

# 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)\*
- Email correspondence between the editorial office and the authors\*

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

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[obgyn@greenjournal.org](mailto:obgyn@greenjournal.org).

**Date:** Sep 25, 2018  
**To:** "Torri Derback Metz" [REDACTED]  
**From:** "The Green Journal" em@greenjournal.org  
**Subject:** Your Submission ONG-18-1655

RE: Manuscript Number ONG-18-1655

Prenatal Marijuana Use by Self-Report and Umbilical Cord Sampling in a State with Legalization

Dear Dr. Metz:

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 21 days from the date of this letter. If we have not heard from you by Oct 16, 2018, we will assume you wish to withdraw the manuscript from further consideration.

#### REVIEWER COMMENTS:

Reviewer #1: For the manuscript titled "Prenatal marijuana use by self-report and umbilical cord sampling in a state with legalization", I have the following comments and queries:

1. Thanks for submission of your work.
2. Line 114. Even if consent is not required for testing discarded specimens, this seems to be an attempt to conceal this practice from your study population, even though anonymity was preserved. The subjects would have no idea that this was occurring, or that such a policy existed.
3. This study clearly demonstrates the lack of a correlation in prenatal marijuana use as assessed by self-reporting and umbilical cord testing.
4. Strengths of the study include a power analysis, the assessment of two different socio-economic populations, and assessment of outcomes in a state where recreational marijuana use is legal.

Reviewer #2:

#### Introduction:

1. While it's important to discuss the discordance between self-reported use of marijuana and detected THC via urine toxicology, I think it's important to better set the stage for why obstetricians even care about marijuana use in the first place (e.g. concerns regarding childhood neurodevelopmental outcomes, smaller birth lengths, smaller head circumference). While much of this is confounded by polysubstance use, socioeconomic status, nutrition, etc, as well as ascertainment bias - I think it's still worth bringing this up to inform readers why this study is important.

#### Methods:

1. For the survey administered to the subjects, was this a validated survey? If so, were other substances also assessed?
2. I do see that assay results were not linked to participants and were not available to the team. Given the fact that in the state of Colorado, perinatal substance use is considered a form of child abuse and mandated reporting is required, were there any other protections in place (e.g. Certificate of Confidentiality) for patient anonymity?

## Results:

1. Pg 11, lines 208-210 - would consider rewording as the sentence is confusing
2. Pg 12, lines 217-218 - would consider highlighting that almost 5-10% of cohort who said they didn't use had positive cord assay, which is an interesting finding. While you kind of get into this with your correlation coefficients, I think providing the proportions in this scenario provide the reader with a clear and tangible statistic to hold onto.

## Discussion

1. Pg 12, lines 234-235 - I would say that there was poor agreement overall regarding self-reporting measures of marijuana use and cord assay
2. Pg 12, lines 237-239 - I would mention that due to the likely ascertainment bias present in some previous studies (e.g. inability to detect a more accurate prevalence of use), the results of aforementioned studies may be biased towards the null hypothesis.
3. Pg 13, lines 255-257 - please explain further why testing for other metabolites might be informative.
4. Pg. 13, lines 273-75 - are there any studies you can cite that could corroborate your incidence of self-report of marijuana (or other substances)? Might be helpful to make your argument
5. Pg 13, lines 283-85 - would move this to the introduction to set the stage as to why marijuana use in pregnancy is important to assess

## Reviewer #3:

1. Although you clearly state that a UDS assess MJ use over the past 2-3 days, why was a UDS not collected at the time of admission, especially since the patient was recruited to the study at the time of admission to L&D? Or why not use UDS that may have been in their chart during this prenatal visits?
2. In your introduction, please provide more information on why and how you chose to analyze the THC-A metabolite versus the other metabolites that you mention in your discussion.
3. The umbilical cord homogenate detects MJ use from the 2nd trimester onwards - is there a correlation with amount of use? For example, if someone smoked marijuana once at 24 weeks, will the metabolite still be present at delivery at 40 weeks? How long does the metabolite last in the blood system? Is it affected by 2nd hand exposure? What is the validity of this metabolite? Please provide some more background information on this. If I understand Figure 2 correctly, then some women who said they never used before had positive homogenates - this makes me wonder if 2nd hand smoke makes the homogenates positive.
4. The words "marijuana use" and "marijuana exposure" appear to be used interchangeably in your manuscript. Exposure to marijuana could also mean exposure to 2nd hand smoke. Consider using the word "use" consistently in your paper versus "exposure" (unless deeming it to be "fetal exposure" which makes sense).
5. Line 123: please provide the IRB number.
6. Line 133: Why was age the only variable that was used to preserve anonymity? You collected several other baseline identifiers that don't preserve anonymity.
7. Line 148 - please clarify what LC-MS/MS is (it is written later in the paragraph on page 9, but would ideally be described earlier)
8. Please clarify your sample size calculations. Why was a prevalence of 15% presumed in your population even the reported prevalence you quoted was between 3-7%? Provide local data if available. You hypothesized that the metabolite would report higher rates, but your sample size calculation is based on equivalent rates. Please clarify.
9. Two additional limitations to discuss are recall bias and lack of correlation with neonatal outcomes. Women may not recall if they had smoked marijuana in the past year or so - this may explain the discord on the number of self-reports and those with positive metabolites. Also, were there any differences in those who tested positive and birth weight, APGARs, GA at delivery?
10. I'm not sure how much extra information Figure 3 adds to your paper. Consider deleting it or revising it.

Reviewer #4: In this article Metz et al report on a cross-sectional study of marijuana use women at two Colorado hospitals comparing used recorded in the H&P with report on a survey and with use as defined by the presence of a metabolite in the umbilical cord tissue. The found that, even in a state with legalized marijuana use, the reported prevalence was much lower than that detected by the active metabolite. These findings are important to the readers of Ob/Gyn as more women are likely to be exposed to marijuana and data on the effects of this use on the pregnancy depends on accurately determining which women and children are exposed. This manuscript suggests that prior studies may be underestimating the exposure, which has implications both for their conclusions as well as how future studies should be designed.

I have the following comments:

Abstract: consider adding the half life of the THC-A

Introduction:

line 62, consider moving "in high risk groups" to after "California study"

Paragraph 1, have there been any studies in non-pregnant populations to support the theory that rates of use are higher after THC is legalized?

Paragraph 2, Please add a line about the half life of the THC-A in serum and as stored in lipophilic tissues. Is it present longer in obese vs normal weight women? Is there any data to suggest that the metabolite is affected by other drug use or cigarettes?

Materials and Methods:

Line 173, Please explain why you chose the cut off of use within the past 30d. Is this related to the half life of the metabolite or just a standard unit of time for the patient survey?

Line 176, Consider adding a line explaining comparison of contingency tables

You did not collect data on maternal weight gain or BMI. Given that the THC-A is lipophilic, would the maternal BMI potentially confound the results?

Results:

Line 214, consider adding that the use of tobacco was low and did not differ between groups.

Discussion:

Lines 265-75, Consider adding that your patients have a low smoking prevalence.

Tables and figures: no comments

#### STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

lines 46-52: Suggest that the proportions reporting marijuana use on surveys, to health care providers and on umbilical cord assay each should include CIs. See later comments re: Fig 3, not convinced that lines 50-52 contribute to the main conclusions of the paper, which is to cite cross sectional estimates of marijuana use in these women and to contrast surveys with assays.

Table 1: The non-random allocation of age strata by THC-A (+) vs THC-A (-) appears to derive most of its discrepancy from the 22-25 yo cohort. Might be worthwhile analyzing by stratum and commenting. The overall test done (Chi-square) cannot directly attribute which stratum by age or by insurance status contributed to the non-random allocation. For the statement on lines 213-215, a pairwise testing should be done.

lines 211-213: Suggest re-wording this, since the 12 samples > 200 pg/g were a subset of the 26 samples > 100 pg/g, lest the reader interpret those groups as being mutually exclusive.

Fig 3 is difficult to interpret, since obviously many of the surveys were incorrectly self-reported. That is, the sample is biased. In any event, the estimates for  $p$  and its CI have too many significant figures. Since the total sample was 116, the precision should be truncated at 2 or at most 3 decimal places.

## EDITOR COMMENTS:

1. Thank you for your submission to Obstetrics & Gynecology. In addition to the comments from the reviewers above, you are being sent a notated PDF that contains the Editor's specific comments. Please review and consider the comments in this file prior to submitting your revised manuscript. These comments should be included in your point-by-point response cover letter.

\*\*\*The notated PDF is uploaded to this submission's record in Editorial Manager. If you cannot locate the file, contact Randi Zung and she will send it by email - rzung@greenjournal.org.\*\*\*

- The objective for the abstract should be a simple "to" statement without background.
- It is not clear from this that how you identified patients. Also, not sure you report the medical record abstraction results other than at time of admission for delivery. Did you collect prenatal data? When was survey done?
- How many women had cord homogenates but no surveys and vice versa?
- in what population? All adults? Only pregnant women? Please clarify.
- When was the Kaiser study done? Is there data to suggest higher usage in states w/ legalization?
- In the first 2/3 of pregnancy, the cord is rather slender without much Wharton's Jelly. While the jelly is largely mucopolysaccharides, there are fats in it. Before much jelly production--mostly in the last 1/3 of pregnancy--presumably there isn't much fat there. Why would it then be a reservoir for lipophilic THC metabolites?
- please add in the introduction something about THC-A. How long does it last in urine, cord homogenate.
- please explicate the primary objectives along with any secondary objectives.
- did you abstract prenatal information?
- when was the survey administered? By whom?
- It is important to know when in relation to the delivery that women completed these samples. Post delivery, possible effects of pain medications, fatigue, heightened fear if results of + use in survey revealed to pediatricians, etc.
- Please clarify: Prenatal marijuana use spanning all of the prenatal period or just peri-delivery?
- Is the cord sample technically "discarded" if the patient knowingly labeled a container and gave it to clinical personnel to retain a segment of cord? Sounds like a special collection of a study segment, rather than a discarded cord segment. One of your reviewers questions the ethics of this--calling it "discarded"--and I have to say I have some questions as well. Can you explain please what the participants were told about what was being done to the cord segment they voluntarily contributed?
- but they were linked to individual patients, correct? What do you mean by "not linked to any identifying information"
- what is this based on?
- The lower bounds is just barely outside of the 15% use you thought likely in your population. (and the upper bound twice that value!). How has that influenced your thinking about your population and maternal/neonatal outcomes?
- please comment about to what degree second-hand exposure to marijuana could result in cord homogenate positive results
- I'm curious about the hypothesis that the legalization of use might mitigate women's hesitancy to report marijuana use, which seems to be your working hypothesis. Women under report both cigarette and alcohol use in pregnancy--both legal. However, marijuana, tobacco use, and alcohol use may not be "approved" by the health care provider (even if legally approved) so the woman may underreport.

2. 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, as well as subsequent author queries. 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:

1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

3. Author Agreement Forms: Please note the following issues with your forms. Updated or corrected forms should be submitted with the revision.

Kennon Heard, MD, PhD - Did not indicate a conflict of interest disclosure.

4. All studies should follow the principles set forth in the Helsinki Declaration of 1975, as revised in 2013, and manuscripts should be approved by the necessary authority before submission. Applicable original research studies should be reviewed by an institutional review board (IRB) or ethics committee. This review should be documented in your cover letter as well in the Materials and Methods section, with an explanation if the study was considered exempt. If your research is based on a publicly available data set approved by your IRB for exemption, please provide documentation of this in your cover letter by submitting the URL of the IRB web site outlining the exempt data sets or a letter from a representative of the IRB. In addition, insert a sentence in the Materials and Methods section stating that the study was approved or exempt from approval. In all cases, the complete name of the IRB should be provided in the manuscript.

5. 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 will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at <http://links.lww.com/AOG/A515>, and the gynecology data definitions are available at <http://links.lww.com/AOG/A935>.

6. 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 appendixes).

Please limit your Introduction to 250 words and your Discussion to 750 words.

7. Specific rules govern the use of acknowledgments in the journal. Please edit your acknowledgments or provide more information in accordance with 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 signature on the journal's author agreement 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).

8. 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 limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

9. 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.

10. 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.

11. 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](http://edmgr.ovid.com/ong/accounts/table_checklist.pdf).

12. Figures

Figure 1: Ok, resubmit as-is.

Figure 2: Per journal style, we try to avoid using patterns in bar graphs. Would it be possible to get a version of this figure with solid colored bars?

Figure 3: Ok, resubmit as-is.

13. If you choose to revise your manuscript, please submit your revision via Editorial Manager for Obstetrics & Gynecology at <http://ong.editorialmanager.com>. It is essential that your cover letter list point-by-point the changes made in response to each criticism. Also, please save and submit your manuscript in a word processing format such as Microsoft Word.

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

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 16, 2018, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD  
Editor-in-Chief

2017 IMPACT FACTOR: 4.982

2017 IMPACT FACTOR RANKING: 5th out of 82 ob/gyn journals

In response to the EU General Data Protection Regulation (GDPR), you have the right to request that your personal information be removed from the database. If you would like your personal information to be removed from the database, please contact the publication office.

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October 16, 2018

Dear Dr. Chescheir,

Thank you for your ongoing consideration of our manuscript entitled "Prenatal marijuana use by self-report and umbilical cord sampling in a state with legalization" for publication in *Obstetrics and Gynecology*. As the lead author, I affirm that this manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of this study have been omitted; and that discrepancies from the study as planned have been explained. This study was approved by the Colorado Multiple Institutional Review Board (COMIRB).

The study is a cross-sectional observational cohort; the study results are therefore reported consistent with STROBE guidelines for reporting observational studies.

The manuscript has not been submitted to any other journal nor will it be submitted to another journal for consideration prior to a decision is made by the editors of *Obstetrics and Gynecology*. All authors approve of the revised version of this manuscript. Each of the reviewer and editor comments have been responded to in a point by point fashion as detailed below. Thank you again for your time and consideration.

Sincerely,



Torri Metz, MD, MS

[REDACTED]

[REDACTED]

[REDACTED]

**REVIEWER COMMENTS:**

**Reviewer #1:** For the manuscript titled "Prenatal marijuana use by self-report and umbilical cord sampling in a state with legalization", I have the following comments and queries:



1. Thanks for submission of your work.

**Response:** None required.

2. Line 114. Even if consent is not required for testing discarded specimens, this seems to be an attempt to conceal this practice from your study population, even though anonymity was preserved. The subjects would have no idea that this was occurring, or that such a policy existed.

**Response:** Thank you for this comment. We appreciate the opportunity to better clarify the details of the IRB approval for this protocol. All women who delivered during the enrollment period for the study had their umbilical cords collected and tested. Over the same time period, all women admitted for delivery were approached for participation in the optional survey portion of the study. We received full waiver of consent to test otherwise discarded umbilical cord samples for all women in order to estimate a point prevalence of marijuana use by umbilical cord sampling as this was felt to be of minimal risk to study subjects, could not practicably be carried out without the waiver, and was not subject to FDA regulations. In addition, the IRB agreed that collecting all cord segments was scientifically important for the proposed research question evaluating the validity of self-report of marijuana use in comparison to measurement via biological sampling. Language regarding the IRB approval process was expanded to provide further clarification in the methods on p. 7-8:

“This study was approved by the Colorado Multiple Institutional Review Board (COMIRB #16-0175). Waiver of consent was granted for collection of umbilical cord segments from all women who delivered over the study time period. Cord segments are routinely collected at both hospitals and would typically be discarded after clinical collection of umbilical cord gases; consent was not required for collection of these otherwise discarded specimens. Waiver of consent was reviewed and approved for the collection of otherwise discarded umbilical cord on all deliveries over the period of the study because the research involved no more than minimal

risk to the subjects; the waiver or alteration would not adversely affect the rights and welfare of the subjects; the research could not practicably be carried out without the waiver or alteration; and the study was not subject to FDA regulations.

Over the same time period, all women were approached for participation in the survey portion of this study. Women were given written IRB-approved instructions explaining that completion of the survey constituted consent for participation in that portion of the study. The consent for the survey did not specifically address anonymous coded correlation between the survey and testing of the umbilical cord segment. This minor deception was determined to be minimal risk, essential to the research question, and therefore appropriate. In addition, the IRB required that the survey and results of the cord testing be coded with an anonymous study identification number, and that assays be performed as a batched analysis at the conclusion of the enrollment period so that cord testing results could not be linked back to any individual research participants. Linkage between the survey, chart abstraction, and umbilical cord result was completed via a shared study identification number. No patient identifiers were recorded at any time.”

3. This study clearly demonstrates the lack of a correlation in prenatal marijuana use as assessed by self-reporting and umbilical cord testing.

**Response:** None required.

4. Strengths of the study include a power analysis, the assessment of two different socio-economic populations, and assessment of outcomes in a state where recreational marijuana use is legal.

**Response:** Thank you. No response required.

**Reviewer #2:**

Introduction:

1. While it's important to discuss the discordance between self-reported use of marijuana and detected THC via urine toxicology, I think it's important to better set the stage for why obstetricians even care about marijuana use in the first place (e.g. concerns regarding childhood neurodevelopmental outcomes, smaller birth lengths, smaller head circumference). While much of this is confounded by polysubstance use, socioeconomic status, nutrition, etc, as well as ascertainment bias - I think it's still worth bringing this up to inform readers why this study is important.

**Response:** We have added information related to the potential implications of perinatal marijuana use to the Introduction on p. 5.

“Marijuana use in pregnancy has been associated with adverse perinatal outcomes such as fetal growth restriction, preterm birth, neonatal intensive care unit admission, and adverse neurodevelopmental outcomes.”

Methods:

1. For the survey administered to the subjects, was this a validated survey? If so, were other substances also assessed?

**Response:** Unfortunately there were no available validated surveys to ascertain detailed information about contemporary cannabis use patterns. The survey was therefore adapted from that used by one of the investigators for a study related to sleep patterns and marijuana use. Those investigators have correlated reported use on the survey with quantified metabolites in blood and urine. However, that work is not yet published and therefore cannot be cited. We have added a limitation to the Discussion on p. 18 to address this concern.

“In addition, we could not identify a validated survey to collect detailed information about contemporary marijuana use patterns prior to starting the study; therefore, we developed the survey questions.”

2. I do see that assay results were not linked to participants and were not available to the team. Given the fact that in the state of Colorado, perinatal substance use is considered a form of child abuse and mandated reporting is required, were there any other protections in place (e.g. Certificate of Confidentiality) for patient anonymity?

**Response:** Please see response to reviewer #1, question #1. The purpose of a Certificate of Confidentiality issued by the NIH is to protect identifiable research information from forced disclosure for civil, criminal, legislative or other proceedings (<https://www.niehs.nih.gov/research/clinical/patientprotections/coc/index.cfm>). Since no identifiers were collected during any part of this research, we did not seek a Certificate of Confidentiality but instead put in place multiple protections to ensure the anonymity of the research participants as described above.

Results:

1. Pg 11, lines 208-210 - would consider rewording as the sentence is confusing

**Response:** We have reworded this sentence for clarity on p. 13.

“Seven women reported marijuana use in the past 30 days on the survey. Among them, the median reported frequency of use was 2.5 of the last 30 days. Three women reported only one day of use, with the four other women each reporting 2, 3, 5 and 10 days of use.”

2. Pg 12, lines 217-218 - would consider highlighting that almost 5-10% of cohort who said

they didn't use had positive cord assay, which is an interesting finding. While you kind of get into this with your correlation coefficients, I think providing the proportions in this scenario provide the reader with a clear and tangible statistic to hold onto.

**Response:** The proportion of women with marijuana use as ascertained by report to the healthcare provider, self-report on a survey, and by biological sampling is included in the Results on p. 13.

“Of the eligible participants, 2.6% (95% CI, 0.5%-7.4%) reported marijuana use to healthcare providers as documented on the admission history. On the self-report survey, 55 (47.4%) women reported marijuana use at some point in their lifetimes while 14.7% (95% CI, 8%-21%) reported past-year use and 6.0% (95% CI, 2.5%-12.0%) reported past-month use.”

“Among 116 umbilical cord homogenate assays, 12 (10.3%, 95% CI, 5.5%-17.4%) had THC-A above the limit of quantification (200pg/g) and 26 (22.4%, 95% CI 15.2%-31.1%) had THC-A above the limit of detection (100 pg/g).”

In response to the reviewer's comment, we have further emphasized the discrepancy between self-report and biological sampling in the Discussion section on p. 16.

“In our cohort, 1 in 10 women tested positive for THC-COOH above the clinical test threshold demonstrating that use was common. In the Kaiser Permanente Northern California study, the prevalence of use was 7.1% based on self-report and urine testing in 2016 with approximately 3-4% disclosing use to a healthcare provider on a prenatal questionnaire.<sup>4</sup> Our results were similar in that 3% of women self-reported use to a healthcare provider. In comparison, 6% of our cohort reported use in the last 30 days on an anonymous survey, 10% had cord results over the limit of quantification (clinical test threshold), and 22% were above the limit of detection (research test threshold). Our higher estimates of prevalence might be expected since cord homogenate testing identifies use from the second trimester onward in comparison to urine

testing which only detects use over 2 to 3 days. Additionally, marijuana is legal for both medicinal and recreational use in Colorado while marijuana was not fully legalized in California when the Kaiser study was performed.”

#### Discussion

1. Pg 12, lines 234-235 - I would say that there was poor agreement overall regarding self-reporting measures of marijuana use and cord assay

**Response:** Thank you for this suggestion. We have made the requested change to the Discussion on p. 15.

“In our study, there was poor agreement between self-reported measures of marijuana use and biological sampling.”

2. Pg 12, lines 237-239 - I would mention that due to the likely ascertainment bias present in some previous studies (e.g. inability to detect a more accurate prevalence of use), the results of aforementioned studies may be biased towards the null hypothesis.

**Response:** Thank you. We added a sentence to the Discussion on p. 15 specifying that differences in ascertainment of use results in uncertainty about the association between marijuana and adverse pregnancy outcomes.

“These differences in ascertainment of marijuana exposure suggest potential uncertainty in prior estimates of the association between marijuana use and maternal and neonatal outcomes.”

3. Pg 13, lines 255-257 - please explain further why testing for other metabolites might be informative.

**Response:** We have removed this sentence from the Discussion due to space limitations.

4. Pg. 13, lines 273-75 - are there any studies you can cite that could corroborate your incidence of self-report of marijuana (or other substances)? Might be helpful to make your argument

**Response:** Please see response to question #2. We have added self-report estimates from the Kaiser Permanente study in which use was ascertained by both report to a provider during prenatal care and urine testing. In addition, a series of references were added to the previous lines 273-5 for studies in which use was ascertained by self-report to a healthcare provider. See updated references.

5. Pg 13, lines 283-85 - would move this to the introduction to set the stage as to why marijuana use in pregnancy is important to assess

**Response:** Please see response to reviewer #2, Intro comment #1. We have added language to the introduction regarding why marijuana use in pregnancy is important to evaluate on p. 5.

“Marijuana use in pregnancy may be associated with adverse perinatal outcomes such as fetal growth restriction, preterm birth, neonatal intensive care unit admission, and adverse neurodevelopmental outcomes.”

**Reviewer #3:**

1. Although you clearly state that a UDS assess MJ use over the past 2-3 days, why was a UDS not collected at the time of admission, especially since the patient was recruited to the study at the time of admission to L&D? Or why not use UDS that may have been in their chart during this prenatal visits?

**Response:** We wanted to collect blood, urine and cord segments from study participants. However, to meet the requirements for waiver of consent, the IRB only allowed for collection of the umbilical cord segment as an otherwise discarded specimen and would not allow for

collection of other biological specimens for the purposes of this study. In addition, we were only able to collect basic demographics at delivery admission rather than a complete chart abstraction. No changes to the text were made.

2. In your introduction, please provide more information on why and how you chose to analyze the THC-A metabolite versus the other metabolites that you mention in your discussion.

**Response:** THC-COOH (formerly referred to as THC-A) is the most stable metabolite of marijuana and is the standard metabolite measured in clinical tests. This information was added to the introduction on p. 5.

“Cord homogenate testing for the most stable marijuana metabolite, 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (THC-COOH), is being used widely clinically as it has a similar performance to meconium testing.”

3. The umbilical cord homogenate detects MJ use from the 2nd trimester onwards - is there a correlation with amount of use? For example, if someone smoked marijuana once at 24 weeks, will the metabolite still be present at delivery at 40 weeks? How long does the metabolite last in the blood system? Is it affected by 2nd hand exposure? What is the validity of this metabolite? Please provide some more background information on this. If I understand Figure 2 correctly, then some women who said they never used before had positive homogenates - this makes me wonder if 2nd hand smoke makes the homogenates positive.

**Response:** The detail of exactly how long marijuana use can be detected by umbilical cord sampling remains unknown. However, umbilical cord testing has been validated and is now widely used clinically with commercially available assays for qualitative testing at the U.S. Drug Testing Laboratory and ARUP Laboratories. This information has been added to the Discussion on p. 16-17. The effect of second hand exposure on umbilical cord testing remains unknown



and was not assessed as part of this protocol, but there are some data in non-pregnant adults that are now referenced.

“Exactly how far back in time marijuana use can be detected with umbilical cord sampling remains unknown. Existing studies compare umbilical cord sampling to meconium sampling and have demonstrated similar detection results.<sup>5,8</sup> However, in order to more thoroughly evaluate the capacity of umbilical cord testing to quantify use over time, women would need to be queried regarding marijuana use throughout pregnancy. In addition, factors which may affect clearance of metabolites such as body mass index or other drug use need to be considered. The impact of second-hand marijuana smoke exposure on cord homogenate results remains unknown, though observational studies demonstrate detectable metabolites in serum and urine of non-pregnant adults with environmental exposure.”

4. The words "marijuana use" and "marijuana exposure" appear to be used interchangeably in your manuscript. Exposure to marijuana could also mean exposure to 2nd hand smoke. Consider using the word "use" consistently in your paper versus "exposure" (unless deeming it to be "fetal exposure" which makes sense).

**Response:** The word “exposure” was changed to use throughout the manuscript except in cases where the meaning was fetal exposure as a predictor of adverse neonatal outcomes. Please see “track changes” throughout.

5. Line 123: please provide the IRB number.

**Response:** The IRB number was added to the Methods on p. 7.

“This study was approved by the Colorado Multiple Institutional Review Board (COMIRB #16-0175).”

6. Line 133: Why was age the only variable that was used to preserve anonymity? You collected several other baseline identifiers that don't preserve anonymity.

**Response:** Age was not the only variable that was categorized. We have clarified that several of the demographic variables were categorized to preserve anonymity in the Methods on p. 9-10.

“In order to preserve anonymity several demographic variables were categorized. Maternal age was categorized as less than 21 years, 22-25 years, 26-29 years, 30-34 years, and 35 years or older. Gestational age at delivery was categorized as less than 37 weeks, 37 weeks and 0 days to 38 weeks and 6 days, 39 weeks and 0 days to 41 weeks and 0 days, and over 41 weeks.”

7. Line 148 - please clarify what LC-MS/MS is (it is written later in the paragraph on page 9, but would ideally be described earlier)

**Response:** LC-MS/MS is now defined with its first use in the Methods on p. 10.

“The cord tissue was processed and analyzed for THC-A by liquid chromatography-tandem mass spectrometry (LC-MS/MS), according to methods similar to those previously published.”

8. Please clarify your sample size calculations. Why was a prevalence of 15% presumed in your population even the reported prevalence you quoted was between 3-7%? Provide local data if available. You hypothesized that the metabolite would report higher rates, but your sample size calculation is based on equivalent rates. Please clarify.

**Response:** We did have preliminary institutional data to guide our sample size calculation. These data are now included to support the rationale behind our sample size calculation in the Methods on p. 11. The sample size calculation was based on the null hypothesis.

“A preliminary anonymous self-report survey at the two enrollment sites estimated that 10% of our cohort would use marijuana during pregnancy. However, given that umbilical cord homogenate sampling will detect use from the second trimester onward, we anticipated that the detected prevalence of use would be slightly higher and closer to 15% in our population.”

9. Two additional limitations to discuss are recall bias and lack of correlation with neonatal outcomes. Women may not recall if they had smoked marijuana in the past year or so - this may explain the discord on the number of self-reports and those with positive metabolites. Also, were there any differences in those who tested positive and birth weight, APGARs, GA at delivery?

**Response:** We added a limitation related to our inability to evaluate neonatal outcomes given our small sample size in the Discussion on p. 18. We are unable to report on birthweight and Apgars as these were not available at the time of admission when demographic characteristics were collected, and we have no identifiers to be able to return to charts to abstract these data. Gestational age at delivery is reported in Table 1.

“Finally, we had insufficient sample size to evaluate differences in perinatal outcomes by marijuana exposure status.

Nothing further was added regarding recall bias as the differences between self-report and cord homogenate testing are now covered in detail in the Discussion in response to other reviewers' comments.

10. I'm not sure how much extra information Figure 3 adds to your paper. Consider deleting it or revising it.

**Response:** Figure 3 demonstrates the correlation between the quantified umbilical cord result and the number of reported days of use in the past 30 days on the self-report survey. We feel

this figure conveys an important result. We have decreased the reported decimal places to two to clean up the figure. If the editors feel that this figure should be removed, we will do so.

**Reviewer #4:** In this article Metz et al report on a cross-sectional study of marijuana use women at two Colorado hospitals comparing used recorded in the H&P with report on a survey and with use as defined by the presence of a metabolite in the umbilical cord tissue. The found that, even in a state with legalized marijuana use, the reported prevalence was much lower than that detected by the active metabolite. These findings are important to the readers of Ob/Gyn as more women are likely to be exposed to marijuana and data on the effects of this use on the pregnancy depends on accurately determining which women and children are exposed. This manuscript suggests that prior studies may be underestimating the exposure, which has implications both for their conclusions as well as how future studies should be designed.

I have the following comments:

Abstract: consider adding the half life of the THC-A

**Response:** See response to reviewer 3, comment #3. Rather than adding the half-life of THC-COOH in the umbilical cord (as this is unknown), we have added detail about the cord homogenate testing and the remaining uncertainty regarding how far back in time use can be detected. We have also clarified that THC-COOH is the most stable metabolite.

Introduction:

line 62, consider moving "in high risk groups" to after "California study"

**Response:** High risk groups only refers to a subset of the women included in the California study. This was clarified by adding the word "overall" to the sentence for clarification on p. 5.

“In a Kaiser Permanente Northern California study, prevalence of first trimester marijuana use as detected by self-report or urine toxicology was 7.1% overall, and exceeded 20% in high risk groups.”

Paragraph 1, have there been any studies in non-pregnant populations to support the theory that rates of use are higher after THC is legalized?

**Response:** The Brown et al (2016) article referenced in our manuscript evaluates trends in use over time for both pregnant and non-pregnant reproductive aged women. Both groups show similar increases in use over time. However, since this manuscript is focused on pregnancy, and the importance of accurate ascertainment of marijuana use during pregnancy on perinatal outcomes, data for non-pregnant women were not added to the Introduction.

Paragraph 2, Please add a line about the half life of the THC-A in serum and as stored in lipophilic tissues. Is it present longer in obese vs normal weight women? Is there any data to suggest that the metabolite is affected by other drug use or cigarettes?

**Response:** We did not utilize any serum samples for this protocol so we opted not to include data regarding the half-life of THC-COOH in serum. Marijuana metabolites are thought to be stored in lipophilic tissues. As such, testing can be affected by body mass index or other drugs. As this is a preliminary assessment of the correlation between self-reported marijuana use and quantitative umbilical cord results, adjustments were not made for factors such as maternal BMI or other drug use. We have now included a statement to that effect in the Discussion on p.15-16.

“However, in order to more thoroughly evaluate the capacity of umbilical cord testing to quantify use over time, women would need to be queried regarding marijuana use throughout

pregnancy. In addition, factors which may affect clearance of metabolites such as maternal body mass index or other drug use will need to be considered.”

The limitations of the umbilical cord assay are now detailed in the manuscript. Please see response to reviewer 3, comment #3.

Materials and Methods:

Line 173, Please explain why you chose the cut off of use within the past 30d. Is this related to the half life of the metabolite or just a standard unit of time for the patient survey?

**Response:** Typical intervals for assessment of drug use are past month and past year use.

Past month use is utilized as the standard for validated surveys such as the National Survey on Drug Use and Health. We clarified that 30 day recall was utilized to estimate past-month use in the Methods on p. 9 and explained that it is a standard measure.

“In addition the survey asked participants to estimate the number of days of use over the past 30 days indicative of past month use. Past month use is a standardized measure of drug use on validated surveys such as the National Survey of Drug Use and Health.”<sup>6</sup>

Line 176, Consider adding a line explaining comparison of contingency tables

**Response:** Contingency tables were not compared. Rather contingency tables were utilized to evaluate differences in the proportion of positive results by categorical group. This was clarified in the text on p. 12.

“Between group comparisons of the proportion of women with positive cord results were made using contingency tables.”

You did not collect data on maternal weight gain or BMI. Given that the THC-A is lipophilic, would the maternal BMI potentially confound the results?

**Response:** We thank the reviewer for this comment. It is true that THC metabolism may be affected by body mass index. We have added a sentence on p. 16 discussing that this will be important in future validation work.

“In addition, factors which may affect clearance of marijuana metabolites such as maternal body mass index or other drug use will need to be considered.”

**Results:**

Line 214, consider adding that the use of tobacco was low and did not differ between groups.

**Response:** Concurrent tobacco use is reported in Table 1. We have now highlighted this finding with text in the Results on p. 13.

“The prevalence of tobacco use did not differ between cord positive and cord negative groups.”

Discussion:

Lines 265-75, Consider adding that your patients have a low smoking prevalence.

**Response:** While we agree that a low smoking prevalence would be a strength in a study evaluating the effect of marijuana on perinatal outcomes—we are not convinced that it is a notable strength of this study focused on prevalence of marijuana use specifically with different means of ascertainment. Therefore, we did not include this as a strength as requested by the reviewer (mostly because of space limitations).

Tables and figures: no comments

**Response:** None required.

**STATISTICAL EDITOR COMMENTS:**

The Statistical Editor makes the following points that need to be addressed:

lines 46-52: Suggest that the proportions reporting marijuana use on surveys, to health care providers and on umbilical cord assay each should include CIs.

**Response:** Confidence intervals for the proportion of women with marijuana use were included in the Results section previously. They have now been added to the abstract.

“Six percent (95% CI 1.7-10.0%) of participants reported use in the last 30 days on survey and 2.6% (95% CI 0.5-7.4%) of participants reported marijuana use to healthcare providers at the time of admission. On umbilical cord assay, 22.4% (95% CI 15.2-31.1%) had detectable THC-COOH.”

See later comments re: Fig 3, not convinced that lines 50-52 contribute to the main conclusions of the paper, which is to cite cross sectional estimates of marijuana use in these women and to contrast surveys with assays.

**Response:** The objective of the paper is both to compare cross sectional estimates of marijuana use, but also to evaluate the utility of a quantitative assay for THC-COOH specifically. Commercially available assays report only a qualitative result. Through this work we can demonstrate both that self-report is an inaccurate measure of use, and that the quantitative cord result is promising for being able to better estimate the amount marijuana use during late pregnancy. We added a sentence to the conclusion of the abstract on p. 4 to clarify this point.

“Umbilical cord assays for THC-COOH demonstrate promise for quantifying use.”

We also more clearly delineated both of these objectives in the Introduction on p. 6.

Our primary objective was to compare the prevalence of self-reported maternal marijuana use to the prevalence of use ascertained by biological sampling of the umbilical cord in a state with legalized marijuana. Our secondary objective was to evaluate if reported frequency of use in the month prior to delivery correlated with the amount of THC-COOH detected in the cord.”



Table 1: The non-random allocation of age strata by THC-A (+) vs THC-A (-) appears to derive most of its discrepancy from the 22-25 yo cohort. Might be worthwhile analyzing by stratum and commenting. The overall test done (Chi-square) cannot directly attribute which stratum by age or by insurance status contributed to the non-random allocation. For the statement on lines 213-215, a pairwise testing should be done.

**Response:** Thank you. We have added a sentence to the results indicating that we also completed a pairwise analysis by stratum and have highlighted the statistically significant difference in the 22-25 year old age group in the Results on p. 13-14. In addition, we have now addressed this in our Discussion on p. 16 as it is an interesting finding in light of the age to purchase marijuana legally being 21 years.

“Demographic characteristics of women by cord homogenate result are presented in Table 1. The observed demographic differences were derived predominantly from a large proportion of women with THC-COOH above the limit of detection being in the 22 to 25 year-old age group (48.0%) with only 15.7% of the cord negative group in this age strata (p<0.001). Similar differences were noted in the insurance category with 80.8% of cord positive women having Medicaid compared to 54.5% in the negative cord group (p=0.016).”

		Positive (n=26)	Negative (n=90)	p
Maternal age	21 years or less	4( 16.0)	20( 22.5)	0.483
	22-25 years	12( 48.0)	14( 15.7)	<.001
	26-29 years	4( 16.0)	19( 21.3)	0.556
	30-34 years	3( 12.0)	26( 29.2)	0.081
	Over 35 years	2( 8.0)	10( 11.2)	0.641
What type of insurance do you have?	Private	5( 19.2)	31( 35.2)	0.123
	Medicaid/care	21( 80.8)	48( 54.5)	0.016
	None/Don't know	0( 0.0)	9( 10.2)	0.089

“Women with a positive cord testing result were more likely to be in the 22 to 25 year-old age range. Marijuana was available for recreational use to women over 21 years of age in Colorado

during the study period. Our results are consistent with other studies demonstrating an increased prevalence of use among younger women.<sup>4</sup> Ultimately, intervention efforts related to encouraging avoidance of marijuana use in pregnancy may need to be targeted to adolescents and young adults.”

lines 211-213: Suggest re-wording this, since the 12 samples > 200 pg/g were a subset of the 26 samples > 100 pg/g, lest the reader interpret those groups as being mutually exclusive.

**Response:** Thank you. This sentence has now been re-worded in the results on p. 13 to clarify this point.

“Among 116 umbilical cord homogenate assays, 26 (22.4%, 95% CI 15.2%-31.1%) had THC-COOH above the limit of detection (100 pg/g), with 12 (10.3%, 95% CI, 5.5%-17.4%) also above the limit of quantification (200 pg/g).”

Fig 3 is difficult to interpret, since obviously many of the surveys were incorrectly self-reported. That is, the sample is biased. In any event, the estimates for  $\rho$  and its CI have too many significant figures. Since the total sample was 116, the precision should be truncated at 2 or at most 3 decimal places.

**Response:** We felt that it was appropriate to include all women in the correlation coefficient calculation despite recognizing that many women denied use when they were clearly using marijuana. A sentence has been added to clarify this point in the Results on p. 14-15. In addition, the precision of  $\rho$  and its CI in Figure 3 has been truncated at 2 decimal places per your request.

“Consistent with the observed differences in prevalence based on self-reported versus biological sampling-detected use, many women who reported no marijuana use in the past 30 days had a

cord result positive for THC-COOH (Figure 3)."

EDITOR COMMENTS:

1. Thank you for your submission to Obstetrics & Gynecology. In addition to the comments from the reviewers above, you are being sent a notated PDF that contains the Editor's specific comments. Please review and consider the comments in this file prior to submitting your revised manuscript. These comments should be included in your point-by-point response cover letter.

\*\*\*The notated PDF is uploaded to this submission's record in Editorial Manager. If you cannot locate the file, contact Randi Zung and she will send it by email - rzung@greenjournal.org.\*\*\*

- The objective for the abstract should be a simple "to" statement without background.

**Response:** The background has been removed from the objective on p. 3.

"To compare self-reported maternal marijuana use to quantitative biological sampling for a marijuana metabolite, 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (THC-COOH), in umbilical cord homogenate in a state with legalized marijuana."

- It is not clear from this that how you identified patients. Also, not sure you report the medical record abstraction results other than at time of admission for delivery. Did you collect prenatal data? When was survey done?

**Response:** The abstract has been updated to clarify that women were approached during the delivery admission, and that reported use to the healthcare provider was recorded based on the admission H&P.

“We conducted a cross-sectional study of women approached at the time of admission for delivery with live, singleton pregnancies  $\geq$  24 weeks at two urban medical centers in Colorado. Maternal marijuana use was estimated by (1) report to the healthcare provider on admission history and physical, (2) survey of self-reported use, and (3) liquid chromatography tandem mass spectrometry analysis of the umbilical cord homogenate for THC-COOH.”

- How many women had cord homogenates but no surveys and vice versa?

**Response:** The number of women with available cords but no surveys and vice versa is included in Figure 1 and in the results section. We had difficulty also incorporating this information into the abstract because of space limitations.

- in what population? All adults? Only pregnant women? Please clarify.

**Response:** The sentence was re-worded to better clarify that this sentence refers to pregnant women.

“Yet, prevalence of past month marijuana use among pregnant women has increased from 2.37% in 2002 to 3.85% in 2014 based on data from the National Survey on Drug Use and Health.”

- When was the Kaiser study done? Is there data to suggest higher usage in states w/ legalization?

**Response:** The reported prevalence from the Kaiser study is in the year 2016. This was added to the Introduction on p. 5. This is also addressed again in the Discussion—specifically we note that marijuana was not fully legalized in California at the time of the Kaiser study. There are not data related to rates of marijuana use in states with and without legalization.

“In a Kaiser Permanente Northern California study, prevalence of first trimester marijuana use as detected by self-report or urine toxicology was 7.1% in 2016, and exceeded 20% in high risk groups.”

- In the first 2/3 of pregnancy, the cord is rather slender without much Wharton's Jelly. While the

jelly is largely mucopolysaccharides, there are fats in it. Before much jelly production--mostly in the last 1/3 of pregnancy-- presumably there isn't much fat there. Why would it then be a reservoir for lipophilic THC metabolites?

**Response:** Of note, we changed THC-A to THC-COOH throughout as this is a more standard abbreviation. In response to your query, the umbilical cord homogenate is thought to detect use from the second trimester onward (similar to meconium). We have removed the sentence about the lipophilicity of marijuana metabolites and clarified that THC-COOH it is a stable metabolite that measures use in the 2<sup>nd</sup> and 3<sup>rd</sup> trimesters of pregnancy. In addition, per a reviewer comment above we added more information to the Discussion regarding the limitations of the test (eg we do not know exactly how far back in time use can be detected).

“While urine testing only detects use over the past 2-3 days, umbilical cord homogenate testing detects marijuana use from the second trimester onward, and may be useful for quantification of use in late pregnancy.<sup>5</sup> Cord homogenate testing for the most stable marijuana metabolite, 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (THC-COOH), is being used widely clinically as it has a similar performance to meconium testing.”

- please add in the introduction something about THC-A. How long does it last in urine, cord homogenate.

**Response:** Please see additions to the Introduction above in response to your previous query. The reference to THC-A was moved earlier to clarify that is the metabolite being evaluated in the assays.

- please explicate the primary objectives along with any secondary objectives.

**Response:** We have clarified the primary and secondary objectives of the study in the Introduction on p. 6.

“Our primary objective was to compare the prevalence of self-reported maternal marijuana use to the prevalence of use ascertained by biological sampling of the umbilical cord in a state with legalized marijuana. Our secondary objective was to evaluate if reported frequency of use in the month prior to delivery correlated with the amount of THC-COOH detected in the cord.”

- did you abstract prenatal information?

**Response:** We were very limited by what our IRB allowed for this project; these restrictions were predominantly to ensure anonymity of the study subjects. Therefore, we were only able to abstract time of admission data in a categorized fashion. We have modified this sentence on p. 6 to clarify that only time of admission data were collected.

“During the delivery admission, maternal marijuana use was estimated by (1) a survey detailing frequency and recency of marijuana use in pregnancy, (2) report to a healthcare provider at time of admission, and (3) assay of the umbilical cord for THC-COOH, which is the most stable marijuana metabolite.”

- when was the survey administered? By whom?

**Response:** The details of the survey administration are in the Methods on p. 7.

“Study staff approached eligible women for participation in a survey about prenatal marijuana use. Approach was completed prior to the time of delivery. Participants were informed that the care team would not have access to the survey responses. They were instructed to complete the survey and return it to the study staff in a sealed envelope with only a study identification number.”

- It is important to know when in relation to the delivery that women completed these samples.

Post delivery, possible effects of pain medications, fatigue, heightened fear if results of + use in survey revealed to pediatricians, etc.

**Response:** We have added a sentence on p. 7 clarifying that approach was completed prior to delivery.

“Approach was completed prior to the time of delivery.”

- Please clarify: Prenatal marijuana use spanning all of the prenatal period or just peri-delivery?

**Response:** The study staff reported data collected on the admission history and physical. This information was not collected in a standardized fashion which is recognized as a limitation of the study—importantly, this reflects real world collection of these data that are used in retrospective cohort studies currently.

“The process by which healthcare providers queried women about use was not standardized; however, this is likely consistent with other studies<sup>11-13</sup> utilizing self-reported measures of marijuana use.”

If the patient noted marijuana use during the pregnancy (past or current) this was recorded. This has been clarified in the methods on p. 7.

“The same study identification number was used to enter self-report data regarding prenatal marijuana use (past or current) from report to the healthcare provider as documented in the history and physical at the time of admission.”

- Is the cord sample technically "discarded" if the patient knowingly labeled a container and gave it to clinical personnel to retain a segment of cord? Sounds like a special collection of a study segment, rather than a discarded cord segment. One of your reviewers questions the ethics of this--calling it "discarded"--and I have to say I have some questions as well. Can you explain please what the participants were told about what was being done to the cord segment they voluntarily contributed?

**Response:** Thank you for your query. We have clarified the study process and the IRB approval in detail in response to your query as well as reviewer 1. We were approved for a

waiver of consent for collection of the cord segments; therefore, participants did not have knowledge cord segments were being collected. We have integrated language from the IRB approval letter to better clarify the conditions under which this study was approved. For the text that was added to the methods, please see our detailed response to reviewer #1, comment #2.

- but they were linked to individual patients, correct? What do you mean by "not linked to any identifying information"

**Response:** We apologize for the confusion and hope that this is now clarified with the language we added to the Methods section on p. 8.

"Linkage between the survey, chart abstraction, and umbilical cord result was completed via a shared study identification number. No patient identifiers were recorded at any time."

- what is this based on?

**Response:** Please see response to reviewer #3, comment #8 for text that was added in response to his/her similar query. Our sample size calculation was based on preliminary institutional data.

- The lower bounds is just barely outside of the 15% use you thought likely in your population. (and the upper bound twice that value!). How has that influenced your thinking about your population and maternal/ neonatal outcomes?

**Response:** We used the clinical test threshold (>200 pg/g) to translate these findings into language on p. 15 that may hit home with the journal readership. Hopefully this will help emphasize how common prenatal use is.



“In our cohort, 1 in 10 women tested positive for THC-COOH above the limit of quantification (the clinical test threshold) demonstrating that use was common.”

We also added language to the first paragraph of the discussion on p. 15 to emphasize that there is uncertainty in the existing literature.

“These differences in ascertainment of marijuana exposure suggest potential uncertainty in prior estimates of the association between marijuana use and maternal and neonatal outcomes.”

- please comment about to what degree second-hand exposure to marijuana could result in cord homogenate positive results

**Response:** We are uncertain how much second hand exposure could contribute to the cord results. However, even if the exposure is second hand, exposure is occurring at a high rate in the prenatal population. We added a sentence about second-hand exposure on p. 17.

“The impact of second-hand marijuana smoke exposure on cord homogenate results remains unknown, though observational studies demonstrate detectable metabolites in serum and urine of non-pregnant adults with environmental exposure.”

- I'm curious about the hypothesis that the legalization of use might mitigate women's hesitancy to report marijuana use, which seems to be your working hypothesis. Women under report both cigarette and alcohol use in pregnancy--both legal. However, marijuana, tobacco use, and alcohol use may not be "approved" by the health care provider (even if legally approved) so the woman may underreport.

**Response:** Anecdotally, pregnant women began to report marijuana use more freely after legalization. This has not been assessed directly in any studies to our knowledge. Our aim was really to evaluate how prevalence of marijuana use differs when ascertained by different means.

This is now clarified as the primary objective above. However, it seems important to also state that these findings are in the setting of a state with legalized marijuana, and make comparisons to the findings of others in states without legalization as we have done on p. 16.

“Our higher estimates of prevalence from biological sampling might be expected since cord homogenate testing identifies use from the second trimester onward in comparison to urine testing which only detects use over 2 to 3 days. Additionally, marijuana is legal for both medicinal and recreational use in Colorado while marijuana was not fully legalized in California when the Kaiser study was performed.”

2. 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, as well as subsequent author queries. 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:

1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.

2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

**Response:** OPT-IN.

3. Author Agreement Forms: Please note the following issues with your forms. Updated or corrected forms should be submitted with the revision.

Kennon Heard, MD, PhD - Did not indicate a conflict of interest disclosure.

**Response:** A new author agreement form has been uploaded for Dr Heard.

4. All studies should follow the principles set forth in the Helsinki Declaration of 1975, as revised in 2013, and manuscripts should be approved by the necessary authority before submission. Applicable original research studies should be reviewed by an institutional review board (IRB) or ethics committee. This review should be documented in your cover letter as well in the Materials and Methods section, with an explanation if the study was considered exempt. If your research is based on a publicly available data set approved by your IRB for exemption, please provide documentation of this in your cover letter by submitting the URL of the IRB web site outlining the exempt data sets or a letter from a representative of the IRB. In addition, insert a sentence in the Materials and Methods section stating that the study was approved or exempt from approval. In all cases, the complete name of the IRB should be provided in the manuscript.

**Response:** The complete name of the IRB that approved this protocol and the protocol number are included in the methods on p. 7.

“This study was approved by the Colorado Multiple Institutional Review Board (COMIRB #16-0175).”

5. 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 will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at <http://links.lww.com/AOG/A515>, and the gynecology data definitions are available at <http://links.lww.com/AOG/A935>.

**Response:** No changes were necessary. Standard definitions are used throughout.

6. 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 appendixes).

Please limit your Introduction to 250 words and your Discussion to 750 words.

**Response:** Word count for the manuscript is now 3118 words. The Introduction is 250 words and the Discussion is 750 words. Additional minor edits were made with track changes throughout both the Introduction and Discussion to reach these word limits.

7. Specific rules govern the use of acknowledgments in the journal. Please edit your acknowledgments or provide more information in accordance with 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 signature on the journal's author agreement 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).

**Response:** All funding is included. The abstract was presented at the SMFM Annual Meeting, and the location and dates of the meeting are included. Please let us know if there is something

missing that is not apparent to the authors.

8. 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 limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

**Response:** The word count for the abstract is now 294 words.

9. 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.

**Response:** We have changed from THC-A to THC-COOH throughout as this is a more standard abbreviation for 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid. No other non-standard abbreviations are used.

10. 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.

**Response:** The virgule symbol was removed from the manuscript in sentences with words. It remains only in descriptions of mass spectrometry and measurement (MS/MS, S/N and pg/g).

11. 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](http://edmgr.ovid.com/ong/accounts/table_checklist.pdf).

**Response:** We confirmed that the tables conform to journal style.

## 12. Figures

Figure 1: Ok, resubmit as-is.

**Response:** No changes were made to Figure 1.

Figure 2: Per journal style, we try to avoid using patterns in bar graphs. Would it be possible to get a version of this figure with solid colored bars?

**Response:** Figure 2 was changed to remove the patterns from the bar graph. A new figure is uploaded with the revision.

Figure 3: Ok, resubmit as-is.

**Response:** Figure 3 was changed per the statistical editor's request to limit the number of decimal places on the reported correlation coefficient. A new figure is uploaded with the revision.

13. If you choose to revise your manuscript, please submit your revision via Editorial Manager for Obstetrics & Gynecology at <http://ong.editorialmanager.com>. It is essential that your cover letter list point-by-point the changes made in response to each criticism. Also, please save and submit your manuscript in a word processing format such as Microsoft Word.

**Response:** A point by point response to reviewers is uploaded with the revision.

Thank you for your ongoing consideration of our manuscript. The comments from the reviewers and editors resulted in revisions that enhanced the quality of the submission.

**From:** [REDACTED]  
**To:** [Randi Zung](#)  
**Cc:** [Denise Shields](#)  
**Subject:** RE: Your Revised Manuscript 18-1655R1  
**Date:** Thursday, October 18, 2018 12:21:02 AM  
**Attachments:** [18-1655R1 ms \(10-17-18v2\) TM.docx](#)

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Please see responses to your queries below and as comments in the attached.  
Thank you!  
Torri

**Torri Metz, MD, MS**

Associate Professor

Maternal-Fetal Medicine

**Department of Obstetrics and Gynecology**

30 North 1900 East, 2B200

Salt Lake City, Utah 84132 | [REDACTED]

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**From:** Randi Zung [RZung@greenjournal.org]  
**Sent:** Wednesday, October 17, 2018 2:17 PM  
**To:** TORRI METZ  
**Cc:** Denise Shields  
**Subject:** Your Revised Manuscript 18-1655R1

Dear Dr. Metz:

Your revised manuscript is being reviewed by the Editors. Before a final decision can be made, we need you to address the following queries. Please make the requested changes to the latest version of your manuscript that is attached to this email. **Please track your changes and leave the ones made by the Editorial Office.** Please also note your responses to the author queries in your email message back to me.

1. General: The Editor has made edits to the manuscript using track changes. Please review them to make sure they are correct.  
Agree with editorial edits.
2. Line 58-59: Please be sure this is stated in the body of your paper. Statements and data that appear in the Abstract must also appear in the body text for consistency.  
Results were fixed to be consistent. See comments in attached.
3. Line 62-64: Please note the recommend change of "impact" to "informs."  
Change to informs is fine.
4. Line 291: More likely than what?  
More likely than women with a negative cord result. This was added to the manuscript. See track changes addition.
5. Line 299: This was added to be perfectly clear you aren't talking about a PUBS.

Agree with this addition. Certainly worth clarifying.

To facilitate the review process, we would appreciate receiving a response within 24 hours. I will be out of the office on October 19, so if you need to return this on Friday, please send it to Denise Shields.

Best,  
Randi Zung

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**Randi Zung (Ms.)**

Editorial Administrator | *Obstetrics & Gynecology*  
American College of Obstetricians and Gynecologists  
409 12th Street, SW  
Washington, DC 20024-2188  
T: 202-314-2341 | F: 202-479-0830  
<http://www.greenjournal.org>



**From:** [TORRI METZ](#)  
**To:** [Stephanie Casway](#)  
**Subject:** RE: O&G Figure Revision: 18-1655  
**Date:** Wednesday, October 17, 2018 11:34:33 PM

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Hi Stephanie,  
You are correct. We need to use THC-COOH in the figures to match the legends. New versions attached. Thank you for catching our error. There is also a small error in the figure legends. There is a 9 missing. This was also our fault. It should be "11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid" in figure legend 2 and 3.  
Thanks,  
Torri

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**From:** Stephanie Casway [SCasway@greenjournal.org]  
**Sent:** Wednesday, October 17, 2018 12:07 PM  
**To:** TORRI METZ  
**Subject:** O&G Figure Revision: 18-1655

Hi Torri,

Your figure has been edited, and PDFs of the figure and legend are attached for your review. Please review the figure and legend CAREFULLY for any mistakes. In addition, please see our query below.

AQ1: The legends for Figures 2 and 3 use THC-COOH; however, the figures use THC-A. Should either of these be updated?

PLEASE NOTE: Any changes to the figures must be made now. Changes made at later stages are expensive and time-consuming and may result in the delay of your article's publication.

To avoid a delay, I would be grateful to receive a reply no later than Friday, 10/19. Thank you for your help.

Best wishes,

Stephanie Casway, MA  
Production Editor  
*Obstetrics & Gynecology*  
American College of Obstetricians and Gynecologists  
409 12th St, SW  
Washington, DC 20024  
Ph: (202) 314-2339  
Fax: (202) 479-0830  
[scasway@greenjournal.org](mailto:scasway@greenjournal.org)