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: Sep 24, 2020
To: "Lauren J Green" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-2160

RE: Manuscript Number ONG-20-2160

Postpartum-specific vital sign reference ranges

Dear Dr. Green:

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

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

Your paper will be maintained in active status for 14 days from the date of this letter. If we have not heard from you by Oct 01, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This is an original observational cohort study of "low risk" or "normal" women followed during pregnancy and for two weeks postpartum to generate normal ranges for maternal vital signs postpartum. Participants assessed vital signs at home daily for two weeks postpartum. Also, trained midwives measured vital signs on days 1, 7 and 14 postpartum. The authors used the final cohort of 909 women to generate normative postpartum data for maternal vital signs. They note a slight increase in BP through day five after birth, with slight decrease after that. They also note a slight decrease in heart rate over 14 days postpartum. The data are somewhat novel with regard to granularity and modernity. The topic is of some interest to readers of the journal and the data may serve as a normative reference. Questions and suggestions for enhancing this manuscript include:

1. The cohort selection may have introduced bias. First, the authors approached a convenience sample about participation. Second, fewer than one fourth approached actually participated. Characteristics of women who did and did not participate should be compared in an attempt to identify bias introduced into the cohort.

2. Generalizability is another concern. Although the authors claim this as a strength, the population was largely white, well off, normal weight and had low rates of complications.

3. The study design has several strengths including enrollment of women during pregnancy, which reduces bias. However, it also is a limitation since women with obstetric complications were included in the "normal" group. Even the restricted analysis still included women with gestational hypertension and preeclampsia without severe features which may skew results. Women with these conditions may have prolonged duration of abnormal vital signs.

4. It would be of interest to assess the subgroup with cesarean delivery. The same is true for women with hemorrhage.

5. It is not clear that the self-measurements of vital signs were validated by trained individuals using standard methods. Simply noting a lack of statistical difference in measurements at varying times is insufficient.

6. There is no mention of or accounting for medication use during pregnancy or postpartum. Did women take low dose aspirin? Anti-hypertensive medications? Etc.

7. Changes in vital signs over the fourteen days postpartum include minor variations in normal ranges. It is unclear how these data can be used to improve clinical care.

8. The paper is quite long, especially the discussion, given the data presented.

9. The authors overstate the clinical utility of these data as providing thresholds for seeking medical attention. In order to justify these statements, they would need to show value by assessing vital signs in women with sepsis, hypertension, etc.

10. Assessment of changes in vital signs during pregnancy and postpartum would be of interest.

Reviewer #2:

The authors present a large prospective longitudinal cohort study looking at daily blood pressure, heart rate, O2 saturation, temperature and respiratory rate in a low risk population immediately after delivery and up to 14 days postpartum. Vital signs were taken by the patient at home in a standardized validated manner. They looked at trends using the median reported blood pressures and other vital signs in the cohort and found the systolic/diastolic BP peaked around day 5 and 6 respectively. All other vital signs remained constant. The relatively small dropout rate (10%) along with a large cohort add valuable information into a critical window of maternal morbidity and mortality. I do think this may be useful in formulating surveillance protocols, particularly with higher risk patients.

Line 39-55 I appreciate the thorough financial disclosure along with details about shareholders and what the company does. Rarely have I seen this much transparency. I usually must query the ticker tape and board of directors online to get this.

Abstract:

Line 84-89 Be more specific as to what population you are looking at. I think this is a worthy endeavor, but state of front what comorbidities were excluded and most importantly if this included the broad range of hypertensive disorders of pregnancy.

Line 103 The conclusion are over-stated. The findings characterize general trends, the majority of which are in the normal, not abnormal range. These physiologic trends "could", not should, inform an evidence based early warning system.

Introduction:

Line 119 I am not sure this is the most recent reference or accurate assessment of US maternal mortality. The report from the maternal mortality review committees is slightly lower. https://reviewtoaction.org/sites/default/files/national-portal-material/Report%20from%20Nine%20MMRCs%20final_0.pdf

Line 143 Describe the scoring system in more detailed cited in reference #19

Line 159-163 I would suggest reference to previous publication in this journal Obstetrics & Gynecology: March 2020 - Volume 135 - Issue 3 - p 653-664. Readers would be interested in both the postpartum and antepartum results.

Materials and methods:

Line 187 Appendix 1 had some contradictory inclusion criteria. The inclusion criteria stated high BP >140/90 at recruitment was OK yet the exclusion criteria stated HTN was an exclusion criterion. Typically, elevated BP prior to 20 wks would be considered chronic HTN.

Line 204-205 Specify how blood pressure was taken. Was it right or left arm at the level of heart sitting or lying? Also what time of day was it taken? Was there any instruction related to medications or caffeine prior to checking?

Line 223 How often did patients seek help for feeling unwell and what differences if any were noted in vital signs for this cohort?

Line 226 Were reported values in the ranges >140/90 repeat and or 4 hours apart?

Line 238 Agree with inclusion of data from withdrawn participants however was there a separate analysis to see how similar they were to the larger cohort?

Line 262 Define bias and limits of agreement for data inclusion.

Line 266-273 Explain the in more detail the purpose of the restrictive population. I noted this was also done in the previous publish study. I assume this would be a purer cohort to look at normal physiologic changes.

Line 275 In addition to post hoc analysis for epidural was there also one done for delivery mode? Greater amount of pain

with recovery from an operative delivery may confound the outcomes of interest.

Results:

Line 280 I would probably not list termination of pregnancy as an adverse outcome. It sounds judgmental. Whether to include data or not is less important.

Table 1

Line 289 The mean age 35 may make this less generalizable and may include more underlying undiagnosed comorbidities that may confound the outcomes. The table looks different and does not seem to be this high. Maternal age (years) (SD) 32.1 (4.7) 34.0 (4.2) 31.5 (5.0) 32.2 (4.7)
The same can be said about the relatively low BMI and homogeneity by ethnicity.
Line 317 0.0003% of visits 3/9621 observations referred for abnormal BP per protocol >140/90 seems very low and below populational ranges.

Table 2

Define use of terms severe pre-eclampsia. Old terminology would include significant proteinuria without having severe range BP. Was this synonymous with severe features?

Figure 2

Describe how and when Day 0 BP were obtained. The day of delivery can include PPH, transient pain issue etc. This needs to be standardized and expanded upon.

The rest of the figures are clear and easy to interpret.

Discussion:

Line 406 Characterizing the 3rd percentile for systolic BP of 97 should be applied to early warning signs of sepsis may be a stretch without other parameters.

Line 410 The 97 percentiles for diastolic BP should be less than 90 not above unless I am misunderstanding the presentation of the data.

The rest of the discussion addresses both the strengths and limitations previously mentioned.

Reviewer #3: This a well written manuscript on a novel topic, which describes a longitudinal cohort study to estimate normal ranges for selected maternal vital signs postpartum.

Abstract: is clear.

Introduction: provides background for conduction of the study, which has an antenatal component, not reported here. There is limited data on ranges of clinical variables in the postpartum period which might inform the degree of complications that patients might present, which are associated with mortality and morbidity. The focus of the study is the population in high income countries, the U.K., Ireland or the United States.

Methods: At three centers in the United Kingdom a cohort study is conducted by asking participants to measure four clinical variables, daily, for two weeks in the postpartum period. Trained midwives complete measurements on three opportunities, adding another variable, not measured by the participants, to estimate a range of variation in the measurements between the participants and trained experts; analyzed using a Bland-Altman method. A description of the sample size included is discussed and an Appendix included. The statistical analysis approach using percentiles and outliers is described. A definition of the population included is provided as those corresponding to Category 1 of the American Society for Anesthesiologists', labelled as a "pragmatic population". A subset of the participants is analyzed and defined as a "restrictive population"; in that group, participants were excluded in complications of pregnancy developed, not the case for the "pragmatic population". Several appendices are included. The STROBE guidelines were followed.

Results: 909 participants included. Table # 1 provides the demographic characteristics of the population included. Table # 2 describes pregnancy complications and birth outcomes Figures are presented to provide the results of the analysis by variable studied.

Discussion: Blood pressure ranges measured are described and a value of 97 mmHg corresponding to the 3rd %, in both groups analyzed is proposed to support the use of that finding with a diagnosis of sepsis, compared to a current range of

90 mmHg used to associate B/P with that diagnosis. No cases of sepsis are included in the analysis. A similar a approach is taken for the reported values for B/P, heart rate, respiratory rate, SpO2 and temperature.

Conclusion: The authors indicate they have established postpartum day-specific reference ranges for important clinical variables that could inform construction of early warning systems to identify women at risk for complications in the postpartum period.

Reviewer Observations:

Methods: The use of the Category 1 of the American Society for Anesthesiologists', definition for the "pragmatic population" group with a sample size calculation based on 1000 participants and then stratification of this group into a 2nd group denominated the "restrictive population", is unclear. The pragmatic population includes participants with risk factors that can be associated with an expected higher rate of complications in pregnancy, at delivery and postpartum. The epigenetic effects in pregnancy and outcomes for example of obesity, cannot be discounted when compared to the population where obesity was not a significant factor. Finding that the variation, as described in the results of the variables studied is not large, but not defined statistically, does not clarify why was the study population not clearly defined from the start and the study completed on a population with the sample size to correspond to either the pragmatic or the restrictive groups.

There is not enough information to describe variations in the population included. Temperature postpartum is associated with breastfeeding or not, as an example. Stratification of the analysis of the variables studied by route of delivery, considering an estimation of blood loss, or postpartum hemorrhage, which would affect all the variables included, is not mentioned and it is only noted in one table. Use of co-interventions that could affect the variables of interest is not discussed such as augmentation of labor with oxytocin, use of IV fluids, use of medications for pain management. It cannot be assumed that the use of those co interventions will be equal by center.

Use of the Bland-Altman analysis presented in Appendix # 3, without reference to quantification of the variation presented and only discussing that there is no evidence of bias is not sufficient. It will be useful to the reader to quantify it, mean? S/D?.

Making the decision to add the measurements made by the participants with those made by the midwives, and including them in the analysis to increase the number of data points, is unclear; why was that decided, when the objective was to demonstrate that the measurements made by the participants are overall accurate.

Interpretation of the meaning of the results found, as discussed for the B/P range for the diagnosis of sepsis is speculative, as no cases of sepsis were identified. A similar consideration needs to be made for the observations made in relation to the ranges described in the rests for all the variables studied. The use of a specific threshold for Spo2 < 95 % to increase concern for poor oxygenation and possible increased risk for pulmonary embolism, is based on the diagnosis of PE. Proposing to change that threshold to sPo2 of 93% is speculative as that number has not been correlated with complications associated with lower oxygenation in this population.

Table # 1: a rounding adjustment is needed as the percentages at the top add to 100.1%.

The appendices include a large and significant amount of information, which are useful to the reader.

STATISTICAL EDITOR COMMENTS:

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

lines 195-198: In this study, there was no duplication or verification of vital sign measurements, while for identification or treatment of hypertension, one would depend on replicated measurements and certainly that would be done before initiating any antihypertensive therapy. Therefore (lines 412-416), these normative data should not be used to establish the diagnosis of hypertension, but rather to investigate further should a BP measurement exceed the highest stratum of centiles.

General: Some Tables have entries whose column total is < 100. For the row entries with that column total, the %s should be rounded to nearest integer %, not cited to 0.1% precision level.

Table 1, Fig 1: Should compare the demographic/clinical characteristics of the women who participated vs those who did not (could be supplemental material), to address issue of generalizability.

EDITORIAL OFFICE COMMENTS:

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

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

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

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

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

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

4. All submissions that are considered for potential publication are run through CrossCheck for originality. The following lines of text match too closely to previously published works.

Please cite Lines 153-157.

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 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.

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 print appendixes) but exclude references.

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

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

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

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

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

12. We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

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

14. Figures 1-6: Please upload as separate figure files on Editorial Manager.

15. Each supplemental file in your manuscript should be named an "Appendix," numbered, and ordered in the way they are first cited in the text. Do not order and number supplemental tables, figures, and text separately. References cited in appendixes should be added to a separate References list in the appendixes file.

16. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at http://links.lww.com/LWW-ES/A48. The cost for publishing an article as open access can be found at https://wkauthorservices.editage.com/open-access/hybrid.html.

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

***

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

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

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

Again, your paper will be maintained in active status for 14 days from the date of this letter. If we have not heard from you by Oct 01, 2020, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Dwight J. Rouse, MD, MSPH

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

_____

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

[redacted]

16th October 2020

Dear Editor,

Thank you for the opportunity to revise our manuscript in light of the reviewers' comments. We believe their suggestions have improved our manuscript and are grateful for the thoroughness of the reviews. We have included a point-by-point response, below, which we are happy for you to publish.

Ethical approval

The study commenced in Oxford as a sub-study of the INTERBIO-21st Fetal Study, Oxford South Central C Research Ethics Committee:08/H0606/139), and then expanded to include two additional centres (Newcastle and London, South East Coast–Brighton and Sussex Research Ethics Committee:14/LO/1312).

Manuscript approval and submission

All authors have approved the manuscript for submission. All persons named in the acknowledgments have given permission for publication. We confirm that the content of the manuscript has not been published or submitted for publication elsewhere.

Guarantor

Peter Watkinson affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and registered) have been explained.

Role of the funding source

The 4P study is supported by the NIHR Biomedical Research Centre, Oxford and the NIHR Biomedical Research Centre of Guy's and St Thomas' NHS Foundation Trust, London. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Meeting presentations

Preliminary data was at the 43rd Annual Meeting of the MacDonald Obstetric Medicine Society on June 28, 2019, Leeds, United Kingdom. No information was made available for publication. There are no postings on a preprint server.

Yours faithfully

Peter J Watkinson MD

Associate Professor of Intensive Care Medicine

REVIEWER COMMENTS:

Reviewer #1: This is an original observational cohort study of "low risk" or "normal" women followed during pregnancy and for two weeks postpartum to generate normal ranges for maternal vital signs postpartum. Questions and suggestions for enhancing this manuscript include:

1. The cohort selection may have introduced bias. First, the authors approached a convenience sample about participation. Second, fewer than one fourth approached actually participated. Characteristics of women who did and did not participate should be compared in an attempt to identify bias introduced into the cohort.

Thank you. As the reviewer and editor will understand we did not have ethical permission to collect descriptive information on those who chose not to take part in the study. We would emphasise that the cohort was never intended to be representative of the whole pregnancy population, but to represent a pragmatic 'low risk' population suitable for defining a normal range for clinical practice and a future early warning score (clarified in the text lines 163-65). Note a quarter of those approached were not eligible; 32% of those who were eligible agreed to participate (comparable with many prospective studies).

2. Generalizability is another concern. Although the authors claim this as a strength, the population was largely white, well off, normal weight and had low rates of complications.

The centres in our study were chosen to reflect the UK population. As we noted we included a pragmatic 'low risk' population who will therefore be more likely to be white, of lower weight, higher socioeconomic status and have fewer complications; the fact that this was the case is reassuring. Despite this, the population included are highly representative of the UK with regard to BMI, ethnicity and age (lines 487-491). Use of this low risk population to derive normal ranges for use in an early warning score will actually make it more responsive to higher risk populations who are likely, for example, to have higher blood pressures, hence our assessment that this design is a strength.

3. The study design has several strengths including enrollment of women during pregnancy, which reduces bias. However, it also is a limitation since women with obstetric complications were included in the "normal" group. Even the restricted analysis still included women with gestational hypertension and preeclampsia without severe features which may skew results. Women with these conditions may have prolonged duration of abnormal vital signs.

Thank you. Our rationale for the pragmatic and normal groups is presented lines 279-286. Rather than being a limitation our findings are representative of these groups, as intended. Whilst it is of course possible to limit the group further by performing another post-hoc subgroup analysis we consider this would be of limited clinical value, reducing the generalisability and our ability to use these normal values in a pragmatic 'low-risk' population without major pregnancy complications. If we apply further exclusions, it is likely that the ranges will have lower utility for use in a standard pregnancy population.

4. It would be of interest to assess the subgroup with cesarean delivery. The same is true for women with hemorrhage.

We agree that there are several subgroup analyses that could be undertaken. In this publication we have included subgroup analyses on parity, the restrictive patient group and the effects of anesthesia. However, as noted previously, our aim was to identify ranges which could be used in a pragmatic early warning tool across both hospital and community settings. Multiple subgroup analyses would infer the need for multiple tools and move away from a simple, pragmatic, easily utilised reference range.

5. It is not clear that the self-measurements of vital signs were validated by trained individuals using standard methods. Simply noting a lack of statistical difference in measurements at varying times is insufficient.

Thank you. We have clarified this (lines 209-10), referring readers to our published study protocol to avoid enlarging our methods section.

6. There is no mention of or accounting for medication use during pregnancy or postpartum. Did women take low dose aspirin? Anti-hypertensive medications? Etc.

Please see answer to question 4. Women receiving low dose aspirin would remain in our study given the aim of producing pragmatic reference ranges for use in clinical populations. Women receiving antihypertensive medications at recruitment were excluded from the study. As only 45 participants developed gestational hypertension (table 2) the effects of inclusion are likely to be minimal and subgroup analysis would not be appropriate.

7. Changes in vital signs over the fourteen days postpartum include minor variations in normal ranges. It is unclear how these data can be used to improve clinical care.

We believe having evidence-based, modern normal ranges is important for modern practice and development of early warning tools. Knowledge of the extent of variation is essential, whether or not variation is considered "minor".

8. The paper is quite long, especially the discussion, given the data presented.

Thank you – we have reduced the length of the manuscript.

9. The authors overstate the clinical utility of these data as providing thresholds for seeking medical attention. In order to justify these statements, they would need to show value by assessing vital signs in women with sepsis, hypertension, etc.

Thank you, we have adjusted these statements (also see answers to reviewer 3). We note that our previous paper presenting antenatal data from the 4P population (in the Green Journal) is currently being used to underpin the development of a national early warning score in England with the results promoted in a "practice pointer" for management of common physical symptoms in pregnancy in the British Medical Journal (*BMJ* 2020; 370 doi: https://doi.org/10.1136/bmj.m2248). The findings postnatally would seem equally relevant to development of an evidence-based early warning score for the postpartum period.

10. Assessment of changes in vital signs during pregnancy and postpartum would be of interest.

We agree with the reviewer and assessed changes in vital signs during pregnancy in our previous paper with this journal and post-partum changes in this manuscript. We have related these papers in the discussion (for example see lines 439 and 451).

Reviewer #2:

The authors present a large prospective longitudinal cohort study….. I do think this may be useful in formulating surveillance protocols, particularly with higher risk patients.

1. Line 39-55 I appreciate the thorough financial disclosure along with details about shareholders and what the company does. Rarely have I seen this much transparency. I usually must query the ticker tape and board of directors online to get this.

Thank you.

Abstract:

2. Line 84-89 Be more specific as to what population you are looking at. I think this is a worthy endeavor, but state of front what comorbidities were excluded and most importantly if this included the broad range of hypertensive disorders of pregnancy.

We used this population description in our previous (antenatal 4P) paper with the journal. We are at the word limit for the abstract, limiting our ability to add detailed descriptors. However, if the editors felt that revision was essential, we are happy to revise and remove detail elsewhere.

3. Line 103 The conclusion are over-stated. The findings characterize general trends, the majority of which are in the normal, not abnormal range. These physiologic trends "could", not should, inform an evidence based early warning system.

We have changed 'should' to 'could' as suggested. See also answer to reviewer 1, point 9.

Introduction:

4. Line 119 I am not sure this is the most recent reference or accurate assessment of US maternal mortality. The report from the maternal mortality review committees is slightly lower. https://reviewtoaction.org/sites/default/files/national-portal-material/Report%20from%20Nine%20MMRCs%20final_0.pdf

Thank you for suggesting this reference. As it includes deaths going back to 2008 for Colorado, includes 9 rather than 52 states data and presents data in a way which would make it more difficult to compare to the

international comparators we have used, we think that it would be more informative to continue to use the reference chosen. We note the reference we chose was published in Obstetrics and Gynecology only 3 years ago and has been referenced over 260 times.

5. Line 143 Describe the scoring system in more detailed cited in reference #19

In the interests of brevity and in order to conform with journal requirements, we have omitted descriptions of the various scoring systems. However, as noted above, if the editors felt that revision was essential are happy to revise and remove detail elsewhere.

6. Line 159-163 I would suggest reference to previous publication in this journal Obstetrics & Gynecology: March 2020 - Volume 135 - Issue 3 - p 653-664. Readers would be interested in both the postpartum and antepartum results.

Thank you – we have added this reference to our previous paper with the journal.

Materials and methods:

7. Line 187 Appendix 1 had some contradictory inclusion criteria. The inclusion criteria stated high BP >140/90 at recruitment was OK yet the exclusion criteria stated HTN was an exclusion criterion. Typically, elevated BP prior to 20 wks would be considered chronic HTN.

We have reviewed the inclusion criteria and ensured that they are provided as written in the published, peer-reviewed protocol.

8. Line 204-205 Specify how blood pressure was taken. Was it right or left arm at the level of heart sitting or lying? Also what time of day was it taken? Was there any instruction related to medications or caffeine prior to checking?

As with our previous (antenatal 4P) publication with the Green Journal, for brevity we have directed the reader to the standard operating procedures for taking each vital sign, which are published with our protocol.

9. Line 223 How often did patients seek help for feeling unwell and what differences if any were noted in vital signs for this cohort?

In line 330 we report the proportion of patients who required referral for raised blood pressure. Whilst interesting, at 3/909 participants, or 3/9621 observations, the numbers are too small for meaningful comparison.

10. Line 226 Were reported values in the ranges >140/90 repeat and or 4 hours apart?

As in line 237, a study standard operating procedure was followed. Participants were instructed to repeat blood pressure measurements >140/90 mmHg after more than 30 minutes and to seek assistance if the blood pressure remained elevated. We have added this SOP to the appendices (new Appendix 2).

11. Line 238 Agree with inclusion of data from withdrawn participants however was there a separate analysis to see how similar they were to the larger cohort?

As the reviewer notes, we included data where possible. We note in our results (line 303-305) that the maternal characteristics were similar in the postpartum cohort to those of all women enrolled. We have added a comparison of the 132 patients included in the antenatal but not the postnatal phase of 4P with those included in the postnatal phase (new Appendix 4) for completeness. However, we would be cautious about interpreting this data given the small numbers and that excluded subgroups such as early miscarriage or early termination did not form part of our intended group to generate post-partum centiles.

12. Line 262 Define bias and limits of agreement for data inclusion.

To facilitate brevity this is explained in appendix 5
– also see reviewer 3 comment 3.

13. Line 266-273 Explain the in more detail the purpose of the restrictive population. I noted this was also done in the previous publish study. I assume this would be a purer cohort to look at normal physiologic changes.

The reviewer is correct. Previous feedback (as with reviewer 1) had suggested that clinicians would be interested in the effect of confining the analysis to those of more optimal health (line 279). As referenced, we were guided by previous work.

14. Line 275 In addition to post hoc analysis for epidural was there also one done for delivery mode? Greater amount of pain with recovery from an operative delivery may confound the outcomes of interest.

We agree that there are many possibilities for subgroup analyses such as the one suggested. Appendix 10 shows results for women who had received epidural or general anaesthetic, which may answer the reviewer's query (heart rates were somewhat higher). However, as noted previously, our aim was to identify ranges which could be used in a pragmatic early warning tool across both hospital and community settings. Multiple subgroup analyses would infer the need for multiple tools and move away from a simple, pragmatic, easily utilised reference range. It is worth noting that studies report women also experience significant pain and complications after vaginal birth over the fourteen day postnatal period covered by this study (Postpartum pain management. Obstet Gynecol 2018;132: e35-e43), and therefore we limited our sub-group analyses to those chosen.

Results:

15. Line 280 I would probably not list termination of pregnancy as an adverse outcome. It sounds judgmental. Whether to include data or not is less important.

Thank you for this suggestion – we have adjusted the wording to avoid this.

16. Line 289 The mean age 35 may make this less generalizable and may include more underlying undiagnosed comorbidities that may confound the outcomes. The table looks different and does not seem to be this high. Maternal age (years) (SD) 32.1 (4.7) 34.0 (4.2) 31.5 (5.0) 32.2 (4.7)The same can be said about the relatively low BMI and homogeneity by ethnicity.

Thank you for spotting this typographical error. The mean age was 32.2 (4.7) as in table 1, which may reassure the reviewer. As noted for reviewer 1 and in lines 487-49, our population sample appears representative of UK practice.

17. Line 317 0.0003% of visits 3/9621 observations referred for abnormal BP per protocol >140/90 seems very low and below populational ranges.

Thank you for spotting this typographical error, we have corrected this to 0.03% visits. In brief, referral to the participant's usual care team only occurred when the blood pressure had not resolved by the time the research midwife became aware of the reading (see line 234, new Appendix 2).

18. Table 2. Define use of terms severe pre-eclampsia. Old terminology would include significant proteinuria without having severe range BP. Was this synonymous with severe features?

Severe pre-eclampsia is defined in our published protocol "Blood pressure is ≥ 160/110mmHg on two occasions, between 4 and 168 hours apart, or if the first measurement was immediately followed by

treatment with an antihypertensive, either of these scenarios being associated with the presence of proteinuria". For brevity, we have referenced the protocol in the text.

19. Figure 2. Describe how and when Day 0 BP were obtained. The day of delivery can include PPH, transient pain issue etc. This needs to be standardized and expanded upon.

Although the reviewer is correct (and indeed, results on each day may be affected by clinical events), the results still record the day 0 BP results for the intended population, the aim of this study. We have added clarification to the methods section regarding how day 0 observations were taken (lines 220-22).

20. The rest of the figures are clear and easy to interpret.

Thank you

21. Discussion: Line 406 Characterizing the 3rd percentile for systolic BP of 97 should be applied to early warning signs of sepsis may be a stretch without other parameters.

This has been adjusted (please see answer to reviewer 1).

22. Line 410 The 97 percentiles for diastolic BP should be less than 90 not above unless I am misunderstanding the presentation of the data.

The statement in the paper is correct, the 97th centile diastolic blood pressures were above 90 mmHg days 2-9 in both pragmatic and restrictive populations – see tables (S6.1 and 7.2)

Reviewer #3: This a well written manuscript on a novel topic, which describes a longitudinal cohort study to estimate normal ranges for selected maternal vital signs postpartum.

1. Methods: The use of the Category 1 of the American Society for Anesthesiologists', definition for the "pragmatic population" group with a sample size calculation based on 1000 participants and then stratification of this group into a 2nd group denominated the "restrictive population", is unclear. The pragmatic population includes participants with risk factors that can be associated with an expected higher rate of complications in pregnancy, at delivery and postpartum. The epigenetic effects in pregnancy and outcomes for example of obesity, cannot be discounted when compared to the population where obesity was not a significant factor. Finding that the variation, as described in the results of the variables studied is not large, but not defined statistically, does not clarify why was the study population not clearly defined from the start and the study completed on a population with the sample size to correspond to either the pragmatic or the restrictive groups.

We have clarified the aim and reasons for choosing a "low-risk" pragmatic population in lines 163-165, in line with our peer-reviewed, published protocol and study registration. Any population of pregnant women could be further subdivided as the reviewer suggests, but we believe the population chosen represents a group who would be monitored with a standard maternal early warning score. We are clear that our "restrictive" population was developed post-hoc (in response in part to feedback from the reviewers of our first 4P paper with the green journal). The other reviewers show the natural curiosity to explore different sub-populations within our large prospective dataset. We believe the "restrictive" groups represents a balance between this curiosity and undertaking an unhelpfully large range of sub-group analyses. Lines 250-254 make clear that we published our sample size determination and that it is large enough for the findings from the restrictive group to be robust. Statistically, we are careful to describe differences between groups as to whether the confidence intervals of our estimates overlap.

2. There is not enough information to describe variations in the population included. Temperature postpartum is associated with breastfeeding or not, as an example. Stratification of the analysis of the variables studied by route of delivery, considering an estimation of blood loss, or postpartum hemorrhage, which would affect all the variables included, is not mentioned and it is only noted in

one table. Use of co-interventions that could affect the variables of interest is not discussed such as augmentation of labor with oxytocin, use of IV fluids, use of medications for pain management. It cannot be assumed that the use of those co interventions will be equal by center.

As the reviewer notes we present pregnancy complications and birth outcomes in table 2. Although further subgroup analyses may be of interest in future work, we believe it is important to present the findings for the whole population. As we note above, multiple subgroup analyses would infer the need for multiple tools and move away from a simple, pragmatic, easily utilised reference range.

3. Use of the Bland-Altman analysis presented in Appendix 3, without reference to quantification of the variation presented and only discussing that there is no evidence of bias is not sufficient. It will be useful to the reader to quantify it, mean? S/D?.

Thank you – we have added the summary numbers to the plots in appendix 5 (previously appendix 3).

4. Making the decision to add the measurements made by the participants with those made by the midwives, and including them in the analysis to increase the number of data points, is unclear; why was that decided, when the objective was to demonstrate that the measurements made by the participants are overall accurate.

The objective of the study has been clarified lines 163-172 (to provide postpartum-specific normal ranges for use in clinical practice). We believe pooling the data is appropriate given no relevant bias was demonstrated.

5. Interpretation of the meaning of the results found, as discussed for the BP range for the diagnosis of sepsis is speculative, as no cases of sepsis were identified. A similar consideration needs to be made for the observations made in relation to the ranges described in the rests for all the variables studied. The use of a specific threshold for Spo2 < 95 % to increase concern for poor oxygenation and possible increased risk for pulmonary embolism, is based on the diagnosis of PE. Proposing to change that threshold to spO_2 of 93% is speculative as that number has not been correlated with complications associated with lower oxygenation in this population.

We have adjusted these statements, see also answer to reviewer 1 point 9, reviewer 2 point 20 and statistical reviewer point 1.

6. Table 1: a rounding adjustment is needed as the percentages at the top add to 100.1%.

Thank you. This is simply a function of rounding to 1 decimal place and therefore it is accepted that the percentages may add up to marginally under or over 100. For example, in a recent study published in the NEJM (N Engl J Med 2020; 383:1447-1457, DOI: 10.1056/NEJMoa2017815), table 1 adds up to 99.9%. This would not be solved by rounding to nearest integer.

7. The appendices include a large and significant amount of information, which are useful to the reader.

Thank you.

Statistical Editor

1. lines 195-198: In this study, there was no duplication or verification of vital sign measurements, while for identification or treatment of hypertension, one would depend on replicated measurements and certainly that would be done before initiating any antihypertensive therapy. Therefore (lines 412-416), these normative data should not be used to establish the diagnosis of hypertension, but rather to investigate further should a BP measurement exceed the highest stratum of centiles.

Thank you – we have added this point into the discussion – lines 428-33.

2. General: Some Tables have entries whose column total is < 100. For the row entries with that column total, the %s should be rounded to nearest integer %, not cited to 0.1% precision level.

Thank you we have made this adjustment

3. Table 1, Fig 1: Should compare the demographic/clinical characteristics of the women who participated vs those who did not (could be supplemental material), to address issue of generalizability.

Thank you – we could not have ethical approval to collect data on those who declined participation (see reviewer1 comment 1), but have presented the data for those who participated in the antenatal, but not the post-natal phase of our 4P study in a new appendix (appendix 4), (see point 8 reviewer 2).

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:

A. OPT-IN: Yes, please publish my point-by-point response letter.

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

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

We have confirmed disclosures are correct

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

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

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

Ethnicity was defined by the participant at baseline visit (as stated in our protocol; Baseline Information CRF in protocol appendix). The option not to give ethnic group information was available to every participant. We used ethnicity classifications as defined by the National Institute for Health and Care Excellence (NICE) guidelines and quality standards, referenced in our published protocol. Race/ethnicity were collected to allow the generalisability of our population to be considered. We have included this explanation as a footnote to Table 1.

4. All submissions that are considered for potential publication are run through CrossCheck for originality. The following lines of text match too closely to previously published works.

Please cite Lines 153-157.

Thank you, we have cited our previous publication with the Green Journal of the antenatal centiles from the 4P cohort.

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 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 have used these definitions as appropriate.

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 print appendixes) but exclude references.

Thank you, we have reduced the length of the manuscript accordingly.

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

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

Thank you, we have complied with these requests.

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 limit for Original Research articles is 300 words. Please provide a word count.

Thank you, we have complied with these requests.

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.

Thank you, we have complied with these requests.

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.

Thank you, we have adjusted the manuscript accordingly.

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

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

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

Thank you, we have complied with these requests.

12. We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

We have avoided making such a claim in our manuscript.

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

Thank you, we believe our tables are compliant.

14. Figures 1-6: Please upload as separate figure files on Editorial Manager.

Thank you, we have complied with this request.

15. Each supplemental file in your manuscript should be named an "Appendix," numbered, and ordered in the way they are first cited in the text. Do not order and number supplemental tables, figures, and text separately. References cited in appendixes should be added to a separate References list in the appendixes file.

Thank you, we have complied with these requests.

16. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at http://links.lww.com/LWW-ES/A48. The cost for publishing an article as open access can be found at https://wkauthorservices.editage.com/open-access/hybrid.html.

It is our intention to publish via open access route.