The Emerging Use of Cannabis in cases of Hyperemesis Gravidarum; A Critical Review

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Abstract

There is emerging documentation in both medical journals and social media of American and Canadian women inflicted by hyperemesis gravidarum (HG), reporting beneficial effects of cannabis on their severe symptoms.

In this review, the risks and benefits of this new therapeutic direction are critically considered. Large numbers of women with HG do not respond favorably to antiemetic medications such as metoclopramide, ondansetron and antihistamines, In contrast, evidence collected in several peer review articles and social media suggest favorable effects of cannabis. While most professional societies warn pregnant women against the use of cannabis due to potential fetal risks, after 40 years and numerous studies, the fetal risks of cannabis have not been clearly substantiated beyond potential intrauterine growth restriction and prematurity. In contrast, there is new evidence of serious fetal neurodevelopmental risks of HG itself.

A risk: benefit analysis presented here suggests that appropriately- powered studies on the efficacy and fetal safety of cannabis for HG are urgently needed.

Key words: cannabis, hyperemesis gravidarum, pregnancy, nausea and vomiting of pregnancy

Introduction:

Hyperemesis Gravidarum (HG) inflicts up to 2% of pregnant women, with compelling evidence of serious physical, emotional and behavioral adverse effects, mostly to the mother (1). Presently the effectiveness of existing anti-emetic medications on HG symptom relief has been partial at best (1). The antiemetic effects of cannabinoid have long been documented and several cannabinoids are on the market for nausea and vomiting relief following cancer chemotherapy (2-4). In parallel there is growing evidence outside the realm of clinical studies suggesting efficacy of cannabis for HG symptoms. On the other hand there are serious concerns regarding potential adverse effects of cannabis on fetal development, while new research suggests that HG itself may adversely affect cognitive development in afflicted children.

With the legalization of cannabis in many countries and states, substantially more women consult their health care providers when standard antiemetic drugs are not addressing their HG symptoms. The aim of this presentation is to synthesize existing evidence in order to better inform practicing physicians on the pros and cons of cannabis use for HG.

Methods:

In order to address this new reality, a narrative review has been conducted which included:

a) Peer and non- peer review data on the efficacy of cannabis in HG;

b) Published data on safety/risk of cannabis on fetal brain development;

c) Published data on fetal neuro-developmental risks of HG;

d) A balance of these aspects and a proposed research agenda to move forward.

Results:

a) Antiemetic effects of cannabis in HG:

There are increasing numbers of peer review publications showing the antiemetic effects of cannabis in non- pregnant individuals, but not in pregnancy (2-4). In contrast, with the legalization of cannabis in the USA and Canada there is wide new evidence from social media and self-help women's websites, describing favorable, and often dramatic effects in women suffering from HG (5). In a proportion of these cases favorable child development is also described, with no reports of adverse fetal outcome. It should be acknowledged that

these lay reports may be biased in that women with favorable effects are more likely to report on them than those experiencing untoward effects, due to fears and guilt and possibly litigious repercussions. Two questionnaire-based studies from British Columbia and Hawaii, published in peer review medical journals, describe high efficacy of cannabis on severe NVP, based on reports by both women and their physicians (6-7).

b) In depth review of cases:

We have reviewed and published 4 cases of HG who were treated with tetrahydrocannabinol at concentrations between18-22% and followed up by us at the Motherisk Program in Shamir Hospital, Israel. In all 4 there was a dramatic improvement in HG with doses of 2-3 puffs every 2-3 hours. Typical use was of 1 g/d. All 4 children have been described to develop normally (8). As these covered all cases consulted by Motherisk, the likelihood of positive bias is small.

c) Child neurodevelopment after cannabis exposure:

Over the last 4 decades, a large number of studies have followed up children exposed *in utero* to cannabis and compared them to non- exposed infants. In all cases the women used cannabis recreationally. Overall, there were no consistent cognitive deficits, ADHD or other adverse effects. A small number of studies claimed small effect size adverse effects, although there is potential confounding by concomitant maternal drinking, smoking and lifestyle (9-10). Most consistent have been reported prematurity and intrauterine growth restriction. Presently, there is no published study following up child development after maternal exposure to medicinal use of cannabis for HG.

d) Cannabinoid hyperemesis syndrome (CHS)

CHS is a rare paradoxical reaction characterized by cyclic severe nausea and vomiting in long-term cannabis users. While the symptoms are unresponsive to antiemetic drugs, compulsive hot baths result in a considerable symptom relief (11). There are several cases of CHS that were described in pregnancy, and their differential diagnosis from HG is important. In CHS prior exposure to cannabis is an impotant clue, and women with HG do not have a tendency to bath excessively, and bathing does not relieve their symptoms (12-13).

Adverse fetal effects of HG:

Several longitudinal studies in Toronto and California have documented loss of IQ points and increased risk of conditions such as ADHD and autism among offspring exposed *in utero* to maternal HG. This evidence is consistent with famine studies in the Netherland and China after maternal starvation documenting similar adverse cognitive fetal effects, consistent with the known nutritional deficits of HG (14-16). A prolonged bout of HG often renders the pregnant woman status of starvation, critically limiting trace elements, proteins and calories needed for healthy fetal brain development (14).

These include:

1) Caloric restriction has been associated with restricted maturation of myelin.
2) Lack of optimal protein intake reduces synaptogenesis.
3) Shortage in vitamin B12 my lead to various degrees of brain atrophy.
4) Vitamin B1 deficiency has been associated with hippocampal hypoplasia.
5) Restricted maternal choline intake leads to acetylcholine and phosphotidylcholine shortage.
6) Vitamin C shortage is affecting adversely hippocampal neurogenesis.
7) Iodine deficiency causes impaired cognition via hypothyroidism.
8) Lack of copper alters dopamine synthesis.
9) Restricted maternal iron intake reduces central myelination.
10) Shortage in dietary zinc reduces hippocampal neurotransmission.

It is conceivable that a combination of these shortages, plus the effects of electrolye and fluid imbalance may have synergistic adverse effects.

Data Synthesis:

The balance of the above data merits a careful analyis:

The antiemetic effects of cannabis in HG appear to be the less problematic issue, as quite a few of the reports describe very dramatic effects among women who have not responded favorably to medicinal antiemetic drugs.

The controversy surrounding potential adverse fetal effects of cannabinoids needs to be put in the context that all past studies were performed on offspring of recreational cannabis users, in whom educational and socioeconomic confounders may play a substantial role (8). While it is likely that

women needing cannabis for HG will not carry these other potential risk, it could be that when used for HG symptoms the dose and duration of cannabis use will be higher. Metz and Stickrath's recent literature review reveals an ongoing concern regarding the use of cannabis in pregnancy due to modern marijuana's high Δ9-tetrahydrocannabinol content, which crosses the placental barrier and can lead to smaller birth weights, still and pre-term births (17).

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The present review suggests that the efficacy and safety of different cannabinoids in HG should be considered and seriously tested. Because of the ethical-medicolegal aspects of such research, it would make sense to study first some of the thousands of the pregnant women using cannabis medically or recreationally in states where cannabis use is legal.

Without well-designed, controlled studies, it would be difficult to address the potential efficacy and safety of cannabis for HG.

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