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Review

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Medical Marijuana: An Overview for Obstetricians/Gynecologists

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Abstract

As of May 2021, 36 states and four territories have approved medical cannabis laws and 17 states, two territories, and the District of Columbia, have approved adult use recreational cannabis laws. Currently, most of the USA is covered by medical cannabis laws in one form or another, so, as with other therapeutics, it behooves us as caregivers to become educated on what cannabis is, how it is given, who is a candidate for treatment, and more importantly, who is not a candidate for treatment. Numerous studies have documented that our caregivers are ill prepared to counsel and utilize cannabis products in our patient populations, considering that approximately 2.5% of the world's population uses cannabis, including 9% of eighth graders and 35% of 12th graders in the USA, as well as 7% of pregnant women. This is a basic expert review of the endocannabinoid system in humans, cannabis constituents and pharmacology, routes of administration, medical cannabis uses, and cautions, designed to address the educational deficits documented by learner analysis of providers.

Keywords: Medical cannabis; Medical cannabis in obstetrics/gynecology; Cannabis pharmacology; Cannabis routes of administration; Medical cannabis uses

Introduction

As of May 2021, 36 states and four territories have approved medical cannabis laws and 17 states, two territories, and the District of Columbia, have approved adult use recreational cannabis laws. South Dakota's and Mississippi's laws were overturned in the courts and are being appealed [1]. Currently, most of the USA is covered by medical cannabis laws in one form or another, so, as with other therapeutics, it behooves us as caregivers to become educated on what cannabis is, how it is given, who is a candidate for treatment, and more importantly, who is not a candidate for treatment. Numerous studies in countries such as Canada, which have a national mandate for cannabis availability, as well as the USA, have shown that our providers, be they attending physicians, physicians in training, advanced practice nurses, pharmacists, or physician assistants, are ill prepared to counsel and utilize cannabis products in our patient populations [2, 3]. Approximately 2.5% of the world's population uses cannabis, including 9% of eighth graders and 35% of 12th graders in the USA [4], as well as 7% of pregnant women [5].

Cannabis has been referenced in man's written word as far back as 2900 BC with the Chinese Emperor Fu Hi, and even further back in archeological excavations. Medical use was documented in Persia, ancient Greece, and India prior to 1 AD [6]. Cannabis was brought to North America with the Jamestown settlers in 1611, and hemp was grown by George Washington and Thomas Jefferson on their farms in the 1700s. Marijuana was added to the US Pharmacopeia in 1850, but marijuana prohibition laws started to be implemented by the states between 1915 and 1927, and by 1970, congress passed the Controlled Substances Act which classified marijuana as a schedule 1 drug with "no accepted medical use", a designation that remains today on the federal level. The 2018 Agricultural Improvement Act (Farm Bill) effectively removed hemp from the Controlled Substances Act but left marijuana. Hemp is defined as cannabis with low levels of THC (delta-9-tetrahydrocannabinol less than 0.3% by dry weight). Marijuana is defined as cannabis with greater than 0.3% THC by dry weight, generally 5-35% [7]. Because of its schedule 1 status, medical cannabis can only be "recommended" in the USA by licensed providers, not prescribed. There are over 100 cannabinoids in cannabis but the most studied are delta-9-tetrahydrocannabinol (Δ-9-THC) and cannabidiol (CBD). This manuscript is roughly divided into major headings which are additionally referenced from an educational presentation compiled at University of Maryland Baltimore School of Pharmacy (MCST program (Masters in Medical Cannabis Science and Therapeutics)) by Stephen Zimberg MD, MCST, Zach Riney MCST, Cameron Howe MCST, and Leslie Mathews MD, MCST (portions used with permission and cited).

The Endocannabinoid System (ECS)

A discussion of medical cannabis and its use is generally divided into four parts: the ECS [8], cannabis constituents, routes of administration, and pharmacology and therapeutics. The ECS is a master regulator of our body systems, and a system that many of us have never heard of. It effects relaxa-

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tion and sleep, protection, mood, memories, appetite (both positive and negative), reproduction, pain sensation, and others. It is composed of three basic components: cannabinoid receptors (primarily cannabinoid 1 (CB1) and cannabinoid 2 (CB2)), though there are more; endocannabinoids (small, internally synthesized lipophilic molecules that engage the cannabinoid receptors); and metabolic enzymes which synthesize the endocannabinoids on demand and metabolize them in a self-regulated manner [9].

The CB1 receptors are abundant in the brain, primarily located in the hippocampus which is responsible for memory, the hypothalamus which is responsible for appetite and body temperature, the substantia nigra and mesolimbic pathways which are the reward center of the brain. Importantly, they are absent in the brainstem, hence the lack of serious side effects with excessive stimulation (overdose). Additionally, CB1 receptors are present in the amygdala, which is responsible for emotions and anxiety, the spinal cord which is responsible for pain transmission, and the basal ganglia and cerebellum, which are responsible for movement. Understanding where the CB1 receptors are located and the different area's responses will help with understanding what to expect when activated by either exogenous phytocannabinoids (from the plant), synthetic cannabinoids, or endocannabinoids [10].

The CB2 receptors are located primarily peripherally. They are seen mainly in lymphoid tissues such as the spleen, tonsils, and thymus. CB2 receptors are also present in microglia immune cells and are present in atherosclerotic lesions. There are also other minor cannabinoid receptors (CB3-5, transient receptor potential vanilloid (TRPV1/2), and G protein receptors (GPR) 18, 55, and 119) that are present in all living organisms except insects [11].

The two primary endocannabinoids are anandamide (arachidonoyl ethanolamide (AEA)), also known as the "bliss molecule" and 2-arachidonoylglycerol (2-AG), which is the most common. These are inhibitory neurotransmitters and are both derived from arachidonic acid. They tend to facilitate lowering of pain, nausea, wasting, and brain damage. They increase communication between the amygdala and the frontal cortex and increase exploratory behavior and learning. They were also responsible for decreasing anxiety. These have similar stimulatory patterns to the phytocannabinoids THC and CBD which act in the same areas [8].

The third portion of the ECS is the metabolic enzymes. The two metabolic enzymes of most interest are fatty acid amide hydrolase (FAAH), which is responsible for metabolizing anandamide to arachidonic acid and ethanolamine, and monoacylglycerol lipase (MAGL), which breaks down 2-AG to arachidonic acid and glycerol. In both, the arachidonic acid is recycled. Both are ubiquitous in nature and constantly altering internal cannabinoid levels. They rapidly degrade anandamide and 2-AG to establish homeostasis by up and down modulation of the ECS. So why is this important? The ECS is the primary homeostatic regulatory system of the body. It can be viewed at the body's internal adaptogenic system, constantly working to maintain a vast range of functions in equilibrium. The endocannabinoids broadly work as neuromodulators, and, as such, regulate a wide scope of physiological processes, from fertility to pain [8].

Cannabis Constituents

Cannabis plants are made up of cannabinoids, terpenes, flavonoids, and other minor constituents [12]. The naturally occurring cannabinoids are known as phytocannabinoids. Cannabis for medicinal or recreational purposes is often described as *Cannabis indica*, *Cannabis sativa*, or hybrid. The strain name often correlates with the genetic makeup of the plant, but the chemical profile is vital to understanding what is going into a patient's body and how it will affect them. The percentage of cannabinoids, terpenoids, and flavonoids thus make up the analytical chemistry profile of the plant [13]. So far, approximately 200 cannabinoids have been discovered throughout the different chemovars or strains of the cannabis plant, though only a handful have been researched [14]. Cannabinoids can activate, deactivate, block, or alter receptor sites and some affect the enzymatic metabolism activity. The cannabinoids are highly lipophilic (and thus hydrophobic) and are relatively non-toxic with exceptionally high lethal dose potential (LD_{50} number (A smoker would theoretically have to consume nearly 1,500 pounds of marijuana within about 15 min to induce a lethal response) [15].

The most prominent cannabinoid found in the cannabis plant is Δ-9-THC. It is known to be psychoactive and intoxicating at elevated doses, the main reason for the "high" or "stoned" effect associated with cannabis resulting from its direct binding to the CB1 receptor as a partial agonist. The THC levels in current plants on the market have seen a significant increase over the past 30 years, the average being about 3% THC in the 1970s, to some varieties showing 30% THC by dry weight currently. The metabolite of THC, 11-hydroxy-THC, is 2 - 7 times more potent (psychoactive) than Δ-9-THC, though the carboxy metabolite (11-carboxy-THC) is non-psychoactive. This is what is measured in the drug testing for THC. Tolerance can develop with chronic cannabis use and withdrawal can occur with the cessation of chronic heavy use. THC side effects include dry mouth, dizziness, sleepiness, rapid heartbeat, red eyes, cough (from inhalation), increased anxiety *(biphasic effect), and paranoia [16].

CBD, the second most researched cannabinoid, has more recently become more popular due to the ability to extract it from legal industrial hemp (removed from schedule 1 status by the Farm Bill of 2018). It is a psychoactive molecule in that it can have sedating effects on mental status (and may moderate the effects of THC), but not one that causes a "high" or intoxication like THC. CBD has been observed to have several therapeutic benefits and is not only influential within the ECS, but it can also have modulating effects elsewhere in other body systems and biological responses. CBD works by several mechanisms, depending on the site of action and the concentration. Unlike THC, its side effects are minimal, but drug-drug interactions need to be monitored due to similarities in the way CBD is metabolized and how other common drugs are metabolized (liver cytochrome P450 enzymes). There are other precursor acids which have some pharmacologic properties, Δ-9 tetrahydrocannabinolic acid (THCA precursor of THC), cannabidiolic acid (CBDA precursor of CBD), cannabigerol (CBG), cannabinol (CBN), cannabichromene (CBC), and other minor cannabinoids which are beyond the scope

of this article. Δ-8-THC deserves some mention as it is being marketed openly now. This is similar to Δ-9-THC but produces 50-60% less intoxication effects and is more stable. It does activate CB1 receptors (like Δ-9-THC), but because it is not specifically defined in the schedule 1 statutes, it is allowed (legal) at the present time [17].

The cannabis plant also contains about 200 terpenoids or terpenes, only 30 of which are primary. These are the aromatic component of all essential plant oils and are present in most fruits and vegetables, not just cannabis. They are basic hydrocarbons and are lipophilic/hydrophobic like cannabinoids and do have some pharmaceutical activity as well as the ability to complement the cannabinoids in their pharmacologic actions. These have some common names such as myrcene (clove, earthy, fruity, and herbal), beta-caryophyllene (spicy, woodsy, and pepper like), limonene (citrusy, orange, and spicy), linalool (citrusy, floral, spicy, and lavender), pinene (pine and skunky), and others. Most appear to have anti-inflammatory effects and can potentiate the effects of THC and CBD, the so-called "entourage effect" [18]. In addition to the terpenes, over 20 flavonoids have been identified in cannabis which are pharmacologically active. These are aromatic phenolic compounds that give plants their pigments, attract pollinators, filter UV light, and prevent plant disease. There are two flavonoids unique to cannabis, cannaflavin A and B. The concept of the entourage effect was advanced by Shimon Ben-Shabat and Raphael Mechoulam in 1998; the concept is that the collective synergistic therapeutic potential of several cannabinoids, terpenes, and flavonoids working together give the therapeutic response [18]. Mechoulam and colleagues, incidentally, are credited with working out the components of the ECS, the structure of THC, and structure of CBD in the mid-1960s.

Routes of Administration

Cannabis is generally administered via oral, inhalation, and other routes [19]. Oral administration encompasses edibles (baked goods, sodas, and candies), pills, capsules, and tincture oils. These can be oils and butters, prescription cannabis, herbal cannabis, and synthetic prescriptions approved by the Food and Drug Administration (FDA) (Epidiolex (CBD) used to treat seizures in children, Marinol (THC and dronabinol) used to treat weight loss in patients with acquired immunodeficiency syndrome, and Cesamet (Nabilone) used for chemotherapy-induced nausea and vomiting, none of which are schedule 1 drugs). Outside the USA, there exists Sativex (Nabiximols), a synthetic THC/CBD 1:1 spray mix for muscle spasms and overactive bladder seen in multiple sclerosis patients [20]. Orally administered drugs must be absorbed through the gut and go through first pass metabolism in the liver which greatly decreases their bioavailability. This also means that orally administered dosing will show effects after a delayed absorption period (as opposed to smoking, vaping, or intravenous use), though it will last longer in the system. Delta-9-THC is also metabolized into 11-hydroxy-THC (11-OH-THC), which is much more potent than Δ-9-THC. Patients are at risk of taking too much orally waiting for a therapeutic response, and thinking they have not taken enough, take more, only to find they have taken too much when the full effects are evident.

For inhaled administration, there is traditional smoking, vaporizing (vaping), metered dose inhalers, and nebulizers. With these, one can inhale cannabis flowers (buds), kief (resin glands that contain terpenes and cannabinoids), resin, concentrates, oils/sprays, wax (a potent cannabis concentrate that looks waxy), shatter (brittle cannabis extract concentrate), hashish (dried flower concentrate), and the illicit synthetic cannabinoids such as K2 and spice. The illicit drugs are manufactured in an effort to avoid the schedule 1 regulations by altering the chemical structure of known cannabinoids, often with dangerous side effects. They exist on the market until regulators notice them and ban them on a one-by-one basis. Inhaled administration of medical cannabis has almost immediate blood levels and physiologic response, though the effects are short lived.

Finally, there are other methods of administration such as sublingual, intranasal, rectal, vaginal, intravenous, buccal, and transdermal for which herbal cannabis, lollipops, lozenges, resins, concentrates, lotions, patches, IVs, Nabiximols (Sativex spray), oral sprays, and synthetic prescription cannabis can be used. These have varying bioavailability and varying half-lives, depending on the route. Cannabis for all routes of administration is labeled as full spectrum (having all the compounds found in the parts of the plant), broad spectrum (pharmacologically active cannabinoids and terpenes are present and specific compounds have been removed), and cannabinoid isolates (everything but the chosen cannabinoid has been removed) [21].

There is no absolute dosing schedule for medical cannabis as there are four conventional FDA approved medications. That is to say, the three approved medications in the USA: Marinol (dronabinol), Cesamet (nabilone), and Epidiolex (cannabidiol), and the Sativex (Nabiximols), not yet approved in the USA, do have standard dosing labeling. For conventional medical cannabis, the dosing recommendations are to "start low and go slow" regarding titration of dose. THC is generally given up to 15 mg in divided dosing 2 - 3 times a day. Doses exceeding 20 - 30 mg/day tend to increase adverse events or induce tolerance without improving efficacy [22]. Similarly, CBD has no established dosing guidelines with the exception of psychosis (800 mg) and seizure disorders (25 - 50 mg/kg). For most other indications, doses of 5 - 20 mg per day in divided doses are used. Interestingly, there are sex differences between the male and female response to cannabinoids that encompass the cannabinoid influence on motivated behaviors and stress responses (males have a higher risk of developing cannabis use disorder but females progress toward cannabis use disorder at a faster rate) [23]. Though cannabis use is multifactorial with genetic and environmental factors (socioeconomic status, smoking, alcohol use, and childhood sexual abuse), the genetic contribution to use and abuse is greater in males with an up to four times male/female ratio of lifetime cannabis use seen by adulthood.

Cannabis Pharmacology

THC is a partial agonist at the CB1 and CB2 receptors in the

endogenous cannabinoid system and exerts psychoactive and pain modulatory effects via CB1 agonism [24]. CBD has relatively little affinity with the orthostatic sites of these receptors and may actually inhibit THC binding at the CB1 receptors via another mechanism. THC is thus psychoactive, and CBD is non-psychoactive. Because of the lack of CB1 receptors in the brainstem, overdose of cannabis does not cause respiratory depression, unlike opioids. Cannabis does produce sedation and has significant pharmacodynamic interactions when administered with other central nervous system (CNS) depressant drugs such as sedatives or hypnotics. Its use is associated with both pathological and behavioral toxicity and THC produces dose-dependent performance impairment. In healthy volunteers, it produced psychotic symptoms, altered perception, increased anxiety and cognitive deficits. Cannabinoids may induce tachycardia, probably via direct agonism of CB1 receptors in cardiac tissue [25]. Interestingly, with chronic cannabis use, a small number of patients may develop cannabis hyperemesis syndrome, which is characterized by abdominal pain, cyclic nausea and vomiting to the point of dehydration, male predominance (more common in males 72.9%) [26], compulsive hot bath/showers for symptom relief, and cessation of symptoms with discontinuation of cannabis. Additionally, approximately 9% of chronic users develop signs of addiction or cannabis use disorder [26].

Though adverse events are mild for adults when taking Δ-9-THC, this is not the case when cannabis is accessed by children and pets. Children (and pets) tend to explore with their mouths and packaging of cannabis, particularly edibles, presents an inviting target. They present with "sudden onset of lethargy or ataxia, hypotonia, mydriasis, tachycardia, and hypoventilation requiring intubation, which are the common clinical findings of cannabis toxicity" [27]. Children and pets are not just small adults, and their volumes of distribution are vastly different.

Regardless of the route of administration, 90% of absorbed cannabis binds to blood proteins and distributes in vascular tissues. Only 1% goes to the brain. THC is metabolized mostly by the liver's cytochrome P450 enzyme systems to 11-OH-THC which is then subsequently excreted in the feces and urine after glucuronidation. Metabolism also occurs in extra-hepatic tissues that express CYP450 such as the small intestine and brain. CBD is also hepatically metabolized by the cytochrome P450 system with primarily fecal excretion [25]. A one-time use of cannabis will show a positive urine THC test from 2.5 h to 1.6 days. Frequent users can test positive from 2.5 h to 30 days after last use, thus the length of time that a test is positive depends of level of use, body weight, body fat, and frequency of use. Hair will show up positive from 7 to 90 days after use [28].

Though the lay press and Internet have touted a multitude of uses for cannabis in the human and veterinary populations, most of the reports are anecdotal. Systematic reviews thus far yield a less optimistic picture of therapeutics. The primary reported uses for cannabis are: 1) Chronic pain syndromes. The Cochrane database reports: "There is no high-quality evidence for the efficacy of any cannabis-based product including herbal cannabis (marijuana) in any condition with chronic neuropathic pain. Some adverse events (particularly somnolence or sedation, confusion, psychosis) may limit the clinical usefulness of cannabis-based medicines. It might be expected that, at best, a few people with neuropathic pain will benefit from long-term use of cannabis-based medicines" [29]. 2) Dementia. Hillen et al in a 2019 systematic review found: "Eight of 12 studies had high risk of bias. While the efficacy of cannabinoids was not proven in a robust randomized control trial, observational studies showed promising results, especially for patients whose symptoms were refractory. In addition, the safety profile is favourable as most of the ADEs reported were mild. Future trials may want to consider dose escalation and formulations with improved bioavailability" [30]. 3) Chemotherapy-induced nausea and vomiting. Cochrane reports: "Cannabis-based medicines may be useful for treating chemotherapy-induced nausea and vomiting that responds poorly to commonly used anti-sickness medicines" [31]. The American Cancer Society reports: "A number of small studies of smoked marijuana found that it can be helpful in treating nausea and vomiting from cancer chemotherapy" [32]. 4) Cancer treatments. American Cancer Society reports: "More recently, scientists reported that THC and other cannabinoids such as CBD slow growth and/or cause death in certain types of cancer cells growing in lab dishes. Some animal studies also suggest certain cannabinoids may slow growth and reduce spread of some forms of cancer. There have been some early clinical trials of cannabinoids in treating cancer in humans and more studies are planned. While the studies so far have shown that cannabinoids can be safe in treating cancer, they do not show that they help control or cure the disease. Relying on marijuana alone as treatment while avoiding or delaying conventional medical care for cancer may have serious health consequences" [30]. 5) HIV-AIDS and associated symptoms. Cochrane reports: "The use of cannabis (marijuana), its active ingredient or synthetic forms such as dronabinol has been advocated in patients with HIV/AIDS, in order to improve the appetite, promote weight gain and lift mood. Dronabinol has been registered for the treatment of AIDS-associated anorexia in some countries. However, the evidence for positive effects in patients with HIV/AIDS is limited, and some of that which exists may be subject to the effects of bias. Those studies that have been performed have included small numbers of participants and have focused on short-term effects. Longer-term data, and data showing a benefit in terms of survival, are lacking. There are insufficient data available at present to justify wide-ranging changes to the current regulatory status of cannabis or synthetic cannabinoids" [33]. 6) Schizophrenia. Cochrane reports: "For some people with schizophrenia, cannabis use clearly makes "positive" symptoms worse. For many, however, using cannabis seems only to have the expected mild soporific effects that probably compound "negative" symptom languor. Trial-based research is so limited that it is uninformative. Whether adding the drug is harmful - or helpful is unclear. How best to help people stop when they ask for help in doing so is not well-researched. There is much work to be done" [34]. 7) Post-traumatic stress disorder (PTSD). Shishko et al reported "Although some positive data exists for the use of marijuana in PTSD, current evidence is limited to anecdotal experiences, case reports,

and observational studies, which leads to a lack of quality evidence to currently support the use of marijuana to treat PTSD" [35].

Additionally, for Crohn's disease and ulcerative colitis: "The effects of cannabis and cannabis oil on Crohn's disease and ulcerative colitis are uncertain. Thus, no firm conclusions regarding the efficacy and safety of cannabis and cannabis oil in adults with active Crohn's disease or ulcerative colitis can be drawn" [36, 37]. Similarly for rheumatoid arthritis: "There is currently weak evidence that oral nefopam, topical capsaicin and oro-mucosal cannabis are all superior to placebo in reducing pain in patients with RA. However, each agent is associated with a significant side effect profile. The confidence in our estimates is not strong given the difficulties with blinding, the small numbers of participants evaluated, and the lack of adverse event data" [38]. Finally, though most every state lists glaucoma as an accepted indication for the use of medical cannabis, a systematic review (2005) in Journal of the American Medical Association (JAMA) found: "One very small crossover trial (6 participants) judged at unclear risk of bias compared tetrahydrocannabinol (THC; 5 mg), cannabidiol (20 mg), cannabidiol (40 mg) oro-mucosal spray, and placebo. This trial found no difference between placebo and cannabinoids on measures of intraocular pressure in patients with glaucoma" [39].

Precautions

We have already established that cannabis has a favorable side effect profile for most people; however, cannabis can represent a serious threat to some classes of patients and should be used with caution or not used at all. The Canadian Government, after years of universal access, has issued some caveats to cannabis use [40].

Youth

The human brain does not finish developing until the age of 25, making youth more vulnerable to the health impacts of cannabis than most adults are. Early use also increases the risk of experiencing psychotic symptoms or developing schizophrenia. There are also lasting structural effects on brain development [40].

Pregnant and breast-feeding women

Using cannabis when pregnant could be harmful to both mom and baby. Heavy cannabis users, particularly those who mix it with tobacco, have a greater risk of having a premature baby. THC passes into breast milk and then enters the baby's brain and fat cells, where it can remain for weeks. Just as in the case of youth, there may be structural brain impacts. Thirty-four to sixty percent of marijuana users continue use during pregnancy and 18.1% meet the criteria for dependency. The American College of Obstetricians and Gynecologists (ACOG) recommends cessation of cannabis upon a finding of pregnancy [41].

History of depression

Cannabis may also worsen the symptoms of depression [39].

Men who want to be fathers

Cannabis suppresses sperm quantity and quality [5].

People with a personal or family history of psychosis, schizophrenia, or bipolar disorder

Studies have found that using cannabis heavily, particularly if there is a history of mental illness in the family, may trigger a psychotic reaction, and regular use may increase the risk that some people will experience longer-lasting psychotic episodes [39].

People with serious liver, kidney, heart or lung disease

People with serious liver, kidney, heart or lung cannabis should be cautious when using cannabis [42-45].

Other medications

These may include sleeping pills, tranquilizers, some pain medications, some allergy or cold medications, or anti-seizure medications. Other products that may interact with cannabis include: antiretroviral drugs used to treat HIV/AIDS, certain anti-depressants, stomach acid inhibitors, certain antibiotic and anti-fungal medications, certain heart medications, especially Warfarin, and Saint John's Wort [39].

The bottom line on cannabis is that THC is commonly used to address pain, glaucoma, insomnia, low appetite, nausea, anxiety, muscle spasms, and movement disorders, despite a lack of supporting evidence from randomized controlled trials. This has not stopped states from approving quite a number of "accepted indications" for medical use. CBD is commonly used to address anxiety, insomnia (both falling and staying asleep), and possibly different types of chronic pain and seizures. CBD, applied to the skin, may help lower pain and inflammation due to arthritis [22, 46]. Despite our best efforts, best practices and best use studies are hindered by cannabis' schedule 1 status and the lack of randomized controlled trials across all of medicine. We are further hindered by a lack of standardization and quality control in the cannabis products available to the public. Product A in one area may well not be the same in another city or dispensary, making efficacy difficult to study. JAMA did a recent study looking at how well the package label reflected what was actually in the CBD products purchased online. They found that 42% were under-

labeled, 26% over-labeled, and 21% had THC detected (in CBD only products) as well as its precursor THCA [47]. Until well-designed, blinded, randomized, placebo-controlled trials are preformed, caregivers will not be certain what disease processes will be best suited for primary or adjunctive treatment with cannabis and which route of administration will be best for each disease state. Still, the multiple cannabinoids, terpenes, and flavonoids present in the cannabis plant represent a wealth of possibilities for treatments, not just for chronic diseases, but for environmental exposures to disease as well, such as multi-drug resistant bacteria [48].

From the standpoint of obstetric/gynecologic physicians, we must be aware of the fact that our patients are using cannabis (whether they tell us or not), both prescribed/recommended and illicit to manage various life events and symptom complexes associated with the following.

Pregnancy and lactation - used for relaxation, pain, and nausea

Surveys show that pregnant women do not perceive cannabis as harmful, despite evidence of harmful effects on infants and children in the literature. One point is that studies from the 1980s that showed somewhat less potential harm had much less THC in the doses studied than the amount of THC available today [49]. Recent studies show that cannabis exposure prenatally was not associated with placental pathology or histology though there was a trend toward lower placental weights in cannabis exposed stillbirths [50]. Cannabis does cross the placenta and passes in breast milk to the baby. There are cannabinoid receptors in the fetal brain and placenta. Though studies are conflicting, the American College of Obstetrics and Gynecology guidelines recommend that women refrain from cannabis, either medical or recreational [51]. The American Academy of Pediatrics similarly discourages cannabis use when breastfeeding and the Centers for Disease Control (CDC) discourages use in pregnancy and lactation [52]. Peer-reviewed studies on the use of medical cannabis in labor and delivery are lacking.

Possible teratogenicity

The literature on possible teratogenicity is mixed with a 2015 study of 4,892 cannabis users reporting no association between cannabis exposure and fetal anomalies, whereas a 2014 study using data from the National Birth Defects Prevention Study finding increased risk of anencephaly (odds ratio (OR) 2.2), esophageal atresia (OR 1.4), diaphragmatic hernia (OR 1.4), and gastroschisis (OR 1.2) [53]. There is no definitive evidence of teratogenicity at this point, but there is evidence of small for gestational infants in users.

Post-operative and post-delivery

Efficacy in patients with acute post-delivery and post-operative pain has not been determined and indeed, the use of cannabis has been linked to cardiac events, upper airway obstruction, and coagulopathy in these states and is not recommended at this point [54].

Gynecologic malignancy

Patients use illicit and prescribed cannabis for cancer and treatment pain control, appetite stimulation, anxiety, insomnia, and nausea. Additionally, though many use non prescribed cannabis and medical cannabis, a significant number in this group have also reported an ability to decrease opioid usage with cannabis as an adjunct [55, 56].

Menstrual and endometriosis pain

Several studies based on surveys indicate that cannabis, THC more so than CBD, may be perceived as helpful in the treatment of pain associated with endometriosis [57, 58].

Sexual enhancement

A 2019 survey showed 38.9% of respondents having enhanced sexual responses, helping with relaxation, and 4.7% reported worse response. Regardless, it is being used across all age groups, especially in combination with alcohol [59].

In another area for obstetricians/gynecologists to be cognizant, the National Epidemiological Survey on Alcohol and Related Conditions (NESARC) finds that there was documented increased use of cannabis both before and during the COVID pandemic, especially with people self-isolating, and this will likely have ramifications for all of us in the future. Twelve states classified cannabis dispensaries as an essential service and home delivery of this service is increasing access to cannabis as well as cannabis use [60, 61]. Hence, all caregivers will need to become better educated on the risks and benefits of cannabis in our individual patient populations, as well as society as a whole.

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Conflict of Interest

The author reports no conflicts of interest.

Data Availability

The author declares that data supporting the findings of this study are available within the article.

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