



## CASE REPORT

## Cannabinoid Hyperemesis Syndrome in Pregnancy: A Case Report and Treatment Overview

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### Abstract

Cannabinoid hyperemesis syndrome (CHS) is characterized by cyclical vomiting, frequent hot water bathing, and chronic cannabis use. Missed diagnosis, especially in pregnancy, may delay treatment and prolong extensive medical assessments. Conventional antiemetics used to control vomiting illnesses are typically ineffective in CHS and pharmacological treatment may be limited due to concern for harm to the fetus during pregnancy. This case report describes a 19-year-old African American female at twenty weeks gestation with CHS. Successful symptom relief was obtained with diphenhydramine, haloperidol, and dronabinol. A literature search identified five case reports regarding cannabinoid hyperemesis syndrome in pregnancy. This case report highlights the importance of recognizing common characteristics of CHS especially in pregnant women with a history of cannabis use. Additionally, the purpose of this article is to review the current literature available for the treatment of CHS and expand recognition of CHS as an increasingly prevalent condition.

### Keywords

Pregnancy, Cannabinoid hyperemesis syndrome

### Abbreviations

CB: Cannabinoid; CBD: Cannabidiol; CBG: Cannabigerol; CHS: Cannabinoid Hyperemesis Syndrome; CVS: Cyclic Vomiting Syndrome; GI: Gastrointestinal; HG: Hyperemesis Gravidarum; TCAs: Tricyclic Antidepressants; THC:  $\Delta$ 9-Tetrahydrocannabinol; TRPV1: Transient Receptor Potential Vanilloid Subtype 1

### Introduction

Cannabinoid hyperemesis syndrome (CHS) is a health condition that has gained recent recognition

after it was first described by Allen, et al. in 2004 as a cyclical vomiting illness induced by chronic cannabis use in which symptoms were relieved by hot water bathing [1]. A growing body of literature has provided guidance in treatment of CHS, however, few articles discuss cases complicated by pregnancy. The purpose of this article is to review available literature regarding treatment, discuss the complications of treatment in pregnancy, and expand recognition of CHS to improve efficiency and accuracy of diagnosis.

### Background

Cannabis is the most commonly used illicit drug in the US averaging 24 million current users ages 12 and older in 2016 [2]. Data from the National Survey on Drug Use and Health identified an increase in past-month cannabis use during pregnancy from 2.85% to 4.98% between the years 2002 and 2016 [3]. Expansion of legalization and an increase in marijuana potency have been proposed as correlating factors in the increase of reports of cannabis-mediated conditions [4,5]. Outside of recreational use, cannabinoids are utilized for chronic pain, chemotherapy-induced nausea/vomiting, appetite stimulation, and seizure disorders [6,7].

While  $\Delta$ 9-tetrahydrocannabinol (THC) is the primary compound in cannabis responsible for psychotropic effects (e.g. euphoria), cannabidiol (CBD) and cannabigerol (CBG) are the non-psychotropic cannabinoids thought to regulate emesis [8]. Two cannabinoid (CB) receptors have been identified. CB1 receptors are found

in the central nervous system and throughout the gastrointestinal (GI) tract, while CB2 receptors are thought to be concentrated in peripheral lymphoid tissue and immune cells [4,8].

In animal models, CB1 agonist activity at GI sites inhibits gastric acid secretion and reduces motility [8]. Although reduced gastric emptying promotes nausea and vomiting, the antiemetic effects of cannabinoids through CB1 activation in the dorsal vagal complex of the brainstem possibly override this [8]. Delayed gastric emptying following use of THC and dronabinol has been noted in humans [8].

Exogenous cannabinoids also activate transient receptor potential vanilloid subtype 1 (TRPV1) [9]. TRPV1 is located in the gastrointestinal tract, vagal sensory neurons, and the chemoreceptor trigger zone [9]. Stimulation of TRPV1 receptors by cannabinoids is a possible mechanism for antiemetic action, however, with chronic cannabinoid use, desensitization of the receptor may result in pro-emetic tendencies [9,10].

Although the pathophysiology of CHS is not completely understood, down-regulation and desensitization of CB1 receptors with chronic cannabinoid use may lead to a pro-emetic state [4,11]. In addition, THC has an estimated half-life of 20-30 hours with subsequent accumulation and storage within body fat, which could be released via lipolysis during periods of stress possibly producing a “re-intoxication effect” [8]. Lastly, delayed gastric emptying and the pro-emetic consequences of CBG and higher doses of CBD have

been postulated to be associated with cyclic nausea and vomiting [8].

The three phases of CHS are comprised of the prodromal, hyperemetic, and recovery phases [4,8]. In the prodromal phase, patients develop nausea, abdominal discomfort, and subsequent distress [8]. Patients may increase use of cannabis due to its perceived antiemetic effects [8]. The hyperemesis phase involves persistent nausea and frequent, profuse vomiting accompanied by abdominal pain, weight loss and dehydration [8]. Patients will take long, hot showers, a learned compulsive behavior to relieve discomfort [8]. The recovery phase is defined as resolution of nausea, vomiting, and abdominal pain [4,8].

As there is no universally accepted diagnostic criterion for CHS, it remains a diagnosis of exclusion [12]. Differential diagnoses should include CHS, cannabis withdrawal, Cyclic vomiting syndrome (CVS), and, in pregnant patients, Hyperemesis gravidarum (HG) [8,13]. Nausea and vomiting of pregnancy occurs in 50-80% of pregnancies and typically resolves before the sixteenth week of gestation [14,15]. Hyperemesis gravidarum, affecting 0.3-3% of pregnancies, is characterized by persistent vomiting, some degree of severe undernourishment, and weight loss [14]. Timeline of cannabis use is key for diagnosis of both CHS and cannabis withdrawal whereas CVS and HG may occur with or without cannabis use. Dehydration and electrolyte abnormalities may occur with CHS, CVS or HG. Cannabi-

**Table 1:** Characteristics of Cannabinoid hyperemesis syndrome, Cyclic vomiting syndrome, Cannabis withdrawal, and Hyperemesis gravidarum.

<b>Cannabinoid Hyperemesis Syndrome [15]</b>	<b>Cyclic Vomiting Syndrome [40]</b>	<b>Cannabis Withdrawal [16]</b>	<b>Hyperemesis Gravidarum [18]</b>
Cyclical severe nausea and vomiting	Cyclical severe nausea and vomiting	Cannabis discontinuation after heavy and long-term use	Continued emesis during pregnancy with no other associated cause
Minimum weekly cannabis use	Accompanying symptoms such as headache, photosensitivity, and/or vertigo	Symptoms often start 24-72 hours after cessation	Typically at least 5% weight loss
Symptom resolution following cannabis cessation	Personal and/or family history of migraines	Condition not ascribed to a separate medical problem	Laboratory abnormalities may be present including electrolyte, thyroid, and liver changes
Brief symptom resolution during hot bathing	Physical and psychological stressors can trigger episodes	A minimum of three of the following within one week of cessation:	History of hyperemesis gravidarum is a risk factor for future pregnancies
Onset before the age of 50 years	Mean age of onset 5 years in children and 37 years in adults	<ul style="list-style-type: none"> <li>- Irrascibility</li> <li>- Anxiousness</li> <li>- Sleep problems</li> <li>- Loss of appetite or weight loss</li> <li>- Edginess</li> <li>- Decreased mood</li> <li>- A physical symptom resulting in distress such as headache, abdominal pain, tremor, diaphoresis, or fever</li> </ul>	Thought to be on the spectrum of nausea and vomiting of pregnancy

bis withdrawal is more likely to present with irritability, anxiety or depressed mood [16] (Table 1).

### CHS treatment

Evidence supports cessation of cannabis use as primary treatment of CHS [4,7,17]. However, patients frequently continue or resume cannabinoid use in belief of its antiemetic properties [8,18]. Conventional antiemetic such as metoclopramide, ondansetron, prochlorperazine, and promethazine have consistently been ineffective or shown minimal symptom relief [4,8,19,20]. Haloperidol has been utilized off-label for its antiemetic properties in treatment of CHS and does have successful case reports at recommended doses of 2.5-5 mg intravenously although none of the patients were pregnant [18,21-23]. Olanzapine and droperidol have been investigated although to a much lesser degree [19].

Tricyclic antidepressants (TCAs) have been studied with some efficacy for “long-term” CHS treatment, although this evidence is taken from trials utilizing TCAs for CVS in which several participants were noted to have concurrent cannabis use [19]. Although several patients either decreased or ceased cannabis use, which may have precipitated symptom improvement, a subset of cannabis users did have symptom improvement with a TCA and ongoing cannabis use [19].

Propranolol has been used successfully in one case report with a patient experiencing emesis termination after administration of two doses of propranolol 1 mg intravenously [24]. In a recent review, benzodiazepines, primarily lorazepam, were noted to be “effective” in five case reports and “helpful” in six case series [19]. Antihistamine agents lack evidence for use with the exception of a few reports that did not demonstrate success with monotherapy [4].

Dronabinol, a schedule III synthesized variant of  $\Delta^9$ -THC, has been proposed as a treatment for CHS to taper patients off cannabis [23]. However, Bonnet, et al. presented a case where CHS symptoms were exacerbated by dronabinol [25].

Hot water bathing is a learned compulsive behavior of CHS and has displayed consistent symptom relief, mediated through hot water activation of TRPV1 [4,9,11,20]. Due to the impracticality of high frequency bathing, other pharmacological treatments such as topical capsaicin has been investigated. Capsaicin also activates TRPV1 and has been shown to be an effective treatment in over twenty case reports [4,9,10]. Heat and capsaicin are proposed to temporarily increase cutaneous TRPV1 firing resulting in antiemetic effects [9]. In an expert consensus treatment guideline, topical capsaicin 0.075% applied three times daily to the back of the arms or abdomen is recommended as a reasonable first-line treatment [17].

The proposed pharmacological treatments for CHS have variable safety profiles in pregnancy. Historically, teratogenic risk has been variably attributed to use of antipsychotics in pregnancy. However, more recent data suggest there is minimal to no increased risk for congenital malformations with these agents, including haloperidol [26,27]. There are reports of congenital abnormalities and low birth weight in women who used propranolol during gestation [28]. When capsaicin is applied topically, insignificant amounts are absorbed transdermally; therefore, adverse effects are considered low risk [29]. A developmental toxicity study in rats and rabbits found no indication that trans-capsaicin (found in chili peppers) should be considered of developmental concern [30]. Benzodiazepines may increase incidence of premature birth and low birth weights with the baby also experiencing withdrawal upon birth [31]. Following extrapolation of the data surrounding marijuana use in pregnancy, dronabinol should be avoided [32]. The risks versus benefits of choosing a treatment will depend on provider comfort level and thorough discussion with the mother. It is important to have a frank and open discussion with the patient regarding cannabis cessation.

### Patient case

A 19-year-old African-American female at twenty weeks gestation presented to the emergency department complaining of nausea, vomiting and upper abdominal pain for 2-3 days with inability to keep food or water down resulting in ten pound weight loss. She endorsed a long history of these episodes, requiring hospital admissions, and prior to pregnancy and a history of gastritis diagnosed as a child. The patient received intravenous fluids for dehydration and promethazine for nausea and vomiting but did not experience relief. She reported that diphenhydramine and hot showers were helpful.

Physical exam and vitals were normal except for heart rate of 106 beats per minute and blood pressure of 163/75 mmHg. Her comprehensive metabolic panel revealed normal liver function, lipase, thyroid stimulating hormone, serum creatinine, and electrolytes except for a mildly low sodium level of 132 mmol/L. Ultrasound was normal apart from the presence of small gallbladder stones and sludge. Abdominal X-ray showed normal bowel gas pattern. Extensive lab work and imaging ruled out ectopic pregnancy and appendicitis. The patient reported daily cannabis use until one week prior to presentation, consistent with the urine drug screen positive for THC.

During admission, the patient often unhooked her lines to lie in the shower. With ongoing emesis, she developed hypokalemia and hypomagnesaemia which necessitated supplementation. Haloperidol was initiated which provided some control. After evaluation by gastroenterology and psychiatry, patient was diag-

**Table 2:** Administered medications during hospitalization.

Day One:	Day Two:	Day Three:
<ul style="list-style-type: none"> <li>• Pantoprazole 40 mg IV Push</li> <li>• Diphenhydramine 25 mg IV Push × 1</li> <li>• Promethazine 12.5 mg IV Piggyback × 1</li> <li>• Sucralfate 1 g suspension PO ACHS</li> <li>• Sodium chloride 0.9% Bolus</li> <li>• Famotidine 20 mg IV Push × 1</li> <li>• Metoclopramide 10 mg IV Push × 1</li> <li>• Promethazine 25 mg IM × 1</li> <li>• Ketorolac 30 mg IV Push × 1</li> </ul>	<ul style="list-style-type: none"> <li>• Pantoprazole 40 mg IV Push</li> <li>• Diphenhydramine 25 mg IV Push × 4</li> <li>• Promethazine 12.5 mg IV Piggyback × 3</li> <li>• Sucralfate 1 g suspension PO ACHS</li> <li>• Sodium chloride 0.9% Bolus</li> <li>• Haloperidol 3 mg SQ × 1</li> <li>• Fentanyl 50 mcg IV Push × 3</li> <li>• Dronabinol 2.5 mg PO BID</li> </ul>	<ul style="list-style-type: none"> <li>• Pantoprazole 40 mg IV Push</li> <li>• Diphenhydramine 25 mg IV Push × 4</li> <li>• Promethazine 12.5 mg IV Piggyback × 3</li> <li>• Sucralfate 1g suspension PO ACHS</li> <li>• Haloperidol 3 mg SQ × 1</li> <li>• Fentanyl 50 mcg IV Push × 3</li> <li>• Dronabinol 2.5 mg PO BID</li> </ul>

ACHS: Before meals and at bedtime; BID: Twice daily; IM: Intramuscular; IV: Intravenous; PO: By mouth; SQ: subcutaneous.

nosed with CHS based on chronic daily cannabis use, cyclic vomiting symptoms, and relief of symptoms with hot showers. Patient denied any previous psychiatric history or current mental health concerns. She was initiated on dronabinol 2.5 mg twice a day to “taper” off cannabis by gastroenterology. She was educated on cannabis cessation for ultimate treatment and complete relief of symptoms. Table 2 details pharmacologic agents utilized over the three-day admission. After improvement, the patient was discharged home on a two-week supply of dronabinol and promethazine. The patient was unable to be contacted for follow-up after several attempts.

## Discussion

Five case reports of CHS in pregnancy have been published at time of writing, in addition to two possible misdiagnosed cases of hyperemesis gravidarum [1]. In 2011, Schmid, et al. reported on a 26-year-old woman at ten weeks gestation [33]. After the patient’s bathing habits were observed coupled with her reported daily cannabis use, a diagnosis of CHS was made. With cannabis cessation, symptoms completely resolved after two weeks [33]. Swanson, et al. reported a case of a 33-year-old woman at seven weeks gestation with cyclical vomiting [34]. The patient’s symptoms improved and she was able to tolerate oral liquids three days following cannabis discontinuation [34]. In one report, a 24-year-old woman at 26 weeks gestation was fluid resuscitated and symptoms resolved with scheduled metoclopramide, 5-6 hot showers daily, additional antiemetics, and cannabis cessation [11]. Manning Meurer, et al. reported a case of CHS, originally diagnosed as hyperemesis gravidarum, associated with preeclampsia and a *Helicobacter pylori* infection. At thirty weeks gestation, a CHS diagnosis was made following a positive urine drug screen for THC [35]. Alaniz, et al. reported a patient who reduced her cannabis use to once daily from an initial report of up to sixteen times daily with subsequent symptom resolution after an unknown time frame [36].

The patient in this case report demonstrated fea-

tures consistent with CHS. The patient showed minimal relief with antiemetics such as promethazine and diphenhydramine but was able to obtain moderate relief with addition of haloperidol and dronabinol. Dronabinol was utilized in this patient to “taper off” recently discontinued cannabis, although mechanistically, dronabinol could worsen nausea and vomiting in addition to concerns related to use in pregnancy [23,25,37]. If the patient had been undergoing cannabis withdrawal, dronabinol could have relieved the symptomatology, although DSM-5 criteria was not met [16,23] (Table 1).

The patient did obtain relief from frequent hot water bathing similar to other patients in the literature. She had also been abstinent from marijuana for one week and appeared to understand the importance of continued abstinence. Moderate relief was obtained with haloperidol and dronabinol, neither of which has published case reports of use in CHS complicated by pregnancy. The patient was educated on the potential risks of dronabinol in pregnancy prior to its initiation, including a correlation between cannabis use during pregnancy with low birth weights and compromised executive functioning such as impulse control, visual memory, and attention [38,39].

Topical capsaicin has limited absorption and the possibility of adverse effects is considered low [29,30]. Use of topical capsaicin is even considered a reasonable first-line option by one expert consensus panel [17]. Its safety profile lends credence to its use as a treatment option in pregnant patients. CHS is frequently misdiagnosed particularly in pregnancy, and the risks versus benefits of pharmacological treatments should be discussed with the patient. Capsaicin could have been considered as a viable alternative although it is unknown if this was considered by gastroenterology.

## Conclusion

It is important to recognize the common characteristics of CHS and ask about all forms of cannabis use. Education is of highest priority and cannabis cessation

should be emphasized, regardless of pregnancy status. As more literature becomes available, it is the hope that increased knowledge of CHS will prompt quicker recognition and diagnosis leading to improved patient outcomes.

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