

Dickson, et al Obstet Gynecol 2018

- 69% of dispensaries (277/400) recommended cannabis products for morning sickness
- Of those who recommended cannabis for morning sickness
 - 65% based their recommendation on personal opinion
 - 36% said cannabis was safe in pregnancy
 - 30% did not specify a reason

OBGYN EXPERT REVIEWS **SMFM Papers**

Marijuana use in pregnancy and lactation: a review of the evidence
Tari D. Metz, MD, MS, Blake H. Nickels, MD

Maternal marijuana use, adverse pregnancy outcomes, and neonatal morbidity
Tari D. Metz, MD, MS, Amanda A. Althouse, MS, Carol J. Hogue, PhD, MPH, Robert L. Goldenberg, MD, Donald J. Dudley, MD, Michael W. Varney, MD, Deborah L. Corney, MD, George N. Sacks, MD, Robert W. Steer, MD

SMFM PAPERS #ajog18 **VIEWPOINT** **The Risks of Marijuana Use During Pregnancy**

Maternal marijuana use and neonatal morbidity
Shayla N. Conner, MD, MSc, Ebony B. Coner, MD, MPH, Melissa G. Tsai, MD, MPH, George A. Macon, MD, MSc, John C. Gallo, MD, MSc

SMFM Papers

Marijuana use and its effects in pregnancy
Kristin C. Chabert, MD, Diana A. Racusin, MD, Kathleen M. Antony, MD, Malika Kehr, MD, Melissa A. Butler, PhD, Juan M. Mastrolonetta, MD, Kjersti M. Aagaard, MD, PhD

Shayla N. Conner, MD, MSc, Victoria Boddie, MD, Kim Elyria, MD, George A. Macon, MD, MSc, Allison G. Gallo, MD, MSc, and Melissa G. Tsai, MD, MPH

Marijuana Use and Pregnancy

- Gunn, BMJ, 2016
- Reviewed literature review up to 2014
- Significant reduction in birthweight by 109 grams compared to nonusers
- No difference in Apgar scores.
- Infants exposed to cannabis had higher admission rates to NICU (rr=2.02)

Conner, et al AJOG 2015

- Retrospective cohort study of all term, nonanomalous deliveries from 2004-2008 at University of Washington in St. Louis
- Two groups: users and non-users during pregnancy
- Primary outcome: neonatal composite of weight <2500g, NICU admit, 5 min APGAR <7, umbilical artery pH <7.10.
- Infants with one or more morbidity were considered positive for the composite outcome

TABLE 1
Baseline characteristics of women who used marijuana during pregnancy compared with those who did not

Characteristic	Marijuana use (n = 680)	No marijuana use (n = 7458)	P value
Age	24.0 ± 5.3	25.0 ± 6.1	< .001
African American race (n = 5863)	87.1%	70.7%	< .001
Smell	32.1 ± 7.2	32.7 ± 7.6	.04
Nativity (n = 3012)	23.2%	27.2%	.04
Tobacco use (n = 1465)	58.1%	14.3%	< .001
Alcohol use (n = 111)	7.6%	0.8%	< .001
Other drug use (n = 220)	10.0%	2.0%	< .001
Private insurance (n = 1255)	2.5%	16.6%	< .001
Medicaid prenatal care (≤5 visits) (n = 1472)	29.6%	17.0%	< .001
Hypertension (n = 945)	11.9%	11.6%	.80
Preeclampsia (n = 505)	6.2%	6.2%	.97
Diabetes (n = 418)	3.1%	5.2%	.01

RR, relative risk.
Conner. Marijuana use and neonatal morbidity. Am J Obstet Gynecol 2015.

Conner, et al AJOG 2015

TABLE 2
Neonatal outcomes of women who used marijuana during pregnancy compared with those who did not

Variable	Marijuana (n = 680)	No marijuana (n = 7458)	RR (95% CI)	aOR (95% CI)*	P value
Birthweight <2500 g (n = 437)	8.5%	5.1%	1.7 (1.3–2.2)	1.3 (0.91–1.8)	.09
NICU admission (n = 58)	1.3%	0.7%	2.0 (1.0–4.1)	1.6 (0.7–3.5)	.25
Five minute Apgar <7 (n = 117)	1.9%	1.4%	1.4 (0.8–2.4)	1.2 (0.7–2.3)	.51
Umbilical artery pH <7.10 (n = 150)	1.6%	1.8%	0.9 (0.5–1.6)	0.9 (0.5–1.7)	.76
Composite (n = 674)	11.6%	8.0%	1.5 (1.2–1.8)	1.3 (0.96–1.6)	.10

aOR, adjusted odds ratio; CI, confidence interval; NICU, neonatal intensive care unit; RR, relative risk.
* Adjusted for smoking, other drug use, and African American race.
Conner. Marijuana use and neonatal morbidity. Am J Obstet Gynecol 2015.

Conclusion: After adjusting for confounders, term infants of women who use marijuana during pregnancy are not an increased risk for neonatal morbidity. The composite and all individual morbidities were the same between groups.

Conner, et al Obstet and Gynecol 2016

- Performed a systemic review and meta-analysis
- Included observational studies (cohort and case control) that compared rates of outcomes between users and non-users in pregnancy (31 studies in final analysis)
- Primary Outcomes: Low birth weight (<2500g) and preterm delivery
 - These were the most commonly evaluated outcomes in the literature
- Secondary outcomes: birth weight, gestational age at delivery, SGA, NICU admission, stillbirth, SAB, low APGAR, abruption, and perinatal death

Conner, et al Obstet and Gynecol 2016

- Pooled **unadjusted** data:
 - marijuana use during pregnancy was associated with an increased risk of low birth weight (15.4% compared with 10.4%, pooled relative risk [RR] 1.43, 95% confidence interval [CI] 1.27–1.62) and preterm delivery (15.3% compared with 9.6%, pooled RR 1.32, 95% CI 1.14–1.54).
- Pooled data **adjusted** for tobacco use and other confounding factors
 - No statistically significant increased risk for low birth weight (pooled RR 1.16, 95% CI 0.98–1.37) or preterm delivery (pooled RR 1.08, 95% CI 0.82–1.43).
- Conclusion: After adjusting for tobacco and other confounders, maternal marijuana use does not appear to be an independent risk factor for low birth weight or preterm delivery

Chabarria, et al AJOG 2016

- Retrospective cohort study at Baylor from 2011 to 2015
- Patients were divided into 4 groups:
 - Non-smokers
 - Tobacco smokers
 - Marijuana smokers
 - Tobacco and Marijuana smokers
- Looked at maternal and neonatal outcomes

Chabarria, et al AJOG 2016

- 12,069 met inclusion criteria
- 106 (0.88%) reported marijuana use
 - Almost half (n=48) also reported concurrent tobacco use
 - Tobacco only smokers (n=242)
- Marijuana smokers were statistically significantly more likely to be:
 - Younger
 - Single
 - African American
 - Primigravid
- Outcomes were adjusted for these differences

Chabarria, et al AJOG 2016

- After controlling for confounders, marijuana use alone was not associated with an increased risk of maternal or neonatal outcomes
- Tobacco and marijuana use combined was associated with an increased risks of:
 - Maternal asthma
 - Preterm birth
 - Decreased head circumference
 - Decreased birth weight
 - Increased risk of preeclampsia

Metz, et al AJOG 2017

- Secondary analysis of singleton live born controls in the Stillbirth Collaborative Research Network dataset
- Aim was to determine if marijuana was associated with increased odds of adverse pregnancy outcomes and neonatal morbidity
 - [SGA, SPTB, HTN], NICU admission, and a neonatal morbidity composite
- Exposure: maternal self-report of marijuana use or the presence of THC in umbilical cord homogenate
- Logistic regression controlling for many covariates

Metz, et al AJOG 2017

Adverse pregnancy outcomes (unweighted sample size)	Any marijuana use, N = 48	No marijuana use, N = 1562	P value
Small for gestational age	8.2	7.4	.83
Spontaneous preterm birth	13.2	6.2	.08
Hypertensive disorder	14.0	9.0	.28
Composite endpoint	31.2	21.2	.13

All results are reported as weighted percentages. P value from weighted χ^2 . Composite endpoint was defined by "any yes" or "all no," as such some item nonresponse is present for individual components.
Metz et al. Maternal marijuana use and adverse outcomes. Am J Obstet Gynecol 2017.

- The composite maternal adverse pregnancy outcome, and each component of the composite outcome, was present more frequently in women with marijuana use compared to nonusers. However, none of these differences were significant in univariable comparisons.

Metz, et al AJOG 2017

Neonatal outcome (unweighted sample size)	Any marijuana use, N = 48	No marijuana use, N = 1562	P value
Neonatal intensive care unit admission	16.9	9.5	.12
Preterm delivery (<37 wk)	17.3	9.0	.07
Composite neonatal morbidity or death	14.1	4.5	.002
-Neonatal pulmonary morbidity	7.5	3.7	.14
-Necrotizing enterocolitis	0.4	0.2	.33
-Seizures	0.3	0.08	.28
-Retinopathy of prematurity	0.6	0.6	.95
-Neonatal infection morbidity	9.8	2.4	<.001
-Anemia requiring blood transfusion	1.3	0.7	.24
-Neonatal surgery	0.3	0.8	.37
-Hyperbilirubinemia	0	0.03	—
-Neonatal neurological morbidity	1.4	0.3	.002
-Neonatal death in labor and delivery suite or prior to discharge	0.4	0.3	.63

Composite neonatal morbidity includes indicated list presented in remaining rows of table.
All results are reported as weighted percentages. "P value from weighted." Composite neonatal morbidity endpoint was defined by "any yes" or "all no," as each same item nonresponse is present for individual components.
Metz et al. Maternal marijuana use and adverse outcomes. Am J Obstet Gynecol 2017.

Metz, et al AJOG 2017

- Maternal marijuana use was not associated with an increased risk for a composite of SGA, SPTB, or HTN
- It is associated with an increased risk of neonatal morbidity
- Agreement between self-reported use and biological sampling was poor
 - Patients are unwilling to disclose use
 - Speaks to importance of using biologic sampling in future studies to better ascertain exposure

Conclusion

- Data is mixed and confusing
- Marijuana may be associated with a mild decrease in birthweight
- Marijuana may be associated with increased neonatal morbidity
- Lots of concern, no clear consensus on the data

What Do We Know About Long Term Neurobehavioral Effects of Prenatal Marijuana Use?

Not much!

Metz and Borgelt. Marijuana Use in Pregnancy and While Breastfeeding, Ob/Gyn, November, 2018

TABLE 1. Summary of Longitudinal Human Studies Evaluating Effect of Prenatal Marijuana Use on Neurobehavioral Outcomes

Study Setting	Population	Major Findings ^{1,49}
Alaska Prenatal Prospective Study (N=698) ⁵⁰ Fairbanks, Alaska, 1978	Middle-income, predominantly Caucasian	Younger than age 4 y: no differences in behavior, intellect, visual perception, language, attention, or memory Age 4–8 y: worse performance on tasks related to visual perception, language comprehension, attention, and memory Age 9–12 y: no difference in global IQ, performance on visual tasks, impulse control
National Health Practices and Child Development Study (N=564), ⁵¹ Pittsburgh, Pennsylvania, 1982	Low-income, predominantly African American	Age 3 y: no differences in intelligence testing Age 6 y: decreased verbal reasoning among offspring with exposure to 1 or more joints/d in the 1st trimester Age 10 y: decreased attention, more hyperactivity and impulsivity, worse academic performance when exposed in the 1st and 3rd trimesters Age 14 y: lower scores in reading, math, and spelling, especially with 1st-trimester exposure
Generation R Study (N=9,778) ⁵² Rotterdam, Netherlands, 2001	Higher socioeconomic status, multiethnic	Age 18 mo: higher aggression scores in exposed girls, but not boys Age 3 y: no differences in behavior Ongoing follow-up planned into adulthood for children born April 2002–January 2006.

Marijuana and Lactation

- 84% of users during pregnancy continue to use while breastfeeding
- Cannabinoids consumed by lactating mothers reach the newborn during breastfeeding
 - The amount that reaches the infant is estimated to be 0.8% of the mother's exposure
- May inhibit milk production by lowering prolactin secretion
- AAP states breastfeeding is contraindicated in women who use illicit drugs...however, expert opinion, given the benefits of breastfeeding and the limited data, patients should still be encouraged to breastfeed.

Drugs in Pregnancy: Original Research

Transfer of Inhaled Cannabis Into Human Breast Milk

Obstet Gynecol 2018

Teresa Baker, MD, Palika Datta, MD, Kathleen Reeves-Felkins, MS, Heather Thompson, MD, Raja R. Kallan, MD, and Thomas W. Hair, MD

- Pilot pharmacokinetic study
- Goal: evaluate the transfer of THC into breast milk after inhalation of 0.1 g of cannabis containing 23% THC

Baker, et al Obstet Gynecol 2018

- 8 women who were 2-5 months post-partum, regular users, and who were exclusively breastfeeding
- Abstained for 24 hours and then collected a baseline sample
- Then smoked marijuana and samples were collected at 20 min and 1, 2, and 4 hours after inhalation
- Measured THC samples in the milk using mass spectrometer

Baker, et al Obstet Gynecol 2018

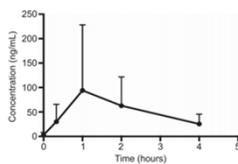


Fig. 2. Mean concentration time profile of delta-9-tetrahydrocannabinol in human breast milk (mean±SD, n=8). Baker. Inhaled Cannabis in Human Breast Milk. Obstet Gynecol 2018.

- THC was detected at low concentrations at all time points but appears to peak at 1 hour
- Infants would get 2.5% of the maternal dose (0.4-8.7%)

Unanswered Lactation Questions

- 1) What is the plasma level in the breastfeeding infant that is exposed to cannabis products through human breast milk?
- 2) What effect would repeated and continuous doses have on breast milk concentrations?
- 3) How much delta-9-tetrahydrocannabinol would transfer into a mother's breast milk after the use of oral cannabis products?
- 4) What do exogenous cannabis products do to the endocannabinoid signaling system?
- 5) What is the lasting effect of exposing developing infants to cannabis?

Synthetic Cannabinoids – K2/Spice products

- Bind more strongly to cannabinoid receptors
- Teratogenic in animals
 - Brain, eye, and facial deformations/clefts in mice
 - Increased risk with increasing doses



ACOG Committee Opinion, 2017

- Before pregnancy and in early pregnancy, all women should be asked about their use of tobacco, marijuana, and other medications used for nonmedical reasons.
- Women reporting marijuana use should be counseled about concerns regarding potential adverse health consequences of continued use during pregnancy
- Women who are pregnancy or contemplating pregnancy should be encouraged to discontinue marijuana use
- Pregnant women or women contemplating pregnancy should be encouraged to discontinue use of marijuana for medicinal purposes in favor of an alternative therapy for which there are better pregnancy specific safety data.
- There are insufficient data to evaluate the effects of marijuana use on infants during lactation and breastfeeding, and in the absence of such data, marijuana use is discouraged.

Concerns with Screening for Use

Screening women for marijuana use does more harm than good

TO THE EDITORS: We read with great interest the report by Ko et al,¹ exploring the prevalence of marijuana use among women who reported marijuana use is artificially inflated. Another concern is that the percentage of pregnant women who reported marijuana use is artificially inflated.

Areas for future research

- Dose
- Frequency of use
- Clinical outcomes

References

- Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. *N Engl J Med*. 2014 Jun 5;370(23):2219-27.
- Ko JY, Farr SL, Tong VT, Creanga AA, Callaghan WM. Prevalence and patterns of marijuana use among pregnant and nonpregnant women of reproductive age. *Am J Obstet Gynecol*. 2015 Aug;213(2):201.e1-201.e10.
- Stadterman JM, Hart CL. Screening women for marijuana use does more harm than good. *Am J Obstet Gynecol*. 2015 Oct;213(4):598-9.
- Brown QL, Sarvet AL, Shmulewitz D, Martins SS, Wall MM, Hasin DS. Trends in Marijuana Use Among Pregnant and Nonpregnant Reproductive-Aged Women, 2002-2014. *JAMA*. 2017 Jan 10;317(2):207-209.
- Schauburger CW, Newbury EJ, Colburn JM, Al-Hamadani M. Prevalence of illicit drug use in pregnant women in a Wisconsin private practice setting. *Am J Obstet Gynecol*. 2014 Sep;211(3):255.e1-4.
- Holland CL, Rubio D, Rodriguez KL, Kraemer KL, Day N, Arnold RM, Tarr JA, Chang JC. Obstetric Health Care Providers' Counseling Responses to Pregnant Patient Disclosures of Marijuana Use. *Obstet Gynecol*. 2016 Apr;127(4):681-7.
- Dickson B, Mansfield C, Gulahi M, Allshouse AA, Borgelt LM, Sheeder J, Silver RM, Metz TD. Recommendations From Cannabis Dispensaries About First-Trimester Cannabis Use. *Obstet Gynecol*. 2018 May 7.
- Metz TD, Stickrat h EH. Marijuana use in pregnancy and lactation: a review of the evidence. *Am J Obstet Gynecol*. 2015 Dec;213(6):761-78.
- Baker T, Datta P, Rewers-Felkins K, Thompson H, Kalleem RR, Hale TW. Transfer of Inhaled Cannabis Into Human Breast Milk. *Obstet Gynecol*. 2018 May;131(5):783-788.
- Alaniz VI, Liss J, Metz TD, Stickrath E. Cannabinoid hyperemesis syndrome: a cause of refractory nausea and vomiting in pregnancy. *Obstet Gynecol*. 2015 Jun;125(6):1484-6.
- Volkow ND, Compton WM1, Wargo EM. The Risks of Marijuana Use During Pregnancy. *JAMA*. 2017 Jan 10;317(2):129-130.

References

- Metz TD, Allshouse AA, Hogue CJ, Goldenberg RL, Dudley DJ, Varner MW, Conway DL, Saade GR, Silver RM. Maternal marijuana use, adverse pregnancy outcomes, and neonatal morbidity. *Am J Obstet Gynecol*. 2017 Oct;217(4):478.e1-478.e8.
- Chabarria KC, Racusin DA, Antony KM, Kahr M, Suter MA, Mastrobattista JM, Aagaard KM. Marijuana use and its effects in pregnancy. *Am J Obstet Gynecol*. 2016 Oct;215(4):506.e1-7.
- Conner SN, Bedell V, Lipsey K, Macones GA, Cahill AG, Tuuli MG. Maternal Marijuana Use and Adverse Neonatal Outcomes: A Systematic Review and Meta-analysis. *Obstet Gynecol*. 2016 Oct;128(4):713-23.
- Conner SN, Carter EB, Tuuli MG, Macones GA, Cahill AG. Maternal marijuana use and neonatal morbidity. *Am J Obstet Gynecol*. 2015 Sep;213(3):422.e1-4.