OBSTETRICS & GYNECOLOGY

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- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

**The corresponding author has opted to make this information publicly available.*

Personal or nonessential information may be redacted at the editor's discretion.

Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office: obgyn@greenjournal.org.

Date: Sep 21, 2020
To: "Roxana Geoffrion" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-2358

RE: Manuscript Number ONG-20-2358

Recreational cannabis use pre- and post-legalization in women with pelvic pain

Dear Dr. Geoffrion:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

Your paper will be maintained in active status for 14 days from the date of this letter. If we have not heard from you by Oct 05, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

Thank you for the opportunity to review your work.
As a gynecologic surgeon taking care of women with pelvic pain and endometriosis, I am very appreciative of authors' efforts to shed more light on the unknown. Quite a few of them use cannabis (although it is still illegal in US and getting is prescribed medically in my state is a major hurdle most patients are not willing to undertake).

Study is well-executed, and paper is well-written.

I have following questions and comments

1. Introduction
Concise and to the point summary of CPP. Research leading up to this is summarized well (minimal, unfortunately)

2. Aims of the study clearly stated
3. Methods-please say more about your prospective registry. What are main goals of the registry? Was this study a side-project and registry is used for other aims? Is this first time this registry used for publication purposes, or are there other publications from this registry?

4. Inclusion and exclusion criteria are clearly stated

5. Questions about cannabis use are explained well in methods.
a. My main question about this is whether it was possible to ask women if they used cannabis for CPP or for some other reason (anxiety, purely recreational, other pain conditions, etc.). That would be a key question to address in this study.
b. What is cannabis climate use in Canada aside from recreational use? In US, we have medical cannabis, CBD, and a million other natural and synthetic derivatives which patients use and those are hard to standardize in questionaries' I would imagine. Can you please expand on that?

6. Metrics entered into database are detailed and clinically relevant

7. Given that ¾ of all patients in registry had endometriosis
a. Would it be possible to analyze women without endometriosis (or are the numbers too small)?
b. If above is not possible, what do authors think might be found if that type of study was possible? Would CPP patients with and without endo differ in their use and response to cannabis?

8. Discussion-addresses limitations sets study into clinical and social context and points out future directions.

Reviewer #2:

Thank you for your submission. Before I get into the meat of the article here are a few grammatical changes you may consider.

1. Line 28: We excluded 18 or younger, and with unknown data..... Consider changing and to or. And means both criteria would need to be met for exclusion.

2. Line 48...they were less likely... Clarify who they were. Instead of they use "cannabis users" if that is the group you are referencing.

3. Line 85 change and to or, for the same reason stated in #1.

4. Line 92 place quotation in front of currently.

5. Tables- clarify what the numbers in parentheses are. I presume they are percentages.

6. Tables- clarify the numbers presented as a fraction. What are the denominators? If denominator is the # of people surveyed for that condition, why is it different from the full cohort?

7. Table 1 Instead of Cannabis User in your second column, change to cannabis use- yes or no. The "no" group are not cannabis users.

Ok, now for your study. You have collected a lot of data and presented them. I have no issues with your methodology. I am having a hard time grasping the clinical significance of all the data presented. I agree with your premise that cannabis as a treatment for CPP needs to be assessed. Your study did not assess that particular question though, it simply assessed frequency of use and the characteristics of the women using it pre and post legalization. While the question above is very much clinically relevant, I am not sure the data presented is. Is there some way you can connect the data you have to the clinically relevant question regarding the use of cannabis for CPP. I understand there is no way to retrospectively assess the effectiveness of cannabis for the treatment of CPP. However, are you able to determine if legalization caused women to even consider the use of cannabis as a treatment option? I am not clear if the women using cannabis were using it for relief of pain or to achieve some other benefit. It is possible that while your survey assessed for pain and other medical descriptors, that was not the goal of use. I think the most clinically significant finding is the reduction in use of narcotics among the cannabis users, but the morbidity was higher among users. My opinion is that after reviewing all this data, I did not have any clear clinical take aways. It did not add to my breadth of knowledge. Again, if analysis of the data can create a statement on whether cannabis use was utilized more as an option for treatment of pelvic pain, any pain, anxiety or depression after legalization that would be helpful.

Reviewer #3:

1. Page 3 "catastrophizing" - is this a medical term?

2. Authors reports different pattern of stage of endometriosis among users and non-users; more information on this would be helpful

3. Perhaps some more information regarding the center at which this study was performed would be useful. It is clear that this is a referral center for chronic pelvic pain & endometriosis. Who is referring? Are these patients who have already had gynecologic care and failed treatment? Or are these patients referred from a primary care doctor/family practice or self referred.

4. Is there a way to assess if those who entered into the study and identified themselves as never users of cannabis then started to use cannabis? This might indicate an effect of legalization

5. After legalization, more people who were previously using may have been more comfortable to admit use.

Reassessment of existing patients in the registry may capture those.

6. I think the key in the conclusion is that "cannabis use reported" increased after legalization. Quantifying actual increase in use would be to re-survey non-users
7. Demographics of users pre and post legailization is an interesting aspect.

8. Tables and charts are good

STATISTICAL EDITOR COMMENTS:

Fig 1: Need to compare baseline characteristics of women who declined consent or declined answering questions re: recreational drug use vs those included in final analyzed cohort to evaluate any issue with generalizability or potential selection bias. Also, did the proportion declining or declining to answer questions re: recreational drug use change from pre to post legalization? That is, could there be potential for selection bias?

Tables 1, 2 and supplemental Tables: Need to specify whether there were missing data for the validated questionnaires and enumerate all missing data.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
A. OPT-IN: Yes, please publish my point-by-point response letter.
B. OPT-OUT: No, please do not publish my point-by-point response letter.

2. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA). When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

3. For studies that report on the topic of race, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes).

Use "Black" and "White" (capitalized) when used to refer to racial categories.

The category of "Other" is a grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. If you use "Other" in your study, please add detail to the manuscript to describe which patients were included in that category.

4. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting observational studies (ie, STROBE) and observational studies using ICD-10 data (ie, RECORD). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at http://ong.editorialmanager.com. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, RECORD, CHEERS, SQUIRE 2.0, or CHERRIES

guidelines, as appropriate.

5. If your study uses ICD-10 data, please make sure you do the following:
a. State which ICD-10-CM/PCS codes or algorithms were used as Supplemental Digital Content.
b. Use both the diagnosis and procedure codes.
c. Verify the selected codes apply for all years of the study.
d. Conduct sensitivity analyses using definitions based on alternative codes.
e. For studies incorporating both ICD-9 and ICD-10-CM/PCS codes, the Discussion section should acknowledge there may be disruptions in observed rates related to the coding transition and that coding errors could contribute to limitations of the study. The limitations section should include the implications of using data not created or collected to answer a specific research question, including possible unmeasured confounding, misclassification bias, missing data, and changing participant eligibility over time.
f. The journal does not require that the title include the name of the database, geographic region or dates, or use of database linkage, but this data should be included in the abstract.
g. Include RECORD items 6.3 and 7.1, which relate to transparency about which codes, validation method, and linkage were used to identify participants and variables collected.

6. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

7. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

8. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

* All financial support of the study must be acknowledged.
* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

9. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limit for Original Research articles is 300 words; Reviews is 300 words; Case Reports is 125 words; Current Commentary articles is 250 words; Executive Summaries, Consensus Statements, and Guidelines are 250 words; Clinical Practice and Quality is 300 words; Procedures and Instruments is 200 words. Please provide a word count.

10. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com/ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

11. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

12. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%").

13. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

14. When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

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Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

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If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded in a word processing format such as Microsoft Word. Your revision's cover letter should include the following:

* A confirmation that you have read the Instructions for Authors (http://edmgr.ovid.com/ong/accounts/authors.pdf), and
* A point-by-point response to each of the received comments in this letter.

If you submit a revision, we will assume that it has been developed in consultation with your co-authors and that each author has given approval to the final form of the revision.

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Oct 05, 2020, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

John O. Schorge, MD
Associate Editor, Gynecology

2019 IMPACT FACTOR: 5.524
2019 IMPACT FACTOR RANKING: 6th out of 82 ob/gyn journals

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: https://www.editorialmanager.com/ong/login.asp?a=r). Please contact the publication office if you have any questions.

RE: Manuscript Number ONG-20-2358

Recreational cannabis use pre- and post-legalization in women with pelvic pain

Dear Editors,

Thank you for considering our manuscript in a revised version. Please see our response to reviewers below.

Sincerely,

Roxana Geoffrion and co-authors

REVIEWER COMMENTS:

Reviewer #1:

Thank you for the opportunity to review your work.
As a gynecologic surgeon taking care of women with pelvic pain and endometriosis, I am very appreciative of authors' efforts to shed more light on the unknown. Quite a few of them use cannabis (although it is still illegal in US and getting is prescribed medically in my state is a major hurdle most patients are not willing to undertake).

Study is well-executed, and paper is well-written.

Response: Thank you

I have following questions and comments

1. Introduction

Concise and to the point summary of CPP. Research leading up to this is summarized well (minimal,

unfortunately)

Response: Thank you

2. Aims of the study clearly stated

Response: Thank you

3. Methods-please say more about your prospective registry. What are main goals of the registry? Was this study a side-project and registry is used for other aims? Is this first time this registry used for publication purposes, or are there other publications from this registry?

Response: This prospective registry, Endometriosis and Pelvic Pain Interdisciplinary Cohort (EPPIC) (Clinicaltrials.gov #NCT02911090), is situated within the BC Women's Centre for Pelvic Pain and Endometriosis (a tertiary referral center in British Columbia, Canada, which provides interdisciplinary care ranging from minimally invasive surgery, medical management, pain education, and psychological and physical therapy) (womenspelvicpainendo.com). We began recruiting new or re-referral patients from the center for the registry in December 2013. The primary goals of the registry are to examine prospective outcomes after interdisciplinary care for endometriosis/pelvic pain, as well as the multifactorial underlying factors associated with baseline and prospective outcomes. Therefore, this registry was not designed to study cannabis – the current study is a side-project, which is why we explicitly stated that this was a retrospective analysis of the prospective registry (page 6). There have been many publications from this registry, some of which are listed on https://clinicaltrials.gov/ct2/show/NCT02911090. The key papers from the registry are:

1. Yosef et al. Multifactorial contributors to the severity of chronic pelvic pain in women. Am J Obstet Gynecol 2016;215(6):760.e1-760.e14
2. Allaire et al. Chronic pelvic pain in an interdisciplinary setting: 1-year prospective cohort. Am J Obstet Gynecol 2018 ;218(1) :114.e1-114.e12

The Yosef paper is referenced in the Methods (reference #2), which describes the details of the registry as summarized above. Also a few sentences have been added to the Methods (see page 6).

4. Inclusion and exclusion criteria are clearly stated

Response: Thank you

5. Questions about cannabis use are explained well in methods.

a. My main question about this is whether it was possible to ask women if they used cannabis for CPP or for some other reason (anxiety, purely recreational, other pain conditions, etc.). That would be a key question to address in this study.

Response: You are correct, this is indeed a key question. Unfortunately our registry only asked the question in regards to "recreational" use. Thus, we are unable to pinpoint the precise reason(s) women started to use cannabis in the cohort. As the reviewer notes, there can be many reasons for using cannabis, including within a given patient (e.g. a patient could be using cannabis for a combination of reasons, in part for CPP, in part for anxiety, and in part recreationally). We are currently planning a survey study to fine tune women's report of indications for cannabis use in this cohort.

b. What is cannabis climate use in Canada aside from recreational use? In US, we have medical cannabis, CBD, and a million other natural and synthetic derivatives which patients use and those are hard to standardize in questionaries' I would imagine. Can you please expand on that?

Response: The cannabis climate in Canada is complex, and constantly evolving. "Medical" cannabis is supplied by approximately 200 Licensed Producers, who are authorized by Health Canada to provide cannabinoid-based products. These initially included dried flower and oils, and have more recently been expanded to include edibles. Products primarily include THC and CBD, although additional cannabinoids look likely in the near future. Medical cannabis requires an authorization by a licensed clinician (the cannabis is not "prescribed" as it does not have a DIN). Many users still consume black-market cannabis, as the cost is substantially cheaper than legally approved medical cannabis. A descriptive sentence was added to the introduction of our revised manuscript (page 5).

6. Metrics entered into database are detailed and clinically relevant

Response: Thank you

7. Given that ¾ of all patients in registry had endometriosis

a. Would it be possible to analyze women without endometriosis (or are the numbers too small)?

Response: We have added the comparison between cannabis users and non-users by endometriosis status to Appendix Table 3. There were 757 subjects without endometriosis, of which 106 were cannabis users (14%). There were 2663 subjects with endometriosis, of which 402 were cannabis users (15%).

Examining the new Appendix Table 3, we see that the differences between cannabis users and non-users are similar between the endometriosis patients and the non-endometriosis patients. The only exception that was both statistically and clinically significant was that cannabis users were more likely to require daily opioids in the subpopulation without endometriosis (28.3% daily opioids), compared to cannabis users in the subpopulation with endometriosis (13.2% daily opioids), although this difference was only present before legalization. These findings were added to the Results section (page 10) and Appendix Table 3 was added.

b. If above is not possible, what do authors think might be found if that type of study was possible? Would CPP patients with and without endo differ in their use and response to cannabis?

Response: Please see response to 7a. It is interesting that cannabis users were more likely to use opioids in the subpopulation without endometriosis, compared to cannabis users in the subpopulation with endometriosis, prior to legalization. The reason why is unclear, and we can only speculate. Perhaps in patients without endometriosis, the primary care providers (before referral to the center, as this is data from baseline at the center) felt more uncertainty about the diagnosis or that there were fewer treatment options (e.g. no option for surgery or the hormonal treatments available for women with endometriosis) – and so opioids were prescribed due to what they perceived as a lack of other options. Two sentences describing possible explanations for this finding were inserted in the discussion.

8. Discussion-addresses limitations sets study into clinical and social context and points out future directions.

Response: Thank you

Reviewer #2:

Thank you for your submission. Before I get into the meat of the article here are a few grammatical changes you may consider.

1. Line 28: We excluded 18 or younger, and with unknown data..... Consider changing and to or. And means both criteria would need to be met for exclusion.

Response: Thank you, done

2. Line 48...they were less likely... Clarify who they were. Instead of they use "cannabis users" if that is the group you are referencing.

Response: Thank you, done

3. Line 85 change and to or, for the same reason stated in #1.

Response: Thank you, done

4. Line 92 place quotation in front of currently.

Response: Thank you, done

5. Tables- clarify what the numbers in parentheses are. I presume they are percentages.

Response: We have clarified this in the table by noting “n (%)” or “mean (SD)” after the variable name to indicate what the numbers in parentheses represent.

6. Tables- clarify the numbers presented as a fraction. What are the denominators? If denominator is the # of people surveyed for that condition, why is it different from the full cohort?

Response: We have added the following footnote to the tables.
“For dichotomized variables with missing data, the denominator represents the number of women with non-missing data.”

7. Table 1 Instead of Cannabis User in your second column, change to cannabis use- yes or no. The "no" group are not cannabis users.

Response: We have changed the heading to from “Yes” and “No” to “Cannabis users” and “Non-users”. We hope this is satisfactory.

Ok, now for your study. You have collected a lot of data and presented them. I have no issues with your methodology. I am having a hard time grasping the clinical significance of all the data presented. I agree with your premise that cannabis as a treatment for CPP needs to be assessed. Your study did not assess that particular question though, it simply assessed frequency of use and the characteristics of the women using it pre and post legalization. While the question above is very much clinically relevant, I am not sure the data presented is. Is there some way you can connect the data you have to the clinically relevant question regarding the use of cannabis for CPP. I understand there is no way to retrospectively assess the effectiveness of cannabis for the treatment of CPP. However, are you able to determine if legalization caused women to even consider the use of cannabis as a treatment option? I am not clear if the women using cannabis were using it for relief of pain or to achieve some other benefit. It is possible that while your survey assessed for pain and other medical descriptors, that was not the goal of use. I think the most clinically significant finding is the reduction in use of narcotics among the cannabis users, but the morbidity was higher among users. My opinion is that after reviewing all this data, I did not have any clear clinical take aways. It did not add to my breadth of knowledge. Again, if analysis of the data can create a statement on whether cannabis use was

utilized more as an option for treatment of pelvic pain, any pain, anxiety or depression after legalization that would be helpful.

Response: Thank you for your analysis. The registry was not designed to go in depth into the reasons for cannabis use, and thus we are unable to pinpoint the precise reason(s) women started to use cannabis in the cohort before and after legalization. There can be many reasons for using cannabis, including within a given patient (e.g. a patient could be using cannabis for a combination of reasons, in part for CPP, in part for anxiety, and in part recreationally). Therefore, we are conducting more research to understand women's detailed reasons for using cannabis (beyond recreational), through a follow-up survey study of the subjects in the cohort. It should be noted that post-legalization users had higher education levels (compared to pre-legalization users), which perhaps suggests that post-legalization more patients (who were less likely to use cannabis historically) became open to trying cannabis for their CPP. But at this point, this is a speculation, and thus we look forward to learning more about this issue in future research.

We also acknowledge, in our limitations, that factors other than legalization may have caused women to increase cannabis use around that time. Nevertheless, in this vulnerable patient population, we observed a significant increase in cannabis use after its legalization, and this is unlikely coincidental or due to other factors only. The government of Canada conducts an annual Canadian Cannabis Survey and results are available online (see reference below). Use of non-medicinal (recreational) cannabis in 2017 and 2018 was the same at 18%, then increased to 21% post legalization in 2019 in women of the general population. In our cohort of women with CPP, there was a parallel albeit higher increase (13.3 to 21.5%), suggesting similarity with national trends. The take away message of our current study is that legalization was temporally associated with an increase in use among women with CPP and this coincided with a desirable decrease in opioid use in this population.

Reference: https://www.canada.ca/en/services/health/publications/drugs-health-products/canadian-cannabis-survey-2018-summary.html

Reviewer #3:

1. Page 3 "catastrophizing" - is this a medical term?

Response: Pain catastrophizing is a term used in pain and psychiatric medicine to describe a negative mental set brought to bear on actual or anticipated pain (e.g. magnification and rumination on symptoms, as well as feelings of helplessness), and widely shown to be associated with poor pain treatment response in patients with chronic pain.

Please see the following references:

Sullivan M, Bishop S, Pivik J. The Pain Catastrophizing Scale: Development and validation. Psychological Assessment. 1995;7(4):524-532.

Darnall BD, Sturgeon JA, Cook KF, Taub CJ, Roy A, Burns JW, Sullivan M, Mackey SC. Development and Validation of a Daily Pain Catastrophizing Scale. J Pain. 2017 Sep;18(9):1139-1149. doi: 10.1016/j.jpain.2017.05.003. Epub 2017 May 19. PMID: 28528981; PMCID: PMC5581222.

2. Authors reports different pattern of stage of endometriosis among users and non-users; more information on this would be helpful

Response: What we found was a different pattern in stage of endometriosis among users before and after legalization – from Table 2:

Endometriosis stage, n (%)	Before legalization	After legalization	P = 0.012
Unknown	82	0	
1	88 (41.3)	34 (31.8)	
2	49 (23.0)	29 (27.1)	
3	35 (16.4)	9 (8.4)	
4	41 (19.2)	35 (32.7)	

Examining this Table indicates that Stage 1 and 3 endometriosis were relatively more common in cannabis users before legalization, while Stage 4 endometriosis was relatively more common in cannabis users after legalization. While this was a statistically significant difference, it is hard to know whether it is clinically meaningful. For this reason, we have decided to not expand on this in the discussion but would be happy to do so if you think it would be useful for readers. For instance, typically Stage 1-2 and

Stage 3-4 endometriosis are grouped together – grouped in this way, there was not a significant difference before and after legalization:

	Before legalization	After legalization	p = 0.39
Stage 1-2	137 (64.3%)	63 (58.9%)	
Stage 3-4	76 (35.6%)	44 (41.1%)	

3. Perhaps some more information regarding the center at which this study was performed would be useful. It is clear that this is a referral center for chronic pelvic pain & endometriosis. Who is referring? Are these patients who have already had gynecologic care and failed treatment? Or are these patients referred from a primary care doctor/family practice or self referred.

Response: The center is the BC Women's Centre for Pelvic Pain and Endometriosis (womenspelvicpainendo.com), which provides interdisciplinary care ranging from minimally invasive surgery, medical management, pain education, and psychological and physical therapy. Referrals can come from either primary care or specialists (gynecology or other specialties), from throughout the province of British Columbia, Canada. There are no self-referrals. This information has been added to the Methods (page 6). Unfortunately we do not have data in registry on the source of the referral. Table 1 allows the reader to draw some conclusions about prior treatments. For example, the stage of endometriosis was known in 83% of patients, suggesting these patients had undergone prior diagnosis and/or treatment via surgery.

4. Is there a way to assess if those who entered into the study and identified themselves as never users of cannabis then started to use cannabis? This might indicate an effect of legalization

Response: You are correct, this would indicate the effect of legalization on women choosing to use cannabis. However, this study was cross-sectional, so we do not have data from the same patients before and after legalization. We were able to see that cannabis use among this population increased from 13.3% to 21.5% pre and post legalization, and are starting a follow up survey study that will investigate the motivations for trying cannabis in this population.

5. After legalization, more people who were previously using may have been more comfortable to

admit use. Reassessment of existing patients in the registry may capture those.

Response: That is an excellent point, thank you. This was added to our limitations (page 13).

6. I think the key in the conclusion is that "cannabis use reported" increased after legalization. Quantifying actual increase in use would be to re-survey non-users

Response: Thank you, we are starting an additional survey study motivated by results from our current cross-sectional study and look forward to reporting on it. You are correct, what increased after legalization in this study was reported cannabis use. As with any questionnaire based study, there may be reporting bias and we cannot assess with certainty the effect that the legal status of cannabis had on accurate reporting of cannabis use. This study used cross-sectional data, so we are unable to report on if use increased among previous non-users post legalization.

7. Demographics of users pre and post legalization is an interesting aspect.

Response: Thank you

8. Tables and charts are good

Response: Thank you

STATISTICAL EDITOR COMMENTS:

Fig 1: Need to compare baseline characteristics of women who declined consent or declined answering questions re: recreational drug use vs those included in final analyzed cohort to evaluate any issue with generalizability or potential selection bias. Also, did the proportion declining or declining to answer questions re: recreational drug use change from pre to post legalization? That is, could there be potential for selection bias?

Response:

The rate of declining to answer the recreational drug question was 242/3002 (8%) for the pre period and 34/700 (5%) for the post period (p=0.004). This was added to the Results section (pages 8,9). Although the difference was statistically significant, the magnitude of the difference was small and so less likely to have major impact on the results. We have also added the following to the discussion (page 13): "The observed increase in cannabis use post legalization may have been due to other unrelated or indirectly related factors such as increased willingness to admit use."

Comparison of baseline characteristics of women who declined answering the recreational drug question (either not provided an answer or selected "preferred not to answer") vs. those who answered and were included in the analysis, has been added to Appendix Table 1. Those who declined to answer had lower education, were less likely to identify as married/common-law, more likely to be smokers or drink alcohol, more likely to be postmenopausal, and had higher scores on the depression (PHQ-9) and anxiety (GAD-7) scales ($p < 0.05$) – although the magnitude of the differences was small (e.g. PHQ-9 score 9.9 vs. 9.0 and GAD-7 score 7.5 vs. 6.8). However, those who declined to answer had similar pain profiles (dysmenorrhea, dyspareunia, dyschezia, other pelvic pain, back pain), similar pain catastrophizing scale and quality-of-life scores, and similar comorbidities (i.e. frequencies of abdominal wall trigger point, pelvic floor myalgia, irritable bowel syndrome, painful bladder syndrome). Our results indicate smoking and drinking alcohol may correlate with cannabis use. Therefore, among non-responders, cannabis use may be higher than that of responders. We added a sentence to the limitations in the discussion section to alert readers to these differences between responders and non-responders (see page 14), and included Appendix Table 1.

Tables 1, 2 and supplemental Tables: Need to specify whether there were missing data for the validated questionnaires and enumerate all missing data.

Response: We have now noted the amount of missing data for continuous/categorical variables and the number of women with non-missing data for dichotomized variables within the tables.