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Associations Among Endocannabinoids, Mental Health, and Obstetric Outcomes in a Pregnancy Cohort: A Preliminary Study

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ABSTRACT

Objective: Endocannabinoids, naturally occurring lipid (fat-based) signaling molecules, play a critical role in fetal development and help regulate pregnancy maintenance, placental functioning, and the timing of labor. In pregnant women, endocannabinoids are found throughout the bloodstream (circulating endocannabinoids) and in the placenta. Elevated concentrations in both blood and placenta have been linked to premature birth in high-risk cohorts. Circulating endocannabinoids have also been associated with depressive symptoms in non-pregnant cohorts. However, little is known about endocannabinoid concentrations in lower-risk pregnancies, their relationship to obstetric outcomes, and their association with maternal depressive symptoms during pregnancy. **Method:** This prospective study recruited 26 pregnant women (29.31 ± 6.36 years) during the first trimester. Participants self-reported depressive symptom severity each trimester using the Center for Epidemiological Studies-Depression Scale. Third-trimester maternal blood and post-delivery placental biopsies were collected to measure two key endocannabinoids: *N*-arachidonoylethanolamine (anandamide, AEA) and 2-arachidonoylglycerol (2-AG), using liquid chromatography-tandem mass spectrometry. Adverse obstetric outcomes were assessed postpartum. **Results:** Higher maternal depressive symptoms in the second trimester were associated with lower third trimester 2-AG concentrations, $t(10) = 2.295$, $p = .045$, a relationship not observed in other trimesters. Additionally, higher placental AEA concentrations were linked to greater risk of adverse obstetric outcomes, $r = .415$, $p = .049$. **Conclusions:** These preliminary findings suggest that endocannabinoids during pregnancy are linked to obstetric outcomes and maternal mental health, even within a lower-risk cohort. This extends prior work in non-pregnant populations and highlights the need for further study.

Key words: anandamide; prenatal; 2-arachidonoylglycerol; depression; maternal-fetal health

Endocannabinoids—*N*-arachidonoylethanolamine (anandamide, AEA) and 2-arachidonoylglycerol (2-AG)—are lipid-based neuromodulators essential for fetal growth

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and development (Kozakiewicz et al., 2021) and are key regulators of pregnancy course (Taylor et al., 2010). Disruptions to endocannabinoid system signaling affect all stages of pregnancy (Correa et al., 2016). Notably, plasma AEA concentrations remain low throughout pregnancy but rapidly rise during labor (Habayeb et al., 2004). In high-risk pregnancies, elevated maternal plasma AEA concentrations have been associated with premature delivery (Bachkangi et al., 2019). However, the role of endocannabinoids in obstetric outcomes among lower-risk pregnancies remains unclear.

In addition to pregnancy physiology, endocannabinoids are implicated in mental health. Pharmacological blockade of cannabinoid type 1 (CB1) receptors—key endogenous targets of AEA and 2-AG—using rimonabant induces significant increases in depressive symptoms (Christensen et al., 2007), highlighting the importance of endocannabinoid tone in mood regulation. In non-pregnant populations, alterations in circulating endocannabinoid concentrations, considered biomarkers of central nervous system signaling (Hillard, 2018), have been associated with depression (Comai et al., 2024; Hill et al., 2008; 2009). For example, Hill et al. (2009) reported lower circulating concentrations of both AEA and 2-AG in unmedicated women with major depressive disorder compared to controls. Our recent systematic review found altered circulating endocannabinoids in individuals with stress-related disorders, though findings varied across studies, likely due to factors such as sex, diagnosis, and comorbid substance use (Gowatch et al., 2024).

Cannabis use during pregnancy is increasingly prevalent, with estimates ranging from 6.3-9% in the U.S. and rising in recent years (Constantin & Jayawardhana, 2026; Young-Wolff et al., 2024), making it the most commonly used illicit substance during pregnancy. Many pregnant individuals use cannabis to manage symptoms such as nausea, anxiety, and pain, often under the misconception that it is safe. The primary psychoactive constituent of cannabis, Δ9-tetrahydrocannabinol (THC), binds to the same CB1 and CB2 cannabinoid receptors as endogenous AEA and 2-AG, thereby mimicking and potentially dysregulating endocannabinoid signaling. Because healthy pregnancy and fetal development depend on tightly regulated endocannabinoid tone, exogenous cannabinoid exposure may interfere with these processes in ways that are not yet fully understood. Studying endogenous endocannabinoid concentrations during pregnancy therefore provides a critical mechanistic foundation for understanding how cannabis use may disrupt placental function, fetal development, and maternal mood.

Despite growing insights into endocannabinoid signaling in mental health, little is known about its role in maternal mental health during pregnancy. Understanding this relationship may be critical for identifying women at risk for maternal depression—a condition affecting approximately 15% of individuals during pregnancy and the postpartum period (Serati et al., 2016), and associated with an increased risk of adverse obstetric outcomes (Staneva et al., 2015; Uguz et al., 2019). Circulating endocannabinoids, measurable via standard blood draw, represent a promising candidate biomarker for maternal depression risk. Blood-based biomarkers are already routinely collected across all trimesters of prenatal care, making endocannabinoid measurement a potentially feasible addition to existing clinical workflows. However, before circulating endocannabinoids can be considered reliable clinical biomarkers, further research is needed to establish their sensitivity, specificity, and stability across pregnancy.

This study begins to lay the foundation for establishing reliable circulating endocannabinoid biomarkers by examining associations among endocannabinoids measured in maternal blood and placental tissues, maternal depressive symptom severity, and adverse obstetric outcomes in a secondary data analysis of a prospective study of primarily low-risk pregnancies (Rajasekera et al., 2024).

METHODS

Participants

This is a secondary data analysis from a previous study examining the relationship between maternal microbiome and mental health outcomes during pregnancy (Rajasekera et al., 2024). Twenty-six English speaking, pregnant individuals were recruited during the first trimester (≤14 weeks gestation) through the Department of Obstetrics and Gynecology at the

Ohio State University Wexner Medical Center. Participants provided verbal and written consent in accordance with the Ohio State University's Biomedical Sciences Institutional Review Board (2017H0362). Exclusion criteria encompassed chronic health conditions (e.g., diabetes, hypertension), documented illicit substance use, any documented cannabis or tobacco use or dependence (i.e., cannabis use disorder) at time of enrollment, and history of preterm birth or preeclampsia. Exclusion criteria were assessed at time of patient recruitment through Electronic Medical Record (EMR) and self-report; cannabis use was assessed via EMR and participants were excluded if cannabis use or dependence was documented.

Study Design and Mental Health Assessments

Data collection occurred at five time points: 1st trimester, 2nd trimester, 3rd trimester, within one week of delivery, and 4-8 weeks postpartum. At the first visit, demographic and clinical characteristics were collected such as age, race, income, and number of previous pregnancies. The Center for Epidemiological Studies Depression Scale (CES-D; Radloff, 1977) was administered at each visit to assess depressive symptom severity. Participants were categorized into high or low depressive symptom groups based on the established cut-off score of 16 (Radloff, 1977).

At the 3rd trimester visit, 13 participants provided serum samples and at birth, 23 participants consented to placenta biopsies, which were used for endocannabinoid quantification. Adverse obstetric outcomes—including preeclampsia, gestational diabetes, Group B streptococcus positivity, chorioamnionitis, low birth weight, and preterm birth—were recorded individually. Due to the lower-risk nature of this cohort, adverse outcomes were combined into a 0–2 scale for analysis: 0 indicating no outcomes, 1 indicating one, and 2 indicating two.

Endocannabinoid Quantification

Serum samples were collected in EDTA tubes, processed, and stored at -80 ^{0}C. Following data collection, samples were transferred to the Wayne State University Lipidomics Core for lipid extraction and quantification via LC-MS/MS (QTRAP7500, Sciex), as previously reported (Marusak et al., 2024; 2025). Qualitative profiling used information-dependent acquisition strategies, while quantitative analysis employed multiple reaction monitoring methods. LipidView (SCIEX, Framingham, Massachusetts) identified lipids and MultiQuant (SCIEX, Framingham, Massachusetts) processed data. Primary outcomes were AEA and 2-AG (pmol/ml); 2-AG was quantified by combining peaks for 2-AG and 1-AG, the latter from isomerization. Due to moderate-to-high skewness (.587-2.476) in AEA and 2-AG concentrations, values were log-transformed. For completeness, we also examined effects on AEA congeners—oleoylethanolamide (OEA), linoleoylethanolamide (LEA), palmitoylethanolamide (PEA), and stearoylethanolamide (SEA)—which share biosynthetic pathways and are involved in inflammation but act through different mechanisms than AEA and 2-AG.

Statistical Analysis

Analyses were conducted using SPSS Statistics (Version 30.0). Descriptive statistics summarized demographics and obstetric outcomes. Pearson correlations assessed relationships between AEA and 2-AG in maternal serum and placental samples and variables such as age and parity. ANOVAs tested differences in endocannabinoid concentrations by race and income. Paired t-tests compared depressive symptoms between time points and Chi-squared tests compared low and high depression groups, defined by CES-D cut-offs (Radloff, 1977), with race, income and adverse obstetric outcomes. Our primary analyses used independent samples t-tests to compare AEA and 2-AG between low and high depression groups, and correlations to examine associations between endocannabinoid concentrations and adverse outcomes. Follow-up analyses explored whether specific adverse outcomes drove associations.

RESULTS

Endocannabinoids, Demographics, and Symptoms

Baseline characteristics of the sample are provided in Table 1. Concentrations of AEA and 2-AG were not correlated in maternal serum (r = -

.022, $p = .942$) nor placental samples ($r = -.152$, $p = .489$). Additionally, maternal concentrations of AEA and 2-AG were not significantly associated with placenta tissue concentrations (AEA: $p > .615$; 2-AG: $p > .615$; see Figure S1). As expected, the AEA congeners, OEA, LEA, SEA, and PEA, were each related to AEA in placenta ($r's > .806$, $p's < .001$) and maternal serum ($r's > .680$, $p's < .011$); except for SEA, $r = .392$, $p = .185$), but not related to 2-AG ($p's > .345$).

Table 1. *Sample characteristics and outcome measures for the study sample (N=26).*

Variable	*M*(*SD*)
Age	29.31(1.24)
Previous pregnancies	2.77 (0.54)
Maternal circulating AEA concentrations, 3rd trimester visit (log)*	0.50 (0.031)
Maternal circulating 2-AG concentrations, 3rd trimester visit (log)	2.38 (0.071)
Placental AEA concentrations, delivery (log)	0.10 (0.054)
Placental 2-AG concentrations, delivery (log)	1.76 (0.056)
Maternal depressive symptom severity (CESD score)	
1st trimester	12.92 (8.84)
2nd trimester	14.48 (7.48)
3rd trimester	11.68 (5.83)
Within 1-week post-delivery	9.70 (6.82)
4-8 weeks postpartum	8.13 (4.32)
Infant Birth Weight (g)	3,244.27 (100.04)
	N(%)
Income	
<$40,000	5 (19.3%)
$40,000 - $44,999	0 (0.0%)
$45,000 - $54,999	1 (3.8%)
$55,000 – $64,999	2 (7.7%)
>$65,000	7 (26.9%)
Not Reported	11(42.3%)
Race/Ethnicity	
Non-Hispanic Black	10 (38.5%)
Non-Hispanic White	14 (53.8%)
Hispanic	2 (7.7%)
Asian	0 (0.0%)
Other	0 (0.0%)
Number of adverse obstetric outcomes	
0 adverse outcomes	13 (50.0%)
1 adverse outcome	12 (46.2%)
2 adverse outcomes	1 (3.8%)
Adverse obstetric outcomes reported	
Preeclampsia	1(3.8%)
Gestational diabetes	2 (7.7%)
Group B strep positive	5 (19.2%)
Chorioamnionitis	2 (7.7%)
Low birth weight (<2494.76g)	2 (7.7%)
Preterm birth (< 36 wk. gestational age)	1 (3.8%)
High depressive symptom severity (≥16 on CES-D)	
1st trimester	6 (23.1%)
2nd trimester	7 (26.9%)
3rd trimester	7 (26.9%)
Within 1-week of delivery	4 (15.4%)
4-8 weeks postpartum	1 (3.8%)

Note. Data are presented as means with standard deviations (*M*(*SD*)) for continuous variables, and as frequencies with percentages (*N*(%)) for categorical variables. See Table S1 for untransformed means and standard deviations. Depressive symptom severity measured using the 20-item Center for Epidemiological Studies-Depression Scale (CESD). See Figure S3 for visual representation of depressive symptom severity mean and standard deviations

Neither AEA nor 2-AG concentrations were associated with maternal age (*p*'s > .14), number of previous pregnancies (*p*'s > .265), race (*p*'s > .263) or income (*p*'s > .25) in maternal serum or placenta.

Overall, depressive symptoms were higher in the first trimester vs. postpartum, $t(15) = 2.189$, $p = .045$, the second trimester vs. delivery, $t(19) = 2.197$, $p = .041$), the second trimester vs. postpartum, $t(14) = 3.202$, $p = .006$, the third trimester vs. delivery, $t(21) = 2.097$, $p = .048$, and the third trimester vs. postpartum, $t(15)=3.520$, $p = .003$. Depressive symptoms did not differ between the rest of the time points (*p*'s > .08) and were not associated with income (*p's* > .089) or adverse obstetric outcomes (*p's* > .15) at any time point. However, depressive symptoms significantly varied by race/ethnicity in the first trimester, $\chi^2(2) = 7.65$, $p = .022$, with Hispanic patients exhibiting higher symptoms; this difference was not observed at latter time points (*p's* > .058).

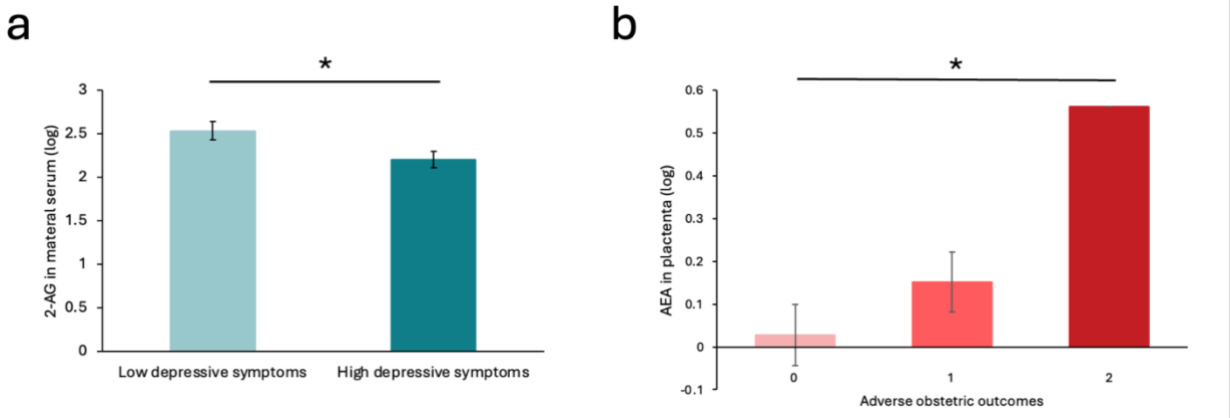
Maternal Circulating Endocannabinoids and Depressive Symptoms

Seven individuals reporting higher second-trimester depressive symptoms showed lower third-trimester circulating 2-AG, $t(10) = 2.295$, $p = .045$ (Figure 1a). Higher concurrent (third-trimester) depressive symptoms were also associated with lower 2-AG, but the difference did not reach significance ($p = .28$). No significant associations between 2-AG and depressive symptoms were found at other time points (*p*'s > .3, see Supplemental Material). AEA and congener concentrations (OEA, LEA, PEA, SEA) did not differ by depressive symptoms at any time point (*p*'s > .5; see Supplemental Material).

Placental Endocannabinoids and Adverse Obstetric Outcomes

Placental AEA concentrations were positively correlated with adverse obstetric outcomes ($r = .415$, $p = .049$; see Figure 1b). Follow-up analyses indicated no specific type of adverse outcome had a significant correlation (*p*'s > .057). Placental 2-AG concentrations were not associated with adverse obstetric outcomes ($r = -.29$, $p = .896$, Figure S2a). Maternal AEA and 2-AG circulating concentrations during the third trimester were also not associated with adverse obstetric outcomes ($r = -.26$, $p = .932$ and $r = -.154$, $p = .615$, respectively, Figure S2b-c). However, exploratory analyses in AEA congeners (LEA, SEA, OEA, PEA) showed a significant positive association between maternal third trimester SEA concentrations and number of adverse obstetric outcomes ($r = .568$, $p = .043$).

Figure 1.



Note. Higher second-trimester depressive symptoms are associated with lower circulating third-trimester 2-AG concentrations (a). Greater number of adverse obstetric outcomes is associated with higher placental AEA concentrations (b). Error bars indicate standard error. Note only one participant had two adverse obstetric outcomes; thus, error bars are not indicated. *$p < .05$.

DISCUSSION

This secondary analysis examined associations between maternal circulating and placental endocannabinoid concentrations, depressive symptom severity, and adverse obstetric outcomes. Consistent with prior findings in non-pregnant women with depression (Hill et al., 2009), higher second-trimester depressive symptoms were associated with lower circulating 2-AG concentrations in the third trimester. Additionally, elevated placental AEA concentrations at delivery correlated with a greater number of adverse obstetric outcomes, extending previous observations from high-risk to low-risk pregnancies (Bachkangi et al., 2019). These results contribute to growing evidence that endocannabinoids play a key role in both maternal mental health and pregnancy outcomes. Mechanistically, endocannabinoids regulate implantation, placentation, and fetal neurodevelopment (Kozakiewicz et al., 2021; Sun & Dey, 2012). They also play a key role in inflammation, a process implicated in both in perinatal depression (Sawyer, 2021) and adverse obstetric outcomes (Mwanyumba et al., 2003). Furthermore, with the increase of exogenous cannabis use throughout pregnancy (Constantin & Jayawardhana, 2026; Young-Wolff et al., 2024), understanding how the endogenous system works can allow us to further determine how exogenous cannabis use relates to maternal depression and obstetric outcomes.

Strengths of this study include integration of targeted endocannabinoid lipidomic analyses with longitudinal maternal mental health and pregnancy outcomes. A primary limitation is the relatively small sample size overall (N = 26), particularly the subsamples available for serum (n = 13) and placental analyses (n = 23). These sample sizes limit statistical power and stability of effect estimates; therefore, findings should be interpreted with caution and require replication in larger studies. The number of analyses conducted also elevates Type I error risk; findings should be considered hypothesis-generating pending replication. Furthermore, though classified as low-risk, our cohort had higher-than-expected rates of adverse obstetric outcomes (50%) and elevated depressive symptoms (3.8–26.9%). This may reflect the modest sample size and the context of enrollment during the COVID-19 pandemic, which has been associated with increased rates of adverse outcomes such as preterm birth and preeclampsia, (Bahado-Singh et al., 2023; Hasbini et al., 2022). Additionally, circulating and placental endocannabinoid concentrations may not directly reflect central endocannabinoid activity in the mother or fetus, limiting inferences. Notably, while prior depressive symptoms were significantly associated with 2-AG concentrations, concurrent depressive symptoms showed a similar negative trend that did not reach statistical significance, highlighting the need for longitudinal, repeated measures to better characterize the temporal relationship between endocannabinoids and maternal mood. Finally, cannabis use was assessed via EMR at a single timepoint; without self-report or urine toxicology, undetected use after enrollment may have influenced endocannabinoid concentrations.

Conclusions

Maternal circulating and placental endocannabinoid concentrations were associated with maternal depressive symptoms and adverse obstetric outcomes in a lower-risk cohort. Lower maternal 2-AG concentrations may represent a candidate biomarker for maternal depression risk, with potential applications in prenatal risk stratification. Specifically, endocannabinoid concentrations measured via standard blood draw—a procedure already integrated into routine prenatal care—could feasibly be added to existing laboratory panels to identify women at elevated risk for depressive symptoms during pregnancy. Additionally, the endocannabinoid system represents a potential therapeutic target; endocannabinoid-targeting treatments are an emerging area of investigation, though none are currently approved for use in pregnancy. These clinical applications remain speculative at this stage and require validation in larger, prospective studies before any recommendations can be made. Growing cannabis use during pregnancy further underscores the importance of understanding endocannabinoid signaling, as exogenous cannabinoids such as THC can act on the same receptors as AEA and 2-AG and may disrupt the endogenous system in ways that affect both maternal mood and obstetric outcomes. These clinical applications remain speculative and

require validation in larger, prospective studies before any recommendations can be made. Future longitudinal studies should replicate these findings, clarify underlying mechanisms, and further explore endocannabinoid signaling in maternal mental health and obstetric outcomes.

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