

CANNABIS USE IN PREGNANCY

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 Psychology Today <http://www.psychologytoday.com/blog/abcs-child-psychiatry>
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DISCLOSURES OF POTENTIAL CONFLICTS

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NIMH	X							
Psychology Today					X			
Guilford Press					X			

OBJECTIVES

- Describe known associations between cannabis use in pregnancy and lactation and various outcomes for both the mother and child/fetus
- Brief coverage of cannabidiol
- Outline some clinical guidelines for addressing this subject with patients

THIS IS WHAT YOUR PATIENTS ARE HEARING

THE DENVER POST

NEWS MARIJUANA
 Nearly 280 marijuana stores in Colorado suggested cannabis for pregnancy-related nausea, a new study shows. Health officials urge the opposite.

- Researchers called and said they were 8 weeks pregnant and had nausea
- 69% recommended cannabis
- Less than 1/3 recommended consulting with a physician
- "The doctor will probably just tell you that marijuana is bad for kids and will just try pushing pills on you. Maybe you have a progressive doctor that will not lie to you. All the studies done back in the day were just propoganda."

RATE OF USAGE AMONG PREGNANT WOMEN

- Ranges widely from 3% to 34% (Metz & Stickrath, 2015)
- Estimates around 8% - similar to smoking, sometime during time unaware of being pregnant
- Significant percentage who use cannabis continue to use into pregnancy (60% in one study - Moore et al, 2010)
- Usage during pregnancy rose from 2.85 to 4.98% from 2002 to 2016, (Argawal et al., 2018)

Figure 1. Adjusted Prevalence of Marijuana Use Among 279 457 Pregnant Females in KPNC by Screening Type, 2009-2016
Source: Self-reported and laboratory-verified marijuana use among pregnant females in California, 2009-2016

WHY ARE PEOPLE USING CANNABIS IN PREGNANCY?

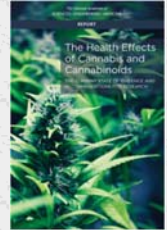
- To get high
- Difficult to stop
- Trying to treat various conditions
 - Nausea [patients report positive results (up to 90%: Westfall et al., 2006) but no controlled studies]
 - Insomnia
 - Anxiety

PHYSIOLOGY

- THC and other active compounds crosses the placenta
- Cannabinoid system involved in many functions during fetal growth (Lubman et al, 2014)
 - Neural stem cell survival and proliferation
 - Migration and differentiation of glial and neural cells
 - Neuronal connectivity and synaptic function
- Secreted in breast milk and can accumulate (Garry et al., 2009)
- Cannabinoid receptors also in other organs (heart, pancreas) and adipose tissue

COMPLICATIONS TO MOTHER OF CANNABIS USE

	Link Found	Quality/comment
Stillbirth and spontaneous abortion	1 of 2 studies	Positive study did not control for other factors
Fetal Distress	No (2 studies)	Both studies old
Maternal Diabetes	No	Smaller retrospective studies
Pre-eclampsia	No	Smaller retrospective studies
Anemia	Yes (not consistently)	Mechanism not understood Driven by one big study



FETAL GROWTH AND DEVELOPMENT

	Link Found	Quality/comment
Length at Birth	No	From meta-analysis (Gunn et al., 2016)
Head circumference	No	From meta-analysis (Gunn et al., 2016)
Birth Weight	Yes	Confounds with tobacco
Fetal growth	Yes	Confounds with tobacco

CANNABIS AND REDUCED FETAL GROWTH

- Studies mixed
 - Assessment of cannabis use variable
 - Control for tobacco smoking
- Effect through
 - Reduced blood flow
 - Glucose and insulin regulation

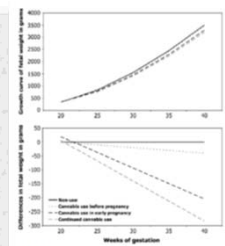
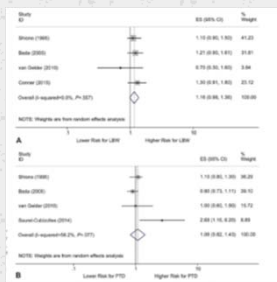


Fig. 1 Estimated growth curve and difference in fetal weight because of cannabis use in pregnancy compared with fetus of mothers who did not use cannabis or tobacco. Estimates of differences were obtained from fitting the fractional polynomial model adjusted for maternal age, body mass index, height, educational level, maternal origin, the trimester of use, parity, gravidity, fetal sex, and maternal psychopathology.

El Marroun et al., JAACAP, 2009

DUELING META ANALYSES

- Two meta-analyses (Conner et al., 2016; Gunn et al., 2016) which looked at similar studies but arrived at *different* conclusions
 - Conner – no increased risk after controlling for other factors (tobacco)
 - Gunn – found significant risk of low birth weight (1/4 to 1/2 lb difference)



OTHER CONSIDERATIONS

- Negative effect of prenatal cannabis may require heavier use
 - Reduction of 55 grams found for group of women with heavier use even after controlling for other substances (Janisse et al., 2014)
- Older negative studies done before significant increase in THC potency of cannabis
- Under-reporting likely HUGE problem with many of these studies

CONGENITAL MALFORMATIONS

- Case control study from National Birth Defects Prevention study found links to the following (van Gelder et al., 2014)
 - anencephaly (posterior OR 1.9 [95% credible interval (CRI) 1.1, 3.2])
 - esophageal atresia (posterior OR 1.7 [95% CRI 1.0, 2.9])
 - diaphragmatic hernia (posterior OR 1.8 [95% CRI 1.1, 3.0])
 - gastroschisis (posterior OR 1.7 [95% CRI 1.2, 2.3])
- Other studies have not found significant links (Warshak et al., 2015)

Alteration in Organ Development in Rats

- THC given to pregnant rats
- Tolerance found with mother rats
- Effect on pups
 - lower birth weight
 - 30% lower heart-to-body wt ratio resulting in decreased stroke volume, decreased cardiac output, increased HR (to compensate)
 - 40% lower liver-to-body wt ratio
 - 20% smaller brain-to-body ratio
 - Smaller pancreas with 60% fewer beta cells, resulting in impaired glucose tolerance
- <https://medicalxpress.com/news/2019-02-ties-heart-disease-diabetes-cannabis.html>



Lutz K. McCarthy K, Lavolette SR, Feng Q, and Dill Hardy. Exposure to Δ9-tetrahydrocannabinol during rat pregnancy leads to impaired fetal growth and postnatal cardiac dysfunction. 6th Annual Meeting of the Canadian National Perinatal Research Meeting, Mt. Tremblant, Quebec, February 2019, Poster 19

NEONATAL CONDITIONS

	Link Found	Quality/comment
Premature birth	No	From meta-analysis (Gunn et al., 2016)
ICU/NICU admissions	Yes	Need better control for confounders
Apgar scores	No	

CHILD OUTCOMES

	Link Found	Quality/comment
SIDS	For <i>fathers</i> only for use around conception or pregnancy	1 study (Klonoff-Cohen et al., 2001)
Physical growth	Yes – smaller head circumference until age 13	Fried et al., 2001
Cognition	Yes – short term memory	Not found on global cognitive measures
Achievement	Yes – lower reading scores, verbal reasoning	See details

PRENATAL CANNABIS AND SCHOOL PERFORMANCE

Table 2
Unadjusted mean scores of WIAT Screener and mediators by levels of first trimester marijuana exposure

	Non exposed N=386	Light/Moderate ^a N=139	Heavy exposure ^b N=79	p ^c
WIAT Screener at 14				
Composite	89.9	89.8	83.9	0.003
Basic Reading	93.8	93.1	87.8	0.001
Mathematics	90.7	90.7	86.0	0.02
Spelling	93.8	94.4	90.1	NS
MIAT composite score at 6	93.8	94.1	87.8	0.002
CDI total score score at 10	8.9	8.9	10.3	0.0002
SNAP inattention at 10	8.7	9.2	9.7	0.02
Marijuana initiation prior to age 14 (No)	15.7	24.5	25.3	0.03

- Maternal Health Practices and Child Development Project (MHPCD) - Lower SES sample
- Findings for heavier use (daily use) during 1st trimester, controlled for ETOH
- Mediating factors – Intelligence (age 6), attention problems and depression (age 10), early adolescent cannabis use

Goldschmidt et al., 2014

CHILD OUTCOMES - BEHAVIOR

	Link Found	Quality/comment
Inattention	Yes	Not consistent
Depression	Yes	Not consistent
Aggression	Yes	Girls only and not after age 3
Rule-breaking	Yes	Mediated by earlier depression and inattention
Substance Use	Yes	Difficult to control for genetics
Psychotic behavior	Yes	2 of 3 studies

Gray et al., 2005; Goldschmidt et al., 2000; El Marroun et al., 2010; Day et al., 2015

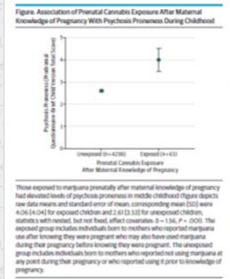
CYCLE OF ADDICTION?

- Prenatal exposure related to increased and earlier use of cannabis in offspring, controlling for other factors (Day et al., 2016; Sonan et al., 2015; Goldschmidt et al., 2016)
 - May operate through depressive symptoms



IN UTERO CANNABIS AND PSYCHOSIS “PRONENESS”

- From Adolescent Brain Cognitive Development Study (ABCD)
- 4.6% of sample (around age 10) were exposed to cannabis in utero (by parent self-report and most prior to knowledge of being pregnant)
- Significant higher score on reporting of psychotic like experiences in children whose mother used cannabis after knowing of pregnancy
- Discussion of how effect of cannabis may be stronger somewhat later in pregnancy but other explanations possible
- Did not find elevations in other behavioral problems



Agrawal et al., JAMA Psychiatry, 2019

Parental THC Exposure Leads to Compulsive Heroin-Seeking and Altered Striatal Synaptic Plasticity in the Subsequent Generation

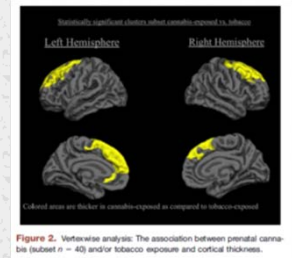
Henrietta Sutorius^{1,2}, Jennifer A DiNieri^{1,3}, Eric Sweet¹, Gabor Egervari^{1,2}, Michael Michaelides^{1,3}, Jenna M Carter^{1,2}, Yanhua Ren^{1,2}, Michael L Miller^{1,2}, Robert D Bitzer^{1,2} and Yasmin L Hurd^{1,2,3,4}

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- THC exposure to rats led to increase opiate seeking behavior and altered brain development in *offspring*
- Found altered mRNA levels of cannabinoid (CB1) receptor and other genes for neurotransmitter receptor subunits in subsequent generation in brains
- “Evidence gathered in the current study now imply a ‘cross-generational’ gateway”.

BRAIN MORPHOLOGY AND CANNABIS EXPOSURE

- MRI of 6-8 year olds in Generation R Study (El Marroun et al., 2016)
- Exposure related to increased thickness of frontal cortex
- Vast majority of cannabis using mothers also used tobacco



MECHANISM OF EFFECTS

Sex-dependent effects of in utero cannabinoid exposure on cortical function

Anissa Bari^{1,2}, Antonia Manduca^{1,2,3}, Axel Bernabeu^{1,4,5}, Milena Borsari¹, Michela Servadei¹, Olivier Lussolier¹, Michele Murphy^{1,6}, Jim Wager-Miller^{1,7}, Kim Mucke^{1,8}, Anne-Laure Palumbo-Altoni^{1,9}, Valérie Trezza¹, Olivier J Manzoni^{1,10}

¹Aix Marseille University, INSERM, IRMHD, Marseille, France; ²CNRS, Centre for Neuroimaging Research International Associated Laboratory, Indiana University, United States; ³Section of Biomedical Sciences and Technology, Department of Science, University Roma Tre, Rome, Italy; ⁴APHM, CHU Conception, Service de Psychiatrie, Marseille, France; ⁵Department of Psychological and Brain Sciences, Indiana University, Bloomington, United States; ⁶IGI Centre, Indiana University, Bloomington, United States; ⁷APHM, CHU Tenon, Adultes, Service de Médecine Légale, Marseille, France

- Changes in function of pyramidal neurons on male rat prefrontal cortex exposed to lose dose cannabis in utero

SUMMARY OF EFFECTS

- Many findings related to link between prenatal cannabis exposure and negative outcomes
 - Most common related to birth weight and fetal growth and cognitive/behavioral outcomes
- Indications that risk more strongly related to higher levels of use
- Studies inconsistent and struggle to overcome some major methodological problems
 - Under-reporting (which would cause underestimation of risk)
 - Confounds (which would cause overestimation of risk)

WHAT ABOUT CANNABIDIOL?

- Side effects (more than 10% of trials and more than placebo)
 - Somnolence/fatigue
 - Decreased appetite
 - Diarrhea
 - LFT elevations
 - Sleep problems
- Dosing 5-20mg per day

WARNINGS AND PRECAUTIONS

- Hepatocellular Injury: EPIDIOLEX can cause transaminase elevations. Concomitant use of valproate and higher doses of EPIDIOLEX increase the risk of transaminase elevations. See Full Prescribing Information for serum transaminase and bilirubin monitoring recommendations. (5.1)

than 20 times the ULN. There were cases of transaminase elevations associated with hospitalization in patients taking EPIDIOLEX. In clinical trials, serum transaminase elevations typically occurred in the first

CANNABIDIOL AND PREGNANCY

Risk Summary

There are no adequate data on the developmental risks associated with the use of EPIDIOLEX in pregnant women. Administration of cannabidiol to pregnant animals produced evidence of developmental toxicity (increased embryofetal mortality in rats and decreased fetal body weights in rabbits; decreased growth, delayed sexual maturation, long-term neurobehavioral changes, and adverse effects on the reproductive system in rat offspring) at maternal plasma exposures similar to (rabbit) or greater than (rat) that in humans at therapeutic doses (see Animal Data). In the U.S. general population, the estimated background risk of

CANNABIDIOL LABELING (BONN-MILLER ET AL., JAMA, 2017)

- Survey of 84 CBD products from 31 companies
- Actual vs Advertised CBD concentration
 - Overlabeled (actual amount of CBD less): 26%,
 - underlabeled (actual amount of CBD more) in 43%,
 - accuracy represented in 31%
- THC detected in 21%



CBD TO THC



- This process is becoming known to public and often used as defense among people who deny cannabis use but test positive for THC

CANNABIDIOL AND BREASTFEEDING

8.2 Lactation

Risk Summary

There are no data on the presence of cannabidiol or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EPIDIOLEX and any potential adverse effects on the breastfed infant from EPIDIOLEX or from the underlying maternal condition.

CANNABIS AND BREASTFEEDING

- AAP and ACOG recommend against cannabis use during lactation
- One study shows infant receives 2.5% of THC dose that mother gets from single exposure (Baker et al., 2018)
 - Can accumulate with repeated exposures
- Practically, many lactation experts recommend continued breastfeeding among cannabis using mothers (Bergeria et al., 2015)
 - Academy of Breastfeeding Medicine changed guidelines - they no longer advise not breastfeeding if going to use cannabis
- Points to difference between recommendations about cannabis vs recommendations about breastfeeding

CLINICAL PROCEDURES

- Both AAP and ACOG recommend screening when a woman enters prenatal care
- If test, urine test most common but length of time someone test positive can vary based on pattern of use

PRIMARY GUIDELINES

- Ask the questions
- Describe the risks (Avoid the "just marijuana" thinking)
- Discuss treatment and alternatives

The American College of Obstetricians and Gynecologists recommends the following:

- Before pregnancy and in early pregnancy, all women should be asked about their use of tobacco, alcohol, and other drugs, including 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 pregnant 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.

MANDATED REPORTING

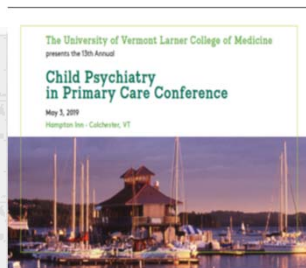
- Wide concern that disclosing cannabis use in pregnancy will result in child protective service action
- Asked DCF Deputy Commissioner Karen Shea
 - "If the reporter believes cannabis use places child at risk, they would need to report. However, DCF would not accept the report if the only concern was prenatal use of cannabis."
 - Investigate for lack of supervision



MORE COMPLEX SCENARIOS

- 25 year old woman who is legally allowed to use cannabis to treat chronic pain. She gave birth to a healthy infant and tried to minimize her cannabis use during pregnancy. She states that the pain is severe and she needs to return to her usual patterns of cannabis administration. She would like to breastfeed but wonders if her baby is better off with her not breastfeeding, as she notes the exposure her baby had already had.
- 30 year woman who reports regular cannabis use as a way to treat her anxiety. She recently found out that she is 6 weeks pregnant. She's reluctant to stop, stating that her being anxious while pregnant or using a prescription medication would also carry risks. She asks for your advice.

WANT MORE MENTAL HEALTH TRAINING?



- Topics: Suicide, cannabidiol, picky eating, happiness, vaping, teen PMDD, and more

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