

# What Every Pediatric Gynecologist Should Know About Marijuana Use in Adolescents



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## ABSTRACT

Use of marijuana in adolescent girls is common and shows no sign of decreasing. With recent trends toward legalization of “recreational” and “medical” marijuana products, adolescents are increasingly faced with information and misinformation about the health effects of marijuana use. We review the current literature on the risks and potential benefits of marijuana use during adolescence with a specific focus on pediatric and adolescent gynecological conditions. Despite limited research on this topic, the many risks associated with marijuana use in adolescents, including negative effects on the developing brain and adverse reproductive, sexual health, and mental health outcomes, likely outweigh potential benefits in this population.

**Key Words:** Adolescent, Gynecology, Cannabis, Substance use, Pregnancy, Dysmenorrhea

## Introduction

Daily use of marijuana has been steadily increasing among adolescents and since 2015, has even surpassed daily tobacco cigarette use in this population.<sup>1</sup> This contrasts with a general trend of decreasing substance use among adolescents over the past 2 decades.<sup>2</sup> Although the correlation between adolescent marijuana use and the increasing legality and availability of marijuana for “medical” and adult use remains controversial, the perceived riskiness of marijuana use is now at its lowest point among teens.<sup>3</sup> Adolescent girls have rates of marijuana use that are slightly lower than that of adolescent boys, however, this gap has been narrowing with time.<sup>4</sup> Although girls tend to initiate use later than boys, use is comparable between both genders by the end of high school.<sup>4</sup>

A rapidly expanding cannabis industry has put forward a plethora of new marijuana products including several formulations manufactured specifically for women such as skin care products and vaginal lubricants. At the same time, pro-marijuana Web sites and social media postings have become omnipresent and practically unavoidable for adolescents, making it challenging to accurately assess the facts regarding the health effects of marijuana.<sup>5</sup>

In this narrative review, we define “recreational” and “medical” marijuana and its effect on the developing adolescent body and brain, with a specific focus on adolescent girls. We then review the literature on the potential risks and benefits of marijuana use for common

pediatric and adolescent gynecological conditions. We conclude by discussing concrete strategies for providers caring for adolescent girls to prevent and address marijuana use and provide recommendations about marijuana use in this population.

## Definitions

Marijuana refers to the cannabis plant, which contains several psychoactive substances, and can be consumed in several forms: smoked or inhaled, ingested, or applied topically or directly on the oral, rectal, or vaginal mucosae.<sup>6</sup> Marijuana contains dozens of different cannabinoid molecules that interact with the body's own endocannabinoid system, a system involved in the regulation of several important brain functions such as emotional regulation, pain, mood, sleep, and appetite.<sup>7</sup> Tetrahydrocannabinol (THC) and cannabidiol (CBD) are the 2 most common cannabinoids. THC has psychoactive properties: it can induce a sensation of euphoria and significantly alter perception, alertness, coordination, mood, and energy.<sup>8</sup> CBD is devoid of psychoactive properties. THC and CBD are purported to have a number of potential health properties, most of which are still being investigated, especially in the pediatric population.<sup>9</sup>

We use quotation marks when speaking about “medical” and “recreational” marijuana because the terms have been coined by the industry and can be misleading. In fact, although “medical marijuana” is often a term loosely used to designate marijuana products used for medical purposes, it is not at all equivalent to pharmaceutical grade cannabinoid products. There are currently only 3 US Food and Drug Administration (FDA)-approved pharmaceutical cannabinoid products: dronabinol (brand names: Marinol [AbbVie Inc.] and Syndros [INSYS Therapeutics Inc.]), nabilone (Cesamet [Meda Pharmaceuticals Inc.]), and CBD (Epidiolex,

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[Greenwich Biosciences Inc.]). The first 2 are made from synthetic THC, whereas the latter is made from the naturally occurring CBD. Of these, only CBD has been approved for use in pediatrics for the treatment of refractory seizures not responding to first-line pharmaceutical treatment.<sup>10</sup>

The Drug Enforcement Agency classifies marijuana as a schedule 1 substance, meaning that it has no accepted medical use, thus the federal FDA does not regulate any “medical marijuana products”<sup>11</sup> except for the 3 pharmaceutical-grade cannabinoid products already mentioned. States that permit the sale of “medical marijuana” are responsible for the regulation and oversight and these products, which do not undergo the extensive quality review and stringent approval processes required by the FDA. Formulation, concentration, and consistency can vary substantially from product to product.<sup>12</sup> This might be particularly problematic for children and young adolescents for whom even relatively small differences in dose might result in large physiological differences.

### Marijuana Use and Its Effects in Adolescents

Earlier age of initiation of marijuana use is strongly associated with the possibility of developing an addiction to marijuana and other substances later in life.<sup>13</sup> Marijuana, a highly lipophilic substance, easily crosses the blood-brain barrier and deposits in the layer of glial cells that coat and protect human neurons. The presence of cannabinoids—molecules found in marijuana—in the central nervous system results in an acute and chronic slowing of cognitive processes and alteration in brain development.<sup>14</sup> In fact, cannabis use during adolescence is associated with a permanent reduction in intellectual capacities, motivation, and lifetime achievement.<sup>15</sup> Marijuana use during adolescence is also associated with a two- to fivefold increase in odds of developing chronic mental health disorders such as depression, anxiety, and schizophrenia later in life.<sup>16,17</sup> Although evidence on the exact mechanisms responsible for the chronic psychological and functional effects seen in adolescents is still emerging, it has been suggested that the disruption in endogenous dopamine secretion resulting from marijuana use might trigger or exacerbate lack of motivation and mental health symptoms.<sup>18</sup> Furthermore, a recent study has shown significant changes in gray matter in key areas of the brain involved with cognition, emotional regulation, and memorization after as little as single-time use of marijuana in youth.<sup>19</sup>

Sex-specific differences in marijuana effects have been described, on the basis of data from emerging preclinical and clinical literature.<sup>20</sup> For reasons that remain poorly characterized and might be a combination of social and genetic, metabolic, and hormonal factors, girls tend to show a telescoping effect with a faster progression from first use of marijuana to problematic use compared with boys.<sup>21</sup> It has been suggested that girls also endorse greater anxiolytic and antinociceptive effects linked to marijuana use than boys, although mechanisms that would explain such differences remain unclear.<sup>20</sup>

Acute marijuana use and intoxication are associated with several physiological symptoms such as increased heart rate

and blood pressure, conjunctival redness, and impaired coordination, that are largely thought to be due to THC.<sup>8</sup> Psychotic symptoms such as paranoia or hallucinations are also common and were reported by 63 out of 146 (43%) adolescents ages 14 to 18 with a history of marijuana use recruited in primary care in a recent observational trial.<sup>22</sup> Although marijuana is considered less addictive than other psychoactive substances such as nicotine, cocaine, or heroin, it remains highly addictive.<sup>23</sup> Newer, more potent “marijuana products” entering the market like waxes and oils might have a higher addiction potential than the traditional cannabis plant upon which most previous studies of addiction potential have been based.<sup>24</sup> Frequent marijuana users commonly endorse *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition substance use disorder criteria, suggesting loss of control over use.<sup>25</sup> In addition, regular marijuana users often develop symptoms of withdrawal, which include irritability, sleep difficulties, loss of appetite, nausea, and abdominal pain, and usually start 1 or 2 days after last use and can extend to 4 to 8 weeks.<sup>26</sup> Women report stronger withdrawal symptoms than men, possibly representing an obstacle for cannabis cessation.<sup>27</sup>

### Marijuana Use and Gynecological Conditions

The cannabis plant has a long history, tracing back to China in 4000 BC, of being used for a range of women’s health conditions including dysmenorrhea, dysuria, and hyperemesis gravidarum.<sup>28</sup> With the increasing availability of “medical” marijuana products marketed for such diverse uses as the treatment of chronic pain including pelvic pain, low mood, low appetite, and nausea or vomiting, more adolescents are using “medical marijuana.”<sup>29</sup> Although research efforts to understand potential benefits of cannabinoid products in adolescents is emerging, evidence remains very limited overall, with refractory epilepsy, and chemotherapy-induced nausea and vomiting—which might be relevant to certain gynecological cancers that present in childhood—being the only recommended use of cannabinoid products in adolescent girls.<sup>30</sup> We discuss current evidence on the risks and potential benefits of cannabinoid use for common gynecological presentations relevant to adolescents. We also note that if cannabinoid therapy is found to be effective in clinical trials of pharmaceutical grade products, how this knowledge translates into a risk-benefit profile regarding the use of “medical marijuana” products remains an open question.

#### *Pelvic Pain, Dysmenorrhea, and Premenstrual Syndrome*

The endocannabinoid system plays an important role in the regulation of pain. In fact, cannabinoid receptors found in the central and peripheral nervous systems exert modulatory action at all stages of pain processing pathways.<sup>31</sup> According to a recent report from the National Academies of Sciences, Engineering, and Medicine, there is “conclusive or substantial evidence” that cannabinoids can be effective for the treatment of chronic pain in adults.<sup>17</sup> There is also increasing interest in investigating the

effectiveness of cannabinoid formulations with varying levels of THC and CBD for the treatment of pelvic pain.<sup>32</sup> However, the evidence remains insufficient to support the effectiveness of use of cannabinoids for pain conditions in children and adolescents, especially in light of known adverse effects in this age group.<sup>30,33</sup>

Some studies have suggested that cannabinoids could be a promising treatment for pelvic pain associated with endometriosis, because of the interactions of the endocannabinoid system with several mechanisms such as inflammation, neuropathic, and nociceptive pain, which all play a prominent role in the pathophysiology of this condition.<sup>34</sup> Specific cannabinoids have been shown to decrease cell proliferation and affect endometrial-associated hyperalgesia and the migration of endometrial cells.<sup>35,36</sup> In a randomized trial of adolescents and young adults ages 16–24 who received a combination of transpolydatin—a precursor molecule of the antioxidant resveratrol—and palmitoylethanolamine—a member of the extended cannabinoid family—108 of the 110 (98%) young women in the treatment group reported a decrease in pelvic pain associated with primary dysmenorrhea or endometriosis compared with 62 out of 110 (56%) in the placebo group.<sup>37</sup> Nonetheless, clinical evidence on the use of cannabinoid products and formulations that would be safe and effective for adolescents with pelvic pain remains very sparse.

Cannabis has been proposed as a nonhormonal treatment for premenstrual symptoms. In a recent study, women older than the age of 18 years who were cannabis users reported expectancies that cannabis use would ameliorate symptoms of premenstrual syndrome (PMS) and premenstrual dysphoric disorder, including irritability, sleep problems, fatigue, and breast tenderness,<sup>38</sup> although these participant claims were not objectively verified in this observational study. It has been suggested that cannabis could be considered as a treatment alternative for PMS and premenstrual dysphoric disorder in adult women because of a favorable side effect profile compared with other hormonal treatments.<sup>28</sup> However, evidence is lacking for adolescents and younger women with a still developing brain who are at increased risk of developing cognitive impairments from cannabis use. Others have claimed that doses of marijuana that are low enough not to cause significant cognitive impairment might be sufficient to bear some effectiveness in treating dysmenorrhea and PMS although because of the lack of rigorous study in this area, this remains mostly hypothetical.<sup>39</sup>

#### *Fertility, Sexuality, and Contraception*

Regular use of marijuana can decrease female fertility through the disruption of the hypothalamic release of gonadotropin-releasing hormone.<sup>40</sup> This can lead to a reduced production of estrogen and progesterone and a subsequent increase in the frequency of anovulatory cycles. Animal studies (mostly done with rhesus monkeys that have ovulatory cycles similar to those of humans) suggest that these effects tend to decrease with time and with the development of increased tolerance to marijuana.<sup>41</sup> A

recent study has also shown that women with regular menstrual cycles and chronic use of tobacco and marijuana tend to have a shorter luteal phase than women who use tobacco only, although further studies are needed to better understand the clinical implications of this finding.<sup>42</sup>

Estrogen secretion generally increases sensitivity to the physiological and psychological effects of marijuana whereas progesterone has the opposite effects,<sup>40</sup> although the clinical significance of this finding remains unclear. Whereas increased drug-liking and euphoria have been reported for other drugs like cocaine and amphetamine during the follicular phase, when estrogen levels are high and progesterone levels are low, this has not been clearly described with marijuana, but might warrant further investigation.<sup>43</sup>

Cannabinoids and oral contraceptives are both metabolized in the liver by cytochrome p450 (CYP) enzymes.<sup>44</sup> THC is an inducer of CYP1A2, which can potentially lead to decreases in levels of certain anti-inflammatory agents, such as naprosyn as well as several antidepressant and antipsychotic medications. CBD is a potent inhibitor of CYP3A4 and CYP2D6 and can lead to significant increases in levels of other medications such as calcium channel blockers, benzodiazepine, tricyclic antidepressants, antipsychotics,  $\beta$ -blockers, and opioids, including codeine and oxycodone.<sup>44</sup> At the time of writing, there were no published accounts of decreased effectiveness of the oral contraceptive pill with concurrent marijuana use, although research on this topic remains limited and caution is advised, especially if using high-potency THC or CBD products, which might also contain other chemicals. If nothing else, the increased risk of unprotected sexual activity, and the risk of forgetting to take oral contraceptives or changing a contraceptive ring or patch while under the influence of marijuana might help explain increased rates of unplanned pregnancies in young women who use marijuana.<sup>45</sup> Of similar concern, marijuana use during adolescence has been shown to be an independent risk factor for sexually transmitted infections.<sup>46</sup>

#### *Pregnancy and Breastfeeding*

The American College of Obstetrics and Gynecology has taken a strong stance on the risks of marijuana use before, during, and after pregnancy, for the mother and the fetus or newborn.<sup>47</sup> It has been shown that at least one-third of female marijuana users report ongoing marijuana use during pregnancy and close to one-fifth of pregnant women who use marijuana, meet criteria for a cannabis use disorder.<sup>48</sup> According to a recent observational study using 2014 data from the National Survey on Drug Use and Health, past-month cannabis use is more common in adolescent and young adult women who are pregnant (7.5% of pregnancies in 18- to 25-year-old women vs 2.1% in 25- to 44-year-old women in sample of 1,117 pregnant women), which is concerning considering the effects that marijuana can have on the developing brain that continues to develop until the mid-twenties.<sup>49</sup>

Marijuana use during pregnancy has been associated with fetal growth restriction, stillbirth, and preterm birth, although existing studies are often confounded by the

effects of other substances, predominantly nicotine/tobacco.<sup>50</sup> Some studies have also suggested that marijuana use during pregnancy might be associated with a small increase in rates of congenital anomalies, but the evidence is conflicting.<sup>51</sup> Maternal marijuana use might also affect fetal neurological development, subsequently leading to increased risks of hyperactivity and poor school and cognitive function during childhood but again, the evidence on this point is conflicting.<sup>52</sup> An important notion is that the nature and potency of cannabis products have evolved tremendously in the past 3 decades. For instance, the average THC content of smoked marijuana has increased at least threefold since the 1990s, from approximately 4% in 1995 to 12% in 2014, without mentioning the increased availability of concentrated forms of marijuana (ie, waxes and oils) that might contain up to 80% or 90% THC.<sup>24</sup> Older studies on the effects of marijuana use during pregnancy were conducted with very different marijuana products than the ones that many young women are using now and might skew the results of systematic reviews and meta-analyses conducted on this topic.<sup>50</sup>

A recent survey of 76 lactation providers in the United States estimated that approximately 15% of breastfeeding mothers (1,203 out of sample of 7,843 breastfeeding mothers) reported using marijuana.<sup>53</sup> Although the exposure to neonates is thought to be small (less than 1% of maternal exposure), and the effects of such an exposure remain largely unknown, the American College of Obstetricians and Gynecologists also recommends avoiding marijuana use during lactation and breastfeeding for similar reasons that they recommend avoiding marijuana use during pregnancy.<sup>47</sup>

### Weight and Eating Disorders

Marijuana has been well known to cause food cravings (often called “munchies”), especially in the period after use. This is thought to be mediated by the activation of cannabinoid type 1 (CB1), which might directly or indirectly increase appetite and stimulate eating.<sup>54</sup> As a corollary, loss of appetite is one of the prominent symptoms of marijuana withdrawal, so much so, that marijuana withdrawal is an important diagnostic consideration in adolescents who present with disordered eating, who might otherwise be diagnosed with an eating disorder.<sup>55</sup> Nevertheless, the association between use of cannabis during adolescence and long-term weight changes remains controversial. In fact, a recent study suggests that use of marijuana during adolescent years had no significant long-term effect on weight into midlife in a cohort of adolescents in Denmark followed over 20 years.<sup>56</sup>

Cannabis hyperemesis syndrome is a rare, yet under-recognized clinical entity characterized by intractable nausea and vomiting (often relieved by taking a hot shower) found in individuals who are regular marijuana users.<sup>57</sup> Affected individuals, who tend to be young (starting in adolescence), often present with weight loss and abdominal symptoms that might resemble other gastrointestinal or gynecological presentations such as ectopic pregnancy or PMS.<sup>58</sup> Clinicians should keep a high level of suspicion for this condition when assessing an adolescent who presents with persistent vomiting and marijuana use.

### Overview of Marijuana Use Prevention and Treatment

Rates of screening for alcohol and substance use among pediatric providers have been increasing steadily over the past 3 decades, offering new opportunities for prevention and early intervention.<sup>59</sup> The American Academy of Pediatrics endorses the use of brief, validated screening tools at each health maintenance visit, but also at specialty and urgent care visits when appropriate.<sup>60</sup> By asking an adolescent a simple question: “In the past year, how many times did you use marijuana” and providing structured response categories (never, once or twice, monthly, weekly or more), providers can obtain a reliable indicator of the level of risk for a mild, moderate, or severe marijuana use disorder.<sup>61</sup>

Although there are currently no approved pharmaceutical treatments for marijuana use disorders in adolescents, brief interventions using motivational interviewing, or longer-term individual or group counseling or therapy might help decrease or stop marijuana use.<sup>62</sup> Pediatric and adolescent gynecologists can play an important role in early detection, brief intervention, and referral to counselors in the community for marijuana use disorder when indicated. This can also help prevent escalation of substance use and use of other substances that might have a negative effect on the health of the adolescent.

### Conclusions

Unlike other substances, use of marijuana has remained relatively stable in the past decade, with increases in daily users among adolescent girls, in the context of a rapidly expanding market of “recreational” and “medical” marijuana products. Although research remains limited, there are very few evidenced-based indications for the use of cannabinoids in pediatric and adolescent gynecological conditions. Further, to the extent that cannabinoids have therapeutic value, administering them in the form of marijuana, and regulating “medical marijuana” loosely, remains highly questionable from a scientific standpoint. Importantly, marijuana carries severe risks to the developing brain and is associated with increased incidence of use of other drugs, mental health problems, decreased fertility, unprotected sexual activity, and teenage pregnancy. Adolescents and young women of childbearing age should be informed that the use of marijuana during pregnancy and lactation is not recommended and might be dangerous for the mother and the fetus. Having open and educated discussions about marijuana use with adolescents might help prevent unwanted harms related to marijuana use. The need for pediatric providers to stay aware of new research advances and product development is also critically important in such a rapidly changing field.

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