RE: Manuscript Number ONG-18-2029

Effect of a Delayed Cord Clamping Protocol on Hyperbilirubinemia in Term Neonates

Dear Dr. Fitzmaurice:

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 Dec 20, 2018, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This is a single institution study evaluating neonatal jaundice and costs after the implementation of universal delayed cord clamping in term infants. This was a retrospective cohort examining pre and post cord clamping implementation. Findings included increased bilirubin levels, increased jaundice, and increased blood draws but no increase in phototherapy or costs. This adds to the existing small body of literature where there are limited increased risks to delayed cord clamping of most infants with some benefits albeit vague.

I'm not sure that you can discuss protocol compliance in a retrospective study although I understand that you are discussing adherence to the delayed cord clamping protocol.

Appropriately you did an a priori power analysis and decided that you could meet the calculation of 211 patients by a 3 month sample. Was the 245 you reviewed in each group, every eligible patient and if not, how did you pick which ones you would review.

In the interest of space, I would eliminate Tables 3 and 4 as they are well described in the body of the paper. I would also eliminate Figure 2 for similar reasons.

Reviewer #2: This article is similar in some ways to past publications/articles/guidelines with respects to delayed cord clamping in term infants resulting in increased bilirubin levels and increased diagnosis of jaundice.

This article is interestingly different from past studies in the following ways:

1) the authors a set time of delayed cord clamping ( 1 minute ) where as past studies have set the delay at much longer time ( 5 minutes ) or not set a specific delay time ( referenced as cessation of pulsation ).

2) the infant population studied is more applicable to the general obstetric population of all term deliveries without the exclusions listed lines 119-121, allowing general OB-GYN's to easier apply this study to their main patient populations as those exclusion criteria listed are often reasons for general practice physicians to not delay cord clamp for an infant.

3) the results showing no increase in incidence of phototherapy in addition to results about cost and length of stay that were addressed and discussed lines 242-252.
Study population differences in breast fed infants before and after protocol implementation was addressed nicely lines 231-239.

Reviewer #3: Review of ONG-18-2029
Effects of delayed cord clamping on term neonates

This is a retrospective study after the institution of delayed cord clamping in a university setting. The adherence to the protocol was an impressive 87%.

1. What was the rate of DCC in the first group? While it may not have been a protocol at the time and lines 106-7 suggest it was rare, there may have been individuals doing it, so that may have affected the comparison group. Lines 114-5 suggest DCC was added to the EMR. Prior to that, how was it determined if it was done on the pre-protocol group (I realize you can't be sure but there may have been some "early adopters" who did it to be ahead of the curve)?

2. You show some significant differences in various lab values, which may or may not have clinical significance. What is the rate of significant effects (blood transfusions, exchange transfusions). As a proponent of the "how do I use this paper to take care of patients" school of literature review, I am not seeing anything that suggests we really need to do DCC in term babies. You mention this on lines 240-1. Any comment on whether we should even be doing DCC in term infants would be appreciated, given the increased annoyance for the baby resulting from the increased testing that was done.

3. What were the levels at which phototherapy was instituted?

4. In Table 1, it seems to me that there is a high rate of cephalohematoma in both groups. How was this diagnosis made?

5. LOS for the mother is sometimes a problem, as there is attention placed on this nationally (CMS criteria). The difference is enough to make a difference in being able to get patients into the hospital in a timely fashion or not. Do you think this is another reason to not do the DCC?

6. Figure 1 should probably have the initial boxes labeled as pre and post protocol like they are in Figure 3 (I'm making an assumption the path on the left is the pre-protocol).

This is a nicely done study with results that are slightly concerning. There is no question that it is a real effect of the DCC to test more, which is a concern for the baby and the parents, but if it makes no substantial clinical difference, we have to ask how much testing is needed and concomitantly, is there a reason to do DCC when it results in more testing with seemingly no change in relevant outcomes. The question is how safe do we have to be? There may be some advantage in less developed countries to do DCC. Perhaps there is a small advantage in the long run to using the DCC if we looked at large populations, but this study can't answer that question. If there are increased interventions that occur because of DCC without obvious long-term benefits or a reduction of significant risks (kernicterus or even transfusions or phototherapy), perhaps we shouldn't be doing this at all. I think some comment on this issue would benefit this paper, using the efficient use of medical care lens to decide how much to push this procedure (I'm not just a grinch; I do DCC with every delivery, but I do wonder if it is worthwhile - this seems to suggest it may not really be worth it). Thanks for your hard work.

Reviewer #4: There is no neonatologist in the authorship. Were they involved in defining the parameters that may be important to determine if there are adverse neonatal effects?

I would ask the authors to clearly spell out their objectives in the introduction. "effect of a delayed cord clamping protocol" doesn't seem enough. Are the authors trying to prove that delayed cord clamping has no adverse effects or are they trying to prove that it does have more adverse effects. Are they trying to suggest that delayed cord clamping is safe or is not safe? What is their hypothesis? Why did they do this study?

The authors should explain the significant differences between the transcutaneous bilirubin measurements and the serum bilirubin measurements. Which one is more meaningful in the context of this study? How should results be interpreted?

In table 2, the serum bilirubin levels were not different but clinical jaundice and "any serum bilirubin" were higher in the breast fed patients. The authors seem to downplay this significance. There's important physiology involved and may have more clinical implications. If all term babies are to have delayed cord clamping should patients who intend to breastfeed be excluded? The authors could spend some time discussing

The last paragraph in the discussion could be more forceful in questioning the benefits of DCC in term infants. This goes back to what the authors' intent is for doing this study.
STATISTICAL EDITOR COMMENTS:

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

Tables 2, 3: Should clearly delineate the primary (peak TcBili) from the secondary outcomes. Were the blood losses normally distributed? If not, should cite as median(IQR or range) and test non-parametrically.

Table 4: Were length of stay or costs normally distributed? If not, should cite as median(IQR or range) and test non-parametrically.

Fig 2: Should cite the median(IQR) number of blood draws for each cohort.

Tables 2, 3: The frequency of phototherapy was low and there was insufficient stats power to generalize this finding. Also, the counts are too few to allow for adjustment for multiple (or even 1) adjustors in the aOR model. For the samples at hand, the post-protocol group would had to have a phototherapy rate >13% to meet criteria for power of 80%. Put another way, in order to detect a pos-protocol phototherapy rate of 2x the pre-protocol rate, the sample sizes would have to be ~ twice as large as in the present study. In short, one cannot conclude that frequency of phototherapy would not be greater if post-protocol cord clamping were universally implemented.

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.

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

- please state how soon after implementation of the protocol that you did this study. An 88% compliance rate seems quite high (congrats) if it was very soon after the this was implemented.

- In the abstract, please provide absolute numbers as well as which ever effect size you are reporting + Confidence intervals. P values may be omitted for space concerns. By absolute values, I mean something like xx (outcome in exposed)/yy(outcome in unexposed) (zz%) (Effect size= ; 95% CI=. ) An example might be: Outcome 1 was more common in the exposed than the unexposed 60%/20% (Effect size=3;95% CI 2.6-3.4)

- you mention LOS for mother and neonate in the methods but provide no results.

- 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.

- The result or the consequence? For some reason that I don't completely understand, the word "impact" has a lot of antibodies for the Journal, perhaps because it really refers to the a physical strike and what happens at the surface.

- whose recommendations?

- why this group?

- Not sure how this was done. You had an a priori number determined. Startin on the first day of the collection period, did you do sequential patients or if that would exceed the number needed, did you randomly select patients to include? Please expand.

- you don't mention discharge on different days but you do report it. Please include if that was one of your outcomes

- It seems reasonable but could you explain why you used this screening test result as the primary outcome, rather than need for phototherapy or exchange transfusion?

- This seems a bit fortuitous since that was exactly your a prior number. Could you please elaborate more on how you got exactly to this number?
Since this is primarily an OB audience reading this (appropriately) could you please give us a sense of normal ranges of bilirubin in term babies?

- what result on the transcutaneous bili read prompts a serum read?

- this group was excluded overall, correct?

- estimated or quantified?

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. In your Abstract, please add the study period dates and the number of neonates.

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. Please include a completed STROBE checklist with your revision.

Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), and quality improvement in health care (ie, SQUIRE 2.0). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at http://ong.editorialmanager.com. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, CHEERS, or SQUIRE 2.0 guidelines, as appropriate.

6. 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.

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

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

8. 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).

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. Please provide a word count.

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

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

12. 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.

13. 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.

14. Figures 1-3 may be resubmitted as-is.

15. 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 Dec 20, 2018, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

2017 IMPACT FACTOR: 4.982
2017 IMPACT FACTOR RANKING: 5th out of 82 ob/gyn journals

In compliance with data protection regulations, please contact the publication office if you would like to have your personal information removed from the database.
Dr. Nancy C. Chescheir  
Editor-in-Chief  
Obstetrics & Gynecology  
409 12th Street, SW  
Washington, DC 20024-2188  

Re: Submission ONG-18-2029  

Dear Dr. Chescheir,  

Thank you for inviting us to revise our manuscript, “Effect of a Delayed Cord Clamping Protocol on Hyperbilirubinemia in Term Neonates” which is being resubmitted for consideration for publication to your journal, Obstetrics & Gynecology. We present the implementation of our universal delayed cord clamping protocol as well as a description of its impact in term neonates. This manuscript has not previously been published nor is it under consideration for publication elsewhere. Further, there are no financial conflicts of interest and the authors have nothing to disclaim. Each author further denies any potential conflicts of interest to disclose. The study described was approved by the institutional review board at the University of California, Irvine.

Responses to the comments by reviewers follow:

Reviewer #1:  
I'm not sure that you can discuss protocol compliance in a retrospective study although I understand that you are discussing adherence to the delayed cord clamping protocol.

_The term compliance has been replaced with the term adherence where appropriate throughout the manuscript._

Appropriately you did an a priori power analysis and decided that you could meet the calculation of 211 patients by a 3 month sample. Was the 245 you reviewed in each group, every eligible patient and if not, how did you pick which ones you would review.

_Following the original identification of the eligible charts by medical records staff based on ICD codes, the charts were reviewed in random order until enough charts were reviewed and determined to be eligible for inclusion that the pre-specified sample size was met. The text surrounding this issue is clarified on lines 136-141._
In the interest of space, I would eliminate Tables 3 and 4 as they are well described in the body of the paper. I would also eliminate Figure 2 for similar reasons.

Table 3 has been eliminated per your recommendation. Table 4, particularly the details of the statistical analyses, is not completely described in the body of the paper, and was left in. Authors feel that the graphic representation of the data in Figure 2 does contribute to readers’ understanding. Since the data described in Figure 2 was evaluated non-parametrically, simply describing the median number of blood draws for each group would not adequately highlight the fact that more serum blood draws were performed on individuals in the post-protocol group. We therefore decided to leave Figure 2 in the manuscript.

Reviewer #2:

This article is similar in some ways to past publications/articles/guidelines with respects to delayed cord clamping in term infants resulting in increased bilirubin levels and increased diagnosis of jaundice.

This article is interestingly different from past studies in the following ways:

1) the authors a set time of delayed cord clamping (1 minute) where as past studies have set the delay at much longer time (5 minutes) or not set a specific delay time ( referenced as cessation of pulsation).

2) the infant population studied is more applicable to the general obstetric population of all term deliveries without the exclusions listed lines 119-121, allowing general OB-GYN's to easier apply this study to their main patient populations as those exclusion criteria listed are often reasons for general practice physicians to not delay cord clamp for an infant.

3) the results showing no increase in incidence of phototherapy in addition to results about cost and length of stay that were addressed and discussed lines 242-252.

Study population differences in breast fed infants before and after protocol implementation was addressed nicely lines 231-239.

Thank you for your comments. No changes were made based on this reviewer’s feedback.

Reviewer #3:

1. What was the rate of DCC in the first group? While it may not have been a protocol at the time and lines 106-7 suggest it was rare, there may have been individuals doing it, so that may have affected the comparison group. Lines 114-5 suggest DCC was added to the EMR. Prior to that, how was it determined if it was done on the pre-protocol group (I realize you can't be sure but there may have been some "early adopters" who did it to be ahead of the curve)?

An institutional quality improvement survey of the obstetrics faculty in May 2016 revealed 25/28 providers reported never or rarely performing delayed cord clamping in term infants. Because the EMR did not have a specific location for data capture of delayed cord clamping prior to protocol initiation, the only method for determining whether or not delayed cord clamping had occurred
would be in the narrative of the delivery note or neonatal admission note. These documents were reviewed for all individuals included in the “pre-protocol” group and there were no cases in which delayed cord clamping was reported in these individuals. However, this data sourcing is subject to the limitations of retrospective data collection and may have missed early adopters if their use of delayed cord clamping was not adequately documented. Therefore, a description of this limitation was added to lines 142-147 in the methods, and lines 299-302 in the discussion.

2. You show some significant differences in various lab values, which may or may not have clinical significance. What is the rate of significant effects (blood transfusions, exchange transfusions). As a proponent of the "how do I use this paper to take care of patients" school of literature review, I am not seeing anything that suggests we really need to do DCC in term babies. You mention this on lines 240-1. Any comment on whether we should even be doing DCC in term infants would be appreciated, given the increased annoyance for the baby resulting from the increased testing that was done.

   In our institution, the rate of phototherapy is approximately 5%. The rate of blood transfusion and exchange transfusions in term infants is very low, well under 1%. The data presented in the present study is therefore not powered to detect group differences in either of these outcomes. The text has been edited to reflect that our outcome is a laboratory outcome which is distinct from these rarer clinical outcomes. As far as the applicability of these data to the practice of delayed cord clamping, prior literature suggests that the benefit of delayed cord clamping in term neonates may include a reduction in iron-deficiency anemia and long term neurocognitive benefit. Neither of these long term clinical outcomes were evaluated in the present study. Therefore, we do not believe the results from this study can be used to suggest that delayed cord clamping in term infants should not be performed. However, we do believe that the long term impact of delayed cord clamping requires further study prior to its universal recommendation, particularly given the increase in neonatal blood draws demonstrated by our data. The text has been updated to clarify this position on lines 310-316.

3. What were the levels at which phototherapy was instituted?

   Paragraph added to address this question, see lines 160-172.

4. In Table 1, it seems to me that there is a high rate of cephalohematoma in both groups. How was this diagnosis made?

   The diagnosis of cephalohematoma is a clinical diagnosis that is indicated on the neonatal admission documentation. Because it is a clinical diagnosis that does not require confirmation on imaging, it is possible that the data reported are an overestimate of the true prevalence. The reason we included this parameter in our data is that infants with cephalohematomas are at an increased risk of hyperbilirubinemia and therefore a difference in the rate of cephalohematoma between the two groups would confound the results. There was no statistically significant difference between the groups and therefore the presence of cephalohematoma likely did not influence the bilirubin levels reported in our groups. Table 1 has been edited to reflect that it is a clinical diagnosis.

5. LOS for the mother is sometimes a problem, as there is attention placed on this nationally (CMS criteria). The difference is enough to make a difference in being able to get patients into the hospital in a timely fashion or not. Do you think this is another reason to not do the DCC?
The half day increase in maternal length of stay in the post-protocol group is interesting because of the national pressure for timely discharge. Whether or not this increase in length of stay is attributable to the delayed cord clamping is difficult to conclude based on this retrospective analysis due to the fact that it is likely multifactorial and was not the primary aim of this analysis. However this finding does speak to the potential cost implications of a universal delayed cord clamping protocol, as noted when we mention discharge-by-noon initiative on line 291. The discussion has been updated to further highlight that these differences need to be further explored, lines 310-316.

6. Figure 1 should probably have the initial boxes labeled as pre and post protocol like they are in Figure 3 (I'm making an assumption the path on the left is the pre-protocol).

Thank you for identifying this correction. The path on the left has been labeled pre-protocol.

This is a nicely done study with results that are slightly concerning. There is no question that it is a real effect of the DCC to test more, which is a concern for the baby and the parents, but if it makes no substantial clinical difference, we have to ask how much testing is needed and concomitantly, is there a reason to do DCC when it results in more testing with seemingly no change in relevant outcomes. The question is how safe do we have to be? There may be some advantage in less developed countries to do DCC. Perhaps there is a small advantage in the long run to using the DCC if we looked at large populations, but this study can't answer that question. If there are increased interventions that occur because of DCC without obvious long-term benefits or a reduction of significant risks (kernicterus or even transfusions or phototherapy), perhaps we shouldn't be doing this at all. I think some comment on this issue would benefit this paper, using the efficient use of medical care lens to decide how much to push this procedure (I'm not just a grinch; I do DCC with every delivery, but I do wonder if it is worthwhile - this seems to suggest it may not really be worth it). Thanks for your hard work.

Reviewer #4:

There is no neonatologist in the authorship. Were they involved in defining the parameters that may be important to determine if there are adverse neonatal effects?

Neonatologists were instrumental in the development of our institution’s delayed cord clamping protocol, as described in lines 110-112. However, they did not contribute to the design or performance of this study. Potential confounders and outcomes were based primarily on prior studies of delayed cord clamping.

I would ask the authors to clearly spell out their objectives in the introduction. "effect of a delayed cord clamping protocol" doesn't seem enough. Are the authors trying to prove that delayed cord clamping has no adverse effects or are they trying to prove that it does have more adverse effects. Are they trying to suggest that delayed cord clamping is safe or is not safe? What is their hypothesis? Why did they do this study?

Thank you for this feedback. Universal delayed cord clamping has been recommended despite a relative paucity of data regarding its benefit in term infants. Our hypothesis was that delayed cord clamping would be associated with increased neonatal hyperbilirubinemia (as measured in transcutaneous bilirubin, clinical jaundice) which may lead to increased need for serum blood draws, phototherapy, increased length of stay and hospitalization costs. Our objective was to
further inform the discussion as to whether the benefits of universal delayed cord clamping outweighs these potential risks. The introduction and conclusion have been edited in lines 99-101 and 310-316, respectively.

The authors should explain the significant differences between the transcutaneous bilirubin measurements and the serum bilirubin measurements. Which one is more meaningful in the context of this study? How should results be interpreted?

Transcutaneous bilirubin is a universally-applied screening test for hyperbilirubinemia, while serum bilirubin is the diagnostic test. Only a subset of infants with suspected hyperbilirubinemia have serum bilirubin measurements drawn, so mean serum measurements are predictably higher than mean transcutaneous measurements. An explanation of when and why each test is obtained has been added to the methods section, lines 160-172, and the screening vs. diagnostic test distinction has been added to the interpretation at the beginning of the discussion, lines 253-254.

In table 2, the serum bilirubin levels were not different but clinical jaundice and "any serum bilirubin" were higher in the breast fed patients. The authors seem to downplay this significance. There's important physiology involved and may have more clinical implications. If all term babies are to have delayed cord clamping should patients who intend to breastfeed be excluded? The authors could spend some time discussing

Thank you for this feedback. We agree that breastfeeding physiology is an important confounder in the relationship between delayed cord clamping and hyperbilirubinemia. Breastfeeding can be a cause of jaundice, and the breastfeeding rate itself can be impacted by intervention for jaundice (such as the introduction of formula). In order to account for this confounding, we used maternal feeding method as a covariate. Table 2 includes both the unadjusted analyses (in which feeding method is not considered in the relationship between jaundice, bilirubin levels and delayed cord clamping) as well as the adjusted analyses. In the adjusted analyses, the relationship between delayed cord clamping and jaundice/transcutaneous bilirubin levels remained significant, indicating that there is a correlation between delayed cord clamping and markers of hyperbilirubinemia, independent of the increase in exclusive breastfeeding noted in the post-protocol group. We feel that using feeding method as a covariate is the most transparent, generalizable way to account for confounders when exploring the relationship between delayed cord clamping and hyperbilirubinemia. We don't feel that this study alone supports a conclusion that the practice of delayed cord clamping should be limited to those planning to supplement or exclusively feed with formula, but absolutely agree that the interaction of delayed cord clamping and feeding method needs to be further investigated. This was added to the discussion in lines 278-280.

The last paragraph in the discussion could be more forceful in questioning the benefits of DCC in term infants. This goes back to what the authors' intent is for doing this study.

Although this study was underpowered to detect significant differences in serious neonatal implications of delayed cord clamping (phototherapy, transfusion exchange), we agree that there are some implications of delayed cord clamping for infants and their families that may outweigh the as-yet theoretical benefits. We have strengthened the last paragraph as can be seen in lines 310-316.

STATISTICAL EDITOR COMMENTS:

Tables 2, 3: Should clearly delineate the primary (peak TcBili) from the secondary outcomes. Were
the blood losses normally distributed? If not, should cite as median(IQR or range) and test non-parametrically.

Table 2 has been edited to identify peak TcBili as the primary outcome. Table 3 has been removed per the recommendation of another reviewer. The blood loss in each group demonstrated a slight skew but was analyzed using a t-test given the large sample size in accordance with the assumptions of the central limit theorem. These data have been re-analyzed using non-parametric tests and the results of Table 2 have been updated accordingly. The corresponding lines in the text have also been updated.

Table 4: Were length of stay or costs normally distributed? If not, should cite as median(IQR or range) and test non-parametrically.

The maternal length of stay was normally distributed so was analyzed using parametric tests. The neonatal lengths of stay and costs data demonstrated a slight skew. They were initially analyzed using t-tests given the large sample size and the fact that the results of nonparametric testing are more difficult to clinically interpret. These data have been reanalyzed using non-parametric tests and Table 4 (now Table 3) has been updated.

Fig 2: Should cite the median(IQR) number of blood draws for each cohort.

The medians and IQRs have been added to Figure 2.

Tables 2, 3: The frequency of phototherapy was low and there was insufficient stats power to generalize this finding. Also, the counts are too few to allow for adjustment for multiple (or even 1) adjustors in the aOR model. For the samples at hand, the post-protocol group would had to have a phototherapy rate >13% to meet criteria for power of 80%. Put another way, in order to detect a post-protocol phototherapy rate of 2x the pre-protocol rate, the sample sizes would have to be ~ twice as large as in the present study. In short, one cannot conclude that frequency of phototherapy would not be greater if post-protocol cord clamping were universally implemented.

Thank you for this feedback. We agree that although we did not demonstrate an increase in phototherapy in the post-protocol group, a relationship between delayed cord clamping and phototherapy may exist but we were underpowered to detect such a relationship. We have edited the discussion in order to clarify this point (lines 257-259).

EDITOR COMMENTS:

Abstract

- please state how soon after implementation of the protocol that you did this study. An 88% compliance rate seems quite high (congrats) if it was very soon after the this was implemented.

The abstract is edited to include this information.

- In the abstract, please provide absolute numbers as well as which ever effect size you are reporting + Confidence intervals. P values may be omitted for space concerns. By absolute values, I mean
something like
xx (outcome in exposed)/yy(outcome in unexposed) (zz%) (Effect size= ; 95% CI= .) An example might be: Outcome 1 was more common in the exposed than the unexposed 60%/20% (Effect size=3;95% CI 2.6-3.4)

These edits have been made and formatted as above for categorical variables. For continuous variables, effect size is described as absolute value ±SD.

- you mention LOS for mother and neonate in the methods but provide no results.

In the interest of keeping to the word count, the list of secondary outcomes for the abstract was shortened to most relevant/interesting.

Introduction

- 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.

  DCC has been changed to delayed cord clamping throughout the manuscript. TcBili and sBili were also removed from the text, since they are similarly not on the list.

- The result or the consequence? For some reason that I don't completely understand, the word "impact" has a lot of antibodies for the Journal, perhaps because it really refers to the a physical strike and what happens at the surface.

  The word impact has been changed to “effect” or “affect,” as appropriate, throughout the manuscript.

- whose recommendations?

  ACOG, this has been updated (line 95).

Materials and Methods

- why this group?

  The text has been updated to explain the rationale for the exclusion criteria in the protocol, lines 121-126.

- Not sure how this was done. You had an a priori number determined. Startin on the first day of the collection period, did you do sequential patients or if that would exceed the number needed, did you randomly select patients to include? Please expand.

  Patients were randomly selected, text has been expanded, lines 136-141.

- you don't mention discharge on different days but you do report it. Please include if that was one of your
outcomes

This secondary outcome has been added, line 158.

- It seems reasonable but could you explain why you used this screening test result as the primary outcome, rather than need for phototherapy or exchange transfusion?

Transcutaneous bilirubin was selected as the primary outcome in an attempt to balance obtaining clinically interesting results with maintaining a feasible sample size. Since phototherapy and exchange transfusion are relatively rare, the sample sizes would have needed to be prohibitively large to detect a reasonably small difference, but we felt that demonstrating a significant change in screening test results would support the need for further, prospective investigation of treatment outcomes in future studies. A brief explanation to this effect was added, lines 151-154.

Results
- This seems a bit fortuitous since that was exactly your a priori number. Could you please elaborate more on how you got exactly to this number?

Following the original identification of the eligible charts by medical records staff based on ICD codes, the charts were reviewed in random order until enough charts were reviewed and determined to be eligible for inclusion that the pre-specified sample size was met. The text surrounding this issue is clarified on lines 136-141.

- Since this is primarily an OB audience reading this (appropriately) could you please give us a sense of normal ranges of bilirubin in term babies?

Excellent point, thank you! A description of how we screened for hyperbilirubinemia and a general idea of normal values has been added to the methods section, lines 160-172.

- what result on the transcutaneous bili read prompts a serum read?

Also now described in the methods section, lines 160-172.

- this group was excluded overall, correct?

This group of individuals were excluded from receiving delayed cord clamping per protocol, but were not excluded from inclusion in the study cohorts. Our study cohorts included all term deliveries as identified by ICD codes. We did identify individuals that inappropriately received delayed cord clamping. The initial analysis included all individuals regardless of whether or not they received delayed cord clamping. The sub-analysis removed all individuals who should have been excluded from the delayed cord clamping protocol (based on predisposition to hyperbilirubinemia) and then compared those that received delayed cord clamping to those that received immediate cord clamping. Since monochorionic twins and abnormal placentations are delivered preterm, the exclusions are limited to infants of diabetic mothers. The text has been edited to make this more clear, line 223-227.

- estimated or quantified?
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.

   Opt-in, thank you.

3. In your Abstract, please add the study period dates and the number of neonates.

   The study periods and number of neonates have been added to the abstract.

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.

   Dr. Yang’s attestation is attached separately, thank you. As senior and corresponding author, I also affirm 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.

5. Please include a completed STROBE checklist with your revision.

   Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), and quality improvement in health care (ie, SQUIRE 2.0). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers.
where each item appears in the margin of the checklist. Further information and links to the checklists are available at https://urldefense.proofpoint.com/v2/url?u=http-3A__ong.editorialmanager.com&d=DwIGaQ&c=dzukdOe-KyRBOwGgecHzPA&r=skrqIAG3buG5CAHt8UgKzboMP8sPJ_bS1C_IOUIUzo&m=f538ikKOP7qiFbtdXCaD5edq764W8Gyc_iB6xnxzFJII&s=ta25rAjpXSx5vbR7Eju6XAq6bjFM06A0E_EU5Tpeiw&c=606f. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STAR, STROBE, CHEERS, or SQUIRE 2.0 guidelines, as appropriate.

* Included, see attachment. *

6. 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 https://urldefense.proofpoint.com/v2/url?u=http-3A__links.lww.com_AOG_A515&d=DwIGaQ&c=dzukdOe-KyRBOwGgecHzPA&r=skrqIAG3buG5CAHt8UgKzboMP8sPJ_bS1C_IOUIUzo&m=f538ikKOP7qiFbtdXCaD5edq764W8Gyc_iB6xnxzFJII&s=JyW0Dg7SJOBeE5Hw6aTWwpH4YyAsca-IR7FSO_JqJ0&c=606f, and the gynecology data definitions are available at https://urldefense.proofpoint.com/v2/url?u=http-3A__links.lww.com_AOG_A935&d=DwIGaQ&c=dzukdOe-KyRBOwGgecHzPA&r=skrqIAG3buG5CAHt8UgKzboMP8sPJ_bS1C_IOUIUzo&m=f538ikKOP7qiFbtdXCaD5edq764W8Gyc_iB6xnxzFJII&s=5Mh7PEmQQR6RZjszawrbMEnx4u_4JJrLJoASFOw8-A&c=606f.

* Acknowledged, thank you. *

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

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

* confirmed *

8. 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).

We have no acknowledgements, thank you.

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. Please provide a word count.

Abstract checked, word count 263.

10. Only standard abbreviations and acronyms are allowed. A selected list is available online at [https://urldefense.proofpoint.com/v2/url?u=http-3A__edmgr.ovid.com_ong_accounts_abbreviations.pdf&d=DwIGaQ&c=dzukdOe-KyRBOwGgecHzPA&r=skrqlAG3buG5CAx8UuqKzbOB8sPJ_bS1C_IOUIUzq&m=f538ikKOP7qiFbtdXCaD5eq764Ws8Gye_iB6xznZJl&f=HwyE7-Z_heHRVGbLmz4_bfLsfjBivLlgMxXm_lGwv&e=](https://urldefense.proofpoint.com/v2/url?u=http-3A__edmgr.ovid.com_ong_accounts_abbreviations.pdf&d=DwIGaQ&c=dzukdOe-KyRBOwGgecHzPA&r=skrqlAG3buG5CAx8UuqKzbOB8sPJ_bS1C_IOUIUzq&m=f538ikKOP7qiFbtdXCaD5eq764Ws8Gye_iB6xznZJl&f=HwyE7-Z_heHRVGbLmz4_bfLsfjBivLlgMxXm_lGwv&e=). 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.

Standard abbreviations have been confirmed. All other abbreviations have been removed.

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

The use of the virgule symbol was restricted to description of measurements.

12. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: [https://urldefense.proofpoint.com/v2/url?u=http-3A__edmgr.ovid.com_ong_accounts_table-5Fchecklist.pdf&d=DwIGaQ&c=dzukdOe-KyRBOwGgecHzPA&r=skrqlAG3buG5CAx8UuqKzbOB8sPJ_bS1C_IOUIUzq&m=f538ikKOP7qiFbtdXCaD5eq764Ws8Gye_iB6xznZJl&f=Vcn2eTpYfxhaOB6oOuFPIJzTcbUmqBvergPMYGYUY3c&e=](https://urldefense.proofpoint.com/v2/url?u=http-3A__edmgr.ovid.com_ong_accounts_table-5Fchecklist.pdf&d=DwIGaQ&c=dzukdOe-KyRBOwGgecHzPA&r=skrqlAG3buG5CAx8UuqKzbOB8sPJ_bS1C_IOUIUzq&m=f538ikKOP7qiFbtdXCaD5eq764Ws8Gye_iB6xznZJl&f=Vcn2eTpYfxhaOB6oOuFPIJzTcbUmqBvergPMYGYUY3c&e=). Table Checklist reviewed.

13. 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 [https://urldefense.proofpoint.com/v2/url?u=http-3A__www.acog.org_Resources-2DAnd-2DPublications&d=DwIGaQ&c=dzukdOe-KyRBOwGgexcHzPA&r=skrLAG3buG5Cat8UqKzboMP8sPJ_bS1C_IOU1Uzo&m=f538ikKOP7qiFbdtXCaD5edq764W8Gyc_iB6xnxzFIJl&s=tPUKvJuaW5RUuXdli62z0n_uMdoQ1TNpcmR4txuJRg&e=].

Reference 3 has been confirmed as current.

Thank you for considering this manuscript for your journal. We look forward to hearing from you.

Sincerely,

Laura Fitzmaurice, MD
Dear Ms. Zung,

Thank you again to you and the editors for the opportunity to improve and revise our manuscript further. We hope that these responses are satisfactory, and we are happy to cooperate with any further requests. Attached are our responses and the word document with tracked changes. I will send the updated figures one at a time because the files are large.

Thank you!

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

2. Dr. Chescheir has reviewed your responses to the Statistical Editor’s comments. She does not believe you have addressed these comments fully. Please make changes to the Tables and Figures based on his original requests.

   - Table 1: Are there any statistically significant or clinically important differences in baseline factors among these cases?

   We found no clinically meaningful difference in age, BMI, race, or comorbidities in the population at the different time points. Because our n’s are so large (57,569; 42,203; 80,178), we found statistical differences that are not meaningful (for example, that the rate of smoking decreased 0.9% across 5 years).
   We have updated the language in line 143 to be more specific. Our understanding is that p-values are typically not presented for a demographics table; however, since this is a persistent issue, we have added the p-values for table 2.

   - Fig 1, 2a, 2b: Either in the figure legends or within the graphs, should include a summary of the stats analysis of the time series.
   - For figs 2a, 2b, should include 95% CIs for the quarterly estimates of proportions.

   Thank you for the opportunity to further improve our manuscript, and many apologies for misunderstanding the initial instructions.
   We have added 95% confidence interval error bars to the figures.
   We have also added a summary of the statistics in the figure legends by rewriting to include an abbreviated description of the interrupted time series data and statistics.

   - Table 2 and the figures cite changes in proportions, but not in annual estimates for number of cases. Either in the main text or as supplemental material, should also show changes in absolute numbers of cases by surgical approach one quarterly or annual basis.

   We chose to present proportions in the figures because NSQIP includes different numbers of hospitals each year, making comparing absolute numbers confusing to a reader. The data in table 2 (now table 3) is presented as n (%), including both n’s and proportions. In response to this comment, we also added a supplemental table (Supplemental Table 2 – now Table 4) with the raw numbers per quarter.

3. eCTA: All authors except Dr. Awtrey will need to complete our electronic Copyright Transfer Agreement, which was sent to them through Editorial Manager.
   We expect that all co-authors have completed this, and would be happy to prompt any coauthors from whom you have not yet received forms.
4. Abstract-Results: Please add absolute values in the Results section. Could you add n’s or something else to accompany the p-values in this section? Please note that any data that is added to the Abstract must also appear in the body text or tables for consistency. Thank you for the opportunity to be more specific in our abstract. We added the value for the percent changes as per the interrupted time series data.

5. Line 202: Please edit to use a word other than “impacting” here and in other instances in the paper. Impact implies a physical blow and as such, we avoid its use in the journal. Thank you. We changed “impacting” to “influencing.”

6. Table 2: The section on co-morbidities should be indented in parallel to the way you present the categories of race. For space considerations, you could remove the word “co-morbidities”. We added indentation as requested. If you preferred to remove this heading altogether for space considerations, we would not disagree with this change.

7. Figures: Please edit these figures as was requested by the Statistical Editor in your original revision letter. When we said that you could resubmit them “as-is,” we meant that the format was generally okay. Please send your updated figure files to me.

   - Fig 1, 2a, 2b: Either in the figure legends or within the graphs, should include a summary of the stats analysis of the time series.
   - For figs 2a, 2b, should include 95% CIs for the quarterly estimates of proportions. Thank you for the opportunity to further improve our manuscript, and many apologies for misunderstanding the initial instructions. We have added 95% confidence interval error bars to the figures. We have also added a summary of the statistics in the figure legends by rewriting to include an abbreviated description of the interrupted time series data and statistics.

To facilitate the review process, we would appreciate receiving a response within 48 hours.

Best,
Randi Zung

There is actually one additional edit that the Editors are requesting. Would you please edit the Precis to say “trend” instead of “effect”? The sentence would be: “Despite early findings of decreased minimally invasive hysterectomy after power morcellation safety warnings, this trend has reversed since March 2015.”

Completed
Hi Stephanie,

The only edited needed is on Figure 1, both of the top boxes (preprotocol and postprotocol) have a misspelling of the word "reviewed."

Otherwise, these look great, thank you!

Take care,
Laura Fitzmaurice