OBSTETRICS & GYNECOLOGY

NOTICE: This document contains correspondence generated during peer review and subsequent revisions but before transmittal to production for composition and copyediting:

- 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: Aug 15, 2022
To: "Tori Valachovic" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-22-1272

RE: Manuscript Number ONG-22-1272

Is the pandemic messing with your period? Associations between COVID-19 stress and menstrual changes

Dear Dr. Valachovic:

Thank you for sending us your work for consideration for publication in Obstetrics & Gynecology. Your manuscript has been reviewed by the Editorial Board and by special expert referees. The Editors would like to invite you to submit a revised version for further consideration.

If you wish to revise your manuscript, please read the following comments submitted by the reviewers and Editors. Each point raised requires a response, by either revising your manuscript or making a clear argument as to why no revision is needed in the cover letter.

To facilitate our review, we prefer that the cover letter you submit with your revised manuscript include each reviewer and Editor comment below, followed by your response. That is, a point-by-point response is required to each of the EDITOR COMMENTS (if applicable), REVIEWER COMMENTS, STATISTICAL EDITOR COMMENTS (if applicable), and EDITORIAL OFFICE COMMENTS below. Your manuscript will be returned to you if a point-by-point response to each of these sections is not included.

The revised manuscript should indicate the position of all changes made. Please use the "track changes" feature in your document (do not use strikethrough or underline formatting).

Your submission will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Sep 05, 2022, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This is a cross sectional study that evaluated the correlation between high stress during the COVID-19 pandemic and menstrual changes. The authors concluded that higher stress was associated with changes in menstrual length, duration and spotting.

The study has multiple strengths. The sample is large and overall representative of the US population when compared to national census data (except for level of education). They used a validated tool to asses COVID-related stress and the questions related to menstrual changes were pre-tested for content and validity. Please see additional questions and comments below:

Line 81 to 185: "High stress is associated with aberrant menstrual changes in women" and "Reports suggest a greater impact of COVID-related stress on women than men during the pandemic". If we know stress causes menstrual changes and COVID-19 increased the levels of stress in women, Isn't it expected that women during COVID have menstrual changes? There are prior published studies answering this question as mentioned on the discussion (lines 284 to 294). Besides the two studies you mentioned, Takmaz et al published in 2021 the result of survey in 952 health care workers with very similar methodology and results. How does your study add to what we already know about the topic?

I suggest to provide more information regarding the company that processed the surveys and the potential for selection bias:

Lines 97 to 101: What type of company is Dynata? Is it a marketing company? How do they recruit their panels? Is it through online advertising in comercial web sites? If so, Wouldn't this prioritize participants with reliable access to internet and free time to perform on line surveys? (This might explain why the education level is higher when compared to national census data) Does the company have experience with non-commercial surveys?

Lines 101: "Our recruitment plan involved the use of demographic quotas". Please provide details about how this was

performed. Did you invite Dynata members with specifics demographic traits in their database to match census data or did you invite all the eligible members and then created the proportions that matched the census?

Lines 174 to 177: "1037 survey takers met the inclusion criteria and consented to participate and 948 (91%) were deemed complete". How big is the Dynata database? What percentage of the eligible women for your survey does the initial 1037 represent? Please clarify that these 1037 participants are the ones that met only the first "round" of inclusion criteria (self-identified women living in the US between the ages of 18 and 45). When the second set of exclusion criteria was applied, you ended up with 374 participants, which would be your actual study sample. Please make sure you clarify this in this section of the manuscript. Why isn't this the group that is compared with the nation census data? Why isn't the calculation of missing data based on this smaller group as opposed to the larger 948 group? Does the percentage of missing data change if applied to the smaller group?

Reviewer #2:

Line 39: "Compared to those with low COVID-19 stress..." Does this not include moderate stress? In previous paragraph, low/moderate stress (scores < 25) was noted so I am curious if the low stress was further delineated or was the PSS-10-C dichotomized and this was just a wording issue.

Lines 47-48: "The estimates for menstrual flow were in the expected direction, but not statistically significant." Does this mean that you expected those numbers to be "abnormal" but they were not statistically significant? Maybe different wording of the sentence will reflect that.

Lines 86-87: "...little research has been conducted on the impact of COVID-19 related stress on women's menstrual cycles, an important indicator of overall wellbeing." This sentence is key and indicates why this study is being conducted.

Lines 88-90: Clear statement on what the study aims to do. Love this.

Lines 90-92: Again, a clear statement on what you think the study will show.

Lines 108-119: Clear inclusion and exclusion criteria are stated.

Lines 125-140: I like how you included the self-reported menstrual parameters in a succinct way.

Lines 152-154: Asking how subjects menses were before the pandemic is important and I like how you asked the question (How many periods they experienced per year prior to the pandemic along with comorbidities...).

Line 174: The survey was active for 3 days. Would there have been more complete participants if the survey had been active for an entire week?

Lines 181-183: Again stating that your sample was representative of a diverse population across the country. This is good as all studies should strive for that goal and have this concept in mind as they devise and conduct studies.

Results section: I like that each parameter was broken down making the article easy to read and digest.

Discussion: I like that you tied in your findings with emerging research.

Limitations: Stating that your study excluded gender minorities is important.
Strengths of the study are listed throughout the article and are not required to be listed again.

Overall, this article is well-devised and important as we learn more about the ramifications of COVID-19 infection.

STATISTICAL EDITOR COMMENTS:

General and lines 95-106: What description was given to the summary for recruitment of women into this study? Specifically, were there any phrases or statements that potentially could have biased selection of women to favor inclusion of women with high levels of stress or of menstrual changes. For example, the phrase used in the title to this article might have encouraged some women to participate. Is there any data available as to the N of all women of the appropriate age available on this platform vs those who agreed to participate in this study?

Abstract: The abstract should include more summary data re: the sample size and proportions of women with high stress

and with some of the primary outcomes of interest, rather than entirely in terms of ORs.

Table 1: Should enumerate all missing data.

lines 211-213, 234: Data not shown should be summarized and analysis shown in supplemental material.

Table 2: Need to enumerate all missing data.

Table 3: The subset with data re: menstrual data is smaller than the cohorts shown in earlier tables. Need to clarify whether they comprise a subset of the larger data set or a separate data set from that in Tables 1, 2. In either event, need to compare the demographic/clinical characteristics of the high stress vs low/medium stress groups with stats analyses. If this sample (~ 350 is a subset of the larger sample (~850), then there is a serious problem with potential for selection bias that must be addressed. That is, more than 1/2 of respondents would have been omitted from the menstrual data analysis, making its estimation of effect, its precision likely biased and not generalizable.

Table 4: Need to clarify for the reader the referent vs the other group(s) in this Table. Should omit the columns of p-values, since CIs are included, and the p-values are therefore redundant.

EDITORIAL OFFICE COMMENTS:

1. If your article is accepted, the journal will publish a copy of this revision letter and your point-by-point responses as supplemental digital content to the published article online. You may opt out by writing separately to the Editorial Office at em@greenjournal.org, and only the revision letter will be posted.

2. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:
* Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and at the end of the abstract. For industry-sponsored studies, describe on the title page how the funder was or was not involved in the study.
* Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).
* Name the IRB or Ethics Committee institution in the Methods section (if applicable).
* Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.

3. Obstetrics & Gynecology's Copyright Transfer Agreement (CTA) must be completed by all authors. When you uploaded your manuscript, each coauthor received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please ask your coauthor(s) to complete this form, and confirm the disclosures listed in their CTA are included on the manuscript's title page. If they did not receive the email, they should check their spam/junk folder. Requests to resend the CTA may be sent to em@greenjournal.org.

4. For studies that report on the topic of race or include it as a variable, 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, describe the reasons that race and ethnicity were assessed in the Methods section and/or in table footnotes. Race and ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and ethnicity as in some cases missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race.

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

List racial and ethnic categories in tables in alphabetic order. Do not use "Other" as a category; use "None of the above" instead.

Please refer to "Reporting Race and Ethnicity in Obstetrics & Gynecology" at https://edmgr.ovid.com/ong/accounts/Race_and_Ethnicity.pdf.

5. ACOG uses person-first language. Please review your submission to make sure to center the person before anything else. Examples include: "People with disabilities" or "women with disabilities" instead of "disabled people" or "disabled women"; "patients with HIV" or "women with HIV" instead of "HIV-positive patients" or "HIV-positive women"; and "people who are blind" or "women who are blind" instead of "blind people" or "blind women."

6. The journal follows ACOG's Statement of Policy on Inclusive Language (https://www.acog.org/clinical-information/policy-and-position-statements/statements-of-policy/2022/inclusive-language). When possible, please avoid using gendered descriptors in your manuscript. Instead of "women" and "females," consider using the following: "individuals;"

"patients;" "participants;" "people" (not "persons"); "women and transgender men;" "women and gender-expansive patients;" or "women and all those seeking gynecologic care."

7. 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.

8. Make sure your manuscript meets the following word limit. The word limit includes the manuscript body text only (for example, the Introduction through the Discussion in Original Research manuscripts), and excludes the title page, précis, abstract, tables, boxes, and figure legends, reference list, and supplemental digital content. Figures are not included in the word count.

Original Research: 3,000 words

9. For your title, please note the following style points and make edits as needed:
* Do not structure the title as a declarative statement or a question.
* Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles.
* Abbreviations, jargon, trade names, formulas, and obsolete terminology should not be used.
* Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," "A Systematic Review," or "A Cost-Effectiveness Analysis" as appropriate, in the subtitle. If your manuscript is not one of these four types, do not specify the type of manuscript in the title.

10. Specific rules govern the use of acknowledgments in the journal. Please review the following guidelines and edit your title page as needed:

* 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 or indicate whether the meeting was held virtually).
* If your manuscript was uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology, add the following statement to your title page: "Before submission to Obstetrics & Gynecology, this article was posted to a preprint server at: [URL]."
* Do not use only authors' initials in the acknowledgement or Financial Disclosure; spell out their names the way they appear in the byline.

11. Be sure that each statement and any data in the abstract are also stated in the body of your manuscript, tables, or figures. Statements and data that appear in the abstract must also appear in the body text for consistency. Make 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 manuscript.

In addition, the abstract length should follow journal guidelines. Please provide a word count.

Original Research: 300 words

12. 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.

13. The journal does not use the virgule symbol (/) in sentences with words, except with ratios. 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.

14. ACOG avoids using "provider." Please replace "provider" throughout your paper with either a specific term that defines the group to which are referring (for example, "physicians," "nurses," etc.), or use "health care professional" if a specific term is not applicable.

15. 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.

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

Express all percentages to one decimal place (for example, 11.1%"). Do not use whole numbers for percentages.

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

17. Please review examples of our current reference style at https://edmgr.ovid.com/ong/accounts/ifa_suppl_refstyle.pdf. Include the digital object identifier (DOI) with any journal article references and an accessed date with website references.

Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the formal reference list. Please cite them on the line in parentheses.

If you cite ACOG documents in your manuscript, be sure the references you are citing are still current and available. Check the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top). If the reference is still available on the site and isn't listed as "Withdrawn," it's still a current document. In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript.

Please make sure your references are numbered in order of appearance in the text.

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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 as a Microsoft Word document. Your revision's cover letter should include a point-by-point response to each of the received comments in this letter. Do not omit your responses to the EDITOR COMMENTS (if applicable), the REVIEWER COMMENTS, the STATISTICAL EDITOR COMMENTS (if applicable), or the EDITORIAL OFFICE COMMENTS.

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

Again, your manuscript will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Sep 05, 2022, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Shannon K. Laughlin-Tommaso, MD, MPH
Associate Editor, Gynecology

Dear Editor,

We thank the reviewers for their comments and are pleased to submit revisions to our manuscript, ***Is the pandemic messing with your period? Associations between COVID-19 stress and menstrual changes***, an original research article, for exclusive consideration for publication. This manuscript is not under consideration elsewhere and will not be submitted to other journals unless a final negative decision is communicated by the Editors of *Obstetrics & Gynecology*. Our study was approved by the University of Rochester Institutional Review Board (STUDY00005980). As previously indicated during initial submission, we as authors have no conflicts of interest to disclose.

Tracked changes are included on the manuscript document. Point by point revisions to address the comments of each reviewer as appropriate are detailed below:

REVIEWER COMMENTS:

Reviewer #1:

1.) **If we know stress causes menstrual changes and COVID-19 increased the levels of stress in women, Isn't it expected that women during COVID have menstrual changes? There are prior published studies answering this question as mentioned on the discussion (lines 284 to 294). Besides the two studies you mentioned, Takmaz et al published in 2021 the result of survey in 952 health care workers with very similar methodology and results. How does your study add to what we already know about the topic?**

Previous epidemiological studies have suggested the association between stress and menstrual cycles, often in the context of more discrete events, not global pandemics. The study by Takmaz et al. was in Turkish healthcare workers, in contrast to our study of a broad spectrum of women in the United States. Despite this difference in populations, our study is consistent with Takmaz in indicating that COVID-19 stress is a predictor of menstrual irregularities. Further discussion of the literature has been added to the manuscript in the discussion (Lines 401-424) as follows:

"To our knowledge, the role of COVID-related stress in relation to menstrual cycle changes has yet to be fully elucidated. In contrast to our findings, Nguyen et al. did not find an association between COVID-related stress and menstrual changes.[43] A potential contributor to this discrepancy could be the fact that the authors of this paper utilized a two question Likert style assessment to query COVID-related stress rather than a validated questionnaire such as the PSS-10-C to more accurately assess stress associated with the pandemic. Unlike Nguyen et al., two other studies have pointed to an association between COVID-related stress and menstrual changes. A recent study of

female healthcare workers in Turkey concluded that reported COVID-19 stress was a significant predictor of menstrual irregularities, although the type of menstrual disturbances were not specified.[44] Similarly, Ozimek et al. observed that women with high perceived stress during the pandemic were more likely to experience a longer duration of menses and heavier bleeding during menses compared to those with moderate stress.[45] However, unlike ours, the study sample was not reflective of US census in multiple demographic factors including race, socioeconomic status and geographic distribution. Our findings demonstrate an association between high COVID-related stress and menstrual changes on a granular level and within a more diverse group of women across various educational, racial/ethnic and regional backgrounds in the US. Because we report menstruation parameters as discrete categories of cycle length, period duration, menstrual flow, and spotting changes, our findings can also be pinpointed to specific menstrual parameters, such as cycle length, which is known to be clinically relevant to future health risks.[14] Additionally, our sampling scheme allowed us to sample US women exposed to varying degrees of COVID-19 infection rates, restrictions, mandates, and policies across the US, and to understand *what* aspects of their menstrual cycle have been affected by these external COVID-related stressors."

2.) **Lines 97 to 101: What type of company is Dynata? Is it a marketing company? How do they recruit their panels? Is it through online advertising in comercial web sites? If so, Wouldn't this prioritize participants with reliable access to internet and free time to perform on line surveys? (This might explain why the education level is higher when compared to national census data) Does the company have experience with non-commercial surveys?**

As indicated in the methods (Lines 101-103), and supported by references 17-19, Dynata is a survey sampling company which maintains a demographically diverse web panel of survey takers across the United States. The company recruits via loyalty panels, open enrollment through a large number of websites, social media influencers and mobile apps, and affiliate networks, such as the websites of schools or communities. Therefore, their recruitment strategy is not limited to only commercial websites. The nature of their surveys, which are online, may favor those with reliable and consistent internet access and extra time as noted by the reviewer however, research shows that those with higher education are more likely to participate in research in general compared to those with lower education (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3276312/

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4129970/

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8231664/#:~:text=In%20one%20study%20measuring%20recruitment,et%20al.%2C%202006).

Therefore, this potential bias in sampling due to internet access/time/education may not be unique to Dynata and/or their method of recruiting participants. Nonetheless, we have added this potential limitation in the discussion section (Lines 440-443) as follows:

"The online nature of the survey could have resulted in a sampling/selection bias favoring individuals with internet access and ample time for research participation, a potential explanation for why the education level of the sample is higher than national averages."

We have also added a comparison of completes and non-completes (data in appendix) and in the results section (Lines 192-205) to further highlight the limited potential for sampling bias inherent in our study.

"A total of 1,037 survey takers met the first set of inclusion criteria and consented to participate in the study and 948 (91%) were deemed "completes," meaning that they proceeded through all questions to the final survey page. The remaining 89 did not make it to the final survey page and were considered "incompletes." Despite being considered a "complete," study participants may have had some missing data and not answered all relevant questions. Thus, we indicate the final sample sizes for each of the analyses in the Tables as appropriate. As shown in the Appendix, the only significant difference between completes and incompletes was race ($p=0.025$) and ethnicity ($p=0.029$); with the incompletes more likely to self-identify as American Indian/Alaska Native, Native Hawaiians, Other, and of Hispanic ethnicity than the completes. Despite ample research showing that minorities, African Americans in particular, are less enthusiastic about research participation than their peers,[26,27] it was encouraging to see a greater proportion of African American/Black participants complete our study than withdraw/drop out (8.48% vs 7.95% respectively, Appendix)."

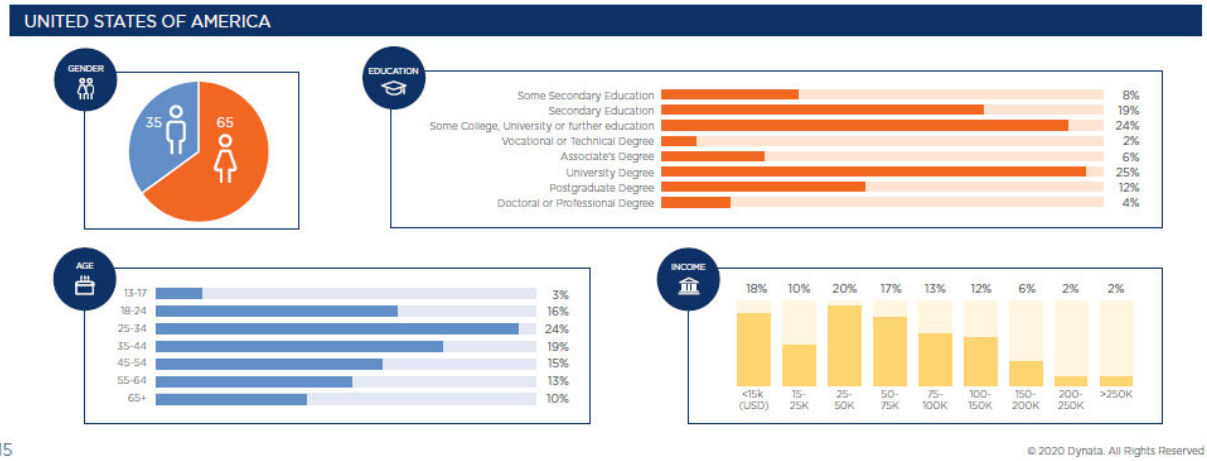
3.) **Lines 101: "Our recruitment plan involved the use of demographic quotas". Please provide details about how this was performed. Did you invite Dynata members with specifics demographic traits in their database to match census data or did you invite all the eligible members and then created the proportions that matched the census?**

We clarified this point with the following additions to the methods (Lines 105-112):

"Our recruitment plan involved the use of "soft" quotas, aligned with the US census data to ensure geographic, racial, and ethnic diversity in our sample. In research, "soft quotas" can either mean an absolute minimum that researchers expect to be exceeded, or a quota for which near enough is good enough.[20] For this study, using 'soft' quotas in our recruitment and sampling scheme allowed us to monitor the geographic, racial, and ethnicity distributions of the study population and modify/target the distribution of subsequent invitations to participate to grossly reflect the US census data."

4.) **Lines 174 to 177: "1037 survey takers met the inclusion criteria and consented to participate and 948 (91%) were deemed complete". How big is the Dynata database? What percentage of the eligible women for your survey does the initial 1037 represent? Please clarify that these 1037 participants are the ones that met only the first "round" of inclusion criteria (self-identified women living in the US between the ages of 18 and 45). When the second set of exclusion criteria was applied, you ended up with 374 participants, which would be your actual study sample. Please make sure you clarify this in this section of the manuscript. Why isn't this the group that is compared with the nation census data? Why isn't the calculation of missing data based on this smaller group as opposed to the larger 948 group? Does the percentage of missing data change if applied to the smaller group?**

Dynata is a global company that maintains a participant database of over 70 million people spanning across North America, South America, Europe, and Asia-Pacific (https://www.dynata.com/). There are over 30 million panelists from the America's alone, and 65% of those from the United States identify as women, over half of the panelists are between the ages of 18-44; falling within the age criteria of the study's "first" round of eligibility criteria (see image below). The educational attainment of the panelists is also quite varied.



Based on the reviewer's comments, we have expanded Tables 1 and 2 to include the data of participants who met BOTH the 1st and 2nd rounds of eligibility criteria to allow for comparisons to each other, and to the census. Comparing these two groups to each

other is more appropriate than comparing to the larger Dynata panel, which includes individuals who would not have met the study's eligibility criteria (ie men, age >45, etc). We have also delineated the proportion of missingness for each variable in Tables 1 and 2.

Additionally, we have also added Figure 1 in the methods to visually demonstrate the study's procedures and the two inclusion/exclusion criteria.

We have also clarified the language for the eligibility criteria in the methods section (Lines 122-130) to read as follows:

"As shown in Figure 1, the study's inclusion criteria included: i) self-identifies as a woman ii) self-reported age between 18-45 years iii) resides in a US state/territory. To capture naturally cycling women meeting the first inclusion criteria for the menstrual assessment questions, we included a second set of gynecological/ reproductive inclusion/exclusion criteria that excluded women who: were menopausal or post-menopausal prior to the pandemic, had undergone a hysterectomy, currently pregnant, were less than 3 months post-partum, currently receiving exogenous glucocorticoids, had received infertility treatments prior to the pandemic, or were currently taking hormonal birth control."

We have also clarified the issue of missing data as follows in the results section (Lines 196-198):

"Despite being considered a "complete" however, study participants may have had some missing data, and not answered all relevant questions. Thus, we indicate the final sample sizes for each of the analyses in the Tables as appropriate"

Reviewer #2:

We appreciate this reviewer's kind comments on the manuscript and hope that our responses adequately address the issues they raised.

1.) **Line 39: "Compared to those with low COVID-19 stress..." Does this not include moderate stress? In previous paragraph, low/moderate stress (scores < 25) was noted so I am curious if the low stress was further delineated or was the PSS-10-C dichotomized and this was just a wording issue**

This was a wording inconsistency. Should be low/moderate vs high. We thank the reviewer for the catch and have fixed this in the abstract (Line 43).

2.) **Lines 47-48: "The estimates for menstrual flow were in the expected direction, but not statistically significant." Does this mean that you expected those numbers to be "abnormal" but they were not statistically significant? Maybe different wording of the sentence will reflect that.**

We adjusted the sentence in the abstract (Lines 50-52) to better reflect our findings that there was a positive association between heavier menstrual flow and high COVID-related stress that was not statistically significant as shown below:

"Our data also demonstrated a nonsignificant trend of heavier menstrual flow amongst women with high COVID-related stress (adj OR: 1.61; 95% CI: 0.77, 3.34)."

3.) **Line 174: The survey was active for 3 days . Would there have been more complete participants if the survey had been active for an entire week?**

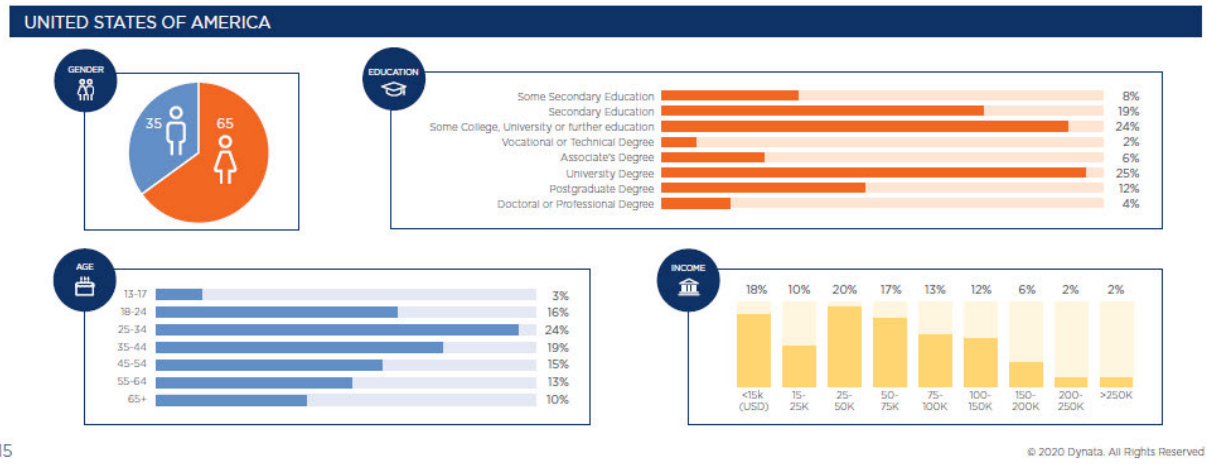
Once we met our total allotted participants (over 1,000) within our Census-guided demographic quotas, the survey was stopped. As with most online recruitment and data collection methods, partnering with Dynata for this research endeavor was expeditious and efficient only lasting 3 days as noted, and with a sample size sufficient enough for univariate, bivariate and multivariate analyses. Thus, missing data would not have been affected by longer active time. Additionally, missing data occurs as participants move through the survey but ultimately go through to the end (thus to be a "complete"). From our experience, it is infrequent (and often times impossible as in our case based on how the survey was designed), for a survey taker to return to a survey they have "completed" (gone all the way through) so perhaps no amount of time would have increased the completeness of participants' responses either.

STATISTICAL EDITOR COMMENTS:

1.) **General and lines 95-106: What description was given to the summary for recruitment of women into this study? Specifically, were there any phrases or statements that potentially could have biased selection of women to favor inclusion of women with high levels of stress or of menstrual changes. For example, the phrase used in the title to this article might have encouraged some women to participate. Is there any data available as to the N of all women of the appropriate age available on this platform vs those who agreed to participate in this study?**

We provided further clarification regarding the description of the survey that was provided to participants in the methods section (Lines 113-116). The title of the survey on Dynata was "Women's Covid-related stress, menstrual health and wellbeing," the summary provided to women who participated outlined that the survey was intended to investigate the impact of Covid-related stress on women's menstrual health. The phrase "Is the pandemic messing with your period?" was not utilized in recruitment information; it is simply the title of our manuscript. As stated in the methods, "All survey questions were reviewed for relevance and context by the research team and pre-tested with a sub-sample of women within the target population for face and content validity" to minimize any additional bias

As stated in response to reviewer 1's comments above, Dynata is a global company that maintains a participant database of over 70 million people spanning across North America, South America, Europe, and Asia-Pacific (https://www.dynata.com/). There are over 30million panelists from the America's alone, and 65% of those from the United States identify as women, over half of the panelists are between the ages of 18-44; falling within the age criteria of the study's "first" round of eligibility criteria (see image below). The educational attainment of the panelists is also quite varied.



2.) **Abstract: The abstract should include more summary data re: the sample size and proportions of women with high stress and with some of the primary outcomes of interest, rather than entirely in terms of ORs.**

We adjusted the “Results” section of our abstract (Lines 39-42) to include more summary data as requested. The additions are shown below:

“A total of 354 women of reproductive age across the US completed both menstrual and COVID-19 stress components of our survey. Over half of these women reported at least one change in their menstrual cycle since the start of the pandemic and 10% reported high COVID-related stress.”

3.) **Table 1: Should enumerate all missing data.**

We have enumerated all missing data for Tables 1 and 2 as appropriate.

4.) **lines 211-213, 234: Data not shown should be summarized and analysis shown in supplemental material.**

We have added all relevant data to the Appendix and noted so in the text (Lines 198, 205, 213, 254, 295).

5.) **Table 2: Need to enumerate all missing data.**

We have enumerated all missing data for Tables 1 and 2 as appropriate

6.) **Table 3: The subset with data re: menstrual data is smaller than the cohorts shown in earlier tables. Need to clarify whether they comprise a subset of the larger data set or a separate data set from that in Tables 1, 2. In either event, need to compare the demographic/clinical characteristics of the high stress vs low/medium stress groups with stats analyses. If this sample (~ 350 is a subset of the larger sample (~850), then there is a serious problem with potential for selection bias that must be addressed. That is, more than 1/2 of respondents would have been omitted from the menstrual data analysis, making its estimation of effect, its precision likely biased and not generalizable.**

The wording of the methods (Lines 122-130) and results sections (Lines 207- 214) were updated to better clarify the identification of groups who met both sets of eligibility criteria with updated tables provided in the text and appendix to further improve this characterization. Specific details of these changes are as follows:

The study's main objective was to evaluate how stress related to the COVID-19 pandemic has impacted women's menstrual cycle length, duration, flow, and frequency of spotting between cycles.

The achieve this, we had to create 2 sets of eligibility criteria:

1. The first was to include participants who i) self-identifies as a woman ii) self-reported age between 18-45 years iii) resides in a US state/territory. This was the population that met the initial screening criteria and were then eligible to continue on to the next level of screening criteria. Using the larger Dynata panel as the denominator, which would have included women who are not of reproductive age, men, and non-US respondents is a population not relevant to the initial eligibility screen.
2. In order to ensure that we were evaluating women who did not have confounding reproductive factors for the menstrual assessment questions, we included a second set of gynecological/ reproductive inclusion/exclusion criteria that excluded from the 1037, women who: were menopausal or post-menopausal prior to the pandemic (n=91), had undergone a hysterectomy (n=61), currently pregnant (n=49), were less than 3 months post-partum (n=30), currently receiving exogenous glucocorticoids/ had received infertility treatments prior to the pandemic (n=38), or were currently taking hormonal birth control (n=569). Please note these groups were not mutually exclusive.

As expected of women's health research of this nature, over half of our study participants were using hormonal birth control (https://www.cdc.gov/nchs/products/databriefs/db327.htm#:~:text=of%20Family%20Growth-,In%202015%E2%80%932017%2C%20approximately%2065%25%20of%20women%20aged%2015,of%20contraception%20(Figure%201)

https://pubmed.ncbi.nlm.nih.gov/31322004/

https://pubmed.ncbi.nlm.nih.gov/28672284) and were excluded to best assess the impact of the COVID-stress on the menstrual functions of women with 'natural' cycles. In the Appendix, we have included a table that compares the excluded non-natural cyclers (n=569) to the included natural cyclers (n=374) on key variables (Lines 207-209). There were no age, race or ethnicity differences between the groups. However, the excluded participants were more likely to be married ($p < 0.001$), have greater educational attainment ($p<0.001$), have a history of tobacco use ($p<0.001$), and not surprisingly, have a history of thyroid ($p=0.027$) and/or reproductive issues ($p<0.001$) that may have necessitated gynecological intervention (e.g. hormonal birth control, surgical methods) to control. Of utmost relevance to the study's aims, was the fact that vaccination rates were lower in the natural cyclers than the non-natural cyclers; meaning that menstrual changes reported by the cohort of natural cyclers in our analyses (Tables 3 and 4) were less attributable to the COVID vaccine.

The choice to focus on those individuals in whom their menstrual cycles occur in the absence of conditions or treatments reasonably suspected to impact their cycles facilitated this study's goal to characterize these subjects' experience as it i) reflects the biology and physiology of women's reproductive health in real world settings, and ii) highlights the herculean recruitment efforts required of women's health researchers to achieve their research goals, which are often under-studied. Natural cyclers are needed for menstruation studies of this nature (https://pubmed.ncbi.nlm.nih.gov/31322004/

https://pubmed.ncbi.nlm.nih.gov/28672284

McNamara, A., Harris, R., Minahan, C. (2020) Menstrual Cycle Change During COVID-19. Sharing some early results. *British Journal of Sports Medicine*. Retrieved from https://blogs.bmj.com/bjsm/2020/11/20/menstrual-cycle-change-during-covid-19/.

Cohut, M. (2021). Long COVID and periods: The unspoken impact on female well-being. *Medical News Today*, Retrieved from https://www.medicalnewstoday.com/articles/long-covid-and-periods-the-unspoken-impact-on-female-well-being)

Thus, this report represents the a priori decision to focus on patients in whom menstrual cycles were proceeding without the listed endogenous or exogenous conditions/treatments known to impact the menstrual cycle. The reporting of the data were clarified to provide the group meeting all eligibility criteria (n = 374) with supporting analysis of comparison between the groups that meet initial criteria (n=1037) and the fully eligible cohort to provide the ability of readers to understand the demographic distribution of those who met all criteria for being 'natural cyclers' as this, in and of itself, is a finding of epidemiologic interest and is relevant to the interpretation of generalizability of the results.

In this way, the data reported in this study are generalizable to the population of women between the ages of 18-45 years across various US regions/states and of varied racial, ethnic, and socioeconomic backgrounds (see Table 1); and the estimations of effect are relevant to people experiencing menstrual cycles without the impacts of this list of endogenous and exogenous conditions/treatments with additional impacts on the menstrual cycle.

We ask the reviewer to clarify this point if we are misunderstanding.

7.) **Table 4: Need to clarify for the reader the referent vs the other group(s) in this Table. Should omit the columns of p-values, since CIs are included, and the p-values are therefore redundant.**

In Table 4, the referent group is the “No Change” group as delineated in the footnote. This group is comprised of the participants who marked that they had not experienced any changes in the parameter in question. Clarification of the referent vs the other group(s) has been made to the table as well. Additionally, the columns of p-values were omitted from Table 4 as recommended.

EDITORIAL OFFICE COMMENTS:

1. If your article is accepted, the journal will publish a copy of this revision letter and your point-by-point responses as supplemental digital content to the published article online. You may opt out by writing separately to the Editorial Office at em@greenjournal.org, and only the revision letter will be posted.

We have noted this comment.

2. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:
*** Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and at the end of the abstract. For industry-sponsored studies, describe on the title page how the funder was or was not involved in the study.**
*** Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).**
*** Name the IRB or Ethics Committee institution in the Methods section (if applicable).**
*** Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.**

Funding information was disclosed on both title page and at the end of the abstract (Lines 60-62). The name of the IRB was included in the original copy of the manuscript (Lines 139-140).

3. Obstetrics & Gynecology's Copyright Transfer Agreement (CTA) must be completed by all authors. When you uploaded your manuscript, each coauthor received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please ask your coauthor(s) to complete this form, and confirm the disclosures listed in their CTA are included on the manuscript's title page. If they did not receive the email, they should check their spam/junk folder. Requests to resend the CTA may be sent to em@greenjournal.org.

All coauthors were instructed to complete the Obstetrics & Gynecology's Copyright Transfer Agreement (CTA).

4. For studies that report on the topic of race or include it as a variable, 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, describe the reasons that race and ethnicity were assessed in the Methods section and/or in table footnotes. Race and ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and ethnicity as in some cases missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race.

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

List racial and ethnic categories in tables in alphabetic order. Do not use "Other" as a category; use "None of the above" instead.

Please refer to "Reporting Race and Ethnicity in Obstetrics & Gynecology" at https://edmgr.ovid.com/ong/accounts/Race_and_Ethnicity.pdf.

The use of "Other" as a category was omitted from the tables in the manuscript. We aimed to ensure that our survey population was racially diverse, as many studies may have disproportionate representation of White individuals. We include discussion of this in our Methods and Results sections (Lines 106-113; 203-206).

5. ACOG uses person-first language. Please review your submission to make sure to center the person before anything else. Examples include: "People with disabilities" or "women with disabilities" instead of "disabled people" or "disabled women"; "patients with HIV" or "women with HIV" instead of "HIV-positive patients" or "HIV-positive women"; and "people who are blind" or "women who are blind" instead of "blind people" or "blind women."

We strove to utilize person-first language throughout the manuscript at all times.

6. The journal follows ACOG's Statement of Policy on Inclusive Language (https://www.acog.org/clinical-information/policy-and-position-statements/statements-of-policy/2022/inclusive-language). When possible, please avoid using gendered descriptors in your manuscript. Instead of "women" and "females," consider using the following: "individuals;" "patients;" "participants;" "people" (not "persons"); "women and transgender men;" "women and gender-expansive patients;" or "women and all those seeking gynecologic care."

We address the limitations of our survey given that we only included participants that self-identified as women in our discussion (Lines 470-475).

7. 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.
We do not find the use of the reVITALize definitions problematic.

8. Make sure your manuscript meets the following word limit. The word limit includes the manuscript body text only (for example, the Introduction through the Discussion in Original Research manuscripts), and excludes the title page, précis, abstract, tables, boxes, and figure legends, reference list, and supplemental digital content. Figures are not included in the word count.

Original Research: 3,000 words

Our original submission was under the 3,000 word limit; however, in order to fully respond to all reviewer and editor comments, we have had to length sections of our manuscript including Methods, Results, and Discussion, which has increased the word count of our submission.

9. For your title, please note the following style points and make edits as needed:
*** Do not structure the title as a declarative statement or a question.**
*** Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles.**
*** Abbreviations, jargon, trade names, formulas, and obsolete terminology should not be used.**
*** Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," "A Systematic Review," or "A Cost-Effectiveness Analysis" as appropriate, in the subtitle. If your manuscript is not one of these four types, do not specify the type of manuscript in**

the title.

No edits were suggested for our title so we kept it as is.

10. Specific rules govern the use of acknowledgments in the journal. Please review the following guidelines and edit your title page as needed:

*** 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 or indicate whether the meeting was held virtually).**
*** If your manuscript was uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology, add the following statement to your title page: "Before submission to Obstetrics & Gynecology, this article was posted to a preprint server at: [URL]."**
*** Do not use only authors' initials in the acknowledgement or Financial Disclosure; spell out their names the way they appear in the byline.**

We have made efforts to ensure that the above rules have been adhered to in the title page.

11. Be sure that each statement and any data in the abstract are also stated in the body of your manuscript, tables, or figures. Statements and data that appear in the abstract must also appear in the body text for consistency. Make 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 manuscript.

In addition, the abstract length should follow journal guidelines. Please provide a word count.

Original Research: 300 words

Our original abstract was under the 300 word limit; however, in order to fully respond to all reviewer and editor comments, we have had to include additions to the Results section of our Abstract, which has lengthened it to 360 words

12. 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.

We have made efforts to ensure than only standard abbreviations and acronyms are utilized and that all abbreviations and acronyms are spelled out the first time they are used in the manuscript.

13. The journal does not use the virgule symbol (/) in sentences with words, except with ratios. 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.

We made efforts to remove any use of the (/) symbol in sentences with words except when using it to express data.

14. ACOG avoids using "provider." Please replace "provider" throughout your paper with either a specific term that defines the group to which are referring (for example, "physicians," "nurses," etc.), or use "health care professional" if a specific term is not applicable.

We adjusted wording in our Discussion to adhere to ACOG's standards (Line 481).

15. 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.

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

Express all percentages to one decimal place (for example, 11.1%"). Do not use whole numbers for percentages.

We have made all efforts to ensure that data is cited in terms of effect size, data presentation is standardized and all percentages are presented to one decimal place.

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

We have reviewed the journal's Table Checklist and have made adjustments such that the formatting and placement, numbering, formatting of the data, table footnotes, and explanation of the data are in accordance with these guidelines. Specifically, we have moved all tables to the end of the manuscript, removed any gray shading, listed racial and ethnic categories in alphabetical order and used "None of the above" instead of "Other."

17. Please review examples of our current reference style at https://edmgr.ovid.com/ong/accounts/ifa_suppl_refstyle.pdf. Include the digital object identifier (DOI) with any journal article references and an accessed date with website references.

Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the formal reference list. Please cite them on the line in parentheses.

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We have reviewed the above comment and will consider publishing open access**.**

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.
We appreciate the guidance regarding next steps if our article were to be accepted.

Regards,

Martina Anto-Ocrah, PhD, MPH, MT(ASCP)

Tori Valachovic, BS

Y. Michael Chen, PhD
Kimberly Tiffany, BA
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