

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

**Date:** Nov 20, 2019  
**To:** "Lauren J Green" [REDACTED]  
**From:** "The Green Journal" em@greenjournal.org  
**Subject:** Your Submission ONG-19-1986

RE: Manuscript Number ONG-19-1986

Pragmatic gestation specific vital sign reference ranges from the Pregnancy Physiology Pattern Prediction Study: a prospective longitudinal cohort study

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 Dec 04, 2019, we will assume you wish to withdraw the manuscript from further consideration.

#### REVIEWER COMMENTS:

Reviewer #1: Precise - gestation specific ranges alter threshold for abnormal BP, HR, RR, O2 sat'n, and temperature  
Abstract - Objective - estimate the underlying normal ranges of maternal vitals - not well defined in a contemporary population  
Methods - prospective longitudinal cohort - 3 centres in UK between 8/12 - 9/17; enrollment < 20 weeks, single pregnancy - vitals q 4-6 weeks  
Results - 1041 women - median SBP/DBP - 114/70 and decrease to 113/69, then increase at 40 weeks to 120/78  
HRT - 12 wk - 81.7, then increase to 90 bpm at 34 weeks; O2 sat'n - 97.5 to 96.5 at 40 weeks, RR - 14.5 - no change, temp - 36.7 to 36.5  
Conclusions - widely relevant gestational specific reference ranges that alter thresholds BP, HR, RR, O2 sat'n and findings refute midtrimester drop in BP after 12 weeks

Intro - maternal death is increasing, so early recognition of unwell patients is important, normal changes complicate recognition of deterioration  
there are no evidence based values of normals

Objective - primary objective - prospective monitoring of vital sign measurements

Methods - study design - multicenter, longitudinal, observational cohort - antenatal, intrapartum, and postnatal setting - 8/12-8/17

Participants - >16 yo, single, no comorbidities

variables - primary outcome - vital signs

Data sources - vitals q 4-6 weeks - BP, HR, O2 sat'n, T, RR

demographics info, medical history, health status, f/u 4-6 week interviews for collection

Personnel - midwives collected data

Bias - measurement not in record unless abnormal

Data quality - duplicate measurements

Study size - 1000 women needed per power analysis

Quantitative variables - smoothed centiles across gestation

Statistical analysis - described

Sensitivity analysis - restricted population to see if difference

Ethical considerations - patients could withdraw at any time

Dissemination and patient involvement

Results - participants - 8/12-12/16 - 1054 agreed and 1041 then participated  
 descriptive data - mean age 31, normal size, multiple visits  
 Outcome data -  
 Main results - SBP/DBP - SBP decreases by 1 mmHG between 12 and 19 weeks and increases by 7 mm Hg from 19 to 40 weeks  
 DBP - increases by 1.4 mmHg from 12 to 19 weeks and increases by 9 from 19-40 weeks  
 HR - 12 wk to 34 weeks - increases by 9.1 bpm to 90.8  
 RR - no change  
 O2 sat'n - 12 wk 97.5 and decrease to 96.5 at 40 weeks  
 temp - decrease from 36.7 to 36.52  
 Other analyses - duplicate readings - no need for a restrictive population as this was not helpful

Discussion - key results - longitudinal data >1000 women  
 BP nadir 19 weeks - decrease by 0.98/1.4 mm Hg, 40 wk - increase by 7/9 mmHg  
 HR - 12 wk - increase by 9 bpm and then decrease by 2 bpm - >10% had HR >100 bpm  
 no change in RR - 20-22 not uncommon  
 O2 sat'n - decrease by 1%, no change in temperature

Interpretation and clinical relevance -  
 normal ranges for vitals  
 midtrimester BP decrease is minimal so hypotension should raise concern for sepsis, upper threshold of HR and RR should be recognized to avoid search for pathology  
 O2 sat'n is normal if >94%

Comparison to other studies  
 SBP/DBP textbooks discuss midtrimester drop of 10-15 mmHg from single center studies and inconsistent methods  
 gestational threshold adjustments could increase detection of deteriorating moms  
 these findings are consistent with ALSPAC study which used records, not validated tools  
 HR - teaching is that HR increases by 10-15 bpm but HR increase is really 7.6 bpm and about 10% have HR >100 bpm  
 RR - no change - >24 o4 25 is abnormal  
 Sat'n - SpO2 <93% abnormal but >94% normal  
 temperature - clinically insignificant change  
 Strengths/limitations/generalizability - largest study with validated techniques for measurement at certain gestational age  
 subsequent analyses - no need for duplicate values  
 small group - but age/ race is representative of UK - not generalizable

Conclusions - gestation specific range SBP/DBP, HR, RR, O2 sat'n, temperature - can facilitate early recognition of unwell patients to decrease morbidity and minimize mortality

Comments -

1) line 606 - says 120 mmHg and should be bpm

2) while it is interesting to see that this is a change in paradigm regarding the classic teaching of a midtrimester drop, it is far too long and redundant  
 it has too many sections that say the same thing - it needs to be consolidated to say more succinctly that people expect a change so they ignore potentially abnormal vitals which could be warning signs, then condense the large amount of data that shows minimal to no change in all vitals, and then 1 conclusion rather than presenting a discussion, an interpretation and clinical relevance, and a conclusion

3) It is a stretch to say that this will lead to a decrease in morbidity and mortality - perhaps this jump should not be made but instead highlight the change in attention and recognition of maternal status

Reviewer #2: Overall, the study is well designed and well written. I do wonder if the presence of midwives in data collection could alter results? Their presence is not common in all clinical practices and could potentially alter results.

Reviewer #3: This manuscript summarizes one aspect of a prospective longitudinal cohort study with the aim of developing a database with gestational age specific vital sign ranges/norms. The work that went into this data collection (namely the sequential assessments of a large number of patients with strong quality assurance measures) is laudable.

Line 179: notes that only "treated" hypertensive patients were excluded. Was there consideration given to excluding

patients with chronic or pre-gestational hypertension who were not currently taking medication. [similar question for decision with regard to women who had a history of pregnancy-related hypertensive disorders (Pre-eclampsia, etc.)

It is this reader's opinion that detailed assessment information on temperature and respiratory rate measurement techniques is extraneous for this journal's readership.

Ultimately the very subtle changes over pregnancy in SBP, DBP, & oxygen saturation and the relatively subtle change in HR (+ the lack of change in temp & respiratory rate) coupled with the wide range of variability in several metrics derived from a cohort with limited ethnic/racial diversity do not represent novel findings that could be applied to clinical practice. I certainly agree with the driving motivation to strengthen the data behind MEWS/MOEWS development but do not think that this work in isolation meets that benchmark.

Perhaps, these data would be better-served presented in concert with other aspects of the prospective study referenced in the manuscript.

#### STATISTICAL EDITOR COMMENTS:

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

lines 94-95, Fig 1: Were the n = 2288 different in any maternal characteristics from the final groups of n = 1041 or those with N = 1004 or n = 987 in the final analyzed groups? That is, was the final group representative and thus could be generalized?

lines 222-224, 293-294: How many women completed all data points (q 4-6 weeks), how many completed 1, 2, 3, etc? Did the women who had complete data differ from those with missing data?

lines 193-194: Why was Bp measured in the dominant arm, rather than consistently in one arm? More detail is required to insure that the BPs were recorded in a basal state. Were the women asked re: smoking or drinking coffee/tea prior to the measurement? Did they sit for a number of minutes prior to the BP measurement? If so, how long? Was the arm at ~ the same level as the heart at the time of measurement? Did they have their feet positioned on the floor, rather than legs crossed at the time of measurement? Was BP measured at a consistent time of day to account for diurnal variation? Were they questioned re: last time they had emptied their bladder at the time of measurement? Was an appropriate cuff size used and placed appropriately? All these (and more variables) are important and could affect BP. There should have been a standard protocol if these are to be taken as normative data. The description on lines 193-194 is much too sparse.

See: (Table 8: Checklist for accurate measurement of Blood pressure) by Whelton PK et al: JACC VOL. 71, NO. 19, 2018 "2017 High Blood Pressure Clinical Practice Guideline: Executive Summary MAY 15)

Table 1: How many women were in overwgt or obese categories? The mean ages, maternal wgt and BMI seem skewed to women with a low risk profile for developing HTN.

General: Was there any analysis undertaken to evaluate whether maternal age, parity or BMI had affected the BP or other vital signs?

#### EDITOR COMMENTS:

Your paper is significantly longer than the word limits for the Journal for Original Research. Please edit to these limits. Much can be moved to Supplemental Digital content, particularly some details in the methods section. You focus a lot of your reporting and introduction on the blood pressure and perhaps other than a brief summary statement of results, the rest could go to SDC?

Rather than report 95% Confidence intervals, given that you are reporting the medians, please provide the ranges for the values. Also, as for these measures (other than temperature) are clinically reported in integers, please report them to the closest integer value (for instance systolic BP of 114 rather than 114.3).

Line 49: please explain how the Sensyne and Oxehealth affiliations relate to this paper.

Line 81: We no longer require that authors adhere to the Green Journal format with the first submission of their papers. However, any revisions must do so. I strongly encourage you to read the instructions for authors (the general bits as well as those specific to the feature-type you are submitting). The instructions provide guidance regarding formatting, word

and reference limits, authorship issues, and other things. Adherence to these requirements with your revision will avoid delays during the revision process, as well as avoid re-revisions on your part in order to comply with the formatting. For instance, note placement of all tables and figures

Line 82: The précis is a single sentence of no more than 25 words, written in the present tense and stating the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstracts conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Précis should be the "hook" for people who scan the Table of Contents to see what to read. It shouldn't include statements like "in this study" or "we found". Just state what you found.

In addition, in the abstract you have provided no evidence that you have "altered" thresholds at all as based on your methods section and results section, you are making no comparisons to any prior work. Please edit here and in abstract. (Line 107-8)

Lines 89-93: Please add a comment about standardization for measuring the vital signs, if any

Line 117: Here must be how Sensyne affiliation is a competing interest. I see from your website that you developed and marketed a system for monitoring and providing a warning score for hospitalized patients. In your declaration of competing interests, please make sure you explain that, in order to provide transparency.

Also in this introductory section its reasonable to make the statement that prior warning scores like MEWS have not proven to be particularly helpful in pregnancy, contrary to your statement on line 132 which is from non pregnant adults. .

Line 122: I'm uncertain that "normal ranges" are not well defined. A very abbreviated look into a single text (Williams, 25th edition) includes a graphic of Systolic and Diastolic BP's taken supine and in left lateral recumbent position adapted from data in 1980. Quite certain a more thorough review would show data for other VS's . It may be reasonable to indicate that normal values from a contemporary cohort have not been reported, but a blanket statement that they are poorly defined isn't well substantiated.

Line 147-150: in your trial registration, you indicate the following: To create a comprehensive database of physiological values during pregnancy, the intrapartum and postpartum periods for 1000 participants.

Secondary outcome measures

1. To develop a centile-based early warning score for pregnancy and the postpartum period.
2. To investigate new patterns within vital signs data in pregnancy

In the manuscript, you only list the primary outcomes. Please comment.

Line 207: which method for respiratory rate was reported? Do you report the results of an analysis of the two different methods in this paper?

Line 211: is this the Sensyne app?: Please so state.

Line 236: were there similar targets for communicating non-BP Vitals to the clinical team?

Line 322: Please include the standard Data Sharing Plan statement noted in the Instructions for authors.

Lines 510-542 is simply a restatement of your results. Please remove. Your "key results" should be in your results section.

Line 601: This is known as a primacy claim: yours is the first, biggest, best study of its kind. In order to make such a claim, please provide the data bases you have searched (PubMed, Google Scholar, EMBASE for example) and the search terms used. IF not done, please edit it out of the paper.

Line 606: Please remove reference to use of the current information to MOEWS in a way that suggests that this would improve its utility. You can say that the 3 and 97th thresholds different when the do from current thresholds in pregnancy, but you have no basis for suggesting how that would alter utility. . You have not studied whether this would change the relatively lack of utility of this, and other VS-based warning systems, in predicting maternal instability.

Line 660'ish: How does the BMI correlate w/ general UK population? Seems low.

Please use American-English spelling for words throughout. (examples: Labor v labour; hemolysis vs haemolysis)

#### 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. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. 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. Obstetrics & Gynecology follows the Good Publication Practice (GPP3)\* guideline for manuscripts that report results that are supported or sponsored by pharmaceutical, medical device, diagnostics and biotechnology companies. The GPP3 is designed to help individuals and organization maintain ethical and transparent publication practices.

(1) Adherence to the GPP3 guideline should be noted in the cover letter.

(2) For publication purposes, the portions of particular importance to industry-sponsored research are below. In your cover letter, please indicate whether the following statements are true or false, and provide an explanation if necessary:

(2a) All authors had access to relevant aggregated study data and other information (for example, the study protocol) required to understand and report research findings.

(2b) All authors take responsibility for the way in which research findings are presented and published, were fully involved at all stages of publication and presentation development and are willing to take public responsibility for all aspects of the work.

(2c) The author list accurately reflects all substantial intellectual contributions to the research, data analyses, and publication or presentation development. Relevant contributions from persons who did not qualify as authors are disclosed in the acknowledgments.

(2d) The role of the sponsor in the design, execution, analysis, reporting, and funding (if applicable) of the research has been fully disclosed in all publications and presentations of the findings. Any involvement by persons or organizations with an interest (financial or nonfinancial) in the findings has also been disclosed.

(2e) All authors have disclosed any relationships or potential competing interests relating to the research and its publication or presentation.

(3) The abstract should contain an additional heading, "Funding Source," and should provide an abbreviated listing of the funder(s).

(4) In the manuscript, a new heading—"Role of the Funding Source"—should be inserted before the Methods and contain a detailed description of the sponsor's role as well as the following language:

"The authors had access to relevant aggregated study data and other information (such as study protocol, analytic plan and report, validated data table, and clinical study report) required to understand and report research findings. The authors take responsibility for the presentation and publication of the research findings, have been fully involved at all stages of publication and presentation development, and are willing to take public responsibility for all aspects of the work. All individuals included as authors and contributors who made substantial intellectual contributions to the research, data analysis, and publication or presentation development are listed appropriately. The role of the sponsor in the design, execution, analysis, reporting, and funding is fully disclosed. The authors' personal interests, financial or non-financial, relating to this research and its publication have been disclosed." Authors should only include the above statement if all of it is true, and they should attest to this in the cover letter (see #2, above).

\*From Battisti WP, Wager E, Baltzer L, Bridges D, Cairns A, Carswell CI, et al. Good publication practice for communicating company-sponsored medical research: GPP3. *Ann Intern Med* 2015;163:461-4.

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

5. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at <https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality->

Improvement/reVITALize. 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. Provide a précis on the second page, for use in the Table of Contents. The précis is a single sentence of no more than 25 words that states the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Please avoid phrases like "This paper presents" or "This case presents."

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

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words; Reviews, 300 words. Please provide a word count.

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

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

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

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

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

13. Line 646: 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 on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

14. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: [http://edmgr.ovid.com/ong/accounts/table\\_checklist.pdf](http://edmgr.ovid.com/ong/accounts/table_checklist.pdf).

15. 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 <http://edmgr.ovid.com/acd/accounts/ifauth.htm>.

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.

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

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

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

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Dec 04, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD  
Editor-in-Chief

2018 IMPACT FACTOR: 4.965  
2018 IMPACT FACTOR RANKING: 7th out of 83 ob/gyn journals

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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.



3<sup>rd</sup> December 2019

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. The study was approved by the relevant research ethics committees, both as a sub-study of the INTERBIO-21<sup>st</sup> Fetal Study, Research Ethics Committee (REC):08/H0606/139), and when expanded to include two additional centres (Newcastle and London, REC:14/LO/1312). We have included a point-by-point response, below, which we are happy for you to publish.

**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 presented at the UK Intensive Care Society State of the Art meeting December 2018 and the UK Obstetric Anaesthetists Association meeting November 2018. No information was made available for publication. There are no postings on a preprint server.

Yours faithfully

A handwritten signature in black ink, appearing to read 'Peter J Watkinson', with a long horizontal flourish underneath.

Peter J Watkinson MD

Associate Professor of Intensive Care Medicine

### REVIEWER COMMENTS:

Reviewer #1:

1. line 606 - says 120 mmHg and should be bpm  
  
corrected – thank you
2. while it is interesting to see that this is a change in paradigm regarding the classic teaching of a midtrimester drop, it is far too long and redundant it has too many sections that say the same thing - it needs to be consolidated to say more succinctly that people expect a change so they ignore potentially abnormal vitals which could be warning signs, then condense the large amount of data that shows minimal to no change in all vitals, and then 1 conclusion rather than presenting a discussion, an interpretation and clinical relevance, and a conclusion

Thank you. We have substantially edited the paper to reduce repetition, reducing our main text to around 3538 words (see editor comment 1) and to re-enforce the lack of a mid-trimester drop in blood pressure in our conclusion.

3. It is a stretch to say that this will lead to a decrease in morbidity and mortality - perhaps this jump should not be made but instead highlight the change in attention and recognition of maternal status

We have removed this statement.

Reviewer #2:

4. Overall, the study is well designed and well written. I do wonder if the presence of midwives in data collection could alter results? Their presence is not common in all clinical practices and could potentially alter results.

We agree with the reviewer that the presence of a midwife may affect results – but in most cases maternal early warning scores will be used based on the readings undertaken by clinical staff. Initial findings from the planned post-partum work, suggest vital signs recorded by midwives have a high degree of concordance with those taken by the mother.

Reviewer #3:

This manuscript summarizes one aspect of a prospective longitudinal cohort study with the aim of developing a database with gestational age specific vital sign ranges/norms. The work that went into this data collection (namely the sequential assessments of a large number of patients with strong quality assurance measures) is laudable.

5. Line 179: notes that only "treated" hypertensive patients were excluded. Was there consideration given to excluding patients with chronic or pre-gestational hypertension who were not currently taking medication. [similar question for decision with regard to women who had a history of pregnancy-related hypertensive disorders (Pre-eclampsia, etc.)

We agree the question of who to include and exclude is interesting. We included these patients in our pragmatic population for our findings to have general relevance. In our "restrictive" population, we excluded patients with any medical co-morbidities (including hypertension not on medication) and those who developed severe pre-eclampsia (lines 251-258 and appendix 8). We have clarified the findings from the restrictive group in light of this question (lines 350-354). We note that even for this highly restrictive population (excluding nearly half the cohort), differences were not clinically meaningful.

6. It is this reader's opinion that detailed assessment information on temperature and respiratory rate measurement techniques is extraneous for this journal's readership.

We have reduced the description as requested and directed the reader to the standard operating procedures published with the protocol (<https://bmjopen.bmj.com/content/7/9/e016034>).

7. Ultimately the very subtle changes over pregnancy in SBP, DBP, & oxygen saturation and the relatively subtle change in HR (+ the lack of change in temp & respiratory rate) coupled with the wide range of variability in several metrics derived from a cohort with limited ethnic/racial diversity do not represent novel findings that could be applied to clinical practice. I certainly agree with the driving motivation to strengthen the data behind MEWS/MOEWS development but do not think that this work in isolation meets that benchmark. Perhaps, these data would be better-served presented in concert with other aspects of the prospective study referenced in the manuscript.

We undertook the 4P study in light of an extensive systematic literature review – now published (<https://bmcmmedicine.biomedcentral.com/articles/10.1186/s12916-019-1399-1>). The paucity of data found, the poor quality of the available studies and the wide confidence intervals that resulted meant it was not possible to provide reliable centiles for clinical practice. To derive reliable centiles, demonstrating a lack of change is just as important as showing where change occurs. This is why a study on the scale of ours, with the strong quality assurance that the reviewer kindly notes, is required. As maternal mortality is rising in the US we believe publication of these centiles could not be more timely.

Statistical Editor:

8. lines 94-95, Fig 1: Were the n = 2288 different in any maternal characteristics from the final groups of n = 1041 or those with N = 1004 or n = 987 in the final analyzed groups? That is, was the final group representative and thus could be generalized?

Although, as the editors will be aware, we cannot record detailed maternal characteristics on women who did not wish to take part (n=2288), we note that in study terms our near 50% recruitment rate represents high participation. Our study population appears representative of pregnant women in the UK (lines 446-447 to which the editor's suggestion to include comparison of BMI has added – table 1; appendices 3, 8 and 9). All 1041 women who contributed data are included in the analysis to maximise generalisability – as the statistical reviewer suggests. We have clarified the text (lines 271-276 and 295) and altered Figure 1 to remove reference to 1004 and 987 women, as we believe this has caused confusion.

9. lines 222-224, 293-294: How many women completed all data points (q 4-6 weeks), how many completed 1, 2, 3, etc? Did the women who had complete data differ from those with missing data?

Thank you – we have clarified this (lines 284-287; appendix 3). 94% of women missed no more than one expected appointment, with 89% achieving all appointments. The effect of missing data will therefore be very small – but we have included maternal characteristics of those who did not achieve all visits in appendix 3 (new).

10. 193-194: Why was Bp measured in the dominant arm, rather than consistently in one arm? More detail is required to insure that the BPs were recorded in a basal state. Were the women asked re: smoking or drinking coffee/tea prior to the measurement? Did they sit for a number of minutes prior to the BP measurement? If so, how long? Was the arm at ~ the same level as the heart at the time of measurement? Did they have their feet positioned on the floor, rather than legs crossed at the time of measurement? Was BP measured at a consistent time of day to account for diurnal variation? Were they questioned re: last time they had emptied their bladder at the time of measurement? Was an appropriate cuff size used and placed appropriately? All these (and more variables) are important and could affect BP. There should have been a standard protocol if these are to be taken as normative data. The description on lines 193-194 is much too sparse. See: (Table 8: Checklist for accurate measurement of Blood pressure) by Whelton PK et al: JACC VOL. 71, NO. 19, 2018 "2017 High Blood Pressure Clinical Practice Guideline: Executive Summary MAY 15)

We recognise the importance of this point. The protocol was developed with extensive consideration of these issues. As a result, study standard operating procedures for each vital sign were designed in light of guidance. These were designed to achieve consistency across the study and reflect clinical practice. As these can be found in the externally refereed published protocol, we have directed the reader to this (in light of reviewer 3 point 6 and the Editor's request to reduce the size of the manuscript, <https://bmjopen.bmj.com/content/7/9/e016034>).

11. Table 1: How many women were in overweight or obese categories? The mean ages, maternal wgt and BMI seem skewed to women with a low risk profile for developing HTN.

We have added the numbers of overweight and obese women to table 1, the new appendix 3 and appendices 8 and 9.

12. General: Was there any analysis undertaken to evaluate whether maternal age, parity or BMI had affected the BP or other vital signs?

Thank you we have improved the clarity of our subgroup analyses in the text. Line 355 and appendix 9 describe the analysis of nulliparous women. Our restrictive cohort analysis excluded women 40 years and above and with BMIs <18.5 and >30 (lines 350-354 and appendix 8)

Editor:

13. Your paper is significantly longer than the word limits for the Journal for Original Research. Please edit to these limits. Much can be moved to Supplemental Digital content, particularly some details in the methods section. You focus a lot of your reporting and introduction on the blood pressure and perhaps other than a brief summary statement of results, the rest could go to SDC?

We have edited to around 3538 words moving information into supplemental digital content as suggested.

14. Rather than report 95% Confidence intervals, given that you are reporting the medians, please provide the ranges for the values. Also, as for these measures (other than temperature) are clinically reported in integers, please report them to the closest integer value (for instance systolic BP of 114 rather than 114.3).

We agree that the presentation of confidence intervals was misleading. In discussion with our statistical author, we have changed these to 3<sup>rd</sup> -97<sup>th</sup> centiles to be concordant with the vital sign diagrams. We have retained the confidence interval of the difference across gestational ages to one decimal for clarity. Similarly in the appendices we have retained the confidence intervals of the presented centiles in order to allow comparison between groups.

15. Line 49: please explain how the Sensyne and Oxehealth affiliations relate to this paper.

The companies have no involvement or relationship with the paper -we have clarified this.

16. Line 81: We no longer require that authors adhere to the Green Journal format with the first submission of their papers. However, any revisions must do so. I strongly encourage you to read the instructions for authors (the general bits as well as those specific to the feature-type you are submitting). The instructions provide guidance regarding formatting, word and reference limits, authorship issues, and other things. Adherence to these requirements with your revision will avoid delays during the revision process, as well as avoid re-revisions on your part in order to comply with the formatting. For instance, note placement of all tables and figures

We have now followed the green journal format.

17. Line 82: The précis is a single sentence of no more than 25 words, written in the present tense and stating the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstracts conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Precis should be the "hook" for people who scan the Table of Contents to see what to read. It shouldn't not include statements like "in this study" or "we found". Just state what you found.

Thank you for this guidance – we have corrected the précis to reflect the abstract conclusion

18. In addition, in the abstract you have provided no evidence that you have “altered” thresholds at all as based on your methods section and results section, you are making no comparisons to any prior work. Please edit here and in abstract. (Line 107-8)

Thank you. Edited.

19. Lines 89-93: Please add a comment about standardization for measuring the vital signs, if any

Added – lines 78-79.

20. Line 117: Here must be how Sensyne affiliation is a competing interest. I see from your website that you developed and marketed a system for monitoring and providing a warning score for hospitalized patients. In your declaration of competing interests, please make sure you explain that, in order to provide transparency.

Added in line with your comments lines 36-41.

21. Also in this introductory section its reasonable to make the statement that prior warning scores like MEWS have not proven to be particularly helpful in pregnancy, contrary to your statement on line 132 which is from non pregnant adults.

We agree that the evidence for current MOEWS is poor. We have used your wording to clarify that our statement applies to non-pregnant adults. We believe there is no reason that the utility of well designed early warning scores will be any less in pregnant women – but that they cannot be reliable without establishment of contemporary reference ranges with robust estimates of where the outer centiles lie.

22. Line 122: I'm uncertain that "normal ranges" are not well defined. A very abbreviated look into a single text (Williams, 25th edition) includes a graphic of Systolic and Diastolic BP's taken supine and in left lateral recumbent position adapted from data in 1980. Quite certain a more thorough review would show data for other VS's . It may be reasonable to indicate that normal values from a contemporary cohort have not been reported, but a blanket statement that they are poorly defined isn't well substantiated.

We have removed this statement as we believe our point is better made further down (lines 126-127) particularly by restricting our statement to contemporary measures as you suggest. We appreciate that textbooks have perpetuated the perception that normal ranges are defined. Our extensive systematic review (<https://bmcmmedicine.biomedcentral.com/articles/10.1186/s12916-019-1399-1>) showed that they were flawed see point 7). Large numbers of contemporary vital signs are required (see statistical appendix) to estimate outer centiles from which thresholds may be derived for an evidence-based MOEWS. The use of contemporary measures is particularly important as our systematic review showed average blood pressure in pregnancy was changing over time. We note that the study used in Williams (Wilson 1980) is included in our discussion but was excluded from our systematic review (though we referenced it as is used by texts such as Williams) as there is insufficient description of the health status of the 69 women included.

23. Line 147-150: in your trial registration, you indicate the following: To create a comprehensive database of physiological values during pregnancy, the intrapartum and postpartum periods for 1000 participants. Secondary outcome measures 1. To develop a centile-based early warning score for pregnancy and the postpartum period. 2. To investigate new patterns within vital signs data in pregnancy. In the manuscript, you only list the primary outcomes. Please comment.

We have added a statement on the secondary objectives (to be undertaken in future work) lines 135-137.

24. Line 207: which method for respiratory rate was reported? Do you report the results of an analysis of the two different methods in this paper?

Both methods are reported - we have moved the counting method to appendix 4.

25. Line 211: is this the Sensyne app?: Please so state.

No – we have clarified this in the text. The study commenced before Sensyne Health existed, and before the pre-Sensyne research-developed System for Electronic Notification and Documentation (SEND) application was put into clinical practice in non-pregnant adults (2015).

26. Line 236: were there similar targets for communicating non-BP Vitals to the clinical team?

No. We considered carefully whether similar targets were necessary for other vital signs with experts in the field. It was decided these were not necessary, an approach with which both the Ethics committee and external reviewers of our protocol were happy.

27. Line 322: Please include the standard Data Sharing Plan statement noted in the Instructions for authors.

Included

28. Lines 510-542 is simply a restatement of your results. Please remove. Your “key results” should be in your results section.

Thank you, we agree removing this section has improved clarity. We were perhaps slightly too literally following STROBE guidance.

29. Line 601: This is known as a primacy claim: yours is the first, biggest, best study of its kind. In order to make such a claim, please provide the data bases you have searched (PubMed, Google Scholar, EMBASE for example) and the search terms used. IF not done, please edit it out of the paper.

We have also tightened this statement in light of this and comment 33, including the databases searched.

30. Line 606: Please remove reference to use of the current information to MOEWS in a way that suggests that this would improve its utility. You can say that the 3 and 97th thresholds different when the do from current thresholds in pregnancy, but you have no basis for suggesting how that would alter utility. You have not studied whether this would change the relatively lack of utility of this, and other VS-based warning systems, in predicting maternal instability.

We have removed this statement.

31. Line 660'ish: How does the BMI correlate w/ general UK population? Seems low.

Thank you for this suggestion. We have now cited work (in the green journal) from our National Perinatal Epidemiology Unit where our BMIs are near-identical to a national survey. We believe this improves the argument that our results are generalisable.

32. Please use American-English spelling for words throughout. (examples: Labor v labour; hemolysis vs haemolysis)

Done

Editorial office:

33. Line 646: 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 on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

See comment 29