

**Increased rates of adverse perinatal outcomes in women with gestational diabetes and depression**

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**Abstract**

**Objective:** We sought to examine the impact of depression on adverse perinatal outcomes in women with GDM.

**Methods:** We performed a retrospective cohort study comparing the rates of perinatal complications among singleton, non-anomalous births to women with GDM and the diagnosis of depression compared to GDM women without depression between 2007 and 2011 in California. Perinatal outcomes were analyzed using Chi square and multivariable logistic regression to compare frequencies of characteristics and outcomes and to determine the strength of association of depression and adverse perinatal outcomes among women with GDM. Statistical comparisons with a p-value of less than 0.05 and 95% CI that did not cross the null were considered statistically significant.

**Results:** Among the cohort of 170,572 women with GDM, 2,090 (1.22%) were diagnosed with antenatal depression. Women with GDM and depression had significantly higher rates of preeclampsia (adjusted Odds Ratio [aOR] 1.28, 95% CI 1.11-1.49) and gestational hypertension (aOR 1.23, 95% CI 1.05-1.44). Women with GDM and depression also had higher rates of preterm delivery at <37, and <34 weeks gestational age (aOR 1.33, 95% CI 1.18-1.50 and 1.36, 95% CI 1.15-1.61 respectively).

**Conclusion:** Women with GDM and a diagnosis of depression have higher rates of adverse perinatal outcomes than women with GDM alone. Identifying and managing depression among women with GDM has the potential to improve the care and health of this high-risk population.

**Introduction**

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Adverse outcomes in women with GDM and depression

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Gestational Diabetes (GDM), impacts approximately 10% of pregnant women and is independently associated with adverse perinatal outcomes.<sup>1,2</sup> Interventions such as nutrition education, exercise, and pharmacotherapy have improved rates of cesarean delivery, LGA, and preeclampsia. However, women with GDM continue to have higher rates of complications compared to women without GDM.<sup>2-6</sup> Approximately 8-12% of all women, and a median of 14.7% of women with GDM experience antenatal depressive symptoms during pregnancy, which is also independently associated with increased adverse pregnancy outcomes, such as preterm birth and preeclampsia.<sup>7-11</sup>

Prior studies have shown that there is an association between GDM and depression in pregnant women.<sup>11,12</sup> However, it is unknown whether having antenatal depression and GDM further increases risks of perinatal complications compared to the increased risk with GDM alone. Whether the pathophysiology of depression or its impact on an individual's ability to manage their GDM leads to worse outcomes in women with GDM remains an unanswered question. Given the high prevalence of depression and the rising rates of GDM (3.7% to 5.8% from 2000 to 2010), it is timely to understand the relationship between these two conditions to potentially reduce adverse pregnancy outcomes in this high-risk population.<sup>13-17</sup>

To address these knowledge gaps, our objective was to investigate the rates of adverse perinatal outcomes among women with GDM, we compared the outcomes of patients affected with coexisting conditions of GDM/depression, compared to those with GDM alone. We hypothesized that women with GDM and depression have higher rates of adverse pregnancy outcomes than women with GDM without depression.

## **Materials and Methods**

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We performed a retrospective cohort study among all singleton, non-anomalous pregnancies diagnosed with GDM in the state of California from 2007 to 2011 to compare rates of adverse perinatal outcomes among women with the diagnosis of GDM and antenatal depression to women with GDM and no depression (referent). Multi-fetal gestations or women who delivered before 23 weeks or after 42 weeks gestational age (GA) at delivery were excluded from analysis. Our primary exposure was antenatal depression, identified by ICD-9 codes in the discharge abstracts. Our outcomes of interest included hypertensive disorders of pregnancy (gestational hypertension and preeclampsia), stillbirth, cesarean delivery, and preterm delivery.

The data was derived from linked mother-infant datasets from the California Vital Statistics Birth Certificate Data, Infant Vital Statistics Death Certificate Data, California Patient Discharge Data, and Vital Statistics Fetal Death File. Data linkage is performed by the California Office of Statewide Health Planning and Development Healthcare Information Resource Center, under the California Health and Human Services Agency, which used a unique “record linkage number” specific to the mother-infant pair. The state of California maintains these linked datasets that include health information from maternal antepartum and postpartum hospital records for the 9 months before delivery and 1 year after delivery, as well as birth records and all infant admissions that occur within the first year of life. We obtained human subjects approval from the Institutional Review Board at Oregon Health & Science University, the California Office of Statewide Health Planning and Development, and the Committee for the Protection of Human Subjects of California. The linked dataset did not contain potential patient privacy/identification information, so informed consent was exempted. All variables were abstracted from the vital statistics data or using ICD-9 Codes from hospitalizations.

Analyses were conducted with Stata software (version 15; Stata Corporation, College Station, TX). Statistical comparisons of categorical variables were measured with univariate analyses. Multivariable logistic regression models were used to determine the strength of association of adverse perinatal outcomes among GDM women with depression compared to women without depression, controlling for potentially biologically plausible and statistical confounding factors. Statistical significance was determined by a p-value of  $<.05$  or 95% confidence intervals that did not include the null.

## Results

After exclusions, 170,572 women with GDM who delivered in California were included for analysis. Of these women with GDM, 2,090 (1.2%) had a diagnosis of antenatal depression. Maternal demographic characteristics are shown in Table 1. In comparison with the referent group, women with both antenatal depression and GDM were more likely to be Black (4.2% vs 3.6%,  $p<0.001$ ), age greater than or equal to 35 (35.6% vs. 32.3%,  $p=0.003$ ), and obese (47.3% vs. 37.0%,  $p<0.001$ ). Parity, insurance status, education status, and number of prenatal visits were not found to be statistically significantly different between groups.

In univariate analysis, rates of hypertensive disorders of pregnancy, including preeclampsia (11.4% vs 7.9%,  $p<0.001$ ) and gHTN (9.9% vs 6.8%,  $p=0.009$ ) were higher in women with GDM and depression, compared to women with GDM alone. Women with GDM and depression were more likely to experience preterm delivery at  $<32$  weeks (4.9% vs 4.0%,  $p=0.045$ ),  $<34$  weeks (7.8% vs 5.7%,  $p<0.001$ ) and  $<37$  weeks gestation (19.1% vs 14.9%,  $p<0.001$ ) compared to women with GDM alone [Figure 1]. Rates of cesarean delivery in women with GDM and depression (45.3% vs 42%,  $p=0.002$ ), were higher compared to women with

GDM alone, and rates of stillbirth were higher in women with GDM and depression (0.7% vs 0.4%,  $p = 0.035$ ) than GDM alone.

After adjusting for confounding variables, including maternal age, maternal education, insurance status, number of prenatal visits, race, ethnicity, parity, BMI, diabetes mellitus and chronic hypertension, we found that depressed women with GDM had significantly increased odds of hypertensive disorders of pregnancy including preeclampsia (adjusted Odds Ratio [aOR] 1.28, 95% CI 1.11-1.49) and gHTN (aOR 1.23, 95% CI 1.05-1.44). There was a significant increase in preterm delivery at <37 and <34 gestational age (aOR 1.33, 95% CI 1.18-1.50 and 1.36, 95% CI 1.15-1.61 respectively). The rates of preterm delivery at <32 weeks, cesarean delivery and stillbirth in depressed women with GDM were not found to be statistically significant once adjusted for potential confounding variables [Table 2].

### **Comment**

Our study demonstrated that in women with a diagnosis of GDM, those with a concurrent diagnosis of antenatal depression were more likely to have adverse perinatal outcomes, including hypertensive disorders of pregnancy and preterm birth, as compared to non-depressed controls, GDM controls.

Although there have been many studies investigating GDM or antenatal depression as independent risk factors for adverse perinatal outcomes, this is one of the first studies to our knowledge to report an increased incidence of adverse perinatal outcomes in women with antenatal depression and GDM.<sup>18,19</sup> Women with GDM in our study have similar rates of preeclampsia as a prior study, however, our study further demonstrates that antenatal depression

may have an additive risk for preeclampsia among women with GDM.<sup>18</sup> There have also been studies in populations of women with antenatal depression showing increased rates of preterm birth compared to non-depressed women, which is consistent with our results<sup>18,20–22</sup>. It is important to consider that a large portion of these preterm births could be due to the increased incidence of preeclampsia in these mothers, as preeclampsia is the most common indication for medically indicated preterm birth.<sup>23</sup> Studies have found that the rate of cesarean delivery was significantly increased in depressed women after adjusting for confounders, however, it was not significantly increased, when adjusted for confounders, in our population of women diagnosed with both conditions (45.3%) as compared to those without depression (42%).<sup>20,24</sup> It is possible that further increases in cesarean delivery rates were not seen from depression because of the clinically high baseline rates observed among women with GDM.<sup>25</sup>

Prior studies suggest that depression is associated with vascular changes that may increase the risk of preeclampsia and hypertension.<sup>19,26</sup> It has also been suggested that both GDM and preeclampsia result from or cause endothelial damage, increasing perinatal risks.<sup>27</sup> Studies have shown that rates of preeclampsia are decreased in women who are treated for their GDM, thus it is possible that women with depression are less likely to optimally treat their concurrent GDM, leading to worse outcomes.<sup>28</sup> However, further research in this area is needed as current published studies are conflicting, the mechanism is not well understood, and our study was not designed to investigate compliance or causality.<sup>10,19,26</sup>

Despite our study being one of the first to examine the additive impact of antenatal depression and GDM, it is not without limitations. Our study is limited given its retrospective design as not all potential confounding variables of interest were available. Particularly, we do

not know if women were undergoing treatment for either depression or gestational diabetes. We also do not have information on the timing of their diagnosis during their pregnancy, which could affect the impact of disease on perinatal outcomes. The data is administrative and thus relies on ICD-9 codes for categorizing all outcomes of interest that may lead to under-identification of the conditions of interest. However, using such data would be less susceptible to institutional bias because of the inclusion of all hospitals and health systems within California. The prevalence of antenatal major depression in our population of women with GDM was 1.22%, which is lower than the national estimated prevalence, which could have led to misclassification bias.<sup>29,30</sup> Such non-differential misclassification would bias our results toward the null, thus the magnitude of the positive associations in our study may represent the lower bounds of the actual impact of depression, and our negative findings may be too conservative.<sup>31</sup> Additionally, the follow-up of our study was just through hospitalization. Hypertensive disorders of pregnancy and GDM have been shown to increase infants' risk for developing programming of adult-chronic diseases and comparisons of such long-term neonatal outcomes were not available in these data for this study.<sup>32,33</sup>

Our data support a strong association between antenatal depression and pregnancy complications in women with GDM. Additional research is needed to explore this association, as this study cannot establish causation. However, these results demonstrate the necessity to identify women at high risk with earlier and more consistent screening for depression and depression prevention with counseling therapy as recommended by the US Preventative Services Task Force in 2019.<sup>34</sup> Future studies are needed to determine if perinatal outcomes can be improved with treatment for depression. Until such time that further studies are available, these



data provide information for clinicians regarding the risks for women with both GDM and depression.

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**Table 1. Maternal Demographic Characteristics**

Characteristic	Depression N=1901	No Depression N= 175,936	P-value
Maternal Age, mean $\pm$ SD	31.93 $\pm$ 5.88	31.5 $\pm$ 5.80	0.001
Older than 35 years, n (%)	690 (35.60%)	58,134 (32.30%)	0.003
Maternal Race, n (%)			
White (Non-Hispanic)	701 (36.62%)	32,952 (18.50%)	<0.001
Black (Non-Hispanic)	80 (4.18%)	6,352 (3.57%)	<0.001
Hispanic	908 (47.44%)	101,226 (56.84%)	<0.001
Asian (Non-Hispanic)	161 (8.41%)	34,122 (19.16%)	<0.001
Pre-pregnancy BMI, mean $\pm$ SD	31.93 $\pm$ 1.36	3.26 $\pm$ 1.28	<0.001
Maternal weight, n (%)			
Underweight (<18.5)	26 (1.45%)	3,209 (1.95%)	<0.001
Normal (18.5-24.9)	450 (25.15%)	52,937 (32.13%)	<0.001
Overweight (25-29.9)	467 (26.10%)	47,622 (28.90%)	<0.001
Obesity I (30-34.9)	412 (23.03%)	32,641 (19.81%)	<0.001
Obesity II (35-39.9)	229 (12.80%)	16,790 (10.19%)	<0.001
Morbid Obesity (40-49.9)	181 (10.12%)	10,206 (6.19%)	<0.001
Superobese (>50)	24 (1.34%)	1,358 (0.82%)	<0.001
Maternal Education n (%)			
< High School	392 (21.27%)	47,483 (27.33%)	<0.001

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High School	470 (25.50%)	41,909 (24.13%)	<0.001
Bachelor's Degree	833 (45.20%)	69,658 (40.10%)	<0.001
Graduate Degree	148 (8.03%)	14,666 (8.44%)	<0.001
<b>Insurance Status, n (%)</b>			
Public	857 (44.22%)	83,777 (46.89%)	0.06
Private	1060 (54.70%)	92,855 (51.97%)	0.06
Self-Pay	21 (1.08%)	2,026 (1.13%)	0.06
<b>Parity, median [IQR]</b>			
Nulliparous n (%)	592 (30.58%)	56,301 (31.30%)	0.52

**Table 2. Perinatal adverse outcomes by depression status in women with GDM**

Adverse perinatal outcomes	Depression	No Depression	p-value	aOR*	95% CI
Preeclampsia	11.4%	7.9%	0.001	1.28	1.11-1.49
gHTN	9.9%	6.8%	0.009	1.23	1.05-1.44
Cesarean delivery	45.3%	42.0%	0.002	0.99	0.88-1.11
Stillbirth	0.7%	0.4%	0.035	1.28	0.68-2.42
Preterm birth <37 weeks	19.1%	14.9%	<0.001	1.33	1.18-1.50
Preterm birth <34 weeks	7.8%	5.7%	<0.001	1.36	1.15-1.61
Preterm birth <32 weeks	4.9%	4.0%	0.045	1.22	0.99-1.51*

aOR, adjusted odds ratio; CI, confidence interval; gHTN, gestational hypertension

\*Multivariable logistic regression analysis adjusting for maternal age (35 years old and <20 years old), maternal education (>12 years vs <12 years), insurance status (private insurance vs public



insurance or no insurance), number of prenatal visits, race/ethnicity, parity, BMI, diabetes mellitus, and chronic hypertension.

Figure 1: Preterm Birth by Gestational Age in Women with GDM

