.8, 1.5]	11 (1.4) 1.3 [0.7, 2.5]
Adjusted Odds Ratio		1.2 [1.0, 1.5]	1.6 [1.1, 2.1]+	1.1 [0.8, 1.4]	1.4 [0.7, 2.6]
Met anxiety criteria Pre-LMP	497 (85.9)	144 (14.1) 1.1 [0.9, 1.3]	48 (4.3) 1.1 [0.8, 1.5]	86 (8.9) 1.1 [0.9, 1.4]	10 (0.9) 0.8 [0.4, 1.5]
Adjusted Odds Ratio		1.1 [0.9, 1.3]	1.1 [0.8, 1.5]	1.1 [0.8, 1.4]	0.8 [0.4, 1.5]
Met anx criteria for the first time in pregnancy	69 (87.0)	18 (13.0) 1.0 [0.6, 1.7]	7 (4.3) 1.1 [0.5, 2.4]	9 (6.6) 0.8 [0.4, 1.7]	2 (2.0) 1.8 [0.4, 8.4]
Adjusted Odds Ratio		1.0 [0.6, 1.7]	1.2 [0.5, 2.6]	0.8 [0.4, 1.7]	1.9 [0.4,8.5]

[1] Weighted for study sampling scheme; + p-value = 0.10 * p-value <0.05; Adjusted Odds Ratio: adjusted for maternal age, race, education and parity

Table 19 Sensitivity analyses excluding women with SNRI use (N=358), unadjusted and adjusted associations of maternal depression/anxiety overlap with hypertension disorder subtypes[1]

	No HTN	AnyHTN	Chronic HTN	Pregnancy HTN	Unspecified HTN
	N= 9629	N=2660	N= 851	N= 1584	N= 225
	N Wt%	N Wt% OR 95%CI	N Wt% OR 95%CI	N Wt% OR 95%CI	N Wt% OR 95%CI
No depression/anxiety	8174 (86.8)	2214 (13.2)	692 (3.9)	1331 (8.2)	191 (1.1)
DeprOne visit≥1 time pt_noanx	224 (85.4)	70 (14.6) 1.1 [0.8, 1.5]	23 (4.5) 1.2 [0.7, 1.9]	40 (8.6) 1.1 [0.7, 1.6]	7 (1.5) 1.3 [0.6, 3.1]
Adjusted Odds Ratio		1.1 [0.8, 1.5]	1.3 [0.8, 2.1]	1.0 [0.7, 1.5]	1.4 [0.6, 3.3]
Depression Pre-LMP-no anxiety	261 (86.0)	78 (14.0) 1.1 [0.8, 1.4]	29 (5.4) 1.4 [0.9, 2.1]	46 (8.1) 1.0 [0.7, 1.4]	3 (0.5) 0.4 [0.1, 1.4]
Adjusted Odds Ratio		1.0 [0.8, 1.4]	1.4 [0.9, 2.2]	1.1 [0.8, 1.5]	0.4 [0.1, 1.4]
Depression in pregnancy-no anxiety	20 (91.1)	4 (8.9) 0.6 [0.2, 1.9]	0 NE	3 (6.7) 0.8 [0.2, 2.7]	1 (2.2) 1.9 [0.2, 14.2]
Adjusted Odds Ratio		0.5 [0.1, 1.5]	NE	0.5 [0.1, 2.2]	1.8 [0.2, 13.9]
No depression-any anxiety	699 (85.3)	212 (14.7) 1.1 [1.0, 1.3]	83 (5.3) **1.4 [1.1, 1.8]***	111 (8.2) 1.0 [0.8, 1.3]	18 (1.1) 1.1 [0.6, 1.7]
Adjusted Odds Ratio		1.1 [0.9, 1.3]	**1.4 [1.1, 1.8]***	1.0 [0.8, 1.2]	1.1 [0.6, 1.7]
Any depression-anxiety overlap	251 (85.1)	82 (14.9) 1.2 [0.9, 1.5]	24 (4.0) 1.0 [0.7, 1.6]	53 (9.7) 1.2 [0.9, 1.7]	5 (1.3) 1.2 [0.4, 3.1]
Adjusted Odds Ratio		1.2 [0.9, 1.5]	1.1 [0.8, 1.7]	1.2 [0.8, 1.6]	1.3 [0.5, 3.3]
No Anxiety/depression	8174 (86.8)	2214 (13.2)	692 (3.9)	1331 (8.2)	191 (1.1)
Anxiety 1visit≥1 time pt/no depr	291 (84.8)	97 (15.2) 1.2 [0.9, 1.5]	40 (6.0) **1.6 [1.1, 2.2]+**	48 (7.9)1.0 [0.7, 1.4]	9 (1.4) 1.3 [0.6, 2.5]
Adjusted Odds Ratio		1.2 [0.9, 1.5]	1.6 [1.1, 2.2]+	1.0 [0.7, 1.3]	1.3 [0.6, 2.5]
Anxiety-Pre-LMP/no depr	359 (85.7)	101 (14.3) 1.1 [0.9, 1.4]	37 (4.8) 1.2 [0.9, 1.8]	56 (8.5) 1.1 [0.8, 1.5]	8 (1.0) 0.9 [0.4, 1.9]
Adjusted Odds Ratio		1.1 [0.8, 1.4]	1.2 [0.8, 1.7]	1.0 [0.7, 1.4]	0.9 [0.4, 1.9]
Anxiety in pregnancy – no depr	49 (86.2)	14 (13.7) 1.0 [0.6, 2.0]	6 (5.3) 1.4 [0.6, 3.2]	7 (7.6) 0.9 [0.4, 2.2]	1 (0.9) 0.8 [0.1, 5.8]
Adjusted Odds Ratio		1.1 [0.6, 2.0]	1.4 [0.6, 3.3]	0.9 [0.4, 2.2]	0.8 [0.1, 5.8]
No anxiety-Any depression	505 (85.9)	152 (14.1) 1.0 [0.9, 1.3]	52 (4.8) 1.2 [0.9, 1.7]	89 (8.3) 1.0 [0.8, 1.3]	11 (1.0) 0.9 [0.5, 1.7]
Adjusted Odds Ratio		1.1 [0.9, 1.3]	1.3 [1.0, 1.8]	0.9 [0.7, 1.2]	0.9 [0.5, 1.8]
Any depression-anxiety-overlap	251 (85.1)	82 (14.9) 1.2 [0.9, 1.5]	24 (4.0) 1.0 [0.7, 1.6]	53 (9.7)1.2 [0.9, 1.7]	5 (1.3) 1.1 [0.4, 3.1]
Adjusted Odds Ratio		1.2 [0.9, 1.5]	1.1 [0.7, 1.8]	1.2 [0.8, 1.6]	1.3 [0.5, 3.3]

Table 20 Sensitivity analyses excluding women with SNRI use (N=358), unadjusted and adjusted associations of maternal anti-depressant /anxiolytic and depression/anxiety status with hypertension disorder subtypes[1].

	No HTN[2]	AnyHTN[3]	Chronic HTN[4]	Pregnancy HTN[5]	Unspecified HTN[6]
	N= 9629	N=2660	N= 851	N= 1584	N= 225
	N Wt%	N Wt% OR 95%CI	N Wt% OR 95%CI	N Wt% OR 95%CI	N Wt% OR 95%CI
No Anti-depressant-No Depression	7948 (87.3)	2069 (12.7)	633 (3.7)	1254 (8.0)	182 (1.1)
Anti-depressant Pre-Pregnancy	931 (83.3)	341 (16.7) **1.4 [1.2, 1.6]***	125 (5.8) **1.7 [1.4, 2.1]***	187 (9.5) 1.2 [1.0, 1.5]	29 (1.4) 1.4 [0.9, 2.1]
Adjusted Odds Ratio		**1.4 [1.2, 1.6]***	**1.8 [1.4, 2.2]***	1.2 [1.0, 1.4]	1.5 [0.9, 2.2]
Anti-depressant Continued	515 (82.6)	196 (17.4) **1.4 [1.2, 1.7]***	74 (6.5) 1**.9 [1.4, 2.4]***	111 (10.0) 1.3 [1.1, 1.7]	11 (0.9) 0.9 [0.5, 1.6]
Adjusted Odds Ratio		**1.4 [1.2, 1.7]***	1**.8 [1.4, 2.3]***	1.4 [1.1, 1.7]	0.9 [0.5, 1.6]
Anti-depressant-Pregnancy Initiated	83 (87.3)	21 (12.7) 1.0 [0.6, 1.7]	6 (2.8) 0.8 [0.3, 1.8]	15 (9.9) 1.2 [0.7, 2.3]	0 NE
Adjusted Odds Ratio		1.0 [0.6, 1.7]	0.8 [0.3, 1.9]	1.2 [0.6, 2.2]	NE
No Anti-depressant-Yes depression	152 (89.8)	33 (10.2) 0.8 [0.5, 1.1]	13 (4.0) 1.1 [0.6, 1.9]	17 (5.3) 0.6 [0.4, 1.1]	3 (0.9) 0.8 [0.3, 2.6]
Adjusted Odds Ratio		0.7 [0.5, 1.7]	1.0 [0.5, 1.7]	0.6 [0.4, 1.0]	0.8 [0.2, 2.5]
No Anxiolytic-No Anxiety	8136 (87.2)	2144 (12.8)	653 (3.7)	1301 (8.0)	190 (1.1)
Anxiolytic Pre-Pregnancy	962 (82.9)	350 (17.0) 1.4 [1.2, 1.6]	135 (6.4) 1.8 [1.5, 2.2]+	191 (9.3) 1.2 [1.0, 1.5]	24 (1.3) 1.2 [0.8, 1.9]
Adjusted Odds Ratio		1.3 [1.1, 1.5]	1.8 [1.5, 2.2]+	1.1 [0.9, 1.3]	1.2 [0.8, 2.0]
Anxiolytic Continued	124 (82.0)	50 (18.0) 1.5 [1.1, 2.1]	29 (10.2) **2.9 [1.9, 4.5]***	17 (6.4) 0.9 [0.5, 1.4]	4 (1.4) 1.4 [0.5, 3.8]
Adjusted Odds Ratio		1.4 [1.0, 1.9]	**2.6 [1.7, 4.0]***	0.8 [0.5, 1.3]	1.4 [0.5, 3.8]
Anxiolytic Pregnancy Initiated	56 (75.7)	31 (24.2) **2.2 [1.4, 3.5]***	5 (4.2) 1.3 [0.5, 3.5]	26 (20.0) **2.9 [1.7, 4.7]***	0 NE
Adjusted Odds Ratio		**2.1 [1.3, 3.4]***	1.3 [0.5, 3.5]	**2.7 [1.7, 4.5]***	
No Anxiolytic-Yes Anxiety	351 (87.5)	85 (12.5)1.0 [0.7, 1.3]	29 (3.7) 1.0 [0.7, 1.5]	49 (7.7) 1.0 [0.7, 1.3]	7(1.0) 0.9 [0.4, 2.1]
Adjusted Odds Ratio		1.0 [0.7, 1.3]	1.0 [0.7, 1.6]	0.9 [0.7, 1.3]	1.0 [0.4, 2.2]

[1] Weighted for study sampling scheme; + p-value = 0.10 * p-value <0.05; Adjusted Odds Ratio: adjusted for maternal age, race, education and parity

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