

OBSTETRICS & GYNECOLOGY



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- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*
- Email correspondence between the editorial office and the authors*

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

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: Jul 13, 2018
To: "Olaide Azizat Ashimi Balogun" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-18-1138

RE: Manuscript Number ONG-18-1138

Serial Third Trimester Ultrasound versus Routine Care in Uncomplicated Pregnancies: A Randomized Controlled Trial (UP Trial)

Dear Dr. Ashimi Balogun:

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

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

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Aug 03, 2018, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

This is a well done RCT aimed at answering an important clinical question: Is routine US helpful a detecting growth and fluid abnormalities in low risk pregnancies? It is a well done, well written paper that will be of interest to the readership of this journal. It can be improved upon in a few key ways.

Abstract

Page 4 - Add the sentence "All women were included in intention to treat analysis" to the methods rather than the result.

Introduction

Page 6, line 83 - I think this should read " >90th percentile for gestational age) AND oligohydramnios or polyhydramnios are unidentified... This removes the comma from the sentence

Materials and Methods

I would recommend putting all the exclusion criteria into a table and the table in an appendix. It is sufficient to say - Women were excluded for any medical complication and for poor obstetric history.

Page 9 - line 157-158 - I think you should say something like the rate is 10% in the literature.

Page 10 line 163-- Consider adding the fact that intention to treat analysis was used to the methods.

Results -

Page 10 Line 177 - could you add to the results and to the table the mean number of US in each group, and if they were different (as I expect they would be).

Page 11 Line 187, 188 -- Since polyhydramnios was the main driver of the composite outcome, could you test for effect modification and see if the intervention was differentially effective in detecting poly.

Discussion

- In the introduction, you state that abnormal growth occurs in 16% of uncomplicated pregnancies. Can you comment on why your rates were so much lower and how this may have impacted the results?

I think that the discussion would benefit from increased discussion of the clinical implications of this trial

How many extra scans did the intervention group have; might similar results be achieved with one third trimester scan?

Do you think that this is sufficient evidence to recommend routine scanning in low risk patients? I think it probably is not, given the lack of maternal or neonatal benefit and in consideration of the cost.

Can you comment on the clinical relevance of identifying polyhydramnios? This seems less urgent to me than FGR or oligo -- do you think the study was underpowered to detect increased detection of those rarer items? If in fact, routine US only increases the detection of poly without other benefits is it worth it?

I think that these components of the discussion can be succinct and set the stage for more evidence to be obtained, addressing them is important.

Reviewer #2:

Balogun et al provide us with a randomized controlled trial on serial third trimester ultrasound examinations in uncomplicated pregnancies. Their recruitment took place between July 2016 and May 2017 with a sample size of 206 patients with 102 randomized to routine care and 104 to serial ultrasounds. They found serial ultrasound was significantly more likely to identify a composite measure of abnormalities in amniotic fluid and fetal growth. I recommend consideration of the following minor revisions.

1. Line #40,209,249 vs 125 - You mention in three places women without complications at 28-30 weeks were randomized but in your methods section you state that the randomization occurred between 24.0 and 30.6 weeks (line 125), please reconcile this discrepancy.
2. Line #103 - would consider clarifying exclusion criteria listed is exclusion criteria if patients had any of the following prior to randomization, given a sizeable portion of your patients went on to develop the antenatal complications such as hypertension/preeclampsia which you included in your exclusion criteria
3. Line #182 - I was left wondering if the results varied among those with antepartum complications and those who were truly uncomplicated pregnancies as the study set out to determine. I would be interested in seeing the results of Table 3 with the complicated pregnancies excluded from the analysis. I understand this would decrease the sample size and may not be adequately powered to detect a difference but would help make the argument for routine screening in truly uncomplicated pregnancies.
4. Line #175 - I understand this was an intent to treat analysis and that ultrasounds were going to be done around 30,34, and 38 weeks (line 124) but it would have been interesting to see more information regarding the actual number of ultrasounds done per patient in each group and the mean/median gestational ages they occurred
5. Line 209-210 - After reviewing your paper around this point I realized what you have come up with is more of a composite measure of detecting four different abnormalities which you also later refer to it as when discussing how your study differs from other prior trials (line #226). I think this aspect should be made more clear to the reader earlier.
6. Line#214 - you say "the rate of induction for cesarean delivery" - please clarify
7. Line#237 - Are you referring to neonatal outcomes or any maternal/neonatal outcomes?
8. Line#242 - I would think more about the strengths of this study - for instance I think the diverse patient population is a strength
9. Line#246 - What evidence do you have to support your trial provides accurate estimates of the rate of FGR, LGA? In Table 3 there were 8 sonographic LGA for the serial 3rd trimester US yet in Table 6 there were only 3 LGA babies on actual birthweight. This is another limitation of ultrasound evaluations.
10. Table 1 - The Maternal age <20 is somewhat deceiving to readers given it really is only 18-20 year olds based on your inclusion criteria
11. Line 187 and Table 3 - I would consider discussing the difference in statistically significant differences versus possible clinically significant differences. The difference in growth abnormalities detected is not statistically significant but trend towards being more detected in the serial 3rd trimester ultrasound and your study was not powered to detect a difference in these small subgroups but a larger trial may.
12. Figure 1 - for the excluded portion you state "22 had first USE after 20 weeks" but your inclusion criteria was ultrasound exam before 22weeks and 0 days - please clarify discrepancy

Reviewer #3:

This is a randomized trial in uncomplicated pregnancies looking at routine prenatal care with fundal height assessment compared to serial ultrasound assessments (USE). The primary outcome was the finding of FGR, LGA or amniotic fluid abnormalities. The secondary outcomes were composite maternal and neonatal morbidities. 206 women met inclusion criteria and were randomized, analysis was on an intent to treat basis. The study found that the two groups had comparable baseline statistics, but that the USE group had a significantly higher incidence of the primary outcome. Secondary outcomes were similar between the two groups. The authors conclude that among uncomplicated women, serial third trimester ultrasound exam was more likely to identify fetal growth or amniotic fluid abnormalities. Ways in which this manuscript could be improved include:

Lines 117-120: Were morbidly obese women excluded? It seems odd than none of the women had a BMI >40. Please clarify.

Line 122-123: Was FHM standardized in this study or left to provider discretion? Please clarify as this might insert some ascertainment bias.

Line 140-142: Why was AF assessment not standardized? It seems odd to not use one standardized process for a randomized trial.

Line 185-188: But there was a trend towards all three of these. Had your study been larger they likely would have reached significance, I think it would be OK to point that out here.

Lines 234-237: Any plans to conduct a larger, multi-centered trial? It seems a waste to not expand this work.

Lines 239-241: But your inclusion and exclusion criteria diminish these differences. Broadening your study would increase its generalizability.

Reviewer #4:

The authors performed a randomized controlled trial to determine if routine serial US identified more abnormalities in fluid and fetal growth. Not surprisingly, the authors found that USE identified fluid and growth more frequently than routine care in uncomplicated pregnancies. They report that 5 women need to be screened to identify one abnormality.

The methods are sound and the manuscript is well written.

The authors found no differences in maternal or neonatal complications, nor did they find differences in management of pregnancies limiting ability to generalize such a practice change into a population.

There are no considerations of cost -- Do the authors know how much on average it would cost to identify a fluid or growth abnormality?

Could they estimate the fewest number of scans required without losing the possibility of identifying a fluid or growth abnormality -- for instance one US at 32-34 weeks?

Perhaps the authors could further emphasize that prior to a practice change - evidence illustrating cost effectiveness and the impact on improved maternal and or fetal outcomes without resulting in increased unneeded interventions is warranted

STATISTICAL EDITOR COMMENTS:

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

lines 157-162: The study design was for a composite primary outcome (any of the 4 metrics being abnormal). The design/sample size does not allow discernment of differences in rates of each of the 4 metrics. That needs to be made clearer in the Abstract, results and discussion.

Table 3: This needs to be re-formatted. The primary outcome is the composite, the others are secondary outcomes. The secondary ones were not individually powered by the composite sample size. The three that were NS cannot be generalized, their individual powers ranged from .06 -.38. The single finding that was statistically significant (polyhydramnios), only had power = 0.62. Therefore one can conclude that the composite primary was significantly different in rates, but one cannot generalize any of the other 4 individual secondary outcomes.

The findings in Tables 4, 5 and 6 are all under powered, except for the relationship of GA at delivery vs treatment arm, which was significant in Table 4 (subset of only women with primary outcome), but not in Table 5.

lines 213-215 (low power) should be modified to reflect low power

lines 245-247: If the Authors want to show that the estimates from this study are accurate (I presume they mean comparable) to all uncomplicated 28-30 wk pregnancies, then their estimates should have CIs, which will be wide and will demonstrate that for that purpose, a much larger study would have to be done.

EDITOR COMMENTS:

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

The notated PDF is uploaded to this submission's record in Editorial Manager. If you cannot locate the file, contact Katie McDermott and she will send it by email – kmcdermott@greenjournal.org.

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

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

3. Based on the forms that have been submitted, Dr. Barrett has not met the criteria for authorship. Dr. Barrett should be moved to the acknowledgments, or he/she could resubmit a revised author agreement form if he/she filled it out erroneously

the first time. All updated and missing forms should be uploaded with the revision in Editorial Manager.

4. Our journal requires that all evidence-based research submissions be accompanied by a transparency declaration statement from the manuscript's lead author. The statement is as follows: "The lead author* 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, if relevant, registered) have been explained." *The manuscript's guarantor.

If you are the lead author, please include this statement in your cover letter. If the lead author is a different person, please ask him/her to submit the signed transparency declaration to you. This document may be uploaded with your submission in Editorial Manager.

5. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at <http://links.lww.com/AOG/A515>, and the gynecology data definitions are available at <http://links.lww.com/AOG/A935>.

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

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

7. Specific rules govern the use of acknowledgments in the journal. Please edit your acknowledgments or provide more information in accordance with the following guidelines:

- * All financial support of the study must be acknowledged.

- * Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.

- * All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your signature on the journal's author agreement form verifies that permission has been obtained from all named persons.

- * If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

8. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.

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; Case Reports, 125 words; Current Commentary articles, 250 words; Clinical Practice and Quality, 300 words; Procedures and Instruments, 200 words. Please provide a word count.

10. Abstracts for all randomized, controlled trials should be structured according to the journal's standard format. The Methods section should include the primary outcome and sample size justification. The Results section should begin with the dates of enrollment to the study, a description of demographics, and the primary outcome analysis. Please review the sample abstract that is located online here: http://edmgr.ovid.com/ong/accounts/sampleabstract_RCT.pdf. Please edit your abstract as needed.

11. 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.

12. 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.

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. The American College of Obstetricians and Gynecologists' (College) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite College documents in your manuscript, be sure the reference you are citing is still current and available. If the reference you are citing has been updated (ie, replaced by a newer version), please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly. If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if a College document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All College documents (eg, Committee Opinions and Practice Bulletins) may be found via the Resources and Publications page at <http://www.acog.org/Resources-And-Publications>.

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

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

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Aug 03, 2018, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2017 IMPACT FACTOR: 4.982

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

If you would like your personal information to be removed from the database, please contact the publication office.

August 10, 2018

The Editors of Obstetrics & Gynecology
Obstetrics & Gynecology
409 12th Street, SW
Washington, DC 20024-2188

RE: Manuscript Number ONG-18-1138

**Serial Third Trimester Ultrasound versus Routine Care in Uncomplicated Pregnancies: A
Randomized Controlled Trial (UP Trial)**

Dear Editors:

Thank you kindly for considering the above-mentioned manuscript for publication in *Obstetrics & Gynecology*.

Per reviewers' comments, we have revised the manuscript. In the following pages, you will find our point-by-point response to the suggestions by reviewers. We are attaching:

1. Revised manuscript, tables and Fig with track changes.
2. Clean copies of the manuscript, tables, and Fig

Please note that in the comments below, the reference to "line_____" refers to manuscript with track changes and not the clean copy.

"The lead author (OAB) 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, if relevant, registered) have been explained." Dr Ashimi Balogun is manuscript's guarantor.

We truly appreciate the opportunity to publish our work in your journal and please do not hesitate contact me with any questions or concerns.

Sincerely,

Olaide Ashimi Balogun, M.D.
Assistant Professor
Department of Obstetrics, Gynecology, and Reproductive Sciences
University of Texas Health Science Center at Houston

[REDACTED]
[REDACTED]

REVIEWER COMMENTS:

Reviewer #1:

This is a well done RCT aimed at answering an important clinical question: Is routine US helpful a detecting growth and fluid abnormalities in low risk pregnancies? It is a well done, well written paper that will be of interest to the readership of this journal. It can be improved upon in a few key ways.

Response: *We truly appreciate the kind summary by the reviewer and the comments below to improve our work in key ways.*

Abstract

Page 4 - Add the sentence "All women were included in intention to treat analysis" to the methods rather than the result.

Response: *We appreciate the suggestion by the reviewer and we have revised the abstract accordingly.*

Introduction

Page 6, line 83 - I think this should read " >90th percentile for gestational age) AND oligohydramnios or polyhydramnios are unidentified... This removes the comma from the sentence

Response: *We appreciate the suggestion by the reviewer and we have revised the introduction accordingly.*

Materials and Methods

I would recommend putting all the exclusion criteria into a table and the table in an appendix. It is sufficient to say - Women were excluded for any medical complication and for poor obstetric history.

Response: *We appreciate the suggestion by the reviewer and in the revision we provide the exclusion criteria in Appendix 1. We have also added the sentence: "Women were excluded for any medical complication and for poor obstetric history." (lines 101-102)*

Page 9 - line 157-158 - I think you should say something like the rate is 10% in the literature.

Response: *While we truly appreciate the suggestion by the reviewer that we should state “the rate is 10% in the literature,” we like the statement as is because with citation of one publication, it is hardly the “literature.”*

Page 10 line 163-- Consider adding the fact that intention to treat analysis was used to the methods.

Response: *We appreciate the suggestion by the reviewer and in the revised manuscript we use the sentence “All randomized women were included in the intent to treat analysis” in the method section (line 157-158). Additionally, we have deleted the sentence from the Results section.*

Results -

Page 10 Line 177 - could you add to the results and to the table the mean number of US in each group, and if they were different (as I expect they would be).

Response: *We appreciate the suggestion and we have provided the total number of ultrasound examinations after the randomization in Appendix 2.*

Page 11 Line 187, 188 -- Since polyhydramnios was the main driver of the composite outcome, could you test for effect modification and see if the intervention was differentially effective in detecting poly.

Response: *We tested for the intervention effect in polyhydramnios which indicated increased detection with serial ultrasounds. The estimated relative risk was 5.4 (95% CI, 1.2-23) (Line 179). We have noted the wide interval in this outcome (Lines 186-187).*

Discussion

- In the introduction, you state that abnormal growth occurs in 16% of uncomplicated pregnancies. Can you comment on why your rates were so much lower and how this may have impacted the results?

Response: *We appreciate the reviewer’s inquiry about why the rate of abnormal growth—SGA plus LGA—was quoted to be 16% in the introduction (10,236/64,436; reference #10) but was lower in the current trial. In our RCT, the overall rate of abnormal growth was 13% (26/205; 95%*

confidence intervals [CI] of 8-18%). Since the 95% CI of our rate crosses 16%, we think the rates are similar.

I think that the discussion would benefit from increased discussion of the clinical implications of this trial

Response: *We appreciate the reviewer's suggestion that we discuss the clinical implications of this trial. We have added a paragraph about this study being a nidus for a larger trial (Lines 264-273).*

How many extra scans did the intervention group have; might similar results be achieved with one third trimester scan?

Response: *We appreciate the reviewer's comment on how many extra scans the intervention arm had. We have provided the results in Appendix 2 and mentioned in lines 174-176.*

Regarding, whether fewer ultrasound exam would have achieved similar results, we would prefer to avoid such post-hoc analysis because we are not powered to answer that and because about one-third of the abnormality were detected before 32 weeks and 1/3 after 37 weeks.

Do you think that this is sufficient evidence to recommend routine scanning in low risk patients? I think it probably is not, given the lack of maternal or neonatal benefit and in consideration of the cost.

Response: *We appreciate the reviewer's comments that the current trial is insufficient to recommend routine USE in the uncomplicated pregnancies. We concur and we have added a paragraph about the need for a larger randomized trial (Lines 264-273)."*

Can you comment on the clinical relevance of identifying polyhydramnios? This seems less urgent to me than FGR or oligo -- do you think the study was underpowered to detect increased detection of those rarer items? If in fact, routine US only increases the detection of poly without other benefits is it worth it?

Response: *We appreciate the reviewer's request to comment about polyhydramnios and if it is associated with adverse outcomes. In lines 223-235 of the manuscript we previously wrote: "Furthermore, pregnancies complicated with oligohydramnios or polyhydramnios are associated with stillbirth, low Apgar score, and neonatal mortality (14-17)." References 15 (co-authored by Dr. Nancy C. Chescheir, the Editor of your journal) and 16 report that indeed polyhydramnios is associated with adverse outcomes, like stillbirth, low Apgar score and neonatal mortality. Thus, we do believe that detection of polyhydramnios is clinically relevant.*

I think that these components of the discussion can be succinct and set the stage for more evidence to be obtained, addressing them is important.

Response: *We appreciate the reviewer's comment that more evidence needs to be obtained. We have clarified this in the very last sentence of the manuscript (Lines 276-278): "Before the clinical practice of serial sonographic examinations is implemented in uncomplicated pregnancies, a larger RCT is warranted (32)."*

Reviewer #2:

Balogun et al provide us with a randomized controlled trial on serial third trimester ultrasound examinations in uncomplicated pregnancies. Their recruitment took place between July 2016 and May 2017 with a sample size of 206 patients with 102 randomized to routine care and 104 to serial ultrasounds. They found serial ultrasound was significantly more likely to identify a composite measure of abnormalities in amniotic fluid and fetal growth. I recommend consideration of the following minor revisions.

1. Line #40,209,249 vs 125 - You mention in three places women without complications at 28-30 weeks were randomized but in your methods section you state that the randomization occurred between 24.0 and 30.6 weeks (line 125), please reconcile this discrepancy.

Response: *We appreciate the reviewer's comment that there was a discrepancy with the dates. We have clarified the dates to be between 24.0-30.6 in lines 36,40,62, 110, 211, 263, 274.*

2. Line #103 - would consider clarifying exclusion criteria listed is exclusion criteria if patients had any of the following prior to randomization, given a sizeable portion of your patients went on to develop the antenatal complications such as hypertension/preeclampsia which you included in your exclusion criteria

Response: *We appreciate the reviewer's suggestion. We have clarified by adding two sentences (Lines 101-103): "Women were excluded for any medical complication or co-morbidity at the time of randomization (Appendix). If a complication developed after randomization, women remained in the group they were randomized to."*

3. Line #182 - I was left wondering if the results varied among those with antepartum complications and those who were truly uncomplicated pregnancies as the study set out to determine. I would be interested in seeing the results of Table 3 with the complicated

pregnancies excluded from the analysis. I understand this would decrease the sample size and may not be adequately powered to detect a difference but would help make the argument for routine screening in truly uncomplicated pregnancies.

Response: *We appreciate the excellent suggestion of determining what was the detection of the primary composite among women who did not develop any complications after randomization. We have described the results of uncomplicated pregnancies in lines 183-188 and in Appendix 3.*

4. Line #175 - I understand this was an intent to treat analysis and that ultrasounds were going to be done around 30,34, and 38 weeks (Line 124) but it would have been interesting to see more information regarding the actual number of ultrasounds done per patient in each group and the mean/median gestational ages they occurred.

Response: *We appreciate the suggestion by the reviewer and we describe this information in lines 174-176 and in Appendix 2.*

5. Line 209-210 - After reviewing your paper around this point I realized what you have come up with is more of a composite measure of detecting four different abnormalities which you also later refer to it as when discussing how your study differs from other prior trials (line #226). I think this aspect should be made more clear to the reader earlier.

Response: *We appreciate the suggestion and in the revised manuscript we use the phrase primary composite outcome seven times (Lines 42,46,53,156,176,184,230).*

6. Line#214 - you say "the rate of induction for cesarean delivery" - please clarify

Response: *We appreciate the reviewer's request to clarify the sentence with the phrase "the rate of induction for cesarean delivery." There was typo error. We have revised the (lines 217)."*

7. Line#237 - Are you referring to neonatal outcomes or any maternal/neonatal outcomes?

Response: *We have deleted the sentence.*

8. Line#242 - I would think more about the strengths of this study - for instance I think the diverse patient population is a strength

Response: *We appreciate the reviewer's suggestion a diverse group of women we recruited is a strength of our trial. We have added a sentence: "The cohort of women we recruited was diverse (line 259)."*

9. Line#246 - What evidence do you have to support your trial provides accurate estimates of

the rate of FGR, LGA? In Table 3 there were 8 sonographic LGA for the serial 3rd trimester US yet in Table 6 there were only 3 LGA babies on actual birthweight. This is another limitation of ultrasound evaluations.

Response: *We appreciate the reviewer's suggestion that our trial does not provide evidence that accurate detection of of the FGR and of LGA is possible. That was not the intent of the trial. Nonetheless, we do acknowledge the reviewer's point. In lines 244-248, we have added the following sentences: "Due to the small number of newborns with actual birth weight less than 10th percentile or greater than 90th percentile, we are unable to ascertain the detection of aberrant growth with sonographic examination. Previous reports, however, have described the accuracy of identifying FGR and LGA with sonographic examinations (1,2,6,9,22,29,30)."*

10. Table 1 - The Maternal age <20 is somewhat deceiving to readers given it really is only 18-20 year olds based on your inclusion criteria

Response: *We appreciate the reviewer's suggestion that in Table 1 maternal age for one group is 18-19 and not < 20 years. We have revised the Table accordingly.*

11. Line 187 and Table 3 - I would consider discussing the difference in statistically significant differences versus possible clinically significant differences. The difference in growth abnormalities detected is not statistically significant but trend towards being more detected in the serial 3rd trimester ultrasound and your study was not powered to detect a difference in these small subgroups but a larger trial may.

Response: *The reviewer has an excellent point: though the identification of abnormal fetal growth was similar in both groups, the trend was towards improved identification with serial USE. Thus, in the revised manuscript we have added: "The likelihood of identifying fetal growth abnormalities or oligohydramnios was similar in both groups but this was because the sample size was not calculated to detect any of the specific abnormalities on sonographic examination. Nonetheless, the trend was toward improved identification of the abnormal growth with serial ultrasound exams. (Lines 240-244)."*

12. Figure 1 - for the excluded portion you state "22 had first USE after 20 weeks" but your inclusion criteria was ultrasound exam before 22weeks and 0 days - please clarify discrepancy

Response: *The reviewer correctly points out the that the GA for the first ultrasound to exclude a woman is stated in correctly in Figure 1. We have corrected the Fig and now it consistently states that if the first ultrasound exam was after 22 weeks, she was excluded.*

Reviewer #3:

This is a randomized trial in uncomplicated pregnancies looking at routine prenatal care with fundal height assessment compared to serial ultrasound assessments (USE). The primary outcome was the finding of FGR, LGA or amniotic fluid abnormalities. The secondary outcomes were composite maternal and neonatal morbidities. 206 women met inclusion criteria and were randomized, analysis was on an intent to treat basis. The study found that the two groups had comparable baseline statistics, but that the USE group had a significantly higher incidence of the primary outcome. Secondary outcomes were similar between the two groups. The authors conclude that among uncomplicated women, serial third trimester ultrasound exam was more likely to identify fetal growth or amniotic fluid abnormalities. Ways in which this manuscript could be improved include:

Lines 117-120: Were morbidly obese women excluded? It seems odd that none of the women had a BMI >40. Please clarify.

Response: *The reviewer's request to clarify if women with BMI ≥ 40 kg/m² were excluded is excellent. In the original manuscript, we had mentioned this but being part of a long sentence, it may have been overlooked. In the revised manuscript, we have enumerated the exclusion criteria in the Appendix and BMI ≥ 40 kg/m² is 2-q*

Line 122-123: Was FHM standardized in this study or left to provider discretion? Please clarify as this might insert some ascertainment bias.

Response: *The reviewer's request for us to clarify about fundal height measurement (FHM) and if it was standardized is excellent. In the revised manuscript, we have added: Obstetrician-gynecologist faculty along with their residents in training under their supervision did all of the FHM measurements. To reflect daily clinical practice standardization of measurements of biometric parts or FHM was not done. (lines 120-122).*

Line 140-142: Why was AF assessment not standardized? It seems odd to not use one standardized process for a randomized trial.

Response: *The reviewer's requests clarification of whether assessment of amniotic fluid (AF) was standardized. We did not standardize the definition of abnormal AF for clinicians in practice are not consistent. As noted in the manuscript (line 260-261), we consider this to be a strength of the study for it reflects current clinical practice.*

Line 185-188: But there was a trend towards all three of these. Had your study been larger they likely would have reached significance, I think it would be OK to point that out here.

Response: *The reviewer's suggestion is excellent. We have the following sentence: "The likelihood of identifying fetal growth abnormalities or oligohydramnios was similar in both groups but this was because the sample size was not calculated to detect any of the specific abnormalities on sonographic examination. Nonetheless, the trend was toward improved identification the abnormal conditions with serial USE (lines 240-244).*

Lines 234-237: Any plans to conduct a larger, multi-centered trial? It seems a waste to not expand this work.

Response: *The reviewer has a superbly encouraging suggestion—a large multi-center study. In the revised manuscript, we have added a paragraph (lines 264-273). Additionally, our very last sentence, with a reference, provides the rationale and the plan for such a multi-center study.*

Lines 239-241: But your inclusion and exclusion criteria diminish these differences. Broadening your study would increase it generalizability.

Response: *The reviewer observes that our inclusion and exclusion criteria diminish the applicability of the findings and we should broaden our criteria. For the following reasons we respectfully disagree: 1) Such an observation is applicable to almost all randomized trial; 2) By expanding the criteria, the sample size, and the intervention would have to be changed; 3) Since upward of half deliveries in the US are uncomplicated (reference # 10), we think the findings are quite generalizable.*

Reviewer #4:

The authors performed a randomized controlled trial to determine is routine serial US identified more abnormalities in fluid and fetal growth. Not surprisingly, the authors found that USE identified fluid and growth more frequently than routine care in uncomplicated pregnancies. They report that 5 women need to be screened to identify one abnormality.

The methods are sound and the manuscript is well written.

Response: *We thank the reviewer for the kind comments.*

The authors found no differences in maternal or neonatal complications, nor did they find differences in management of pregnancies limiting ability to generalize such a practice change into a population.

Response: *We agree with the reviewer that the positive findings of the RCT are not enough to change practice patterns. In concordance with the reviewer, the very last statement of the*

manuscript states “Before the clinical practice of serial sonographic examinations is implemented in uncomplicated pregnancies, a larger RCT is warranted to determine if increased detection of the four conditions improves outcomes (32)” (Lines 276-278).

There are no considerations of cost -- Do the authors know how much on average it would cost to identify a fluid or growth abnormality?

Response: *We agree with the reviewer that we do not provide any consideration to the cost of the intervention. In the revised manuscript, we added: “Lastly, we did not undertake a cost-effective analysis to determine if the intervention justifies the cost (Lines 255-256).”*

Could they estimate the fewest number of scans required without losing the possibility of identifying a fluid or growth abnormality -- for instance one US at 32-34 weeks?

Response: *The reviewer asks an interesting question about the fewest number of ultrasound exams required to increase the detection of abnormality of fetal growth or of amniotic fluid. As noted in Table 4, about 1/3 of the abnormalities were noted before 32 weeks; 1/3 at 32-34 week and; 1/3 at 37 weeks or more. Thus, we are not able to estimate the fewest number of ultrasound exam needed to maximize detection of abnormalities.*

Perhaps the authors could further emphasize that prior to a practice change - evidence illustrating cost effectiveness and the impact on improved maternal and or fetal outcomes without resulting in increased unneeded interventions is warranted

Response: *As noted above, we agree with the reviewer that our RCT should not be an impetus for practice change but rather a reason to do a sufficiently powered intervention trial to determine if serial USE improves outcomes. We have clearly stated this in a new paragraph (lines 264-273) and in our last statement: “Before the clinical practice of serial sonographic examinations is implemented in uncomplicated pregnancies, a larger RCT is warranted to determine if increased detection of the four conditions improves outcomes (32)” (Lines 276-278).*

STATISTICAL EDITOR COMMENTS:

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

lines 157-162: The study design was for a composite primary outcome (any of the 4 metrics being abnormal). The design/ sample size does not allow discernment of differences in rates of each of the 4 metrics. That needs to be made clearer in the Abstract, results and discussion.

Response: We appreciate the statistical editor's comment *that the sample size was powered to only detect a difference in the primary composite outcome. We have reworded throughout the manuscript to indicate that the study was powered for the primary composite outcome.*

Table 3: This needs to be re-formatted. The primary outcome is the composite, the others are secondary outcomes. The secondary ones were not individually powered by the composite sample size. The three that were NS cannot be generalized, their individual powers ranged from .06 -.38. The single finding that was statistically significant (polyhydramnios), only had power = 0.62. Therefore one can conclude that the composite primary was significantly different in rates, but one cannot generalize any of the other 4 individual secondary outcomes.

Response: *We appreciate the statistical reviewer's point that the trial did not have the sufficient power to detect a difference in the four components of the primary composite outcome. In the revised manuscript we have added a footnote to Table 3: "*The trial was not powered to detect a difference in the four components of the primary composite outcome."*

The findings in Tables 4, 5 and 6 are all under powered, except for the relationship of GA at delivery vs treatment arm, which was significant in Table 4 (subset of only women with primary outcome), but not in Table 5.

Response: *We appreciate the statistical reviewer's comments. We have noted in the text that the study was not powered for these outcomes (Lines 57, 65, 181, 199, 203, 216, 248). The GA shown in Table 4 refers to when the initial detection of an ultrasound abnormality. Table 5 show GA at delivery.*

lines 213-215 (low power) should be modified to reflect low power

Response: *We appreciate the statistical reviewer's comments. In lines 215-218 we state: "Though the trial is underpowered for assessment of peripartum outcomes, the maternal and neonatal adverse outcomes were similar, as were gestational age at delivery, the rate of induction and of cesarean delivery."*

lines 245-247: If the Authors want to show that the estimates from this study are accurate (I presume they mean comparable) to all uncomplicated 28-30 wk pregnancies, then their estimates should have CIs, which will be wide and will demonstrate that for that purpose, a much larger study would have to be done.

Response: *We appreciate the statistical reviewer's comments. In lines, we now state that "The*

trial provides accurate estimates of the rate of the composite outcome of FGR, LGA, oligo- or poly-hydramnios in uncomplicated pregnancies at 24-30.6 weeks."

EDITOR COMMENTS:

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

Response: *We truly appreciate the Editor's specific comments. To respond to the editor, we have cc each of the comments in the PDF and provide our response below.*

"Please make it clear in the methods that your primary end point is a composite of abnormalities of fluid volume and growth abnormalities. As written on line 41, its not clear that its a composite of these findings. This needs to be really clear in the methods section of the paper as well. Several of your reviewers commented that this was not clear."

Response: *Since we used the terms composite maternal morbidity or composite neonatal morbidity, we tried to avoid using "composite outcomes" and instead chose the phrase "four abnormal conditions." We realize that it consistently confused the reviewers and the editors. Thus, we have deleted the phrase four abnormal conditions, and replaced it with "composite of abnormalities of fluid volume and growth abnormalities." We appreciate the suggestion and in the revised manuscript we use the phrase primary composite outcome seven times (Lines 42,46,53,156,176,184,230).*

"It is reasonable to not use abbreviations for words that are seldom used in the paper. As well, please consult the Instructions for Authors regarding the use of abbreviations, and what constitutes an acceptable abbreviation. This is not an acceptable abbreviation. Please spell the words out throughout the manuscript."

Response: *We appreciate the Editor's suggestion that we delete the abbreviation "USE" for ultrasonographic examination. We have done so, 18 times throughout the manuscript.*

Please see instructions for authors to see how to include your clinical trials registry. As well, there is a unique abstract we use for RCT's that can be found in editorial manager, On editorialmanager1.com/ong on the landing page, click on the 2nd link under Instructions for Authors to take you to the structured abstract example for randomized clinical trials."

Response: *We appreciate the Editor's suggestion and we have complied with it.*

"This is actual a composite outcome, right? Please so describe. Noted by most of your reviewers."

Response: *We appreciate the Editor's suggestion and we have deleted the primary outcome and replaced it with "composite of abnormalities of fluid volume and growth abnormalities" 7 times (Lines 42,46,53,156,176,184,230).*

"Methods should include some information about analysis, including intent to treat analysis."

Response: *We appreciate the Editor's suggestion and we have added the phrase "All women were included in the intent to treat analysis" in the methods section (lines 48,157,158). We have also added a sentence—Fisher exact, χ^2 tests or 2-sample t-tests were used to assess group differences—to the Method section in the abstract (Lines 48-49).*

"852 women were screened for eligibility and 206 were randomized as follows:..."

Response: *We appreciate the Editor's suggestion and we have revised the sentence in the abstract (lines 51-52).*

"By abnormality, you mean of the 4 things in your composite, correct? Abnormality can be misconstrued to mean fetal abnormality. Could you say ...number needed to identify at least one of the composite ultrasound abnormalities or something of that nature? ?"

Response: *We appreciate the Editor's suggestion and we have changed the sentence in the abstract to read (lines 55-56): The primary outcome was significantly higher among women who were in the ultrasound examinations group than the routine care group (27% vs. 8%; RR 3.43; 95% CI 1.64-7.17) with the number of women needed to identify at least one of the composite ultrasound abnormalities, 5 (95% CI 3-11).*

"These secondary endpoints were part of composite endpoints and should be reported in this manner. Given that you were likely underpowered to be able to draw conclusions about the lack of a difference, its important to be cautious about how you frame this."

Response: *We appreciate the Editor's suggestion and we have revised the results section of the abstract in the following manner: Though we were underpowered to detect a significant difference, the following secondary endpoints occurred with similar frequency in the control and intervention group: delivery due to abnormal ultrasound examinations findings...(lines 57-60).*

“To avoid spin, it would be reasonable to state the no differences in outcomes was found, although underpowered for this.”

Response: *We appreciate the Editor’s suggestion and we have added the following as the last sentence of the abstract: No differences in maternal and neonatal outcomes were noted, although we were underpowered to do so (Lines 57, 65, 203,216).*

“Specifically amniotic fluid volume, correct?”

Response: *We appreciate the Editor’s request for clarify in the introduction that it was abnormalities in amniotic fluid volume we were assessing. We have revised this sentence in the introduction (line 71): Currently, American College of Obstetricians and Gynecologists (ACOG) recommends that the first step in screening for abnormalities of fetal growth or amniotic fluid volume in uncomplicated pregnancies is serial measurements of fundal height, starting at 24 weeks.*

If there is a discrepancy between gestational age and fundal height measurement, then a sonographic examination to...

Response: *We appreciate the Editor’s suggestion to improve the wording in the 2nd sentence of the Introduction. We have done so. The new statement reads (Lines 72-74): If there is a discrepancy between gestational age and fundal height measurement, then a sonographic examination is done to assess fetal weight and amniotic fluid volume (1,2).*

Highlighting words that need editing. for example: more likely to result Abnormalities....occur

Response: *We truly appreciate the Editor’s suggestions to improve our syntax. We have done so.*

There is an impetus to improve identification..... among uncomplicated pregnancies (lines 83-85).

Response: *We truly appreciate the Editor’s suggestions to improve our sentence. We have done so.*

Can you offer an explanation why these 4 were chosen? I assume because that their identification might alter perinatal management going forward. But why not fetal structural abnormalities, placenta previa, etc etc.

Response: *The Editor has an excellent question: Why focus on a composite of these 4 abnormalities and not others (e.g. previa and anomalies)? We chose to focus on these four abnormalities because 1) after a normal second trimester anatomy ultrasound they are the*

most common abnormalities noted, and; 2) the purpose of the fundal height measurements is to detect these conditions. In the revised manuscript, we have provided the rationale for focusing on the four conditions. Specifically we have added the following sentence: We focused on this composite because after a normal second trimester anatomy ultrasound examination, these are the most common abnormalities identified (6) and because the purpose of fundal height measurements is to screen for these four abnormal conditions (Lines 91-94).

Name the IRB; no need to provide the number

Response: *The Editor has a nice suggestion about naming the IRB and deleting the IRB number. We have done so in line 97-98*

Please clarify that you did not exclude women who had an anomaly detected only postnatally. Perhaps "no major prenatally diagnosed fetal anomalies"

Response: *The Editor has a very nice request on clarification on when the anomalies were noted which were excluded. Using the Editor's suggestion, we have added the phrase "no major prenatally diagnosed fetal anomalies (lines 99-100)."*

Women were excluded if they had any of the following complications or co-morbidities diagnosed prior to randomization: (Recommended change because some of these aren't obstetrical complications and some of these women developed gestational hypertension later and were still included, correct?)

Response: *The Editor nicely points out that regarding the description of exclusion criteria, we acknowledge that some were complications and / or co-morbidities. Per reviewer #1 suggestion we have made an appendix of the complications or comorbidities which excluded them. We have also clarified that if complication developed after randomization the woman was retained in the group assigned. Specifically, we note in lines 101-103 that "Women were excluded for any medical complication or co-morbidity at the time of randomization (Appendix 1). If a complication developed after randomization, women remained in the group they were randomized to."*

"Although with this small number of patients (n=206) in uncomplicated pregnancies, fetal and neonatal death would be rare, since when these do occur it is more likely in the setting of FGR and fluid abnormalities--the components of the composite primary outcome. Why did you exclude them?"

Response: *The Editor has a good question about why did we exclude women with history of fetal or neonatal death. The reasons we excluded them are: 1) History of prior death would*

make them “high-risk”; 2) They would get 3rd trimester ultrasounds examination for growth and / or antepartum surveillance; and 3) Our faculty did not feel comfortable to these women being allocated to fundal height alone in the 3rd trimester.

“As per the CONSORT guidelines and checklist: how was the randomization done? Who did the randomization? How was allocation concealed?”

Response: *Our apologies to the Editor for not having this in the manuscript originally. In the revised manuscript we have added the modified the sentence (lines 104-106): “Eligible women who consented to participate in the trial were randomly assigned in a 1:1 ratio, using permuted block randomization in order to prevent imbalances between groups. The concealment was done by the statistician (CP).*

“No other indications or are these just examples?”

Response: *The Editor has understandably requests clarification on whether the listed reasons for additional ultrasound examinations examples or an exhaustive list. We have modified the sentence to state that these are examples. Specifically, now the statement is (lines 115-118): “In both groups, additional ultrasound exams could be obtained if deemed necessary by the obstetric provider if complications developed (e.g. preterm labor, decreased fetal movements, or development of hypertensive disease). The letters in red are to highlight the change in the sentence.*

ABOG prefers to avoid the terminology “Board Eligible.”

Response: *We appreciate the Editor pointing out that ABOG does not like the term board eligible. We have deleted the descriptor “a board eligible or certified.” The revised sentence is: Registered diagnostic medical sonographers (RDMS) did all the sonographic examinations and a maternal-fetal medicine sub-specialist reviewed all ultrasound exams (lines 118-120).*

For this readership, probably OK just to say Hadlock's formula and not mention the components

Response: *The Editor makes a good point that the readers of Obstet Gynecol do not need to know what components of biometric parameters were used to derive the estimated fetal weight. If at all possible, we would like to keep this sentence—The fetal weight was estimated by obtaining measurements of the bi-parietal diameter, head circumference, abdominal circumference and femoral diaphysis length—because researchers on accuracy of predicting birth weight and identification of aberrant growth would appreciate how estimate was derived. For example, we have seven publications on factors which influence accuracy of birth weight, or identification of SGA or macrosomia. One of the factors which influences the accuracy is what biometric parameter was used to derive the estimate.*

“Fetal growth abnormalities were defined if the EFW was < 10th percentile or > 90th percentile for gestational age.”

Response: *The Editor makes a good point that our sentence “Fetal growth restriction was EFW < 10th percentile for gestational age (GA) and sonographic LGA was EFW > 90th percentile for GA (1, 21, 22)” can be simplified. We have done so in lines 126, 127.*

One reviewer asked why this wasn't standardized.

Response: *The Editor nicely echoes one of the reviewer’s concern regarding why was the definition of oligo- and poly-hydramnios not standardized. We previously noted that, “We did not standardize the definition of abnormal AF for clinicians in practice are not consistent. As noted in the manuscript (line 259-261), we consider this to be a strength of the study for it reflects current clinical practice.”*

All ultrasound reports were made available to the treating providers.

Response: *The Editor is kind to point out that we could delete the following sentence—ViewPoint or Digisonic software (Waukesha, WI) were used to generate the reports and were uploaded into the subject’s electronic medical record—and replace it with “all ultrasound reports were made available to the treating providers.” We have done so in lines ____.*

Nomogram published by Alexander et al (23) was used to categorize newborns as SGA (birthweight < 10th percentile for GA) or as actual LGA (birthweight > 90th percentile for GA).

Response: *The Editor kindly points out that the sentence about Alexander et al nomogram should begin with “The.” We have revised sentence accordingly (line 132).*

Abstracted rather than culled. Who did this abstraction? Were they blind to the allocation of the patient?

Response: *The Editor points that instead of “culled” we should use the word “abstracted.” We have done so in the revised manuscript. We have also added a sentence “To keep abstracted data consistent, one author (OAB) reviewed all the charts and was aware of the group allocation (lines 135-136).”*

You had said above that women with stillbirth or neonatal death were excluded. This would suggest they were not. Please clarify.

Response: *The Editor request clarification: if women with stillbirth or neonatal death were excluded, how can these outcomes be part of composite neonatal morbidity. We excluded women with history of stillbirth or neonatal death in prior pregnancy. Women who had stillbirth*

after randomization or neonatal death in the index pregnancy were included. We have modified the sentence to clarify this: Composite neonatal morbidity was defined as any of the following: 1) Apgar score < 5 at 5 min, 2) umbilical arterial pH < 7.00, 3) intraventricular hemorrhage grade III or IV, 4) periventricular leukomalacia, 5) intubation for over 24 hrs., 6) necrotizing enterocolitis grade 2 or 3, 7) stillbirth after randomization or 8) neonatal death, within 28 days of birth, in index pregnancy (lines 137-144).

I actually prefer that you use "routine care" to two-step schema." Either way, be consistent.

Response: *The Editor suggest that "routine care" would be preferable to "two-step schema." Upon reflection, we agree with the Editor. We have deleted the phrase two-step schema at both places it was mentioned (lines 75, 145, 212) and ensured that "routine care" is used. In the revised manuscript we use "routine care" 19 times.*

It would be good to consider describing the control arm and intervention arm as such in your materials and methods section. You variously use routine vs serial USE, two step schema, etc. Please pick a lexicon and stick w/ it.

Response: *The Editor's suggestion is good one that we should define which arm is control and which the intervention and we should be consistent with our terminology. Starting with the abstract, we have defined what is control arm and intervention arm (line 41, 42).*

The Journal style does not include the use of the virgule (/) except in numeric expressions. Please edit here and in all instances.

Response: *We appreciate the Editor's reminder that virgule should be avoided. We have revised the manuscript to ensure that we do not use virgule.*

The following sentence belongs in the method section: "All randomized women were included in the intent to treat analysis."

Response: *We appreciate the Editor's reminder that the above quoted sentence should be in the material and methods section. We have revised the manuscript and now the statement about intent to treat analysis is the last sentence of methods section (lines 48, 157, 158).*

Please describe as "number needed to treat" rather than number needed to identify.

Response: *We struggled with this verbiage. While the computation is for number needed to treat, the ultrasound exam does not "treat" anything, as a pharmacological intervention might. We also thought of the verbiage number needed to diagnose but with oligo- and polyhydramnios, we are uncertain about the accuracy of diagnosis, even after delivery. Thus, it's not*

number to diagnosis. Thus, we came up with the descriptor “number needed to identify” for all the sonographic exam did was identify the composite.

Though we have revised the manuscript, and use “number needed to treat,” (lines 155,) we think it is somewhat of a mischaracterization of sonographic findings.

This is tricky--see statistical editor comments. You are underpowered for the individual components of the composite US findings and should probably frame it as such. The very wide CI's for poly should be noted in discussion as well.

Response: *Both the Editor and the statistical editor nicely point out that we were underpowered to detect a difference in the components of the composite. We acknowledge that in the revised manuscript (lines 180-182): “...there was not a significant difference in detection of FGR, LGA, and oligohydramnios between the two groups, but the study was not powered to detect differences in the components of the composite (Table 3).”*

We have also noted the very wide 95% CI about the identification of polyhydramnios.

Provide the data (what GA was noted in the 2 groups? provide CI's; p values optional)

Response: *Understandably, the Editor inquires about the gestational age when the composite abnormality was initially detected in the two groups. As noted in Table 4, we categorized the GA when the abnormality was initially identified in four groups i.e. < 32.0 weeks, 32.0-34.6 weeks, 35.0 to 36.6 weeks and > 37.0 weeks. The P value of 0.02 for this comparison is chi-square test for trend. So, while we can say that the GA at initial identification was different, we cannot pinpoint when. I hope keeping the statement as is, is acceptable.*

Not sure what you mean here. The rate of BPP and UA Doppler? Do you mean performance of these tests? If so, this is really important as you have stated that routine care resulted in women not having benefit of antenatal surveillance but if the rates of BPP's and Dopplers were no different, can you draw that conclusion later. Also, do you NOT do NST's at UT_H?

Response: *The Editor justifiably requests clarification on what the rate of BPP and UA Doppler in the control and intervention arms. We have revised the statement to say: The rate of having biophysical profile or umbilical artery Doppler, because of the abnormality noted on sonographic examination (i.e. polyhydramnios or IUGR), were similar between the two groups (lines 190-192). The Editor is correct we do not NST as the first step of fetal surveillance. We usually do NST if the BPP is abnormal or if there are other concerns.*

Do you mean induction of labor or do you mean iatrogenic delivery? IE, were some of these women primarily sectioned instead of being induced?

Response: *The Editor requests clarification regarding “induction of labor prior to 37 weeks.” According to the Meriam-Webster dictionary iatrogenic means, “induced inadvertently by a physician or surgeon or by medical treatment or diagnostic procedures.” Since the indications for the inductions were complications (i.e. severe preeclampsia) we think that the descriptor “induction of labor prior to 37 weeks” is apropos. None of the women had primary cesarean delivery secondary to abnormality noted on the sonographic exam.*

Please report your composite secondary outcomes after your composite primary outcome. Then if you wish to comment on other things you looked at that fine but avoid "spin" if there are no differences and you aren't powered to say anything about it.

Response: *We were mistaken in presenting the data chronologically i.e. demographics, antepartum complications after randomization, primary composite outcome, intrapartum events, and lastly adverse outcomes to mother-newborn dad. We have now learned that secondary outcome after primary outcome. We have done so and re-numbered the tables to illustrate this.).*

The additional information we provide is not to “spin” for we know the readers of your journal are discriminatory. We provide the details for clinicians and researchers interested on the topic. But your point is quite valid and we have summarized in the limitations section that “This single center trial was not powered to detect differences in any obstetric or neonatal outcomes (lines 247-248).

Please present your composite maternal and neonatal secondary outcomes before looking at any other outcomes or the components of the outcomes. Again, please be careful in your discussion that you don't suggest lacks of differences for things you are underpowered for.

Response: *The Editor’s suggestion about the order we present outcomes and that we were underpowered is astute. We have revised the manuscript accordingly. In lines 215-217 we wrote: Though the trial is underpowered for assessment of peripartum outcomes, the maternal and neonatal adverse outcomes were similar, as were gestational age at delivery, the rate of induction and of cesarean delivery.*

Upwards of two-thirds

Response: *The Editor’s suggestion of rephrasing is understandable. We have revised the sentence.*

Low-risk pregnancies may have adverse outcomes... other etiologies of course are possible--undiagnosed fetal abnormalities, abruption, PTL, prolapsed cord, development of preeclampsia, trauma, etc., etc. I think you are trying to say, as I mentioned above, that low risk pregnancies may unexpectedly develop fetal growth abnormalities and abnormalities of amniotic fluid volume which can be associated with adverse pregnancy outcomes and which could be amenable to perinatal management that could reduce the associated risks by antenatal testing and iatrogenic delivery prior to labor.

Response: *The Editor accurately points out that aside from abnormalities of fetal growth and of amniotic fluid, there are several possible causes of adverse outcomes in seemingly uncomplicated pregnancies. We have revised this statement to reflect the multiple causes of poor outcomes with low-risk pregnancies and that aberrant fetal growth and abnormalities of amniotic fluid are just some of them. In lines 219-221, now we note that “While there are multiple potential etiologies of adverse outcomes in low-risk pregnancies, the most common ones which are amenable to interventions are aberrations of fetal growth or of amniotic fluid (6,10-17).”*

Is there evidence to support this statement?

Response: *The Editor inquires about the evidence behind our statement that “combination of surveillance and interventions could mitigate adverse outcomes” associated with abnormalities of fetal growth and / or amniotic fluid. We do “fervently” believe that our statement is supported (references 1, 7, 8, and 21). ACOG Practice Bulletins on Fetal Growth Restriction (#134), Fetal Surveillance (#145) and Fetal Macrosomia (#173), as well as SMFM Clinical Guideline on intrauterine growth restriction provide evidence that identification and interventions (e.g. antepartum testing, Doppler, induction or cesarean delivery) improve outcomes. Though not cited in the manuscript because of the limitation in number of references we can cite, other national guidelines from Canada, England, Ireland and France also suggest the identification and intervention improve outcomes. It is unlikely that all these guidelines misrepresent the evidence but I am willing to debate that if the journal will permit.*

Placental grading is not on of the ones you mentioned so "not on all four abnormal conditions" doesn't quite fit this. Please edit.

Response: *The Editor inquired about the comparison of our primary outcomes versus those of other randomized trials on third trimester ultrasound. Our apologies that our sentence—“Prior randomized trials on ultrasound exam after 24 weeks focused on growth restriction (26,28-30) or placental grading, (27) but not on all four abnormal conditions—was somewhat confusing. We were trying to draw the attention that prior trial focused on either growth restriction or placental grading but not the composite of four conditions. We have revised the sentence in the following manner (words are red ink to highlight the change; lines 229-232): Prior randomized trials on ultrasound exam after 24 weeks focused on either growth restriction (26,28-30) or*

placental grading, (27), **while we focused on a composite of abnormal conditions and did not assess placental grade.** We hope this address Editor's concern.

~~Unlike hypertensive disease of pregnancy or diabetes (1,7,8), where there is a predilection of what abnormality may be noted on sonographic exam, among uncomplicated pregnancies it is uncertain what abnormal findings may be identified.~~

Response: *The Editor has crossed out the sentence noted above. On closer inspection, we see why it may seem unnecessary. Nevertheless, please permit us to revise and point out the importance of our thoughts. With hypertensive disease of pregnancy, it is well accepted that growth abnormality is IUGR and abnormality of amniotic fluid is oligohydramnios; with diabetes it is large for gestational and polyhydramnios. Among uncomplicated pregnancies, however, it is uncertain which aspect of abnormality in growth or amniotic fluid will predominate. Our randomized is one of the few trials to provide unbiased estimates (prospectively collected in prescribed manner) of these four conditions in uncomplicated pregnancies.*

While we have deleted the crossed out sentence, we hope the editor would permit us to use the following statements (lines 232-235): With hypertensive disease of pregnancy, it is well accepted that growth abnormality is IUGR and abnormality of amniotic fluid is oligohydramnios; with diabetes it is large for gestational and polyhydramnios. Among uncomplicated pregnancies, however, it is uncertain which aspect of abnormality in growth or amniotic fluid predominates (6).

Really not powered for the individual components of your composite outcomes nor for your composite maternal outcomes. It was only powered for the composite ultrasound findings.

Response: *Quite accurately, the Editor notes that the study was only powered to detect the primary composite of the abnormalities on sonographic examinations. In the revised manuscript we address this in the paragraph describing the shortcoming. Specifically in lines 239-243 we state: The likelihood of identifying fetal growth abnormalities or oligohydramnios was similar in both groups but this was because the sample size was not calculated to detect any of the specific abnormalities on sonographic examination. Nonetheless, the trend was toward improved identification of the abnormal growth with serial ultrasound exams. This single center trial was not powered to detect differences in any obstetric or neonatal outcomes.*

RDMS is the name of an organization. Your sonographers are RDMS certified.

Response: *The Editor kindly points out the RDMS refers to an organization, while sonographers are RDMS certified. We have revised the manuscript accordingly.*

Typically one presents the strengths first, followed by limitations.

Response: *The Editor appropriately points out that traditionally in the discussion section of manuscript researchers mention strength followed limitation. While this is good convention, we would like to upend the tradition for the following reasons: 1) changing the format does not misrepresent the objective findings of the trial; 2) there is no known clinical benefits of keeping the format; 3) to end the manuscript with enumeration of shortcoming is an immodest proposition.*

What about at the other 3 time frames? Does your data allow you say which gestational age in the 3rd trimester has the "biggest bang for the buck" if one were to want to do a bigger study to see if outcomes changed? Scanning every 2 weeks x 3 is a lot. Was the detection of the composite US outcome more likely at scan 1, 2 or 3? Would there be time to intervene with testing protocol if not until scan 3? etc.

Response: *The Editor asks a series of poignant questions about the frequency of ultrasound and when may be the optimum time to get these examinations in low risks pregnancy. Due to the small sample size, we are not powered to answer the question of "biggest bang for the buck." Considering 36% of the primary composite were detected before 32 weeks, we think the starting serial ultrasound at 28-30 weeks is reasonable.*

This is a very important point that you spend almost no attention on in your discussion. You should state in the discussion that you are not powered to look at actual maternal and neonatal outcomes which is really where the potential value is of 3rd trimester ID of abnormal growth and fluid volumes. To avoid "spin" in your manuscript, perhaps you could do an estimate of how many patients would need to be enrolled to look at maternal and neonatal outcomes, given the relative rarity of bad outcomes.

Importance of such of trial should be emphasized:

1. Your trial helps inform us about rates of the composite US outcome in low risk women.
2. Costs of serial scans in terms of charges to patient, resource utilization quite large.
3. Costs also include costs of monitoring, interventions if abnormalities found
4. Benefits--decreased neonatal and maternal poor outcomes.

Response: *Previously we thought we understate the need for a large multicenter to show an improvement in peripartum outcomes, especially considering we previously published an article entitled "Screening for intrauterine growth restriction in uncomplicated pregnancies: time for action (reference # 32)." Upon further reflection, we understand why the Editor suggests that in discussion we elaborate on the need for a large randomized trial and provide a sample size. Towards this end, we have added a paragraph (lines 168-173): "Our trial should be a nidus for a larger multi-center trial with sufficient power to determine if serial ultrasound exam improve peripartum outcomes. Previously, investigators suggested that a trial of 6,000 low-risk*

pregnancies, randomized to routine care compared to serial sonographic examination, has the power to detect a 36% difference, assuming the risk of neonatal morbidity is about 4% in the control arm (32). Such a large trial would permit better assessment of costs of serial scans (including interventions) in terms of charges to patient, and resource utilization. It may also demonstrate potential maternal benefits like decreased rate of cesarean delivery or greater satisfaction (33).”

The notated PDF is uploaded to this submission's record in Editorial Manager. If you cannot locate the file, contact Katie McDermott and she will send it by email – kmcdermott@greenjournal.org.

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

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

3. Based on the forms that have been submitted, Dr. Barrett has not met the criteria for authorship. Dr. Barrett should be moved to the acknowledgments, or he/she could resubmit a revised author agreement form if he/she filled it out erroneously the first time. All updated and missing forms should be uploaded with the revision in Editorial Manager.

Response: Thank you for pointing out the discrepancy. The form was incorrectly filled for T. Barrett, and a revised author agreement form has been uploaded.

4. Our journal requires that all evidence-based research submissions be accompanied by a transparency declaration statement from the manuscript's lead author. The statement is as follows: "The lead author* 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, if relevant, registered) have been

explained." *The manuscript's guarantor.

If you are the lead author, please include this statement in your cover letter. If the lead author is a different person, please ask him/her to submit the signed transparency declaration to you. This document may be uploaded with your submission in Editorial Manager.

Response: We have added this statement to our cover letter above.

From: [REDACTED]
To: [Randi Zung](#)
Cc: [REDACTED]
Subject: Re: Your Revised Manuscript 18-1138R1
Date: Tuesday, September 11, 2018 4:59:50 PM
Attachments: [18-1138R1 \(9-11-18v7\)--SPC.docx](#)
[UP Trial Clean v7.docx](#)

Hello,

Attached is the corrected version with the requests made by Dr. Chescheir. I have deleted all the sentences she wanted in the manuscript with track changes, and I have attached a clean version of the manuscript. For her question about Line 149 (now line 135 due to deletions made in the paper), we replied to the comment with the following:

Our sincerest apologies for the continued confusion.

Hopefully, the revised sentence will be clearer:

“To reflect daily clinical practice, the standardized measurement of biometric parts, amniotic fluid or fundal height was continued before, during and after the trial.”

If this sentence is still confusing, we would truly appreciate additional direction.

Please let me know if there is anything else you need.

Best,

Olaide

Olaide Ashimi Balogun, MD

[REDACTED]
[REDACTED]
[REDACTED] [REDACTED]
[REDACTED] [REDACTED]

From: Randi Zung <RZung@greenjournal.org>
Sent: Monday, September 10, 2018 8:09 AM
To: Ashimi, Olaide A
Subject: RE: Your Revised Manuscript 18-1138R1

Dear Dr. Balogun:

Dr. Chescheir has reviewed your version from September 5. She has made final edits to the manuscript file and we would like you to review to make sure everything is correct (version 6). We are asking you to make final deletions, as noted in the file, and listed below. The version of the manuscript that you send back to me will be considered final for the author queries stage. Please make all of your final edits in the version that you send back to me next.

If possible, we would appreciate receiving your manuscript by September 12.

Queries:

- Line 129-136: Dr. Chescheir would like you to delete this section. She has crossed it out so you can review the deletion, but please make your edit directly to this file. We realize deleting this will remove this comment from the file. That is fine.
- Line 149: I remain confused by this. Don't your RDMS-certified sonographers use standardized approaches to biometry and AFI measurements?
- Line 204-241: As above, please delete the text that Dr. Chescheir has crossed out. It should not appear in the final version of the manuscript.
- Line 262-263: Please delete the bolded sentence. We realize that deleting this will delete this comment.

Thank you,
Randi

From: Ashimi, Olaide A [REDACTED]
Sent: Wednesday, September 5, 2018 4:20 PM
To: Randi Zung <RZung@greenjournal.org>
Subject: Re: Your Revised Manuscript 18-1138R1

Hello Ms. Randi,

Thank you for getting back to me with comments. Attached are the answers to the questions sent by Dr. Chescheir, the manuscript with edits (track changes), and a clean version of the manuscript. Please let me know if you need anything further.

Sincerely,

Olaide

Olaide Ashimi Balogun, MD

Chief Administrative Fellow, Maternal-Fetal Medicine , PGY 7

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

From: Randi Zung <RZung@greenjournal.org>
Sent: Friday, August 31, 2018 9:26 AM
To: Ashimi, Olaide A
Subject: RE: Your Revised Manuscript 18-1138R1

Dear Dr. Balogun:

Dr. Chescheir has reviewed your latest version and she has a few follow up queries for you to address. In the attached manuscript (v4), her new comments to you are highlighted in green. She also made a few comments in the point-by-point letter that you submitted. Her new comments in both files are as follows:

Point-by-point letter:

Query 5: Please see suggested changes. The statistician created the randomization allocation sequence. Please see question in last line. It seems like the study was unblinded entirely. If so, please so state. Also in the discussion then, please list that as a limitation and explain why the abstractor, sonographer, and sonologists couldn't be blinded as these are limitations.

Query 5: Don't you mean "was not blinded"?

Query 13: My point is that the fetus or newborn is stillborn and the mother has a stillbirth. Please rephrase.

Version 4 of manuscript:

Line 99: Please note the edit to "performing."

Line 121: Please see my comments on your point by point rebuttal with respect to this paragraph. Please make your corrections and additions to the resubmitted manuscript.

Line 220: Please provide the weeks at ID, not just the p values.

Line 231: Note this addition ("a composite of").

Line 268-269: I deleted the above phrase because it is speculation that the reason you did not see a difference was because of the small sample size. You don't know that. Perhaps there is truly no difference..

Line 282: Please comment here about total lack of blinding with potential for introduced bias.

Please edit the version of your manuscript that is attached to this message (v4). Please send me back your next version when you are finished. Please note that ACOG will be closed on September 3. You may return your updated file by September 6.

Thank you,
Randi Zung

From: Ashimi, Olaide A [REDACTED]
Sent: Wednesday, August 29, 2018 4:10 PM
To: Randi Zung <RZung@greenjournal.org>
Subject: Re: Your Revised Manuscript 18-1138R1

Hello Ms. Randi,

Attached are the UP trial revisions with answers to the questions and changes to the manuscript made with track changes. We truly appreciate your patience with us.

Sincerely,

Olaide

Olaide Ashimi Balogun, MD

[REDACTED]

From: Randi Zung <RZung@greenjournal.org>
Sent: Tuesday, August 28, 2018 8:06 AM
To: Ashimi, Olaide A
Subject: RE: Your Revised Manuscript 18-1138R1

Dear Dr. Balogun:

Thank you for letting me know. An extension will be fine.

Thanks,
Randi

From: Ashimi, Olaide A [REDACTED]
Sent: Monday, August 27, 2018 11:59 PM
To: Randi Zung <RZung@greenjournal.org>
Subject: Re: Your Revised Manuscript 18-1138R1

Good Evening Ms. Zung,

While we had every intention of getting the revisions back to you today, we are awaiting final comments from our statistician, who is also one of the senior authors. She just returned to town this evening and has asked for 48 hours to respond to our questions. Attached are the responses to all of your questions below in red, however the yellow highlighted portions are areas where we need final approval from our statistician. We are asking for a two day extension to get this back to you. We sincerely apologize and hope to get this back to you as

soon as possible.

Sincerely,

Olaide

Olaide Ashimi Balogun, MD

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

From: Randi Zung <RZung@greenjournal.org>

Sent: Thursday, August 23, 2018 2:36 PM

To: Ashimi, Olaide A

Subject: Your Revised Manuscript 18-1138R1

Dear Dr. Balogun:

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

1. General: The Editor has made edits to the manuscript using track changes. Please review them to make sure they are correct.
2. Please ask Dr. Blackwell to respond to his authorship confirmation email. The email contains a link that needs to be clicked on. The sender of the email is EM@greenjournal.org. Please have him contact Randi Zung at rzung@greenjournal.org if he cannot locate the message.
3. Line 53 and elsewhere: Please expand these acronyms throughout the paper, except in tables and figures. For readers, it would be very hard to distinguish CMM v. CNM. They look almost identical to each other if one is skimming an article.
4. Line 67-68: Where are these data stated in the body of your paper? If the data are not contained in the text, tables, or figures, please add them.
5. Line 116: Please see CONSORT checklist as there are some missing details:
 - 8a: What method was used to generate the random allocation sequence? (Coin flip? Computer program and if so which one?)

- 9. Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned.

Did you use NOSE? Or at consent, was randomization done by computer program? Was the statistician called? Please explain further.

- 10: Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions
- 11. Please discuss blinding efforts. Clearly, the patients were not blinded to their group assignment. Presumably, the investigators would know in the US unit which group people were in based on frequency of their US's. What about people abstracting data? Were they blinded?

6. Line 133: Didn't you do standardize fetal biometry? It was just amniotic fluid measurement that wasn't standardized if I recall from first draft. If so, please state.

7. Line 148: This non-blinded abstractor should be listed as a potential limitation in the discussion.

8. Line 185-187: Move the highlighted statement to after the part about demographics.

9. Line 192: On line 189, you ordered the results as Intervention group vs control (27% v 8%) but elsewhere, you order it (Control vs Intervention) (at least that what it seems to be). Please be consistent as it is quite confusing this way. Convention is that you report Control vs Intervention in the results.

10. Line 195: Recommended language change to emphasize early in sentence re: being underpowered.

11. Line 196: Recommended language change to emphasize early in sentence re: being underpowered.

12. Line 201: Interesting that due to small n that these numbers, including the CI are identical to the whole group. You talk about the CI being wide here—but it's the same. Is this perhaps a typo? If the CI is wide for subgroup, it would be wide for the whole group also, if identical.

13. Line 226: You have retained the "two step schema" terminology here, instead of referring to routine care. Was this an oversight or did you have a reason to retain it?

14. Line 237: Odd phrasing to suggest that a newborn can have a stillbirth. This gets a bit into some nuance here. Are sonographically LGA fetuses more likely to be stillborn or have neonatal morbidities independent of maternal diabetes? We know that SGA newborns are more likely to have these problems, but you are identifying FGR fetuses. The point of trying to identify aberrations of fetal growth and fluid problems are to put into place perinatal care steps to prevent stillbirth and neonatal morbidity. Do you mean to be talking about neonatal SGA and LGA or do you mean to be talking about FGR and sonographic LGA here?

15. Line 247-251: This just seems to flow better. Is it OK with you?

16. Line 253-222: Please avoid single sentence paragraphs.

17. Line 272: Also lack of blinding or allocation concealment by abstractor of data.

18. Line 278: How do you know they are accurate? Is this generalizable?

19. Appendix (Page 24): Your appendixes can stay in print, since your manuscript isn't overly long. The appendixes have been incorporated into the manuscript as a box and tables, and the tables/appendixes were renumbered.

To facilitate the review process, we would appreciate receiving a response by August 27.

Best,
Randi Zung

--

Randi Zung (Ms.)

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

FROM RESPONSE DATED AUGUST 29, 2018

RE: Serial Third-Trimester Ultrasound Compared With Routine Care in Uncomplicated Pregnancies: A Randomized Controlled Trial

Dear Ms. Denise Shield and Dr. Nancy C. Chescheir:

Thank you for considering our manuscript and your thoughtful edits / questions, which have truly enhanced the quality of the manuscript and taught us.

Below you will find point-by-point response to your editorial questions.

Please do not hesitate to contact me if I can be of any further assistance.

Looking forward to seeing the manuscript in print!

Sincerely,

Olaide Ashimi Balogun, M.D.

A large black rectangular redaction box covers the signature and any accompanying text or contact information that might have been present.

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

1. General: The Editor has made edits to the manuscript using track changes. Please review them to make sure they are correct.

2. Please ask Dr. Blackwell to respond to his authorship confirmation email. The email contains a link that needs to be clicked on. The sender of the email is EM@greenjournal.org. Please have him contact Randi Zung at rzung@greenjournal.org if he cannot locate the message.

Response: Thank you for letting us know this information. Dr. Blackwell stated he has responded to the email on 8/23/18.

3. Line 53 and elsewhere: Please expand these acronyms throughout the paper, except in tables and figures. For readers, it would be very hard to distinguish CMM v. CNM. They look almost identical to each other if one is skimming an article.

Response: We appreciate the suggestion by the editors and we have revised the manuscript accordingly and removed these acronyms.

4. Line 67-68: Where are these data stated in the body of your paper? If the data are not contained in the text, tables, or figures, please add them.

Response: We appreciate the request for clarification about the data in the abstract versus text / tables. It seems that in the multiple revisions, the data about delivery due to abnormal ultrasound examination findings (6% vs. 14%) was deleted.

In the revised manuscript, we have: 1) Clarified that it's "induction due to abnormal ultrasound examination findings"; 2) Added the data to Table 8.

Regarding your inquiry about where is the data of "cesarean delivery in labor (6% vs. 5%)" please note it is in Table 6.

5. Line 116: Please see CONSORT checklist as there are some missing details:

Response: We understand that the Editor wants us to clarify our randomization sequence using the CONSORT checklist. We would like to clarify by replacing the paragraph beginning with "Eligible women..." With the following:

Trained research staff approached eligible women and obtained informed, written consent between 24.0 to 30.6 weeks after it was determined they did not have gestational diabetes (19). Enrolled participants were randomly assigned in a 1:1 ratio, using permuted block randomization in order to prevent imbalances between groups. The random allocation was done in R software by the statistician (CP), who was not involved in the conduct of the study. The randomization table was uploaded to RedCap (Research Electronic Data Capture), where it was implemented using the randomization module. Once a woman consented to participate in the study, their demographic information was entered into RedCap, and allocated into one of the two arms. Women randomized were assigned to either routine care which included serial FHM at each clinical appointment prompting an ultrasound exam if a discrepancy was present (routine arm) or ultrasound exam every 4 weeks (at approximately 30, 34, and 38 weeks), regardless of FHM (intervention arm). After allocation was made to either group, neither the women nor sonographers performing the US were blinded to the study.

- 8a: What method was used to generate the random allocation sequence? (Coin flip? Computer program and if so which one?)

Response: Thank you for inquiring about how the random allocation sequence was generated. As noted in the revisions above computer Program, RedCap (Research Electronic Data Capture)

- 9. Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned.

Did you use NOSE? Or at consent, was randomization done by computer program? Was the statistician called? Please explain further.

Response: The random allocation was done in R software by the statistician (CP), who was not involved in the conduct of the study. The randomization table was uploaded to RedCap (Research Electronic Data Capture), where it was implemented using the randomization module. Once a woman consented to participate in the study, their demographic information was entered into RedCap, and allocated into one of the two arms.

- 10: Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions

Response: The random allocation sequence was done by our statistician-Claudia Pedroza. Participants were enrolled by UT Health Research Staff and Maternal-Fetal Medicine Fellows, all of whom had approval by our IRB.

- 11. Please discuss blinding efforts. Clearly, the patients were not blinded to their group assignment. Presumably, the investigators would know in the US unit which group people were in based on frequency of their US's. What about people abstracting data? Were they blinded?

Response: Everyone but the statistician was blinded to the allocation sequence. Once patients were consented to the study, their information was entered into computerized system, RedCap, to allocate them to Control vs. Intervention group. RedCap (Research Electronic Data Capture), is a secure web application for building and managing online surveys and databases. After allocation was made to either group, neither the women nor sonographers performing the US were blinded to the study. The person abstracting the data was not blinded.

6. Line 133: Didn't you do standardize fetal biometry? It was just amniotic fluid measurement that wasn't standardized if I recall from first draft. If so, please state.

Response: The Editor has a nuanced question, which needs clarification. For the purpose of the trial, the following were not standardized: measurements of biometric parameters, amniotic fluid and FHM. Thus, we have revised the statement (underlined words are new): To reflect daily clinical practice standardization of measurements of biometric parts, amniotic fluid, or FHM was not done for this trial (lines 134-136).

7. Line 148: This non-blinded abstractor should be listed as a potential limitation in the discussion.

Response: Thank you for suggestion, we have made this revision in line 280.

8. Line 185-187: Move the highlighted statement to after the part about demographics.

Response: Thank you for this suggestion. This has been revised and moved to line 181-183.

9. Line 192: On line 189, you ordered the results as Intervention group vs control (27% v 8%) but elsewhere, you order it (Control vs Intervention) (at least that what it seems to be). Please be consistent as it is quite confusing this way. Convention is that you report Control vs Intervention in the results.

Response: The editor's comment about being consistent and compliant with convention is understandable and we have been compliant with it in almost all instances. With the primary composite outcome, however, because of relative risk is > 1 and because of our emphasis is that the outcome is significantly more common with intervention (27%) than control (8%), we have chosen to reverse the order.

If we stayed with the convention, than the conclusion would be with routine care the primary composite outcome is significantly less than with intervention, which is somewhat of a defeatist and deflating conclusion.

Thus, while we will always defer to the editors, please permit us to be unconventional with this.

10. Line 195: Recommended language change to emphasize early in sentence re: being underpowered.

Response: We appreciate the editor's revision.

11. Line 196: Recommended language change to emphasize early in sentence re: being underpowered.

Response: We appreciate the editor's revision.

12. Line 201: Interesting that due to small n that these numbers, including the CI are identical to the whole group. You talk about the CI being wide here—but it's the same. Is this perhaps a typo? If the CI is wide for subgroup, it would be wide for the whole group also, if identical.

Response: We appreciate the clarification. While the number needed to treat is similar from the overall and those without complications after randomization, the 95% confidence interval does differ, slightly.

	Number Needed to Treat	95% Confidence Interval
Overall (N = 206)	5.2	3.4-11.0
Without any complications after randomization (N = 141)	5.1	3.2-12.8

We have revised the sentence (with the new number underlined): The number needed to treat was also 5 women (95% CI 3– 13).

13. Line 226: You have retained the “two step schema” terminology here, instead of referring to routine care. Was this an oversight or did you have a reason to retain it?

Response: We apologize this was an oversight. This revised sentence is: Our randomized trial suggests that among women with uncomplicated pregnancies at 24.0 - 30.6 weeks, serial third-trimester ultrasound examinations are more likely to identify abnormalities of fetal growth or amniotic fluid than routine care.

14. Line 237: Odd phrasing to suggest that a newborn can have a stillbirth. This gets a bit into some nuance here. Are sonographically LGA fetuses more likely to be stillborn or have neonatal morbidities independent of maternal diabetes? We know that SGA newborns are more likely to have these problems, but you are identifying FGR fetuses. The point of trying to identify aberrations of fetal growth and fluid problems are to put into place perinatal care steps to prevent stillbirth and neonatal morbidity. Do you mean to be talking about neonatal SGA and LGA or do you mean to be talking about FGR and sonographic LGA here?

Response: This is an exceptionally good question by the Editor. Let me take several components of the remark above, answer it individually, and then sum it up.

1. A stillborn at birth, we think, is a newborn. Stated alternatively, newborns can have Apgar of 0, 0, and 0.
2. Fetuses with estimated fetal weight < 5th or > 95th percentile are at risk for stillbirth (reference 11 being the best for it is prospective and multi-center) and when born they are newborn. Additional examples for EFW < 10th percentile being linked with stillbirth are GRITT and TRUFFLE trials.
3. Newborns with actual weight < 10th percentile or > 90th percentile are at increased risk of being stillborn (ACOG practice bulletin on fetal growth restriction and macrosomia) and then being newborn.

Thus, respectfully, we submit that our original sentence (line 241-242) is accurate: SGA and LGA newborns are significantly more likely to have stillbirths and neonatal morbidities (1,11,21).

Alternatively, we could say: Fetuses and newborns with growth abnormalities are more likely to have stillbirths and neonatal morbidities.

15. Line 247-251: This just seems to flow better. Is it OK with you?

Response: We appreciate the suggestion. Yes this is acceptable with me.

16. Line 253-222: Please avoid single sentence paragraphs.

Response: We apologize. This was meant to be the last sentence of the above paragraph. It is now line 254-257.

17. Line 272: Also lack of blinding or allocation concealment by abstractor of data.

Response: We appreciate the Editor's suggestion. We have added this sentence on line 277-278.

18. Line 278: How do you know they are accurate? Is this generalizable?

Response: The Editor raises a good question about the accuracy and generalizability of results of randomized trial. Perhaps a better word than "accurate" is unbiased. Hence, we have revised the sentence, with new words being underlined: "Being a randomized trial, our results provide unbiased estimates of the rate of the composite outcome of FGR, LGA, oligo- or polyhydramnios in uncomplicated pregnancies at 24-30.6 weeks (lines 288-290)."

Regarding the question about whether the results are generalizable, our sentence does not imply it or we did not mean to imply that with the word "accurate."

19. Appendix (Page 24): Your appendixes can stay in print, since your manuscript isn't overly long. The appendixes have been incorporated into the manuscript as a box and tables, and the tables/appendixes were renumbered.

Response: Thank you for that revision.

FROM RESPONSE DATED SEPTEMBER 5, 2018

RE: Serial Third-Trimester Ultrasound Compared With Routine Care in Uncomplicated Pregnancies: A Randomized Controlled Trial

Dear Ms. Denise Shield and Dr. Nancy C. Chescheir:

Thank you for considering our manuscript and your thoughtful edits / questions, which have truly enhanced the quality of the manuscript and taught us.


Below you will find point-by-point response to your editorial questions.

Please do not hesitate to contact me if I can be of any further assistance.

Looking forward to seeing the manuscript in print!

Sincerely,

Olaide Ashimi Balogun, M.D.



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- 8a: What method was used to generate the random allocation sequence? (Coin flip? Computer program and if so which one?)

Response: Thank you for inquiring about how the random allocation sequence was generated. As noted in the revisions above computer Program, RedCap (Research Electronic Data Capture)

- 9. Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned.

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Commented [c1]: Please see suggested changes. The statistician created the randomization allocation sequence. Please see question in last line. It seems like the study was unblinded entirely. If so, please so state. Also in the discussion then, please list that as a limitation and explain why the abstractor, sonographer, and sonologists couldn't be blinded as these are limitations.

Commented [Oab2R1]: You are correct in your statements and we have edited the statement to clarify the study was not blinded. This new statement is underlined. Finally we stated this as a limitation and explained why in lines 293-300 in the discussions section.

Commented [c3]: Official name is REDCap

Response: Everyone but the statistician was not blinded to the allocation sequence. Once patients were consented to the study, their information was entered into computerized system, RedCap, to allocate them to Control vs. Intervention group. RedCap (Research Electronic Data Capture), is a secure web application for building and managing online surveys and databases. After allocation was made to either group, neither the women nor sonographers performing the US were blinded to the study. The person abstracting the data was not blinded.

Commented [c4]: Don't you mean "was not blinded"?

Commented [Oab5R4]:

Commented [Oab6R4]: Yes, you are correct in this statement and it has been clarified in the manuscript.

6. Line 133: Didn't you do standardize fetal biometry? It was just amniotic fluid measurement that wasn't standardized if I recall from first draft. If so, please state.

Response: The Editor has a nuanced question, which needs clarification. For the purpose of the trial, the following were not standardized: measurements of biometric parameters, amniotic fluid and FHM. Thus, we have revised the statement (underlined words are new): To reflect daily clinical practice standardization of measurements of biometric parts, amniotic fluid, or FHM was not done for this trial (lines 134-136).

7. Line 148: This non-blinded abstractor should be listed as a potential limitation in the discussion.

Response: Thank you for suggestion, we have made this revision in line 280.

8. Line 185-187: Move the highlighted statement to after the part about demographics.

Response: Thank you for this suggestion. This has been revised and moved to line 181-183.

9. Line 192: On line 189, you ordered the results as Intervention group vs control (27% v 8%) but elsewhere, you order it (Control vs Intervention) (at least that what it seems to be). Please be consistent as it is quite confusing this way. Convention is that you report Control vs Intervention in the results.

Response: The editor's comment about being consistent and compliant with convention is understandable and we have been compliant with it in almost all instances. With the primary composite outcome, however, because of relative risk is > 1 and because of our emphasis is that the outcome is significantly more common with intervention (27%) than control (8%), we have chosen to reverse the order.

If we stayed with the convention, than the conclusion would be with routine care the primary composite outcome is significantly less than with intervention, which is somewhat of a defeatist and deflating conclusion.

Thus, while we will always defer to the editors, please permit us to be unconventional with this.

I am not entirely certain I understand what you mean here—the results are the results whether you present them in one direction or another. However, as an example of why its important to be consistent please note the following. I am OK with you being unconventional by reporting Intervention vs routine results but I have to insist that you be consistent and clear in each description what is being compared to what to result in the RR's you report. True in text and in table.

Numbering may differ a bit.

Line 266-267: You report your RR Intervention vs Routine

Line 270" I believe you are reporting your RR in terms of Routine vs Intervention.

Line 313: You seem to be re porting Routine vs Intervention

Line 315-317: Routine v intervention

Line 323: No data provided other than P value so I don't know what to make of it.

Line 329-330: you give a p value but no indication of order of comparison

Response: We now understand what you mean when you are saying making the reporting of results order consistent throughout the paper. We have edited the results section to read as follows:

—The primary composite outcome was more frequently identified among women who had serial ultrasound examinations than those who received routine care (27% vs. 8%; RR 3.4; 95% CI 1.6-7.2). The number needed to treat was five women (95% CI 3 to 11). Although the study was not powered to detect differences in the individual components of the composite outcome, there was a difference in identification of polyhydramnios between the serial ultrasound examination and routine care (11% vs 2%; RR 5.4; 95% CI 1.2-23.7). No significant difference in the detection of FGR, LGA, and oligohydramnios was noted. (Table 4). Analysis limited to women who did not develop any complications after randomization (e.g. preterm labor or hypertensive disease) also indicated the primary composite outcome was significantly more frequent among women who serial ultrasound than routine care (27% vs. 8%; RR 3.7 (1.5 – 9.4). The detection of polyhydramnios differed between the two groups but the 95% confidence interval was

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Commented [NCC7]: AQ: On line 189, you ordered the results as Intervention group vs control (27% v 8%) but elsewhere, you order it (Control vs Intervention) (at least that what it seems to be). Please be consistent as it is quite confusing this way. Convention is that you report Control vs Intervention in the results.

Commented [Oab8R7]: **Response:** The editor's comment about being consistent and compliant with convention is understandable and we have been compliant with it in almost all instances. With the primary composite outcome, however, because of relative risk is > 1 and because of our emphasis is that the outcome is significantly more common with intervention (27%) than control (8%), we have chosen to reverse the order.

If we stayed with the convention, than the conclusion would be with routine care the primary composite outcome is significantly less than with intervention, which is somewhat of a defeatist and deflating conclusion.

Thus, while we will always defer to the editors, please permit us to be unconventional with this.

Commented [NCC9]: AQ: Recommended language change to emphasize early in sentence re: being underpowered.

Commented [Oab10R9]: We appreciate the editor's revision.

Commented [RZ11R9]: AUTHOR APPROVES.

Commented [NCC12]: This is a subgroup analysis, not described in the methods section. See Consort 12b. 12b. You 12b

Commented [Oab13R12]: Subgroup analysis was done using the same methods for the primary analysis. This was mentioned in line 167.

Commented [RZ14R12]: AUTHOR HAS ADDRESSED EARLIER IN THE TEXT.

wide due to the sample size (Table 5). The number needed to treat was also 5 women (95% CI 3–13). Pre-specified composite maternal morbidity was similar in both groups (9% in both serial ultrasound examinations vs routine care group; RR 1.0; 95% CI 0.4–2.3) but we were not powered to detect a difference. There were no episodes of deep venous thrombus or pulmonary embolism, admission to the intensive care unit, or maternal deaths in either groups. The pre-specified composite neonatal morbidity was also similar in both groups (1% in serial ultrasound exam group vs. 4% in routine care group; RR 0.2; 95% CI 0.03–2.1) but we were underpowered to detect a difference. The GA when the initial sonographic abnormal condition was noted differed between the groups ($P = 0.02$). *The gestational age epoch (< 32.0, 32.0 to 34.6, 35.0 to 36.6, or at least 37.0 weeks) when the abnormal condition was initially identified differed between the groups ($P = 0.02$).* The rate of having biophysical profile or umbilical artery Doppler, because of the abnormality noted on sonographic examination (i.e. polyhydramnios or IUGR), were similar between the two groups (Table 7).

Commented [c15]: AQ: Please provide the weeks at ID, not just the p values.

Commented [CSP16R15]: Dr. Chescheir we have revised the sentence and hopefully it is more understandable. Since $P = 0.02$ is from chi square test for trend, we can only provide the GA by groups. We sincerely apologize for any opacity and truly appreciate all suggestions to improve our syntax. We would like to replace this statement with the highlighted sentence.

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10. Line 195: Recommended language change to emphasize early in sentence re: being underpowered.

Response: We appreciate the editor's revision.

11. Line 196: Recommended language change to emphasize early in sentence re: being underpowered.

Response: We appreciate the editor's revision.

12. Line 201: Interesting that due to small n that these numbers, including the CI are identical to the whole group. You talk about the CI being wide here—but it's the same. Is this perhaps a typo? If the CI is wide for subgroup, it would be wide for the whole group also, if identical.

Response: We appreciate the clarification. While the number needed to treat is similar from the overall and those without complications after randomization, the 95% confidence interval does differ, slightly.

	Number Needed to Treat	95% Confidence Interval
Overall (N = 206)	5.2	3.4-11.0
Without any complications after randomization (N = 141)	5.1	3.2-12.8

We have revised the sentence (with the new number underlined): The number needed to treat was also 5 women (95% CI 3– 13).

13. Line 226: You have retained the “two step schema” terminology here, instead of referring to routine care. Was this an oversight or did you have a reason to retain it?

Response: We apologize this was an oversight. This revised sentence is: Our randomized trial suggests that among women with uncomplicated pregnancies at 24.0 - 30.6 weeks, serial third-trimester ultrasound examinations are more likely to identify abnormalities of fetal growth or amniotic fluid than routine care.

14. Line 237: Odd phrasing to suggest that a newborn can have a stillbirth. This gets a bit into some nuance here. Are sonographically LGA fetuses more likely to be stillborn or have neonatal morbidities independent of maternal diabetes? We know that SGA newborns are more likely to have these problems, but you are identifying FGR fetuses. The point of trying to identify aberrations of fetal growth and fluid problems are to put into place perinatal care steps to prevent stillbirth and neonatal morbidity. Do you mean to be talking about neonatal SGA and LGA or do you mean to be talking about FGR and sonographic LGA here?

Response: This is an exceptionally good question by the Editor. Let me take several components of the remark above, answer it individually, and then sum it up.

1. A stillborn at birth, we think, is a newborn. Stated alternatively, newborns can have Apgar of 0, 0, and 0.
2. Fetuses with estimated fetal weight < 5th or > 95th percentile are at risk for stillbirth (reference 11 being the best for it is prospective and multi-center) and when born they are newborn. Additional examples for EFW < 10th percentile being linked with stillbirth are GRITT and TRUFFLE trials.
3. Newborns with actual weight < 10th percentile or > 90th percentile are at increased risk of being stillborn (ACOG practice bulletin on fetal growth restriction and macrosomia) and then being newborn.

Thus, respectfully, we submit that our original sentence (line 241-242) is accurate: SGA and LGA newborns are significantly more likely to have stillbirths and neonatal morbidities (1,11,21).

Alternatively, we could say: Fetuses and newborns with growth abnormalities are more likely to have stillbirths and neonatal morbidities.

My point is that the fetus or newborn is stillborn and the mother has a stillbirth. Please rephrase.

RESPONSE: Truly sorry we missed the nuanced difference between stillborn and stillbirth. Darn English as a second language or daydreaming during English classes! We have learned and rephrased (new words are bolded): “SGA and LGA newborns are significantly more likely to **be stillborn** and **have** neonatal morbidities (1,11,21).”

15. Line 247-251: This just seems to flow better. Is it OK with you?

Response: We appreciate the suggestion. Yes this is acceptable with me.

16. Line 253-222: Please avoid single sentence paragraphs.

Response: We apologize. This was meant to be the last sentence of the above paragraph. It is now line 254-257.

17. Line 272: Also lack of blinding or allocation concealment by abstractor of data.

Response: We appreciate the Editor’s suggestion. We have added this sentence on line 277-278.

18. Line 278: How do you know they are accurate? Is this generalizable?

Response: The Editor raises a good question about the accuracy and generalizability of results of randomized trial. Perhaps a better word than “accurate” is unbiased. Hence, we have revised the sentence, with new words being underlined: “Being a randomized trial, our results provide unbiased estimates of the rate of the composite outcome of FGR, LGA, oligo- or poly-hydramnios in uncomplicated pregnancies at 24-30.6 weeks (lines 288-290).”

Regarding the question about whether the results are generalizable, our sentence does not imply it or we did not mean to imply that with the word “accurate.”

Response: We would like to state the following instead:

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“Being a randomized trial where neither participants nor clinicians were blinded, our results provide reasonable estimates of the rate of the composite outcomes of FGR, LGA, oligo- or poly-hydramnios in uncomplicated pregnancies which are managed routinely or with serial ultrasounds examinations in the third trimester.”

19. Appendix (Page 24): Your appendixes can stay in print, since your manuscript isn't overly long. The appendixes have been incorporated into the manuscript as a box and tables, and the tables/appendixes were renumbered.

Response: Thank you for that revision.

From: Stephanie Casway
To: [REDACTED]
Subject: RE: O&G Figure Revision: 18-1138
Date: Tuesday, August 21, 2018 8:36:00 AM
Attachments: [18-1138 Legend.pdf](#)

Good Morning Olaide,

We have included the explanation for comorbidity in the legend (see attached). If you have any questions or concerns, just let me know. Thanks so much!

From: Ashimi, Olaide A [REDACTED]
Sent: Monday, August 20, 2018 3:47 PM
To: Stephanie Casway <SCasway@greenjournal.org>
Subject: Re: O&G Figure Revision: 18-1138

Hello Ms. Casway,

The figure itself looks fine, however the explanation that I had for co-morbidity was left out. If you don't think that it is necessary, then that is fine. This means we need to remove the asterisk from co-morbidity. Another option is to list/state that the co-morbidities are listed in Appendix 1. Please let me know your thoughts.

Thank you,

Olaide

Olaide Ashimi Balogun, MD

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

From: Stephanie Casway <SCasway@greenjournal.org>
Sent: Monday, August 20, 2018 1:33 PM

To: Ashimi, Olaide A

Subject: O&G Figure Revision: 18-1138

Good Afternoon Dr. Balogun,

Your figure has been edited, and a PDF of the figure is attached for your review. Please review the figure CAREFULLY for any mistakes.

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

To avoid a delay, I would be grateful to receive a reply no later than Wednesday, 8/22. Thank you for your help.

Best wishes,

Stephanie Casway, MA
Production Editor

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