Marijuana Use in Pregnancy and Lactation: A Review of the Evidence

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Reprints will not be available.
Condensation: With the increasing legalization of marijuana more data are needed to counsel women regarding potential short- and long-term adverse effects of marijuana in exposed offspring.

Short Title: Marijuana in Pregnancy
Abstract

With the legalization of recreational marijuana in many states, we anticipate more women will be using and self-reporting marijuana use in pregnancy. Marijuana is the most common illicit drug used in pregnancy with a prevalence of use ranging from 3-30% in various populations. Marijuana freely crosses the placenta and is found in breast milk. It may have adverse effects on both perinatal outcomes and fetal neurodevelopment. Specifically, marijuana may be associated with fetal growth restriction, stillbirth and preterm birth. However, data are far from uniform regarding adverse perinatal outcomes. Existing studies are plagued by confounding by tobacco, other drug exposures, as well as socio-demographic factors. In addition there is a lack of quantification of marijuana exposure by trimester of use, and a lack of corroboration of maternal self-report with biologic sampling which contributes to the heterogeneity of study results. There is an emerging body of evidence indicating that marijuana may cause problems with neurological development resulting in hyperactivity, poor cognitive function, and changes in dopaminergic receptors. In addition, contemporary marijuana products have higher quantities of delta-9-tetrahydrocannabinol (THC) than in the 1980s when much of the marijuana research was completed. The effects on the pregnancy and fetus may therefore be different than those previously seen. Further research is needed to provide evidence-based counseling of women regarding the anticipated outcomes of marijuana use in pregnancy. In the meantime women should be advised not to use marijuana in pregnancy or while lactating.

Key Words: cannabis, lactation, marijuana, pregnancy
**Background**

Marijuana is the most frequently used illicit drug in Western countries. In 2013, 19.8 million, or 7.5% of the United States population, reported use within the last month, an increase from 2007 when only 5.8% of the population had used marijuana within the past month.\(^2\,^3\)

Reported prevalence rates of marijuana use in pregnancy vary from as low as 3% to as high as 34%.\(^4\,^5\) We anticipate an increase in marijuana use in pregnancy as legalization of marijuana increases throughout the United States. This review is intended to provide practicing clinicians with an understanding of existing literature and recommendations for managing women who use marijuana during pregnancy as this will be an increasingly encountered clinical scenario.

The term, ‘marijuana’, is used throughout this article to represent cannabis use globally. Technically the active psychogenic component of marijuana is a cannabinoid called delta-9-tetrahydrocannabinol (THC).\(^6\)

**Search Methodology**

Ovid Medline (PubMed) and Embase were searched on December 11, 2014 for relevant articles. A focused search was conducted with the search terms “marijuana” and “marihuana” or “cannabinoids” and “pregnancy”, “lactation” and outcomes including adverse perinatal outcomes and neurodevelopment. A search without any language or year limits yielded 615 unique citations. Abstracts were reviewed by the authors and all pertinent articles were obtained and reviewed individually. In addition, references of pertinent articles were reviewed to find any additional articles that were not identified with the initial search (n=43). All pertinent articles are summarized here. Our goal was...
not to provide a systematic review of a specific research question but rather to provide practicing clinicians with a comprehensive overview of the existing marijuana in pregnancy and lactation literature.

**Legalization of Marijuana**

Currently both recreational and medical marijuana remain illegal by federal law in the United States. However, the legalization of medical and recreational marijuana at the state level is increasing throughout the United States. At this point, 23 states have legalized the use of medical marijuana and 4 states have legalized both medical and recreational marijuana (Figure 1).

*The Colorado Experience*

Medical marijuana was legalized in Colorado in the year 2000. However, it was not until 2009 when the United States Attorney General issued a statement passing the jurisdiction of marijuana law enforcement to state governments, that we saw a sharp increase in the number of medical marijuana users in the state. In 2012, recreational marijuana was legalized in the state of Colorado with the passing of Amendment 64. There is no stipulation in the law stating that pregnant women cannot purchase or possess marijuana.

Sales of recreational marijuana have been steadily increasing since the opening of the first recreational dispensaries on January 1st of 2014. The state of Colorado does not publish overall sales amounts, but does publish tax revenue on a monthly basis. In January 2014, the revenue was 3.5 million dollars. The monthly tax revenue is now up to 7.6 million dollars for the month of October 2014 showing a steady increase in sales
and consumption. In addition, there has been an increase in the use of alternative forms of consumption such as vaping (heating the cannabis to release THC and cannabinoids without making it smoke), lotions, and edibles.

Following the legalization of marijuana, we have noted several unanticipated adverse consequences of the increase in marijuana availability including an increase in pediatric overdoses and emergency visits for marijuana toxicity.

Attitudes and Beliefs

When women have been followed longitudinally during pregnancy, a decrease in use has been noted across trimesters of pregnancy. In a one-year prospective cohort study, marijuana use in pregnancy declined from 32% in the first trimester to 16% in the third trimester.

Similarly a longitudinal prospective study on drug use in pregnancy (n=86), the Development and Infancy Study (DAISY), found that the percentage of women who used marijuana throughout the pregnancy declined. However, approximately 60% of women who used marijuana in the year prior to pregnancy continued to use more than 10 joints per week, indicating that many women continue use throughout pregnancy. It should be noted that the women in the DAISY study smoked an average of 21 joints per week in the month prior to pregnancy and may not be representative of less frequent users of marijuana.

Two-thirds of adults surveyed in a United Kingdom study noted that cannabis was either “not very harmful” or “not at all harmful”. This is in contrast to other recreational drugs such as heroin or cocaine in which less than 5% of adults surveyed...
perceived them to be either “not very harmful” or “not at all harmful”. The perceived safety likely contributes to the high prevalence of use in pregnancy.

**Screening and Testing for Marijuana Use**

The American College of Obstetricians and Gynecologists and the American Academy of Pediatrics support screening all women for drug use at the time of entry to prenatal care. Verbal screening for self-reported use was noted to be acceptable to patients in one study. Women who report use should then be encouraged to stop and referred to local substance use disorder programs if needed.

Unfortunately maternal and fetal testing for marijuana exposure is fraught with error. Maternal urine testing is the most accurate method of testing. However, the duration of a positive urine toxicology result from the last use depends on many factors including chronicity of use (Table 1). Despite its limitations, urine is easy to obtain, has a high concentration of metabolites, and is therefore the preferred method of screening. Testing of maternal hair samples is inaccurate, and may remain positive despite no recent use. Neonatal hair and meconium can also be tested (Table 1); however, because of the cost of testing, delay in results, and high false positive rate in laboratory testing of meconium by different techniques, neonatal testing is rarely used in clinical practice.

There are no good methods to quantify the amount of marijuana ingested using biologic sampling in a clinical setting. The amount of THC in various forms of marijuana varies by the extraction process from the plant, Cannabis sativa, which also results in challenges in quantifying self-reported use. In addition, the various forms of consumption result in different rates of absorption and peak blood concentrations.
report from the University of Mississippi’s Potency Monitoring Project, the average concentration of THC in seized samples in the United States in 2008 was 13.0% which was an increase from 3.2% in 1983.16

**Nausea and Vomiting of Pregnancy**

As with any drug or medication in pregnancy, possible benefits must be weighed against possible adverse effects. There are little data on possible benefits of marijuana use in pregnancy. Interest in the use of marijuana as an anti-emetic has been propagated by its efficacy in oncology patients.17,18

There are two studies investigating the relationship between marijuana use and nausea and vomiting of pregnancy.19,20 Roberson et al used Pregnancy Risk Assessment Monitoring System (PRAMS) data (n=4,375) and found that women who used marijuana in pregnancy were more likely to report severe nausea (3.7 vs 2.3%, prevalence ratio 1.63, 95% CI 1.08-2.44).20 The treatment of nausea with marijuana was not specifically addressed.

Westfall et al19 reported on the prevalence of nausea among 79 women who used medicinal marijuana in pregnancy. Forty of these women (51%) used marijuana to treat nausea and vomiting of pregnancy and 92% of them felt it was effective. There was no control group, no documentation of quantity used, nor demonstration of effect on symptoms of nausea other than subjective report by survey after the pregnancy.

In summary, the effect of marijuana use on nausea and vomiting of pregnancy is unknown.

**Anesthetic Considerations**
Marijuana use can affect the safety and administration of anesthesia surrounding delivery. In high doses, marijuana can cause bradycardia and hypotension, but more commonly low or moderate doses can cause tachycardia.\textsuperscript{21} If tachycardia is present or marijuana use is suspected, drugs that increase heart rate such as ketamine, pancuronium and epinephrine should be avoided. As marijuana is often inhaled, it can also cause upper airway irritation and edema making anesthetic administration more complicated.\textsuperscript{21}

**Adverse Perinatal Outcomes**

**Fetal Growth**

Many of the human studies of marijuana in pregnancy focus on fetal growth (Table 2).\textsuperscript{4,22-35} Abnormalities in growth are biologically plausible given the passage of cannabinoids across the placenta. There are some data suggesting that cannabis affects glucose and insulin regulation and therefore may affect the fetal growth trajectory.\textsuperscript{25} However, data regarding fetal growth with marijuana exposure are mixed with some studies demonstrating a decrease in birth weight and/or growth and others demonstrating no association (Table 2). In part, the controversy may be a result of differing methodology for ascertainment of marijuana exposure varying from a single question about self-reported use at study entry to detailed longitudinal frequency of use data and biologic sampling (Table 2). In addition, many early studies did not account for concurrent exposure to tobacco.\textsuperscript{36}

A meta-analysis by English et al (1997) focused on the association between marijuana exposure and birth weight.\textsuperscript{36} This meta-analysis included 10 studies in which the investigators adjusted for the effect of tobacco exposure. While women who
consumed large quantities of marijuana (greater than 4 times per week) had babies that weighed less than non-users by 131 grams on average, the pooled odds ratio for low birth weight with any marijuana use was 1.09 (95% CI 0.94-1.27).\textsuperscript{36}

Most of the trials included in the meta-analysis utilized self-report of marijuana use as the predictor of low birth weight rather than biologic sampling. Zuckerman et al found an association between a positive urine toxicology screen for THC and lower birth weight (79 gram decrease in birthweight, \(p=0.04\)).\textsuperscript{35} However, there was no observed association when only self-report was considered. These authors argued that a lack of association between marijuana and lower birth weight in other studies may have been a result of incomplete ascertainment of exposure by relying on self-report.\textsuperscript{35}

There is only one study, a secondary analysis of the Generation R data (a large prospective trial to assess early environmental and genetic determinants of health in the Netherlands), in which serial ultrasounds were performed to assess fetal growth rather than using birth weight as the outcome.\textsuperscript{25} Women were followed prospectively with growth ultrasounds at \(<18\) weeks, \(18-25\) weeks and \(\geq 25\) weeks. Marijuana exposure data were by self-report. Fetuses exposed to marijuana in early pregnancy (\(n=214\)) grew 11.2 grams/week less than non-users and this effect was more pronounced in women with continued use throughout pregnancy (Table 2). The long-term effects of this small growth decrement are unknown.

A small subset of the Generation R cohort had Dopplers performed between 28 and 34 weeks.\textsuperscript{37} Women with cannabis use in early pregnancy (\(n=14\)) and women with ongoing cannabis throughout pregnancy (\(n=9\)) were compared to non-users. There was no difference in the umbilical artery pulsatility index or fetal cerebral blood flow. Women
who used cannabis throughout pregnancy had a higher uterine artery pulsatility index and resistance index than non-users after adjusting for fetal weight, fetal sex and maternal education. The authors appropriately cautioned against drawing widespread conclusions from these data given the small sample size.

It should be noted that in contrast to all other studies finding a small growth decrement or no difference in birth weight, one prospective study noted an increase in birth weight among neonates exposed to heavy use of marijuana (> 1 joint/day) in the third trimester (3357 gms versus 3215 grams, p=0.04). This finding has not been replicated in any other studies, and was not demonstrated with use in other trimesters.

In summary, there may be a small decrease in growth with exposure to marijuana in pregnancy. However, the clinical significance of this decrease is questionable with reported growth differences on the order of a hundred grams.

**Stillbirth**

Many of the prior studies of marijuana in pregnancy exclude women with a stillbirth so data regarding stillbirth and marijuana use are scant. However, a recent case-control study by Varner and colleagues in the Stillbirth Collaborative Research Network demonstrated an increased risk of stillbirth among women who used marijuana in pregnancy as demonstrated by THC in the umbilical cord homogenate (OR 2.34, 95% CI 1.13-4.81). These data are valuable given their cross-sectional nature, diverse population and objectivity. However, there are limitations including lack of quantification and timing of marijuana use. In addition, the authors noted concern for possible residual confounding by tobacco use which attenuated the association between THC in the cord
homogenate and stillbirth by approximately 10% thereby further stressing the importance of accounting for concurrent tobacco use in marijuana research.

*Preterm Birth*

Data on the association between marijuana use and preterm birth are mixed with some studies demonstrating an increased risk of preterm birth and others demonstrating no association (Table 3). This is likely a result of differing methodological approaches including poor quantification of marijuana exposure and lack of documentation of the indication for preterm birth in many studies (Table 3). Only two studies specify an outcome of spontaneous preterm birth\textsuperscript{4,39} rather than a generic outcome of any preterm birth (<37 weeks).

There are two, large retrospective population-based Australian studies supporting an increased risk of preterm birth with marijuana use. The first was a cohort (n=24,874) who self-reported marijuana use at their intakes for prenatal care. After adjusting for alcohol, tobacco and other illicit drugs, marijuana use was associated with preterm birth (OR 1.5, 1.1-1.9).\textsuperscript{23} A second study using ICD-10 codes for substance use similarly noted an increased incidence of preterm birth among marijuana users (18.8% vs 5.8%, p<0.001).\textsuperscript{24}

In contrast, in the Avon Longitudinal Study of Pregnancy and Childhood which is a population-based cohort from the United Kingdom to study environmental exposures that affect the health and development of children (n=12,129), the preterm birth rate in women who used marijuana weekly beyond the first trimester was exactly the same as non-users at 4.6% (p=0.976).\textsuperscript{22}
One prospective multi-center study by Shiono et al highlights one of the difficulties in marijuana research.\textsuperscript{40} Only 31% of the women with a positive serum screen for THC (n=585) also self-reported use in a structured interview. Conversely only 43% of women who self-reported use had a positive serum assay for THC. These investigators grouped women who reported use and/or had a positive drug assay for THC and demonstrated no association between preterm birth and marijuana use (OR 1.1, 95% CI 0.8-1.3).\textsuperscript{40} There was however an association with preterm birth in women when only women with a positive serum assay (possibly more chronic users) were considered marijuana-exposed (OR 1.3, 95% CI 1.0-1.7).

Multiple other prospective cohort studies and secondary analyses fail to provide a definitive answer regarding preterm birth and marijuana use (Table 3). The majority of studies demonstrate no increased risk of preterm birth. However, the two studies mentioned above that use spontaneous preterm birth as the outcome demonstrate an association with marijuana use (Table 3).\textsuperscript{4,39} Further research with detailed documentation of obstetrical history (specifically history of preterm birth and risk factors for preterm birth), quantification of marijuana use, and indication for delivery is needed.

\textit{Congenital Anomalies}

There are two studies in which data were collected prospectively to assess for an association of marijuana exposure with congenital anomalies (Table 4). Neither of these demonstrated an association between marijuana use and major congenital anomalies. There are also several large retrospective cohort studies examining whether there is an association between marijuana and birth defects with mixed results (Table 4).\textsuperscript{41-43} Unfortunately, the majority of these studies are based on birth defects registries with
incomplete ascertainment of confounding factors and potential for recall bias with exposure data collected long after delivery.

Current evidence does not support an association between marijuana exposure and any specific congenital birth defect (Table 4).

**Neurodevelopment**

There have been multiple animal studies and retrospective human studies looking at the effect of maternal marijuana use during pregnancy and the effects on neurodevelopment, behavior and intelligence.

Animal studies have shown alterations in neurotransmitter and neuroendocrine systems in the offspring of rodents exposed to cannabinoids. This effect is particularly pronounced within dopaminergic pathways. In addition, there have been some animal studies that show a marked increase in hyperactivity and exploratory behaviors in female rats. Other rat studies have shown persistent deleterious effects on learning and memory functions in exposed offspring. While rodent animal studies cannot be extrapolated directly to humans, they can help elucidate some of the mechanisms by which marijuana affects the developing brain.

In human research, there is one published series of post-mortem fetal brains (n=44) from 17-22 week elective terminations exposed to marijuana. Dopamine receptors were reduced in the amygdala of marijuana exposed compared to non-exposed fetuses. This effect was most prominent in male fetuses, and was directly correlated with the amount of marijuana used during the pregnancy.
Human research on drug exposure in utero and its subsequent effects is challenging due to confounding psychosocial issues and ongoing exposures that are impossible to fully adjust for in multivariable modeling. The following data must therefore be interpreted with caution.

One study assessed 26 infants born to adolescent mothers who were exposed to marijuana in utero compared to non-exposed infants of demographically matched mothers. Exposure was confirmed by maternal hair samples and neonatal meconium testing. Those exposed to marijuana had significantly different arousal, regulation and excitability on the Neonatal Intensive Care Unit Network Neurobehavioral Scale.

There are two large cohorts with both short- and long-term follow-up of children exposed to marijuana in utero. The Ottawa Prenatal Prospective Study (OPPS) looked at the effects of prenatal marijuana and tobacco use on 180 offspring of primarily middle class, Caucasian, low-risk patients in Ottawa, Canada at various developmental ages. Younger than age 4, there were no differences in behavior problems, intellect, visual perception, language or sustained attention and memory tasks between children born to mothers that used marijuana and those who did not. However, after the age of 4, there were differences in behavioral problems, poorer performance on visual perception tasks as well as language comprehension and sustained attention and memory difficulties in exposed children. By the age of 9-12 years, there was no difference between exposed and unexposed children in global IQ scores or performance on visual tasks and impulse control.

While the OPPS provides much needed long-term follow-up of exposed children, it has limitations. It does not adequately correct for environmental factors, does not
clearly report differences based on the quantity of marijuana used, and is a relatively homogenous population.

The other large cohort with long-term follow-up is the Maternal Health Practices and Child Development Project (MHPCD) out of Pittsburgh, Pennsylvania which consists of mostly high-risk, low-income minority women and their children. While there were no differences in intelligence testing at 3 years of age, maternal use of one or more joints per day during the first trimester was associated with decreased verbal reasoning by the age of 6.

The MHPCD cohort was examined again at age 10 (n=636). Those children exposed during the first and third trimesters demonstrated decreased attention, and more hyperactivity and impulsivity. Academic performance in reading, spelling and by teacher report was worse in those exposed to at least one joint per day during pregnancy. In the last assessment of the MHPCD cohort at the age of fourteen (n=524), maternal use was associated with lower scores in reading, math and spelling, most notably in those exposed to heavy use in the first trimester. In addition, there was an earlier age of onset of substance use and greater duration of use than their matched counterparts even after adjustment for home environment and parental substance use.

Although the human research in neonatal and childhood development following marijuana exposure is flawed by factors including the concurrent use of other substances, variability in exposure dosing and frequency, other genetic or environmental factors, and a reliance on self-reported data, there is a concerning pattern of altered neurodevelopment with early, heavy maternal use of marijuana.
Breastfeeding

Cannabinoids consumed by lactating mothers reach the newborn during breastfeeding. The amount that reaches the infant is estimated at 0.8% of the mother’s exposure. There is some evidence that marijuana use inhibits milk production by inhibiting prolactin secretion.

Astley et al attempted to determine the effects of marijuana use on infant development at one year. Infants exposed to marijuana during lactation scored poorly on the Psychomotor Developmental Index compared to those not exposed. However, this result could not be separated from the effect of marijuana use during pregnancy. Eighty-four percent of users during pregnancy continued use during lactation.

The American Academy of Pediatrics policy statement on “Breastfeeding and the Use of Human Milk” states that breastfeeding is contraindicated in women using illicit drugs. The statement does not address whether hospitals should withdraw lactation support in the form of facilitation of breastfeeding by nursing and lactation consultants. In our opinion, given the paucity of data regarding ongoing exposure to marijuana through breast milk, and multiple known benefits of breastfeeding, lactation support should not be withdrawn. However, women should clearly be educated regarding the potential adverse effects of ongoing marijuana exposure through breast milk and encouraged to stop using marijuana while lactating.

Future Research
Despite a large volume of literature on the topic of marijuana in pregnancy, there is still a need for high quality, contemporary, prospective data to better understand the effects of marijuana use in pregnancy and lactation.

We have identified the following research gaps as areas of focus for future studies: (1) determining whether there is an association between marijuana use and congenital anomalies, spontaneous preterm birth, pregnancy loss and stillbirth, or poor fetal growth by serial ultrasound assessments, (2) confirming the long-term neurobehavioral consequences of marijuana exposure with longitudinal follow-up, (3) establishing whether there are adverse effects of breastfeeding in the setting of ongoing marijuana use, (4) characterizing the changes in prevalence of use during pregnancy in states with legalized marijuana for medical and recreational use, (5) understanding women's attitudes and beliefs regarding marijuana in pregnancy in the setting of increasing legalization, (6) understanding the impact of different modes of consumption on outcomes with increased use of edible forms of marijuana that contain high concentrations of THC.

While performing any study on marijuana, it will be important to collect participant's socioeconomic status, medical history, obstetrical history, use of other drugs, alcohol and tobacco in a detailed, methodical manner. In addition, studies will need to quantify the timing and the amount of marijuana ingested and corroborate self-report with biologic specimens.

Ultimately high quality data will enable obstetricians to appropriately counsel women regarding marijuana use in pregnancy. If adverse effects are confirmed,
intervention and education programs can be developed to minimize morbidity to mothers and their babies.

**Summary**

Summary recommendations for the practicing clinician are in Table 5. These recommendations are made after a thorough review of the existing literature, but are based on studies of varying methodologic quality with mixed results, and reflect the opinions of the authors after completing this extensive review. Until further data are available, we should continue to discourage women from using recreational drugs, including marijuana, during pregnancy and lactation given the uncertain short- and long-term outcomes.
Acknowledgements

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References


50. Fried PA. The Ottawa Prenatal Prospective Study (OPPS): methodological issues and findings--it's easy to throw the baby out with the bath water. *Life Sci.* 1995;56(23-24):2159-2168.


Table 1. Testing for Marijuana in Biological Samples

<table>
<thead>
<tr>
<th>Biological Sample</th>
<th>Duration of Positive Result</th>
<th>Test Limitations</th>
</tr>
</thead>
</table>
| Maternal urine    | 2-3 days in occasional users<sup>63</sup>  
Several weeks in chronic users<sup>54</sup> | Chronicity of use determines duration of positive result<sup>63</sup> |
| Maternal serum    | 2-3 days in occasional users<sup>6</sup>  
Several weeks in chronic users<sup>6</sup> | Chronicity of use determines duration of positive result<sup>63</sup>  
Invasive sample  
Shorter half-life than urine<sup>6</sup> |
| Maternal hair     | Several weeks<sup>65</sup> | Less accurate for marijuana than other drugs<sup>65</sup>  
False positives from passive exposure<sup>65</sup>  
Not clinically used due to cost and inaccuracy |
| Meconium          | Positive result indicates second and third trimester exposure<sup>26,66,67</sup> | Small amount of detectable THC in the samples<sup>68</sup>  
High false positive rate (up to 43%)<sup>15</sup>  
Send out to reference laboratory  
Costly and impractical at many sites |
| Neonatal hair     | Positive result indicates third trimester exposure<sup>66</sup> | Costly and impractical at many sites  
Less sensitive than meconium<sup>66</sup> |
Table 2. Summary of Marijuana and Fetal Growth Restriction Studies

<table>
<thead>
<tr>
<th>Study and Number in Cohort</th>
<th>Marijuana Exposed Women, n(%)</th>
<th>Setting</th>
<th>Data Source</th>
<th>Marijuana Measure</th>
<th>Other Variables Considered in Analysis</th>
<th>Findings (adjusted odds ratios or regression coefficients with 95% confidence intervals reported when available)</th>
<th>Limitations and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prospective Cohort Studies</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Day 1991 22</td>
<td>324 (62)</td>
<td>Single institution</td>
<td>Self-report by prenatal interview in each trimester of pregnancy</td>
<td>Frequency: light (0-2.9 joints/wk), moderate (3-6.9/wk) and heavy (≥ 1 joint/day)</td>
<td>SES, OB hx, medical hx, standard demo, other drugs, EtOH, tobacco</td>
<td>No association with SGA</td>
<td>Increase in birth weight in marijuana users compared to non-users Women who use marijuana were intentionally over-sampled</td>
</tr>
<tr>
<td>El Marroun 2009 25</td>
<td>459 (6)</td>
<td>Population-based study in the Netherlands</td>
<td>Self-report at study enrollment</td>
<td>Frequency: daily, weekly, monthly Reported use: only before pregnancy, use in early pregnancy, or ongoing use</td>
<td>Standard demo, psych hx, EtOH, fetal sex, tobacco Excluded women with other drugs</td>
<td>Use before pregnancy did not affect growth Early pregnancy use decreased growth 11.18 gms (-15.26 to -7.10)/wk Ongoing marijuana use decreased growth 14.44 gms (-22.94 to -5.94)/wk</td>
<td>Only study with serial ultrasounds to assess fetal growth (detailed in fetal growth section of text) Marijuana use not well-quantified</td>
</tr>
<tr>
<td>Fergusson 2002 22</td>
<td>606 (5)</td>
<td>Population-based study in Great Britain</td>
<td>Self-completed questionnaire at 18-20 weeks gestation</td>
<td>Frequency: 1x/day, 2-4x/wk, 1/wk, &lt;1/wk pre-pregnancy, 1st trimester and ongoing</td>
<td>Standard demo, other drugs, EtOH, tobacco</td>
<td>Ongoing use ≥1/wk throughout pregnancy was not associated with lower birth weight -84.20gms (-174.70 to 6.40)</td>
<td>Self-report data collected at 18-20 weeks gestation, no later pregnancy data</td>
</tr>
<tr>
<td>Fried 1984 24</td>
<td>84 (14)</td>
<td>Referred to study by primary OB/study ads</td>
<td>Self-report by prenatal interview in each trimester of pregnancy</td>
<td>Frequency: irregular users (≤1 joint/wk, moderate (2-5/wk), heavy (&gt;5/wk)</td>
<td>SES, OB hx, medical hx, standard demo, other drugs, EtOH, tobacco</td>
<td>No association with LBW</td>
<td>Marijuana use not well quantified, averaged over the course of pregnancy</td>
</tr>
<tr>
<td>Gray 2010 26</td>
<td>38 (44)</td>
<td>Single institution</td>
<td>Self-report by prenatal interview in each trimester of pregnancy Biologic samples</td>
<td>Frequency: number of joints/day by trimester Presence of THC in maternal saliva and meconium</td>
<td>Standard demo, OB hx (parity only), tobacco Excluded women with other drugs, or heavy EtOH</td>
<td>THC in meconium associated with lower birth weight (3429 gms vs 2853 gms, p&lt;0.001), persistent effect in multivariable logistic regression Self-report alone was not associated with lower birth weight</td>
<td>Study designed to assess tobacco exposure primarily Sampling strategy for high prevalence of use not reported</td>
</tr>
<tr>
<td>Hatch 1986 29</td>
<td>366 (10)</td>
<td>Planned delivery at single institution</td>
<td>Self-report by structured interview early in pregnancy</td>
<td>Frequency: none, occasional (≤1x/month), regular (≥2/month)</td>
<td>OB hx, standard demo, other drugs EtOH, tobacco</td>
<td>Regular use in white women associated with LBW (OR 2.6, 1.1-6.2)</td>
<td>Self-report data collected at early in pregnancy, no later pregnancy data Differing results by racial group Marijuana use not well-quantified</td>
</tr>
<tr>
<td>Hingson 1982 34</td>
<td>237 (14)</td>
<td>Single institution</td>
<td>Self-report by structured interview</td>
<td>Frequency: &lt;1x/month, &lt;1/wk, 1-2x/month</td>
<td>SES, OB hx, medical hx, standard demo,</td>
<td>Neonates 95 grams smaller than non-users with use &lt;3x/wk (p&lt;0.01)</td>
<td>Possible recall bias, most exposure data collected postpartum, small subset with</td>
</tr>
<tr>
<td>Study</td>
<td>N</td>
<td>Institution</td>
<td>Interview Method</td>
<td>Sample Description</td>
<td>THC in Maternal Urine or Meconium</td>
<td>Self-Reported Use</td>
<td>Other Drugs, EtOH, Tobacco</td>
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<tr>
<td>Hurd 2005&lt;sup&gt;27&lt;/sup&gt;</td>
<td>139</td>
<td>Women undergoing elective termination at a single center at 17-22 weeks</td>
<td>Self-report by structured interview at time of termination</td>
<td>Frequency: light (0-0.4 joints/day), moderate (0.41-0.88/day) and heavy (≥ 0.89/day)</td>
<td>Standard demo, gestational age at termination, EtOH, tobacco</td>
<td>Excluded women with use ≥ 3x/week</td>
<td>Increasing self-reported use not associated with decreasing weight</td>
</tr>
<tr>
<td>Kliegman 1994&lt;sup&gt;70&lt;/sup&gt;</td>
<td>425</td>
<td>Single institution</td>
<td>Self-report by structured interview at time of delivery</td>
<td>THC in maternal urine at time of delivery</td>
<td>SES, OB hx, standard demo, other drugs, EtOH, tobacco</td>
<td>No association with LBW (OR 2.28, 0.27-19.5)</td>
<td>Study designed to assess cocaine exposure primarily</td>
</tr>
<tr>
<td>Linn 1983&lt;sup&gt;71&lt;/sup&gt;</td>
<td>12,424</td>
<td>Single institution</td>
<td>Self-report by structured interview postpartum</td>
<td>Frequency: occasional, weekly or daily use</td>
<td>SES, OB hx, medical hx, standard demo, other drugs, EtOH, tobacco</td>
<td>No association with LBW for any use of marijuana (OR 1.07, 0.87-1.31)</td>
<td>Possible recall bias, exposure data collected postpartum</td>
</tr>
<tr>
<td>Tennes 1985&lt;sup&gt;5&lt;/sup&gt;</td>
<td>756</td>
<td>Two affiliated institutions</td>
<td>Self-report by structured interview at one prenatal visit and postpartum</td>
<td>Frequency quantified by trimester: light (≤1 X/wk), moderate (&gt;1/wk but &lt;1/day), heavy (≥1/day)</td>
<td>SES, OB hx, medical hx, standard demo, other drugs, EtOH, tobacco</td>
<td>No effect on birth weight when considered by trimester or as a total amount consumed during pregnancy</td>
<td>Possible recall bias, only two sessions of self-report which was then reported by trimester of use</td>
</tr>
<tr>
<td>Zuckerman 1989&lt;sup&gt;35&lt;/sup&gt;</td>
<td>1,226</td>
<td>Single institution</td>
<td>Self-report by structured interview at one prenatal visit and postpartum</td>
<td>Reported use: yes/no THC in maternal urine at time of prenatal or postpartum interview</td>
<td>SES, OB hx, medical hx, standard demo, other drugs, EtOH, tobacco</td>
<td>Positive urine toxicology screen for THC associated with 79 gm decrease in birth weight (p=0.04)</td>
<td>Possible recall bias, only two sessions of self-report</td>
</tr>
<tr>
<td>Bada 2005&lt;sup&gt;28&lt;/sup&gt;</td>
<td>8,637</td>
<td>Multicenter, 4 university-based centers</td>
<td>Self-report by structured interview prior to delivery</td>
<td>Reported use: yes/no</td>
<td>SES, OB hx, medical hx, standard demo, other drugs, EtOH, tobacco</td>
<td>No association with LBW (OR 1.08, 95% CI 0.85-1.36) or SGA (OR 0.9, 0.73-1.11)</td>
<td>Not designed to assess marijuana specifically (Maternal Lifestyle Study&lt;sup&gt;72&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Gibson 1983&lt;sup&gt;73&lt;/sup&gt;</td>
<td>7,301</td>
<td>Two affiliated institutions</td>
<td>Self-report by structured interview at one prenatal visit</td>
<td>Frequency: ≤1x/wk, &gt;1/wk</td>
<td>Standard demo, OB hx (parity only), EtOH, tobacco</td>
<td>No association with LBW after excluding premature neonates</td>
<td>Marijuana use not well-quantified</td>
</tr>
<tr>
<td>First Name</td>
<td>Year</td>
<td>N</td>
<td>Study Design/methodology</td>
<td>Data Collection</td>
<td>Gestational age</td>
<td>Marijuana Use Reporting</td>
<td>Fetal Outcomes</td>
</tr>
<tr>
<td>------------</td>
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</tr>
<tr>
<td>Janisse</td>
<td>2014</td>
<td>748</td>
<td>Single institution</td>
<td>Self-report by structured interview at each prenatal visit</td>
<td>Proportion of prenatal visits with reported use: 1-33%, 34-66%, or 67-100%</td>
<td>SES, OB hx, medical hx, standard demo, other drugs, EtOH, tobacco</td>
<td>55 gram decrease in fetal growth with ongoing marijuana use (reported at 67-100% of visits) (p&lt;0.004)</td>
</tr>
<tr>
<td>Kline</td>
<td>1987</td>
<td>275</td>
<td>Two overlapping prospective cohorts at three urban hospitals</td>
<td>Self-report by structured interview at one prenatal visit</td>
<td>Frequency: &lt;1x/month, 2-4/month, 2-3/wk, 4-6/wk, daily</td>
<td>SES, OB hx, medical hx, standard demo, other drugs, EtOH, tobacco</td>
<td>No association with FGR in early cohort. Decreased growth with increased use (127g less with 2-3/wk, 143g less with 4-6/wk and 230g less with daily) in late cohort.</td>
</tr>
<tr>
<td>Saurel-Cubizolles</td>
<td>2014</td>
<td>156</td>
<td>Population-based study, all births in France during a single week</td>
<td>Self-report by structured interview 2-3 days postpartum</td>
<td>Frequency: &lt;1x/month, 1-9/month, ≥10/month</td>
<td>SES, standard demo, EtOH, tobacco</td>
<td>No association with SGA for &lt;1x/month use (OR 1.29, 0.61-2.72) or for use ≥1x/month use compared to non-users (OR 1.30, 0.66-2.56). Also no association with SGA for non-tobacco users, marijuana only.</td>
</tr>
<tr>
<td>Shiono</td>
<td>1995</td>
<td>822</td>
<td>Multicenter, 7 university-based clinics</td>
<td>Self-report by structured interview at one prenatal visit Biologic samples</td>
<td>Frequency: number of times/wk THC in maternal serum</td>
<td>SES, OB hx, medical hx, standard demo, other drugs, EtOH, tobacco</td>
<td>No association with LBW when marijuana use assessed by self-report or positive serum assay for THC (OR 1.1, 0.9-1.5). Increased odds of LBW with positive serum assay in isolation but not with self-report.</td>
</tr>
<tr>
<td>Teitelman</td>
<td>1990</td>
<td>95</td>
<td>Planned delivery at single institution</td>
<td>Self-report by structured interview early in pregnancy</td>
<td>Reported use: yes/no</td>
<td>OB hx, standard demo, other drugs, ETOH, tobacco</td>
<td>No association with LBW (OR 1.57, 0.54-4.52).</td>
</tr>
<tr>
<td>van Gelder</td>
<td>2010</td>
<td>189</td>
<td>Population-based, U.S. National Birth Defects Prevention Study</td>
<td>Self-report by structured interview 6 wks to 24 months post-delivery</td>
<td>Reported use: yes/no by trimester</td>
<td>SES, OB hx, medical hx, standard demo, other drugs, EtOH, tobacco</td>
<td>No association with LBW (OR 0.7, 0.3-1.6). No difference in mean birth weight (-17gms, p=0.65) No difference by trimester of use.</td>
</tr>
</tbody>
</table>

THC is delta-9-tetrahydrocannabinol. SGA is small for gestational age (birth weight <10%ile). LBW is low birth weight (defined <2500 gms unless otherwise noted). FGR is fetal growth restriction (estimated fetal weight <10%ile). PTB is preterm birth (<37 weeks). SAB is spontaneous abortion. SES is socioeconomic status. OB hx is obstetrical history. Medical hx is medical history. Standard demo is some measure of standard demographics including maternal age, race, body mass index. ETOH is alcohol use. Wk is week.

a Studies that did not adjust for tobacco use and retrospective cohorts are not included in this summary table.
Table 3. Summary of Marijuana and Preterm Birth Studies

<table>
<thead>
<tr>
<th>Study and Number in Cohort</th>
<th>Marijuana-Exposed Women, n (%)</th>
<th>Study Design and Setting</th>
<th>Data Source</th>
<th>Marijuana Measure</th>
<th>Other Variables Considered in Analysis</th>
<th>Findings (adjusted odds ratios with 95% confidence intervals reported when available)</th>
<th>Limitations and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1991</td>
<td>324 (62)</td>
<td>Single institution</td>
<td>Self-report by prenatal interview in each trimester of pregnancy</td>
<td>Frequency: light (0-2.9 joints/wk), moderate (3-6.9/wk) and heavy (≥ 1 joint/day)</td>
<td>SES, OB hx, medical hx, standard demo, other drugs, EtOH, tobacco</td>
<td>No effect on length of gestation No association with PTB</td>
<td>Women who use marijuana were intentionally over-sampled</td>
</tr>
<tr>
<td>Dekker 2014</td>
<td>213 (7) with pre-pregnancy exposure</td>
<td>International multicenter</td>
<td>Self-report by structured interviews at 20 weeks</td>
<td>Timing of use: pre-pregnancy, 1st trimester</td>
<td>SES, OB hx, medical hx, standard demo, other drugs, EtOH, tobacco</td>
<td>Pre-pregnancy use associated with spontaneous PTB with intact membranes (OR 2.34, 1.22-4.52)</td>
<td>Study designed to develop screening tests for PTB and other adverse obstetrical outcomes Marijuana use not quantified</td>
</tr>
<tr>
<td>Fried 1984</td>
<td>84 (14)</td>
<td>Referred to study by primary OB/study ads</td>
<td>Self-report by prenatal interview in each trimester of pregnancy</td>
<td>Frequency: irregular users (≤1 joint/wk, moderate (2-5/wk), heavy (&gt;5/wk)</td>
<td>SES, OB hx, medical hx, standard demo, other drugs, EtOH, tobacco</td>
<td>Heavy use of marijuana reduced the length of gestation by 0.8 weeks (p=0.008) Increasing use associated with decreasing length of gestation</td>
<td>Marijuana use not well-quantified, especially for more frequent users Self-report data collected at early in pregnancy, no later pregnancy data</td>
</tr>
<tr>
<td>Hatch 1986</td>
<td>366 (10)</td>
<td>Planned delivery at single institution</td>
<td>Self-report by structured interview early in pregnancy</td>
<td>Frequency: none, occasional (≤1x/month), regular (&gt;2/month)</td>
<td>OB hx, standard demo, other drugs EtOH, tobacco</td>
<td>Use associated with increased rate of PTB (&lt;37 wks) in white women (OR 1.9, 95% CI 1.0-3.9) No association with PTB in women of other races</td>
<td>Marijuana use not well-quantified, especially for more frequent users Self-report data collected at early in pregnancy, no later pregnancy data</td>
</tr>
<tr>
<td>Kliegman 1994</td>
<td>34 (8)</td>
<td>Single institution</td>
<td>Self-report by structured interview at time of delivery Biologic samples</td>
<td>THC in maternal urine at time of delivery</td>
<td>SES, OB hx, standard demo, other drugs, EtOH, tobacco</td>
<td>No association with PTB (OR 1.89, 0.34-10.50)</td>
<td>Study designed to assess cocaine exposure primarily Marijuana use not quantified</td>
</tr>
<tr>
<td>Linn 1983</td>
<td>1,246 (10)</td>
<td>Single institution</td>
<td>Self-report by structured interview postpartum</td>
<td>Frequency: occasional, weekly or daily use</td>
<td>SES, OB hx, medical hx, standard demo, other drugs, EtOH, tobacco</td>
<td>No association with PTB (OR 1.02, 0.82-1.27)</td>
<td>Possible recall bias, exposure data collected postpartum Marijuana use not well-quantified</td>
</tr>
<tr>
<td>Tennes 1985</td>
<td>257 (34)</td>
<td>Two affiliated institutions</td>
<td>Self-report by structured interview at one prenatal visit and postpartum</td>
<td>Frequency quantified by trimester: light (≤1 X/wk), moderate (&gt;1/wk but &lt;1/day), heavy (&gt;1/day)</td>
<td>SES, OB hx, medical hx, standard demo, other drugs, EtOH, tobacco</td>
<td>No odds ratio reported for PTB (0% PTB rate in ≥3x/wk users and 7% in non-users) Total marijuana use in pregnancy positively correlated with increased gestational age at birth (r=.10), average of</td>
<td>Possible recall bias, only two sessions of self-report No PTB (0%) in the non-users as comparison group Finding of longer length of gestation</td>
</tr>
</tbody>
</table>
### Secondary Analysis of a Prospective Cohort

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Sample Size</th>
<th>Study Design</th>
<th>Data Collection Method</th>
<th>Postpartum</th>
<th>SES, OB hx, Other Drugs, EtOH, Tobacco</th>
<th>PTB Association</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bada 2005</td>
<td>812 (9)</td>
<td>Multicenter, 4 university-based centers</td>
<td>Self-report by structured interview prior to delivery</td>
<td>Reported use: yes/no</td>
<td>SES, OB hx, medical hx, standard demo, other drugs, EtOH, tobacco</td>
<td>No association with PTB (OR 1.21, 0.9-1.61)</td>
<td>Not designed to assess marijuana specifically (Maternal Lifestyle Study) Marijuana use not quantified</td>
</tr>
<tr>
<td>Gibson 1983</td>
<td>392 (5)</td>
<td>Two affiliated institutions</td>
<td>Self-report by structured interview at one prenatal visit and postpartum</td>
<td>Frequency: ≤1x/wk, &gt;1/wk</td>
<td>Standard demo, OB hx (parity only), EtOH, tobacco</td>
<td>High proportion of PTB among &gt;1x/wk users (25% vs 6% in non-users, p&lt;0.001)</td>
<td>Marijuana use not well-quantified</td>
</tr>
<tr>
<td>Janisse 2014</td>
<td>748 (24)</td>
<td>Single institution</td>
<td>Self-report by structured interview at each prenatal visit</td>
<td>Proportion of prenatal visits with reported use: 1-33%, 34-66%, or 67-100%</td>
<td>SES, OB hx, medical hx, standard demo, other drugs, EtOH, tobacco</td>
<td>Not associated with PTB</td>
<td>Study designed to assess EtOH exposure primarily Population limited to African Americans Marijuana use not well-quantified</td>
</tr>
<tr>
<td>Saurel-Cubizolles 2014</td>
<td>156 (1)</td>
<td>Population-based study, all births in France during a single week</td>
<td>Self-report by structured interview 2-3 days postpartum</td>
<td>Frequency: &lt;1x/month, 1-9/month, ≥10/month</td>
<td>SES, standard demo, EtOH, tobacco</td>
<td>Any marijuana use associated with spontaneous PTB (OR 2.15, 1.10-4.18) No association with PTB when only women with marijuana use and no concurrent tobacco use were analyzed (OR 1.22, 0.29-5.06) Recall bias Low prevalence of use concerning for ascertainment bias for marijuana exposure Marijuana use not well-quantified</td>
<td></td>
</tr>
<tr>
<td>Shiono 1995</td>
<td>822 (11)</td>
<td>Multicenter, 7 university-based clinics</td>
<td>Self-report by structured interview at one prenatal visit Biologic samples</td>
<td>Frequency: number of times/wk THC in maternal serum</td>
<td>SES, OB hx, medical hx, standard demo, other drugs, EtOH, tobacco</td>
<td>No association with PTB when marijuana use assessed by self-report or positive serum assay for THC (OR 1.1, 0.8-1.3) Increased odds of PTB with positive serum assay in isolation but not with self-report</td>
<td>Study designed to assess association between vaginal infections and PTB Marijuana use not well-quantified</td>
</tr>
<tr>
<td>van Gelder 2010</td>
<td>189 (3)</td>
<td>Population-based, U.S. National Birth Defects Prevention Study</td>
<td>Self-report by structured interview 6 wks to 24 months post-delivery</td>
<td>Reported use: yes/no by trimester</td>
<td>SES, OB hx, medical hx, standard demo, other drugs, EtOH, tobacco</td>
<td>No association with PTB (OR 1.0, 0.6-1.9) No difference by trimester of use</td>
<td>Recall bias, interview up to 2 years postpartum Not designed for marijuana exposure specifically (birth defects registry) Marijuana use not well-quantified</td>
</tr>
</tbody>
</table>

THC is delta-9-tetrahydrocannabinol. PTB is preterm birth (<37 weeks). SAB is spontaneous abortion. SES is socioeconomic status. OB hx is obstetrical history. Medical hx is medical history. Standard demo is some measure of standard demographics including maternal age, race, body mass index. EtOH is alcohol use. Wk is week.

* a Studies that did not adjust for tobacco use and retrospective cohorts are not included in this summary table.
<table>
<thead>
<tr>
<th>Study and Number in Cohort</th>
<th>Marijuana-Exposed Women, n(%)</th>
<th>Study Design and Setting</th>
<th>Data Source</th>
<th>Marijuana Measure</th>
<th>Other Variables Considered in Analysis</th>
<th>Findings (adjusted odds ratios with 95% confidence intervals reported when available)</th>
<th>Limitations and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Major Congenital Malformation</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Linn 1983&lt;sup&gt;15&lt;/sup&gt; N=12,424</td>
<td>1,246 (10)</td>
<td>Prospective cohort Single institution</td>
<td>Self-report by structured interview postpartum</td>
<td>Frequency: occasional, weekly or daily use</td>
<td>SES, OB hx, medical hx, standard demo, other drugs, EtOH, tobacco</td>
<td>Rate of major malformation: 2.6% non-users, 3.2% occasional, 3.9% weekly, 3.6% daily No association with major congenital anomalies (OR 1.36, 95% CI 0.97-1.91)</td>
<td>Possible recall bias, exposure data collected postpartum No data on trimester of exposure Marijuana use not well-quantified</td>
</tr>
<tr>
<td>Gibson 1983&lt;sup&gt;14&lt;/sup&gt; N=7,301</td>
<td>392 (5)</td>
<td>Secondary analysis of a prospective cohort Two affiliated institutions</td>
<td>Self-report by structured interview at one prenatal visit and postpartum</td>
<td>Frequency: ≤1x/wk, &gt;1/wk</td>
<td>Standard demo, OB hx (parity only), EtOH, tobacco</td>
<td>Rate of major malformation: 4.2% in cohort, rates by non-users and users of marijuana not provided No association with congenital anomalies, no odds ratio reported</td>
<td>No data on trimester of exposure Marijuana use not well-quantified</td>
</tr>
<tr>
<td>Gastroschisis</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Forrester 2006&lt;sup&gt;41&lt;/sup&gt; N=316,508</td>
<td>829 (0.3)</td>
<td>Retrospective cohort from a Hawaiian birth defects registry</td>
<td>Self-report in medical record or positive urine toxicology screen at delivery</td>
<td>Reported use: yes/no THC in maternal urine at time of delivery (ordered clinically)</td>
<td>None</td>
<td>N=109 total cases of gastroschisis, N=3 cases of gastroschisis in marijuana-exposed Rate ratio of marijuana users compared to women with other live births 23.11, 95% CI 4.69-69.34</td>
<td>Low prevalence of marijuana use (0.3%) indicates incomplete ascertainment of exposure No adjustment for possible confounders No data on trimester of exposure Marijuana use not well-quantified</td>
</tr>
<tr>
<td>van Gelder 2009&lt;sup&gt;42&lt;/sup&gt; N=10,241 cases with anomalies and 4,967 controls</td>
<td>610 (4)</td>
<td>Retrospective cohort from a multi-state birth defects registry</td>
<td>Self-report by structured interview 6 wks to 24 months post-delivery</td>
<td>Reported use: yes/no from 1 month pre-pregnancy to end of pregnancy</td>
<td>Standard demo including maternal age at delivery, ETOH, tobacco, folate use, maternal diabetes</td>
<td>N=485 total cases of gastroschisis, N=189 cases of gastroschisis in marijuana-exposed No association with gastroschisis (OR 1.3, 0.9-1.8)</td>
<td>Possible recall bias, women interviewed 6 weeks to 24 months after delivery No data on trimester of exposure Marijuana use not well-quantified</td>
</tr>
<tr>
<td>Ventricular Septal Defect (VSD)</td>
<td></td>
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<tr>
<td>Williams 2004&lt;sup&gt;43&lt;/sup&gt; N=122 cases with a VSD and 3,029 controls</td>
<td>253 (8)</td>
<td>Retrospective cohort from Atlanta Birth Defects Case-Control Study</td>
<td>Self-report by structured telephone interview postpartum</td>
<td>Reported use: ≤ 2 days/wk, ≥ 3 days/wk from 3 months pre-pregnancy to end</td>
<td>Cases matched to controls by birth year, race, birth period, and hospital of birth Adjusted for maternal</td>
<td>N=122 total cases of VSD, N=20 cases of VSD in marijuana-exposed Marijuana use associated with VSD (adjusted OR 1.90, 1.29-1.81)</td>
<td>Possible recall bias, women interviewed after delivery Incomplete ascertainment of confounding factors</td>
</tr>
<tr>
<td>van Gelder 2009&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Retrospective cohort from a multi-state birth defects registry</td>
<td>Self-report by structured interview 6 wks to 24 months post-delivery</td>
<td>Reported use: yes/no from 1 month pre-pregnancy to end of pregnancy</td>
<td>Standard demo including maternal age at delivery, EtOH, tobacco, folic acid use, maternal diabetes</td>
<td>Marijuana use not well-quantified</td>
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</tr>
<tr>
<td>N=10,241 cases with anomalies and 4,967 controls</td>
<td>610 (4)</td>
<td></td>
<td></td>
<td>N= 927 total cases of perimembranous VSD, N=34 cases of perimembranous VSD in marijuana-exposed</td>
<td>Possible recall bias, women interviewed 6 weeks to 24 months after delivery</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No association with VSD (OR 0.9, 0.6-1.4)</td>
<td>No data on trimester of exposure</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Marijuana use not well-quantified</td>
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</tr>
</tbody>
</table>

### Anencephaly

<table>
<thead>
<tr>
<th>van Gelder 2009&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Retrospective cohort from a multi-state birth defects registry</th>
<th>Self-report by structured interview 6 wks to 24 months post-delivery</th>
<th>Reported use: yes/no from 1 month pre-pregnancy to end of pregnancy</th>
<th>Standard demo including maternal age at delivery, EtOH, tobacco, folic acid use, maternal diabetes</th>
<th>Marijuana use only associated with anencephaly in a sub-analysis restricted to 1&lt;sup&gt;st&lt;/sup&gt; month after conception exposure (OR 2.5, 95% CI 1.3-4.9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=10,241 cases with anomalies and 4,967 controls</td>
<td>610 (4)</td>
<td></td>
<td></td>
<td>N=244 total cases of anencephaly, N=12 cases of anencephaly in marijuana-exposed</td>
<td>Possible recall bias, women interviewed 6 weeks to 24 months after delivery</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Marijuana use only associated with anencephaly in a sub-analysis restricted to 1&lt;sup&gt;st&lt;/sup&gt; month after conception exposure (OR 2.5, 95% CI 1.3-4.9)</td>
<td>No data on trimester of exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Marijuana use not well-quantified</td>
<td></td>
</tr>
</tbody>
</table>

95% CI is 95% confidence interval for reported odds ratio. THC is delta-9-tetrahydrocannabinol. SES is socioeconomic status. OB hx is obstetrical history. Medical hx is medical history. Standard demo is some measure of standard demographics including maternal age, race, body mass index. EtOH is alcohol use. Wk is week.

<sup>a</sup> Rates of other birth defects that were higher in women with isolated (no other drug use) marijuana use in Forrester et al (2006) study were encephalocele, hydrocephaly, microcephaly, anotia/microtia, tetralogy of Fallot, atrial septal defect, pulmonary valve atresia/stenosis, hypoplastic left heart syndrome, cleft lip and palate, pyloric stenosis, anal/rectal/large intestinal atresia/stenosis, obstructive genitourinary defect, polydactyly, syndactyly, and reduction deformity of upper limbs. These findings are not further described given the limitations in the methodology of this study with no correction for possible confounders.

<sup>b</sup> No association was found between marijuana and several other birth defects in the van Gelder et al (2009) study including spina bifida, anotia/microtia, d-transposition of the great arteries, tetralogy of Fallot, hypoplastic left heart syndrome, coarctation of the aorta, pulmonary valve stenosis, atrial septal defect, cleft lip and palate, esophageal atresia, anorectal atresia, hypospadias, transverse limb deficiency, craniosynostosis, and diaphragmatic hernia.
Table 5. Recommendations for Clinicians Regarding Marijuana Use in Pregnancy

Screen all women verbally for marijuana use at intake to obstetrical care
   Consider re-screen later in pregnancy
   Consider urine toxicology screening in high-risk patients
Recommend avoiding marijuana in pregnancy
   Marijuana crosses the placenta
Counsel women regarding uncertainty of effects on perinatal outcomes
   Possible increased risk of stillbirth
   Possible increased risk of preterm birth (mixed data)
Counsel women regarding uncertainty of effects on offspring
   Possible adverse effects on neurodevelopment
   Possible increased risk of fetal growth restriction (mixed data)
   No established association with specific congenital anomalies
Refer women who use marijuana and desire cessation to appropriate resources
   Local substance use programs
Do not otherwise modify clinical care
   Growth ultrasounds not indicated outside of study protocols
   Screening for preterm birth with cervical length not indicated
   Antenatal surveillance not indicated
Recommend avoiding marijuana while lactating
   Marijuana is passed to the neonate in breastmilk
   Possible adverse effects on early neurodevelopment
   Provide counseling, but do not withdraw lactation support

Recommendations in the Table above reflect the opinions of the authors after a thorough review of the existing literature on marijuana in pregnancy and lactation.
Figure Legends

Figure 1. An increasing number of states in the United States have legalized both medicinal and recreational marijuana use.
Map of Legalization of Marijuana in the United States

- Green: Recreational and Medical
- Light Green: Medical Marijuana only