The Contribution of Untreated and Treated Anxiety and Depression to Prenatal, Intrapartum, and Neonatal Outcomes

Dotun Ogunyemi, MD[1,2] Andrew Jovanovski, MD[2] James Liu, MD[1,2] Perry Friedman, MD[1,2] Nathaniel Sugiyama, MD[3] James Creps[2] Ichchha Madan, MD[1,2]

[1] Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Beaumont Hospital, Royal Oak, Michigan
[2] Department of Obstetrics and Gynecology, Oakland University, William Beaumont School of Medicine, Rochester Hills, Michigan
[3] University of Vermont Robert Larner College of Medicine, Burlington, Vermont

Address for correspondence Dotun Ogunyemi, MD, System Vice Chair of Patient Safety and Quality, Beaumont Health, MFM Fellowship Director, Beaumont Hospital, Royal Oak, Professor, Oakland University, William Beaumont School of Medicine, 3601 West 13 mile rd. Royal Oak, MI 48073 (e-mail: dogunye@outlook.com).

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Abstract

Objective To determine independent perinatal associations of anxiety and depression in women who were and were not treated with psychotropic drugs in comparison to unaffected pregnancies.

Study Design From 2013 to 2014, 978 (6.3%) cases of anxiety/depression, of which 35% used psychotropic drugs, were compared with 14,514 (93.7%) unaffected pregnancies using logistic regression.

Results Subjects were more likely to be Non-Hispanic Whites, use tobacco and illegal substances, be unmarried, use public insurance, and have medical complications of pregnancy. For independent maternal outcomes, untreated anxiety/depression was associated with labor induction (adjusted odds ratio [aOR] = 2.02), cesarean deliveries (aOR = 1.69), longer length of stay (aOR = 1.96), readmission (aOR = 2.40), fever (aOR = 2.03), magnesium exposure (aOR = 1.82), and postpartum hemorrhage (aOR = 2.57), whereas treated cases were associated with increased blood transfusion (aOR = 4.81), severe perineal lacerations (aOR = 2.93), and postpartum hemorrhage (aOR = 3.85), but decreased risk of cesarean deliveries (aOR = 0.59). Independent neonatal outcomes included small for gestational age (aOR = 3.04), meconium-stained fluid (aOR = 1.85; 2.61), respiratory failure (aOR = 5.84), neonatal adaptation syndrome (aOR = 11; 10.2), and neonatal seizures (aOR = 12.3) in treated cases, whereas untreated cases were associated with hypoxia (aOR = 2.83), low Apgar score (aOR = 3.82), and encephalopathy (aOR = 18.3). Exposure to multiple psychotropic medications independently increased the risk of neonatal adaptation syndrome, neonatal length of stay, and hypoglycemia.

Conclusion Untreated cases were associated with increased maternal adverse outcomes, whereas treated cases were associated with more adverse neonatal outcomes when compared with unaffected pregnancies.

Keywords
- anxiety
- depression
- psychotropic medication
- maternal outcome
- neonatal outcome
- neonatal adaptation syndrome

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Identifying risk factors for mental disorders that may affect pregnancy is an important prerequisite in developing interventions to lower adverse maternal and neonatal outcomes. The estimated prevalence of perinatal anxiety and depression varies in published studies and is estimated to be between 7 and 20%.[1,2] Previous studies have reported associations of perinatal anxiety and depression with obstetrical and neonatal factors such as substance abuse, socioeconomic factors, and medical complications of pregnancy, small for gestational age (SGA),[1–5] and postpartum depression. However, lacking from the literature are comprehensive reports from the same cohort simultaneously studying prenatal, intrapartum, and neonatal outcomes to assess associations of untreated and treated anxiety and depression in comparison to unaffected pregnancies.

An important consideration is the medical management of these mental disorders in pregnancy and the potential consequences.[6] Hanley et al estimated that 10.3% of all pregnancies may have some exposure to psychotropic medications.[6] Currently, psychotropic medications require more extensive risk–benefit analyses to determine efficacy and safety in pregnancy. For example, evidence from a large study of publicly insured pregnant women[7] and a recent meta-analysis[8] are consistent with a potential increased risk of persistent pulmonary hypertension associated with maternal use of selective serotonin reuptake inhibitors (SSRIs) in late pregnancy. However, the absolute risk was noted to be small, and the risk increase appears more modest than suggested in previous studies. Other studies have shown a significantly increased risk of spontaneous abortion, preterm birth, and low birth weight. All of the observed risks were of a very low magnitude, and the clinical significance of these results is unknown.[9] However, benefits of antidepressant medication in pregnancy include prevention of possible relapse of illness, with resultant hospital admission and suicidal ideations.[9] Consequently, studies analyzing the interactive effect of psychotropic treatment on mental disorders with obstetrical and neonatal outcomes are required for counseling and clinical management.

Therefore, the objectives of this study were (1) to determine the independent prenatal, intrapartum, and neonatal correlates of pregnancies affected by depression and anxiety and (2) to evaluate the differences in outcomes between cases of depression and anxiety treated and not treated with psychotropic medications when compared with unaffected pregnancies.

Materials and Methods

This was a retrospective cohort study of all women with singleton pregnancies and their newborns who delivered from January 1, 2013, through December 31, 2014, in the Beaumont Health System. An obstetrical outcomes database was developed using a combination of International Classification of Diseases, ninth edition (ICD-9), coding and direct querying of the electronic medical record. The extracted data were audited and verified by manual chart review as indicated. The database included a maximum of 18 months hospital follow-up data.

Beaumont Health is a not-for-profit health system located in suburban southeastern Michigan and services a diverse population of approximately 5 million, comprising Non-Hispanic Whites (68.5%), Blacks (21.6%), Asians (3.6%), and Hispanics (3.9%).

Cases of anxiety and depression were retrieved using the ICD-9 codes 293.84, 300.00, 300.01, 300.02, and 300.09 for anxiety and 296.2, 296.3, and 311 for depression (please refer to the ►**Appendix A** for more details). A comprehensive manual chart review was completed on all women identified as having depression or anxiety to determine treatment with psychotropic medications during the antepartum period. This was accomplished by review of the admission history, and physical activity as well as medication prescription during the hospital admission. Those who had a positive history and were prescribed psychotropic medication during the hospital admission were classified as "treated," whereas those who were not prescribed medication during the hospital admission were classified as "untreated." Cases of treated and untreated anxiety, depression, and comorbid anxiety and depression were compared with unaffected pregnancies regarding various prenatal, intrapartum, and maternal and neonatal factors and outcomes that were selected based on literature reviews and biological plausibility.

Prenatal factors that were analyzed included maternal age, body mass index, gestational age, self-reported race or ethnicity, parity, marital status, medical insurance type, tobacco use, drug use, diabetes (gestational and pregestational), hypertensive disorders (chronic hypertension, gestational hypertension, severe preeclampsia, and superimposed preeclampsia), and previous cesarean delivery.

Intrapartum and maternal factors included induction of labor, exposure to cervical ripening agents (misoprostol, dinoprostone, oxytocin, and Foley catheter), abnormal fetal heart rate (ICD-9 code 659.71), systolic and diastolic blood pressures, pulse rate, temperature, exposure to intravenous antibiotics (gentamicin or clindamycin), exposure to intravenous antihypertensive medications (labetalol and hydralazine), exposure to magnesium, exposure to insulin, preterm birth less than 37 weeks' gestation, type of delivery, severe perineal laceration, chorioamnionitis, placental abruption, postpartum hemorrhage, blood transfusion, postpartum readmission, preterm rupture of membranes, shoulder dystocia, and length of stay (LOS).

Neonatal variables included infant sex, birth weight, Apgar scores, meconium-stained amniotic fluid, birth defects, admission to the neonatal intensive care unit (NICU), sepsis, persistent pulmonary hypertension, respiratory failure, hypoxia, hypoglycemia, seizure, encephalopathy, abstinence syndrome, umbilical arterial and venous blood gases, LOS, and a composite neonatal adverse outcome consisting of 5-minute Apgar score less than 4, umbilical artery pH less than 7, umbilical artery base excess greater than –12, sepsis, seizures, encephalopathy, and respiratory failure. Please refer to the Appendix for a complete list of ICD-9 codes used.

Univariate analyses of associations between maternal and neonatal factors and psychiatric diagnoses were performed by Student's *t*-test and chi-square test for continuous and categorical data, respectively. The associations that were significant on univariate analysis were further evaluated by multinomial logistic regression comparing each group to the unaffected referent pregnancies to calculate adjusted odds ratios (aORs) controlling for baseline differences. Because of the large numbers of cases and to assure clinical relevance, we only reported odds ratios greater than or equal to 1.5 or less than 0.9. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). This study was approved by our hospital's institutional review board.

Results

A total of 19,072 unique maternal–neonatal pairs were assessed for eligibility. Of these, 915 were excluded for multiple gestations and 2,665 for incomplete records, the majority of which were because of missing cord gas results. The remaining 15,492 (81.2%) deliveries were analyzed for this study. Of these, depression or anxiety was present in 978 (6.3%), including anxiety alone ($n = 453$; 2.9%), depression alone ($n = 305$; 2%), and comorbid depression and anxiety ($n = 220$; 1.4%). These cases were further subdivided based on treatment with psychotropic medications as follows: treated anxiety alone ($n = 101$), treated depression alone ($n = 123$), treated comorbid depression and anxiety ($n = 92$), untreated anxiety alone ($n = 351$), untreated depression alone ($n = 182$), and untreated comorbid depression and anxiety ($n = 129$). These groups were compared with the 14,514 (93.7%) unaffected reference pregnancies.

Considering significant maternal characteristics, patients with anxiety and depression were more likely to self-report as Non-Hispanic Whites, use tobacco and illegal substances, and be unmarried. Additionally, both treated depression and untreated depression were associated with public health insurance, multiparity, and hypertension. Both treated and untreated comorbid anxiety and depression were associated with hypertension, whereas treated comorbid anxiety and depression were associated with diabetes and untreated with public insurance. Only untreated anxiety was associated with decreased odds of previous cesarean delivery. Maternal age, body mass index, gestational age, and infant gender were similar across groups (►**Table 1**).

Significant independently associated intrapartum and maternal factors are listed in ►**Table 2**. This shows that untreated anxiety was associated with increased risks of cesarean deliveries (aOR = 1.69), induction of labor (aOR = 2.02), and longer maternal LOS (aOR = 1.85), risks not present among patients with treated anxiety. Those with untreated depression had higher odds of magnesium exposure (aOR = 1.82) and readmission within 6 weeks of delivery (aOR = 2.40), whereas treated depression was associated with decreased odds of cesarean delivery (aOR = 0.59) but increased odds of requiring a blood transfusion (aOR = 4.81). Untreated comorbid anxiety and depression were associated with increased risks of cesarean delivery (aOR = 1.59), fever $> 38°C$ (aOR = 2.03), postpartum hemorrhage (aOR = 2.57), and maternal LOS (aOR = 1.96), whereas treated comorbid anxiety and depression were associated with increased risks of severe perineal lacerations (aOR = 2.93) and postpartum hemorrhage (aOR = 3.85). There were no significant associations with abnormal fetal heart rate ICD-9 code, systolic or diastolic blood pressure, pulse rate, exposure to intravenous antibiotics, exposure to intravenous antihypertensive medications, insulin therapy, preterm birth before 37 weeks' gestation, operative vaginal delivery, chorioamnionitis, placental abruption, preterm rupture of membranes, and shoulder dystocia.

Significant independent associations of neonatal outcomes are listed in ►**Table 3**. This showed that untreated anxiety was associated with 5-minute Apgar score < 4 (aOR = 3.82) whereas treated anxiety was associated with meconium-stained amniotic fluid (aOR = 1.85), respiratory failure (aOR = 5.84), and neonatal abstinence syndrome (aOR = 11). Neonates of mothers with untreated depression had increased odds of hypoxia (aOR = 2.83), but treated depression was associated with neonatal seizures (aOR = 12.3) and neonatal abstinence syndrome (aOR = 10.2). Untreated comorbid anxiety and depression were associated with encephalopathy (aOR = 15), whereas treated comorbid disease was associated with increased odds of being SGA (aOR = 3.04), meconium-stained amniotic fluid (aOR = 2.61), arterial base excess greater than –12 (aOR = 3.42), and venous base excess greater than –12 (aOR = 5.62). There were no significant differences in admission to the NICU, birth defects, persistent pulmonary hypertension, sepsis, hypoglycemia, arterial and venous pH < 7, LOS, and the neonatal composite adverse outcome.

Psychotropic medications were used by 339 subjects (34.6%). The most common medications were SSRIs ($n = 271$; 79.9%), benzodiazepines ($n = 54$; 15.9%), and other antidepressants ($n = 35$; 10.3%). Other medications included serotonin–norepinephrine reuptake inhibitors ($n = 18$; 5.7%), antiepileptics ($n = 13$; 4.4%), and antipsychotics ($n = 10$; 3.2%). A single drug was used by 285 (84.1%) and multiple drugs by 54 (15.9%). We did a subanalysis and compared those with multiple drugs (polypharmacy) with those who used single psychotropic drugs regarding neonatal outcomes. On univariate analysis, neonates born of mothers with multiple prenatal psychotropic drug use were significantly more likely to be SGA and have neonatal hypoglycemia, neonatal abstinence syndrome, NICU admission, and longer neonatal LOS; however, on adjusted regression analysis, NICU admission and neonatal LOS were no longer significant (►**Table 4**)

Discussion

In this hospital system, the prevalence of anxiety and depression overall was 6.3%, which is somewhat lower than observed in other studies.[6] This is probably because most previous reports used self-reported screening instruments in the identification of cases—a process that may overestimate with a resultant higher prevalence in comparison to this study, which used ICD-9 coding and detailed chart review for identification of cases.[1,10] However, the low

Table 1 Baseline characteristics of patients with anxiety and depression ($n = 978$) compared with unaffected reference pregnancies ($n = 14,514$)

Variable	Anxiety, untreated ($n = 351$)	Anxiety, treated ($n = 101$)	Depression, untreated ($n = 182$)	Depression, treated ($n = 123$)	Comorbid depression and anxiety, untreated ($n = 129$)	Comorbid depression and anxiety, treated ($n = 92$)	Unaffected ($n = 14,514$)
Maternal age (y)	31.8 ± 5.5	31.4 ± 5	29.7 ± 5.8	31.5 ± 6.1	29.9 ± 5.4	32.3 ± 5.5	31 ± 5.2
Body mass index (kg/m^2)	31.6 ± 6.2	32 ± 6.8	33.2 ± 6.8	32.5 ± 5.3	33.1 ± 7.1	32.1 ± 6.9	31.5 ± 6.1
Gestational age (wk)	39 ± 2.2	38.6 ± 2.6	38.7 ± 2.7	38.3 ± 2.2	38.8 ± 2.7	38.3 ± 2.4	39.1 ± 1.7
White race	279 (79.5) **1.91 (1.47–2.48)**[a]	88 (87.1) **3.33 (1.86–5.97)**[a]	123 (67.6)	99 (80.5) **2.03 (1.30–3.18)**[b]	103 (79.8) **1.95 (1.30–3.18)**[b]	80 (87) **3.28 (1.79–6.02)**[b]	9,726 (67)
Nulliparous	174 (49.6)	49 (48.5)	60 (33) **0.67 (0.49–0.91)**[c]	40 (32.5) **0.66 (0.45–0.96)**[c]	62 (48.1)	40 (43.5)	6,154 (42.4)
Married	257 (73.2) **0.71 (0.56–0.90)**[b]	73 (72.3)	111 (61) **0.40 (0.30–0.55)**[a]	82 (66.7) **0.52 (0.36–0.75)**[b]	74 (57.4) **0.35 (0.25–0.49)**[a]	65 (70.7)	11,533 (79.5)
Public insurance	72 (20.5)	23 (22.8)	79 (43.4) **2.60 (1.93–3.49)**[a]	40 (32.5) **1.63 (1.12–2.38)**[c]	44 (34.1) **1.75 (1.21–2.53)**[b]	28 (30.4)	3,312 (22.8)
Tobacco use	34 (9.7) **2.30 (1.60–3.30)**[a]	13 (12.9) **3.17 (1.76–5.70)**[a]	21 (11.5) **2.80 (1.76–4.44)**[a]	18 (14.6) **3.68 (2.22–6.10)**[a]	20 (15.5) **3.85 (2.17–6.83)**[a]	14 (15.2) **3.93 (2.43–6.38)**[a]	647 (4.5)
Drug use	20 (5.7) **2.77 (1.74–4.41)**[a]	8 (7.9) **3.94 (1.90–8.19)**[a]	21 (11.5) **5.98 (3.74–9.55)**[a]	5 (4.1)	20 (15.5) **8.41 (5.15–13.7)**[a]	15 (16.3) **8.93 (5.08–15.7)**[a]	310 (2.1)
Diabetes	24 (6.8)	13 (12.9)	17 (9.3)	9 (7.3)	13 (10.1)	13 (14.1) **1.90 (1.05–3.42)**[c]	1,158 (8)
Hypertension	56 (16)	17 (16.8)	33 (18.1) **1.63 (1.12–2.39)**[c]	22 (17.9) **1.61 (1.01–2.55)**[c]	26 (20.2) **1.86 (1.21–2.87)**[b]	21 (22.8) **2.18 (1.34–3.56)**[b]	1,734 (12)
Previous cesarean	53 (15.1) **0.67 (0.50–0.90)**[a]	16 (15.8)	43 (23.6)	28 (22.8)	25 (19.4)	22 (23.9)	3,043 (21)
Male infant	171 (48.7)	41 (40.6)	98 (53.9)	62 (50.4)	60 (46.5)	45 (48.9)	7,626 (52.5)

Note: Data are presented as mean ± standard deviation or *n* (%) and odds ratio (95% confidence interval).
[a] $p < 0.0001$.
[b] $p < 0.01$.
[c] $p < 0.05$.

Table 2 Intrapartum and maternal factors independently associated with anxiety and depression ($n = 978$) compared with unaffected reference pregnancies ($n = 14,514$)

Variable	Anxiety, untreated ($n = 351$)	Anxiety, treated ($n = 101$)	Depression, untreated ($n = 182$)	Depression, treated ($n = 123$)	Comorbid depression and anxiety, untreated ($n = 129$)	Comorbid depression and anxiety, treated ($n = 92$)	Unaffected ($n = 14,514$)
Induction of labor	96 (27.4) **2.02 (1.56–2.61)**[a]	18 (17.8)	32 (17.6)	18 (14.6)	25 (19.4)	19 (20.7)	2,229 (15.4)
Fever > 38°C	16 (4.6)	3 (3)	10 (5.5)	4 (3.3)	11 (8.7) **2.03 (1.07–3.86)**[b]	4 (4.4)	618 (4.3)
Magnesium exposure	25 (7.2)	7 (6.9)	21 (11.5) **1.82 (1.04–3.20)**[b]	6 (4.9)	8 (6.3)	8 (8.8)	719 (5)
Cesarean delivery	167 (47.6) **1.69 (1.31–2.18)**[a]	42 (41.6)	70 (38.5)	41 (33.3) **0.59 (0.36–0.96)**[b]	64 (49.6) **1.59 (1.04–2.42)**[b]	35 (38)	5,862 (40.4)
Severe laceration	6 (1.7)	3 (2.9)	3 (1.7)	3 (2.4)	2 (1.5)	4 (4.5) **2.93 (1.02–8.38)**[b]	284 (2)
Postpartum hemorrhage	10 (2.9)	1 (1)	5 (2.8)	7 (5.7)	8 (6.2) **2.57 (1.23–5.35)**[b]	9 (9.8) **3.85 (1.90–7.82)**[c]	398 (2.7)
Blood transfusion	3 (0.9)	1 (0.9)	2 (1.1)	5 (4.1) **4.81 (1.86–12.4)**[c]	3 (2.3)	2 (2.2)	128 (0.9)
Readmission within 6 wk of delivery	6 (1.7)	4 (4)	7 (3.9) **2.40 (1.10–5.21)**[b]	1 (0.8)	4 (3.1)	2 (2.2)	229 (1.6)
Length of stay > 5 d	31 (8.8) **1.85 (1.21–2.84)**[b]	5 (5)	17 (9.3)	7 (5.7)	10 (7.8) **1.96 (1.07–3.61)**[b]	8 (8.7)	598 (4.1)

Note: Data are presented as *n* (%) and adjusted odds ratio (95% confidence interval). Adjusted for maternal age, body mass index, gestational age, race/ethnicity, parity, marital status, smoking status, and history of drug use. There were no significant associations for abnormal fetal heart rate ICD-9 (International Classification of Diseases) code, systolic or diastolic blood pressure, pulse rate, exposure to intravenous antibiotics, exposure to intravenous antihypertensive medications, insulin therapy, preterm birth <37 weeks' gestation, operative vaginal delivery, chorioamnionitis, placental abruption, preterm rupture of membranes, and shoulder dystocia.

[a] $p < 0.0001$.

[b] $p < 0.05$.

[c] $p < 0.01$.

Table 3 Neonatal outcomes independently associated with anxiety and depression ($n = 978$) compared with unaffected reference pregnancies ($n = 14,514$)

Variable	Anxiety, untreated ($n = 351$)	Anxiety, treated ($n = 101$)	Depression, untreated ($n = 182$)	Depression, treated ($n = 123$)	Comorbid depression and anxiety, untreated ($n = 129$)	Comorbid depression and anxiety, treated ($n = 92$)	Unaffected ($n = 14,514$)
Birth weight (g)	3,340 ± 617	3,220 ± 643	3,228 ± 670	3,156 ± 608	3,351 ± 653	3,036 ± 601 **0.89 (0.84–0.93)**[a]	3,383 ± 542
Small for gestational age	22 (6.3)	4 (4)	15 (8.2)	6 (4.9)	10 (7.8)	13 (14.1) **3.04 (1.63–5.70)**[b]	672 (4.6)
Five-minute Apgar score < 4	1 (0.3) **3.82 (3.23–4.52)**[a]	1 (1)	2 (1.1)	0 (0)	1 (0.8)	0 (0)	11 (0.1)
Meconium-stained amniotic fluid	47 (13.4)	18 (17.8) **1.85 (1.10–3.11)**[c]	25 (13.7)	18 (14.6)	16 (12.4)	21 (22.8) **2.61 (1.58–4.32)**[a]	1,705 (11.8)
Admission to neonatal intensive care unit	57 (16.2)	26 (25.7)	28 (15.4)	31 (25.2)	19 (14.7)	26 (28.3)	2,030 (14)
Birth defect	17 (4.8)	3 (2.9)	10 (5.5)	4 (3.3)	6 (4.7)	3 (3.3)	491 (3.4)
Persistent pulmonary hypertension	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	29 (0.2)
Sepsis	2 (0.6)	0 (0)	2 (1.1)	0 (0)	1 (0.8)	0 (0)	20 (0.1)
Respiratory failure	1 (0.3)	2 (2) **5.48 (1.07–28.1)**[c]	2 (1.1)	0 (0)	0 (0)	1 (1.1)	32 (0.2)
Hypoxia	5 (1.4)	2 (2)	7 (3.9) **2.83 (1.15–7.01)**[c]	2 (1.6)	3 (2.3)	3 (3.3)	127 (0.9)
Hypoglycemia	17 (4.8)	11 (10.9)	11 (6)	13 (10.6)	6 (5.7)	9 (9.8)	736 (5.1)
Seizures	0 (0)	0 (0)	0 (0)	1 (0.8) **12.3 (1.28–119)**[c]	0 (0)	0 (0)	9 (0.1)
Encephalopathy	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8) **18.3 (2.16–156)**[c]	0 (0)	7 (0.1)
Adaptation syndrome	3 (0.9)	5 (5) **11 (3.41–35.7)**[a]	1 (0.6)	4 (3.3) **10.2 (2.98–34.7)**[b]	0 (0)	2 (2.2)	31 (0.2)
Arterial base excess greater than –12	5 (1.4)	1 (1)	0 (0)	0 (0)	2 (1.6)	3 (3.3) **3.42 (1.05–11.1)**[c]	124 (0.9)
Arterial pH < 7	2 (0.6)	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (1.1)	44 (0.3)
Venous base excess greater than –12	2 (0.6)	1 (1)	0 (0)	0 (0)	1 (0.8)	3 (3.4) **5.62 (1.63–19.4)**[b]	62 (0.4)
Venous pH < 7	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.1)	19 (0.1)
Length of stay > 3 d	47 (13.4)	14 (13.7)	25 (13.7)	17 (13.8)	18 (13.7)	18 (20.2)	1,409 (9.7)

(*Continued*)

Table 3 (*Continued*)

Variable	Anxiety, untreated ($n = 351$)	Anxiety, treated ($n = 101$)	Depression, untreated ($n = 182$)	Depression, treated ($n = 123$)	Comorbid depression and anxiety, untreated ($n = 129$)	Comorbid depression and anxiety, treated ($n = 92$)	Unaffected ($n = 14,514$)
Neonatal composite adverse outcome	9 (2.6)	4 (4)	4 (2.2)	1 (0.8)	4 (3.1)	4 (4.4)	168 (1.2)

Note: Data are presented as mean ± standard deviation or *n* (%) and adjusted odds ratio (95% confidence interval). For birth weight, the odds ratio refers to a 100-g increase. Adjusted for maternal age, body mass index, gestational age, race/ethnicity, parity, marital status, smoking status, history of drug use, and mode of delivery. Composite neonatal adverse outcome: 5-minute Apgar score < 4, umbilical arterial pH < 7, umbilical arterial base excess greater than −12, sepsis, seizures, encephalopathy, and respiratory failure.

[a] $p < 0.0001$.

[b] $p < 0.01$.

[c] $p < 0.05$.

prevalence noted in this study could also be because of potential misclassification of both "noncases" and "cases." It is likely that there are several missed cases of depression or anxiety in the reference group. The findings in this study support other previous reports showing associations between anxiety/depression and smoking, substance abuse, and unmarried status.[11–17] But in contrast to most other studies that have likewise shown associations with minority ethnic groups, our study showed an association with Non-Hispanic white women.[11–17] The increased risk of perinatal anxiety and depression in minority groups has been explained by stress-related discrimination in addition to financial and social disadvantages.[18] However, another report in support of our findings demonstrated higher levels of depression among White mothers compared with black and Hispanic mothers as well as women of other ethnicities.[19] As an explanation, other studies have demonstrated that prolonged and repeated exposure to adversity might provide minority women with greater resilience and skills to manage psychological distress in addition to having higher levels of social support, spirituality, and self-esteem resources.[20] Correspondingly, our study highlights that Non-Hispanic Whites may also be at increased risk of anxiety and depression during pregnancy and the need for universal screening of all pregnant women.

In this study, untreated prenatal anxiety and depression were associated with more adverse maternal outcomes than treated (7 vs. 3, respectively) when both groups were compared with those without anxiety and depression. Both prenatal anxiety and comorbid anxiety and depression when untreated were associated with an increased risk of cesarean birth, whereas treated depression demonstrated a decreased risk. A past history of cesarean delivery has been found to be associated with a high incidence of antenatal anxiety and depression.[21,22] However, our study did show a decreased risk of previous cesarean delivery with those with untreated anxiety. The association of anxiety with previous cesarean birth may not be very reliable since its validity would depend on the following: (1) if the patient did have a diagnosis of anxiety during the previous pregnancy and (2) if she was treated in that pregnancy. Our study's finding of increased risk of cesarean birth with untreated prenatal anxiety and depression with a corresponding decrease when treated is intriguing. Other studies have found no association between mode of delivery and antenatal depression,[23,24] whereas another previous study did show an association between untreated depression and cesarean section.[25] A recent systemic review showed that those requesting elective cesarean sections had higher antepartum depression and anxiety levels but no different postpartum depression levels than women who delivered vaginally.[26] It is important to note that in a Finnish study on major depression in pregnancy, after a history of depression, the second strongest associated factor for major depression was fear of childbirth, with a 2.6-fold increased prevalence.[10] Furthermore, other studies have shown that patients with antenatal anxiety and depression have a fear of childbirth and show a preference for an elective cesarean delivery.[1] These findings

Table 4 Significant associations of prenatal single versus multiple psychotropic drug use with neonatal outcomes ($n = 339$)

Neonatal factor	Single psychotropic drug, $n = 285$	Multiple psychotropic drugs, $n = 54$	Univariate p-value (OR)	Independent p-value (OR) [95%CI]
Male gender	134 (47%)	29 (53.7%)	ns	ns
Birth weight	3,058.86 (43.6)	2,877.17 (100.58)	ns	ns
Neonatal hypoglycemia	25 (8.8%)	11 (20.4%)	(2.66)[a]	(2.6) [1.04–6.55][a]
Neonatal abstinence syndrome	3 (1.1%)	8 (14.8%)	(16.348)[b]	(8.3) [1.72–39.9][c]
Admission to neonatal intensive care unit	80 (28.1%)	25 (46.3%)	(2.2)[a]	ns
SGA	18 (6.3%)	8 (14.8%)	(2.57)[a]	
Length of stay > 3 d	50 (17.5%)	22 (40.7%)	(3.23)[b]	(3.2) [1.15–9.09][a]

Abbreviations: CI, confidence interval; ns, not significant; OR, odds ratio; SGA, small for gestational age.
Note: There were no significant associations with the neonatal composite score, arterial pH < 7, venous base excess greater than –12, venous pH < 7, 5-minute Apgar score < 4, and meconium-stained amniotic fluid. The independent p-value was adjusted for maternal age, body mass index, gestational age, race/ethnicity, parity, marital status, smoking status, history of drug use, and mode of delivery.
[a] $p < 0.05$.
[b] $p < 0.0001$.
[c] $p < 0.01$.

suggest a need for greater attention to continuous assessment of psychological well-being among women, especially those requesting elective cesarean birth, as a potential intervention for the current major public health concern with the increasing prevalence of cesarean delivery. Further prospective studies are required to test this hypothesis.

In this study, treated prenatal anxiety and depression were also associated with more adverse neonatal outcomes than untreated cases (7 versus 3 respectively) when both groups were compared with those without anxiety and depression. The increased association of treatment of anxiety/depression with psychotropic drugs during pregnancy with neonatal adaptation syndrome supports previous findings.[9] Furthermore, treatment of comorbid anxiety and depression was associated with a threefold risk for SGA neonate, whereas there was no association with preterm birth. The impact of antidepressants on fetal growth has been evaluated with inconclusive results, with most studies reviewed lacking adequate control groups with heterogeneity of outcomes.[9] In contrast to our findings, a recent study demonstrated an association of a positive screen for depression using Edinburgh Postnatal Depression Scale (EPDS) with preterm birth and SGA, but it noted that such risk was not apparent among women who were treated with an antidepressant medication.[27] The difference in results may be partially explained by methodology since in our study we identified patients with depression or anxiety based on ICD-9 coding and we compared identified patients with depression or anxiety with those who were not unaffected based on the use of psychotropic drugs. In the aforementioned study, patients were identified by EPDS, and all patients who received antidepressants (either screen-positive or screen-negative) were compared with all those who did not use antidepressants (both screen-positive and screen-negative). Meconium-stained fluid, which is associated with intrauterine hypoxia, was also increased in treated cases in our study. Our findings and those of previous reports do support that psychotropic medications in pregnancy are associated with some neonatal morbidity.

It should also be noted that untreated anxiety and depression were not without neonatal morbidity and were associated with increased risks including low Apgar scores and neonatal hypoxia. It conceivable that the increased maternal morbidity associated with untreated anxiety and depression noted in this study and previous works can predispose to neonatal morbidity.[1,10,27,28] For example, maternal fever, which is a predictor of neonatal sepsis and morbidity, was only associated with untreated comorbid anxiety and depression. Furthermore, studies in pregnant women have shown increased relapse rates in those who discontinued their psychotropic medication during pregnancy, with increased risks of hospitalization and suicide ideation.[29,30] Neonatal adaptation syndrome, which is the main neonatal morbidity associated with antidepressant use, is known to be transient with the symptoms resolving within a week with no apparent long-term adverse effects.[9] Correspondingly, the risks associated with pharmacological treatment must be balanced with the effects of untreated antenatal maternal depression on the mother–fetus dyad, which have the potential to be devastating.

Limitations

There are several limitations to this study. This is a retrospective cohort study design, which has inherent limitations including missing data and accuracy of data. Specifically, the used of ICD-9 codes for identifying cases has intrinsic limitations, namely, accuracy of diagnostic code, potentially

nonactive diagnoses, and noncoded cases (i.e., unidentified cases). The latter is supported by the fact that the prevalence of anxiety/depression in our study (6.3%) is lower than that reported in the literature.[31] Additionally, there were no data regarding the adequacy of prenatal care, duration of anxiety and depression, and the level of control entering the pregnancy. However, we did manual review and audits of the charts for verification and confirmation of the data. We also performed multivariate logistic regression to eliminate potential confounders, but it is possible that there are other factors that were not measured. Such potential cofounders include quantity, timing, and duration of psychotropic medication therapy. We also did not assess postpartum depression; however, multiple studies have already confirmed the strong association of prenatal anxiety and depression with postpartum depression.[30] We also did not directly compare treated cases versus untreated cases of anxiety and depression, which would have provided differential effects of the exposure of medications, but compared against unaffected pregnancies to determine the baseline burden of disease and treatment. Moreover, there are always concerns with medication compliance, and modest associations regarding medication treatment and outcomes can be attributed to misclassification because nondifferential misclassification of the exposure or the outcome will tend to bias results toward the null hypothesis.[32,33] Another limitation is that many of the neonatal adverse outcomes such as respiratory failure, neonatal seizures, encephalopathy, low Apgar score, and abnormal blood gases had very small numbers with correspondingly very wide 95% confidence intervals. Hence, these findings, though significant, may not be clinically relevant. Furthermore, this is a single-system study in southeastern Michigan; therefore, the findings may not be applicable to different centers with different populations. Strengths of this study include assessment of a large cohort of mother–fetus dyads using uniform methodology and ascertainment of depression, anxiety, and maternal and neonatal outcomes by the electronic health record with detailed review, thus avoiding the risk of recall bias and overestimation seen in some earlier studies. Through detailed categorization of these pregnant women, we were able to control for important confounding variables associated with maternal and neonatal morbidity.

Conclusion

In contrast to the majority of previous studies, Non-Hispanic White mothers were at a greater risk of prenatal anxiety and depression in addition to other social disadvantaged factors, substance use, and medical disorders. Women with untreated anxiety and depression in pregnancy had more adverse maternal outcomes. Untreated anxiety appeared to be a risk factor for induction of labor and cesarean delivery. Treated patients with anxiety and depression had more neonatal adverse outcomes; however, untreated patients still had some neonatal morbidity presumably as a consequence of significant maternal morbidity. A third of women used psychotropic medications during pregnancy, with an increased risk of neonatal adaptation syndrome, which is known to be transient without long-time sequelae. The universal identification of women at risk of anxiety and depression during pregnancy may provide opportunities for therapy and promote well-being of mothers and babies.

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Appendix A ICD-9 codes

Diagnosis	Code	Description
Maternal		
Abnormal fetal heart rate	659.71	Abnormality in fetal heart rate or rhythm, delivered
Anxiety	293.84	Anxiety disorder in conditions classified elsewhere
	300.00	Anxiety state, unspecified
	300.01	Panic disorder without agoraphobia
	300.02	Generalized anxiety disorder
	300.09	Other anxiety states
Chorioamnionitis	658.4x	Infection of amniotic cavity
Depression	296.2x	Major depressive disorder, single episode
	296.3x	Major depressive disorder, recurrent episode
	311	Depressive disorder, not otherwise classified
Diabetes, gestational	648.8x	Abnormal maternal glucose tolerance
Diabetes, pregestational	250.x	Diabetes mellitus
	648.0x	Diabetes mellitus of the mother complicating pregnancy
Hypertension, chronic	401.x	Essential hypertension
	402.x	Hypertensive heart disease
	403.x	Hypertensive chronic kidney disease
	404.x	Hypertensive heart and chronic kidney disease
	405.x	Secondary hypertension
	642.0x	Benign essential hypertension complicating pregnancy
	642.1x	Hypertension secondary to renal disease complicating pregnancy
	642.2x	Other preexisting hypertension complicating pregnancy
Hypertension, gestational	642.3x	Transient hypertension of pregnancy
	642.4x	Mild or unspecified preeclampsia
	642.5x	Severe preeclampsia
	642.6x	Eclampsia
	642.7x	Preeclampsia or eclampsia superimposed on preexisting hypertension
	642.9x	Unspecified hypertension complicating pregnancy
Placental abruption	641.2x	Premature separation of the placenta
Postpartum hemorrhage	666.0x	Third-stage postpartum hemorrhage
	666.1x	Other immediate postpartum hemorrhage
	666.2x	Delayed and secondary postpartum hemorrhage
	666.3x	Postpartum coagulation defects
Preterm rupture of membranes	658.11	Premature rupture of membranes, delivered, with or without mention of antepartum condition
Previous cesarean	654.21	Previous cesarean delivery, delivered
Severe laceration	664.2x	Third-degree perineal laceration during delivery
	664.3x	Fourth-degree perineal laceration during delivery
Shoulder dystocia	660.4x	Shoulder (girdle) dystocia during labor and delivery
Neonatal		
Abstinence syndrome	292.0	Drug withdrawal
	779.5	Drug withdrawal syndrome in newborn

Appendix A (*Continued*)

Diagnosis	Code	Description
Maternal		
Birth defects	Numerous	http://www.mdch.state.mi.us/pha/osr/CHI/birthdefects/BXDefectCodeGroups.html
Encephalopathy	348.3x	Encephalopathy
	768.7x	Hypoxic–ischemic encephalopathy
	779.2	Cerebral depression, coma, and other abnormal cerebral signs in fetus or newborn
Hypoglycemia	251.2	Hypoglycemia, unspecified
	775.6	Neonatal hypoglycemia
Hypoxia	768.7x	Hypoxic–ischemic encephalopathy
	768.9	Unspecified birth asphyxia in liveborn infant
	770.12	Meconium aspiration with respiratory symptoms
	770.88	Hypoxemia of newborn
	775.81	Other acidosis of newborn
Persistent pulmonary hypertension	747.83	Persistent fetal circulation
Respiratory failure	V46.11	Dependence on respirator, status
	518.81	Acute respiratory failure
	518.83	Chronic respiratory failure
	518.84	Acute and chronic respiratory failure
	770.84	Respiratory failure of newborn
	770.87	Respiratory arrest of newborn
Seizures	345.x	Epilepsy and recurrent seizures
	779.0	Convulsions in newborn
Sepsis	038.x	Septicemia
	771.81	Septicemia of newborn
	785.52	Septic shock
	995.91	Sepsis
	995.92	Severe sepsis

Abbreviation: ICD-9, International Classification of Diseases, ninth edition.