

# CHARACTERISTICS OF WOMEN USING MARIJUANA IN PREGNANCY AND THEIR REPORTED EFFECTS ON SYMPTOMS OF NAUSEA AND VOMITING OF PREGNANCY: A PROSPECTIVE, CONTROLLED COHORT STUDY

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## ABSTRACT

### **Background**

Nausea and Vomiting of Pregnancy (NVP) affects the majority of pregnant women. Marijuana has been documented to have antiemetic properties and some pregnant women report to us using marijuana to help them with their NVP.

### **Objective**

To investigate characteristics of women using marijuana for symptoms of NVP and their reports on its effectiveness in pregnancy.

### **Patients and Methods**

One hundred and seventeen women calling the Motherisk Alcohol and Substance Use Help-line regarding marijuana exposure during pregnancy were asked through a standard questionnaire whether they experienced any NVP and the severity of the nausea, vomiting and retching symptoms. The same questionnaire was also used on three hundred and eighty nine women recruited from the Motherisk Helpline who did not have an exposure to marijuana during pregnancy.

### **Results**

In the multivariate analysis, the use of marijuana during pregnancy was associated with a significant reported decrease in nausea symptoms during pregnancy with no apparent decrease in vomiting and/or retching symptoms.

### **Discussion**

While the use of marijuana appears to relieve reported symptoms of nausea during pregnancy, women should be informed about its unproven fetal safety and existing evidence of potential behavioural teratogenesis.

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## INTRODUCTION

**N**ausea and Vomiting of Pregnancy (NVP) affects up to 80% of all pregnant women<sup>1</sup>. Although self-limiting, NVP can cause severe distress and it impacts negatively on women's quality of life<sup>3</sup>. The delayed released combination of 10 mg doxylamine succinate (an antihistamine) and 10 mg pyridoxine hydrochloride (vitamin B6), marketed as Diclectin<sup>®</sup>, is currently the drug of choice in Canada. However other treatments have been used for NVP including phenothiazines<sup>4</sup>, antihistamines<sup>4,5</sup>,

metoclopramide<sup>4,6</sup> and ondansetron<sup>4,7</sup>.

The Motherisk Program shows that some women report using marijuana to alleviate NVP symptoms<sup>8</sup>, despite the fact that its efficacy for treating NVP is undocumented and fetal safety is not known. Presently marijuana is the most popular illicit drug used by pregnant women<sup>9</sup> and inadvertent fetal exposure may occur since a large proportion of pregnancies are unplanned. Natural and synthetic cannabinoids (e.g. dronabinol and nabilone) are known to possess antiemetic effects<sup>10,11</sup>. These medicinal

preparations are used with cancer chemotherapy for that purpose<sup>12-15</sup>.

The objective of the present study was to investigate whether marijuana use is associated with reported alleviation of NVP symptoms.

## CASE REPORTS

### *Case 1:*

A 32-year old, multi-gravida (G3, SA2) woman contacted the Motherisk Alcohol and Substance Use Helpline after initiating use of marijuana "joints" to relieve her severe NVP. She was 25 weeks pregnant, weighed 115 pounds, and smoked 7-10 cigarettes daily in addition to the marijuana. She had been hospitalized eight times in her pregnancy because of hyperemesis gravidarum (HG) and was using Diclectin<sup>®</sup> (doxylamine succinate and vitamin B6, 10mg each in a delayed release combination) and dimenhydrinate to manage ongoing symptoms. She reported that these medications did not alleviate her NVP. With these conventional antiemetics and regular hospital visits, she was still not able to gain any weight.

Due to HG she also reported suffering social consequences including loss of employment and difficulties with her partner. She considered terminating her pregnancy because of HG. Her previous two pregnancies were also complicated by HG. The first resulted in a spontaneous abortion at 8 weeks of gestation and the subsequent pregnancy was diagnosed as ectopic.

At 12 weeks gestation, she started smoking marijuana joints as a last resort for managing her uncontrolled NVP. Unlike the other antiemetic treatments she reported that marijuana was effective in easing her symptoms of NVP. With marijuana use, there was a significant decrease in NVP symptoms and an increase in her weight. She no longer required hospital visits. At 24 weeks gestation, she discontinued the use of marijuana because its antiemetic effects began to wear off, with recurring HG. Consequently, she was hospitalized once again and Diclectin<sup>®</sup> and dimenhydrinate therapy resumed.

### *Case 2:*

A 34-year old woman (G4 P1 SA2) suffering from HG reported the use of Cesamet<sup>®</sup> (nabilone), a synthetic cannabinoid indicated for

cancer chemotherapy-induced nausea and vomiting. She was 30 weeks pregnant at the time of contact, consumed tobacco (5 cigarettes a day) and was maintained on methadone (40mg a day) due to I.V. drug use 2 years before. She was also smoking marijuana joints infrequently. Her HG was not managed by the use of Diclectin<sup>®</sup> or dimenhydrinate. In the second trimester, her ongoing HG led her to self-medicate with her partner's prescription of nabilone, once a day for three days. Although she reported that nabilone was effective in diminishing symptoms of NVP, she discontinued use because of her concern for the potential risks of exposure to her unborn baby.

## PATIENTS AND METHODS

The Motherisk Program is a counseling service for women and their health professionals inquiring about the risk of drugs, chemicals, radiation and infections during pregnancy and lactation. In 1998 the Motherisk Alcohol and Substance Use Helpline (1-877-327-4636) was established to provide information and counseling about alcohol and recreational drug exposures during pregnancy and lactation. The design of the study was observational and prospective. Two groups of women were recruited. The study group consisted of all pregnant women calling the Alcohol and Substance Use Helpline about exposure to marijuana. Pregnant women who called the Motherisk Program general line (416-813-6780) reporting exposure to non-recreational drugs, served as the comparison group.

At the time of the initial call, demographics, medical and obstetrical information was collected for all study participants, with a particular focus on details of occurrence of NVP and its severity. The following NVP details were solicited from the callers: self-assessment of the NVP severity (mild, moderate and severe), duration of daily nausea, frequency of vomiting and/or retching and use of antiemetic therapy. Information about additional exposures such as medications, vitamins/minerals, chemicals, cigarettes, alcohol or illicit drugs was also collected.

Demographics and characteristics of NVP among women in the marijuana-exposed group were compared to women in the comparison

group using parametric or non-parametric statistics as applicable. Determinants that may affect NVP severity, NVP duration, symptoms of nausea, vomiting and/or retching were identified through multivariate analysis. We included in the model all factors known to affect the severity of NVP, including maternal age, gravidity, use of multivitamins, use of antiemetics, cigarette consumption and marijuana use. The Hospital for Sick Children Research Ethics Board and informed verbal consent was obtained from all participants.

## RESULTS

A total of 506 women participated in the study. One hundred and seventeen women who were exposed to marijuana during pregnancy were recruited from the Alcohol and Substance Use Helpline. Three hundred and eighty nine women who were not exposed to marijuana were recruited from the Motherisk Helpline. Maternal characteristics, drug use in pregnancy and obstetrical history of the 506 participants are

summarized in Tables I and II. The pregnant women who used marijuana were younger than the pregnant women in the comparison group. Marijuana users also smoked cigarettes significantly more commonly, and took less folic acid and prenatal and /or multivitamins during pregnancy (Table I). Although marijuana users had more previous pregnancies, they had fewer live births compared to non-marijuana users. An analysis of previous spontaneous and therapeutic abortions indicated similar miscarriage rates between the two groups but statistically more elective abortions among marijuana users (Table II). The majority of women in both groups described their NVP as mild (Table III). In the univariate analysis, marijuana users reported having less nausea but more vomiting than non-users. Although not statistically significant, duration of NVP tended to be shorter among marijuana users, lasting on average 6 weeks compared to 8 weeks among controls.

**Table I: Maternal characteristics and drug history of cohort (N=117) and comparison (N=389) groups – values are numbers of patients unless stated otherwise**

Characteristics	Cohort	Control	Significance (p)
<b>Age</b>			
Mean (sd)	26.9 yrs (6.5)	31.1 yrs (4.4)	< 0.001***
<b>Gestational Age</b>			
Mean (sd)	12.7 wks (8.6)	17.2 wks (9.5)	< 0.001***
<b>Antiemetic Use n* (%)</b>			
Yes	23 (28)	18 (12)	0.002****
No	59 (72)	138 (88)	
Missing	0	102**	
<b>Folic Acid n (%)</b>			
Yes	11 (9)	101 (26)	< 0.001****
No	106 (91)	288 (74)	
<b>Vitamin Use n (%)</b>			
Yes	61(52)	357 (92)	< 0.001****
No	56 (48)	32 (8)	
<b>Nicotine Use n (%)</b>			
Yes	75 (64)	16 (4)	< 0.001****
No	42 (36)	373 (96)	

sd = standard deviation

\*Number of women who used antiemetics for NVP.

\*\*Not all endpoints were available for all patients.

\*\*\*Probability of difference between cohort and control by t-test.

**Table II: Obstetrical history of cohort (N=117) and comparison (N=389) groups – values are numbers of patients unless stated otherwise**

Characteristics	Cohort - n (%)	Control - n (%)	Significance (p)*
<b>Gravida</b>			
G1	39 (33)	163 (42)	0.025
G2	37 (32)	140 (36)	
G3	20 (17)	50 (13)	
G>3	21 (18)	36 (9)	
<b>Parity</b>			
P0	74 (63)	186 (48)	
P1	28 (24)	150 (38)	
P2	9 (8)	34 (9)	
P3	5 (4)	16 (4)	
P>3	1 (1)	3 (1)	
<b>Spontaneous Abortions</b>			
SA0	93 (80)	332 (85)	0.461
SA1	18 (15)	37 (9)	
SA2	4 (3)	12 (3)	
SA3	2 (2)	7 (2)	
SA>3	0 (0)	1 (0.3)	
<b>Therapeutic Abortions</b>			
TA0			< 0.001
TA1	76 (65)	377 (97)	
TA2	28 (24)	10 (3)	
TA3	8 (7)	1 (0.3)	
TA>3	3 (3)	0 (0)	
	2 (1)	1 (0.3)	

\* Probability of difference between cohort and control by chi-square.

**Table III: Nausea and vomiting characteristics of cohort (N=117) and comparison (N=389) groups - values are numbers of patients unless stated otherwise**

Characteristics	Cohort - n (%)	Control - n (%)	Significance (p)**
<b>NVP</b>			
Yes	82 (70)	258 (66)	0.517
No	35 (30)	131 (34)	
<b>NVP Severity</b>			
Mild	36 (44)	119 (46)	0.796
Moderate	29 (35)	94 (36)	
Severe	17 (21)	45 (18)	
<b>Nausea</b>			
Always	10 (14)	63 (24)	< 0.001
Most of the time	18 (24)	67 (26)	
Some of the time	22 (29)	97 (38)	
Rarely or never	25 (33)	31 (12)	
<b>Vomiting/Retching</b>			
>5/day	5 (7)	7 (3)	< 0.001
2-5/day	15 (20)	40 (16)	
once/day	22 (29)	37 (14)	
never	33 (44)	174 (67)	
<b>NVP Duration*</b>			
Mean (sd) [n]	5.96 wks (3.43) [23]	8.16 wks (3.19) [118]	0.086

sd = standard deviation

\*NVP Duration = Gestational age in weeks of when NVP stopped minus gestational age of when NVP started. Not all endpoints were available for all patients because either they did not report when NVP started/stopped or their NVP was ongoing.

\*\*Probability of difference between cohort and control by chi-square.

The demographics of the pregnant marijuana users and the characteristics of their use are described in Table IV. The typical pregnant marijuana user was employed, single and Caucasian. Most of the women had unplanned pregnancies (81%). The average history of using marijuana was 7.8 years and the most common patterns of use was daily or weekly. A small proportion of women (19%) reported experiencing positive or negative effects associated with marijuana use. The majority of reported adverse effects ranged from insomnia, anxiety, dizziness, tiredness, paranoia and memory loss. Twelve women reported having used marijuana in previous pregnancies and a

considerable proportion (61%) reported that marijuana use helped them with their NVP.

Table V outlines the results of the multivariate analysis of determinants that may affect symptoms of nausea, vomiting and/or retching, NVP severity and NVP duration. The total number of women who used antiemetics was not sufficient to include it in the multiple regression analysis. Cannabis and nicotine use were associated with decreased nausea but with increased vomiting and/or retching. Maternal age was associated with decreased vomiting and/or retching. NVP severity was not affected by any of the potential predictors while NVP duration was shortened by cannabis use.

**Table IV: Demographics and characteristics of pregnant marijuana users (N=117) - values are numbers of patients unless stated otherwise**

<b>Ethnicity (n)</b>		<b>History of Use</b>	
<i>White</i>	55	<i>mean (sd)</i>	7.8 yrs (6.3)
<i>Black</i>	7	<i>max</i>	25 yrs
<i>Aboriginal</i>	3	<i>min</i>	0.25 yrs
<i>Asian</i>	2		
<i>Hispanic</i>	1		
<i>Other</i>	3		
<i>Missing</i>	46		
<b>Marital Status (n)</b>		<b>Pattern of Use (n)</b>	
<i>Married</i>	12	<i>Daily</i>	59
<i>Single</i>	32	<i>Weekly</i>	40
<i>Common Law</i>	24	<i>Every 3 wks</i>	1
<i>Divorced</i>	3	<i>Monthly</i>	11
<i>Engaged</i>	1	<i>Every 2 months</i>	1
<i>Missing</i>	45	<i>Every 3 months</i>	1
		<i>Yearly</i>	2
		<i>Missing</i>	2
<b>Education (n)</b>		<b>Side Effects (n)</b>	
<i>&lt; Highschool</i>	12	<i>Yes</i>	22
<i>Highschool</i>	20	<i>No</i>	93
<i>College/University</i>	29	<i>Missing</i>	2
<i>Professional Degree</i>	2		
<i>Missing</i>	54		
<b>Employment (n)</b>		<b>Efficacy for NVP (n)</b>	
<i>Employed</i>	47	<i>Yes</i>	47
<i>Unemployed</i>	22	<i>No</i>	30
<i>Social Assistance</i>	5	<i>Missing</i>	5
<i>Missing</i>	43		

sd = standard deviation

Not all endpoints were available for all patients.

**Table V: Multiple regression analysis of determinants affecting outcomes of NVP severity, nausea, vomiting/retching and NVP duration**

	correlation	p-value
<b>NVP Severity</b>		
<i>Maternal Age*</i>	-0.053	0.330
<i>Gravidity*</i>	-0.022	0.717
<i>Folic Acid Use**</i>	-0.002	0.972
<i>Vitamin Use**</i>	0.004	0.949
<i>Nicotine Use**</i>	0.048	0.375
<i>Cannabis Use**</i>	0.029	0.595
<b>Nausea</b>		
<i>Maternal Age</i>	0.028	0.610
<i>Gravidity</i>	-0.044	0.424
<i>Folic Acid Use</i>	0.039	0.476
<i>Vitamin Use</i>	0.077	0.161
<i>Nicotine Use</i>	-0.140	0.011
<i>Cannabis Use</i>	-0.186	0.001
<b>Vomit/Retch</b>		
<i>Maternal Age</i>	-0.144	0.008
<i>Gravidity</i>	0.075	0.171
<i>Folic Acid Use</i>	-0.060	0.278
<i>Vitamin Use</i>	-0.101	0.066
<i>Nicotine Use</i>	0.149	0.006
<i>Cannabis Use</i>	0.187	0.001
<b>NVP Duration</b>		
<i>Maternal Age</i>	0.074	0.381
<i>Gravidity</i>	0.046	0.589
<i>Folic Acid Use</i>	-0.045	0.597
<i>Vitamin Use</i>	0.093	0.271
<i>Nicotine Use</i>	-0.101	0.234
<i>Cannabis Use</i>	-0.230	0.006

\*Scores by Pearson correlation.

\*\* Scores by Spearman's rho correlation.

## DISCUSSION

Marijuana is produced from the plant *Cannabis sativa*. It contains more than 400 chemicals including delta-9-tetrahydrocannabinol (9-THC) which possesses psychoactive and antiemetic properties<sup>16</sup>. Anecdotal accounts<sup>2,3</sup> and clinical investigations<sup>12-15</sup> of the effectiveness of cannabinoids in alleviating nausea and vomiting of cancer chemotherapy have been reported.

A recent systematic review of 30 randomized comparisons of cannabis with placebo or antiemetics, confirmed that cannabinoids (oral nabilone and dronabinol, and intramuscular levonantradol) were effective in controlling chemotherapy-related nausea and vomiting<sup>15</sup>, however no smoking of cannabis was included in this analysis. Adverse effects such as withdrawal, dizziness and paranoia were

commonly reported in the studies suggesting the potential severity of these side effects.

Given the wide use of marijuana<sup>11</sup>, inadvertent exposure during pregnancy is probable and likely. Although marijuana has not been implicated as an agent that causes birth defects<sup>16-18</sup> there is evidence for adverse neuro-developmental effects after prenatal exposure<sup>19-21</sup>.

Many women who smoke marijuana during pregnancy also use other illicit drugs, making it difficult to interpret the effects of marijuana in isolation. Moreover, socioeconomic status, family structure and maternal personality play a role in the long-term neurodevelopment of children<sup>22</sup>. In heavy marijuana users adverse effects identified in tobacco users can be

expected<sup>16-18, 23-25</sup>.

Our experience at the Motherisk Program includes numerous anecdotal reports from pregnant marijuana users suggesting that marijuana alleviates NVP<sup>8</sup>. Our design of the present study aimed at trying to control for various factors, other than cannabis use, which may affect symptoms of NVP such as vitamin consumption and maternal age. Our multivariate analysis may suggest that the use of marijuana helped to alleviate symptoms of nausea during pregnancy. Most of the study participants had a history of using marijuana and they may have had prior knowledge of its antiemetic effects, or may have incidentally discovered a decrease in NVP symptoms while using marijuana during pregnancy. As a result, the pregnant women experiencing NVP may have decided to continue or wished to increase the marijuana intake.

In contrast, marijuana use was not associated with relief of vomiting or retching and in fact, these symptoms seemed to increase. The mode of using marijuana by the participants of this study was through smoking and this may explain the mechanism of action of marijuana. Smoking leads to a rapid systemic exposure, therefore it may provide instant relief for nausea symptoms, a more central effect, while the act of smoking itself may increase vomiting and/or retching through a more peripheral effect. This difference may suggest two distinct mechanisms for nausea versus vomiting and/or retching. We were not able to measure the relationship between marijuana dose and efficacy for NVP since the dose was estimated by the number of joints smoked, hence making it impossible to quantify the amount of marijuana used by each participant.

Consistent with other studies<sup>15</sup>, a number of women reported experiencing potentially serious adverse effects when smoking marijuana. In spite of the fact that neither fetal nor maternal safety has yet been established, many of the participants of this study continued to smoke marijuana during pregnancy and have had previous pregnancy exposures. Smoking nicotine has also been documented to

help with NVP<sup>26</sup> thus corroborating our findings. Our study confirmed that cigarette smoking helped with nausea but not with vomiting, again suggesting the instant effect of the route of delivery as well as suggesting two different mechanisms for nausea and vomiting and/or retching. To gain more insight into the effects of marijuana as an anti-emetic in pregnancy, one would have to measure these effects alone. This would be difficult since many of the women who smoke marijuana also smoke nicotine during pregnancy and it is conceivable that they probably started smoking cigarettes first.

We found that younger maternal age was a predictor of symptoms of vomiting and/or retching. This agrees with previous studies and lends credibility to our analysis<sup>27</sup>. In a similar manner, vitamin use showed a trend to less vomiting and/or retching, possibly due to the vitamin B6 content which is currently recommended for NVP treatment<sup>28-31</sup>.

NVP severity, as rated objectively by the women, has been shown by us recently to be poorly associated with the self-assessment severity of the physical symptoms of NVP<sup>32</sup>. Thus it is not surprising that this subjective measure was not predicted by any of the putative factors tested by us. Whether a woman has mild physical symptoms or not, she may perceive herself as being severe, depending on how the NVP is affecting her quality of life. On the other hand, the duration of NVP was reportedly shortened by cannabis use but not by nicotine use, further elucidating the pharmacological effects of cannabis on NVP.

The purpose of this study was to analyze a regimen widely practiced by women. This study should not be interpreted as support for the use of marijuana as treatment for NVP. Women who choose to do so should be informed and warned that they may enjoy antiemetic benefits in exchange for potential risks to their unborn. While cannabinoids appear to be effective for nausea and length of NVP, the safety of these potent chemicals require further studies in pregnancy as well as in the general population.

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