

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)*

**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: Apr 11, 2019
To: "Monique Marie Hedderson" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-461

RE: Manuscript Number ONG-19-461

Enhanced recovery after surgery implementation in elective cesarean deliveries within an integrated healthcare delivery system

Dear Dr. Hedderson:

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 May 02, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: The authors present the outcomes of having implemented an obstetrical enhanced recovery system within an health system in California aimed at improving outcomes after elective cesarean delivery. This is important work, especially given the unacceptable rate of maternal morbidity and mortality in the United States as compared to other western nations. The authors should be commended for their work. However, there are several issues that the manuscript needs to address.

General comments:

- 1* The manuscript contains lots of jargon terms that are not clearly defined. Readers of the manuscript are most likely not used to terms such as "process metrics" and "regional dashboards".
- 2* While the authors attempt to look at multiple aspects of post-elective cesarean delivery, the scope of the manuscript strongly focuses on administration of opioids vs non-opioid analgesia and patients' pain scores. This is not clear when the authors express the objective of the study (Lines 29-31). The use of non-opioid pain medication should be a primary focus of the paper and others made secondary (Lines 88-89).
- 3* The authors should refer to a recently published quality improvement study by Holland et al from January 2019 published in Obstetrics & Gynecology titled "Evaluation of a Quality Improvement Intervention That Eliminated Routine Use of Opioids After Cesarean Delivery" that performed similar work. The authors should review this paper in the context of their work.

Specific comments:

- 4* Line 68: ". . .postoperative phrases" should read "postoperative phases".
- 5* Line 85: ". . .other stakeholders". Who are these other stakeholders? These are never defined.
- 6* Lines 98-99, 149-150: The study regimen for non-opioid analgesia should be clearly defined.
- 7* Line 105: Which EHR was used? Is this consistent throughout all hospitals?
- 8* Line 115: What are regional performance dashboards?

9* Line 118: What is the role of nurse consultant mentors?

10* Lines 124-127: Are the hospitals treating different patient populations? Were language barriers considered when analyzing data?

11* Line 139: "process of care metrics". Define these.

12* Lines 150-153: Do the authors have information on pain scores from day 2 or day 3, as it is known that post-cesarean patients have worsening of pain at that juncture.

13* Lines 179-181, 239: It is unclear as to why depression was evaluated as an outcome. Clarify this, as currently it does not appear relevant to ERAS evaluation.

14* Lines 240-241: What were the authors using pre-ERAS for surgical site infection prophylaxis? Was the ERAS designed to evaluate a practice change?

15* Lines 297-298: "...opioid safety initiative". No information is provided regarding what this initiative exactly is.

16* Table 1: In the preoperative section for patient education, verbal counseling and written brochures are mentioned, but this is not enumerated in the text. How are patients counseled? Is there uniformity between hospitals?

Reviewer #2: To evaluate implementation of an Enhanced Recovery After Surgery (ERAS) program for patients undergoing elective cesarean deliveries by comparing process and outcome measures before and after implementation. ERAS program was implemented among elective cesarean delivery patients in 2016 within the Kaiser Permanente Northern California integrated healthcare delivery system. pre-post study of ERAS implementation to compare changes in process and outcome measures during the 12 months before (Pre: n = 4,689) and 12 months after (Post: n = 4,624) implementation.

Objective is well defined

Abstract: well done

Materials and Methods: What did your standard order set look like pre ERAS for NPO after MN or eating before cesarean? How about eating and ambulation and removal of foley and pain meds? From Figure 1 it looks like multi-modal pain management and pre-op nutrition and early ambulation were new goals. This is important to understand the differences between pre and post op metrics. How did you measure time to first ambulation retrospectively. Was this written or checked by nurses. This would seem to me a difficult calculation and very resource heavy. Given that ambulation wasn't mandated as it was post ERAS and that ambulation is dependent on many factors (nursing time, breastfeeding, pain control).

Instead of comparing groups before and after (really an impossible task because the groups are so different) why don't you simply report on the percent of women that achieved each metric after ERAS implementation. The comparison before and after ERAS seems like an artificial comparison for some of the metrics because the process was completely different. Granted it does show the change that was needed and gives some perspective.

Figure 1 is excellent

Was all the data present in the EHR for the retrospective data? Was a percent of data missing?

Did the patients have to buy their own special drink or could they simply drink apple juice? please explain

IV Acetaminophen is expensive and some hospitals discourage its use, please comment

Did you increase any resources (personnel) for implementation at any of the 15 hospitals or simply reorganized. "Nursing and physician leads at each site were supported by local quality and multidisciplinary clinical teams that led ERAS pathway implementation"

One of the process items was avoid exteriorization of the uterus / was this accomplished? data pre and post ERAS?

Discussion: could you describe challenges and obstacles in implementation? This is both a change management and an implementation. Was there much heterogeneity between hospitals? What did those scorecards look like. Was there a steady change over time. When did they reach a steady state in implementation

Comment on patient satisfaction / sustainability and any changes that you made to teams after 3, 6, 9, 12 months after implementation.

Do you have any plans to extend this in a modified/streamlined approach for unscheduled cesareans.?

Reviewer #3: Very timely study in the era of opioid overuse/abuse.

1. Please clarify (line 134) operating room tables? I assume that this was a query in the OR scheduling data base tables in the EHR?
2. Were there any interfacility differences in the outcome data?
3. What were the exclusion criteria?
4. Were there any outcome differences between nulliparous and multiparous patients or between patients with no previous cesarean sections compared to prior cesarean sections?
5. Did intraoperative or postpartum hemorrhage / anemia affect the any of the outcome or process measures?
6. In table 3, early ambulation was 60.9% in the post-ERAS cohort, but the mean hours to first ambulation was 13.82 hours, please elaborate.
7. Please clarify the use of acetaminophen, was IV acetaminophen scheduled or was it only given as an IV if oral acetaminophen was not effective?
8. What was the duration of time patients received scheduled non-narcotic medications intravenous? First 24 hours, first 48 hours?
9. What percentage of patients did not require any narcotics?
10. How was it determined how many tablets of narcotics to prescribe in the pre-and post-ERAS cohorts? Was there a change in the prescription recommendation or standards?
11. What percentage of patients requested a refill of narcotics after discharge?
12. Were you able to determine if the number of narcotic refills changed between the two cohorts?
13. Were there any racial/ethnic differences in narcotic use?
14. Were you able to calculate any cost benefit from the ERAS implementation?

STATISTICAL EDITOR'S COMMENTS:

1. lines 108-111, 122-127 and Fig 1: First, the Fig needs a legend to explain for the reader the meaning of the time scale along the x-axis, (ie, that the calendar times may be different for the transition for individual centers and whether the 2 pilot centers were/were not included in the analysis.) It appears from Fig 1 that there were changes in each metric that preceded month "0". Was there communication among the centers or crossover by providers that could have affected the transition. Another aspect that may be confusing for the reader is that the graphs display monthly metrics (presumably mean or median values for each month), but the graphs imply a continuous change. For example, time zero was excluded from analysis (lines 126-127), but the crossover at time zero is shown in all the graphs. Should change format to individual indicators for each month (excluding time zero). The early ambulation and early nutrition metrics appear to be changing at -2 months.
2. Table 2: Need units for BMI.
3. Table 3: Need to address issues cited above re: Fig 1. Might have been better addressed with time series analysis.
4. The morphine equivalents are cited as "average" values, but Fig 1 cites as median and the column headings in Table 3 refer to mean and adjusted mean values. If median was the more appropriate descriptor for the distributions, then should consistently cite and analyze as medians.
5. Table 4: The counts of 30-day ICU admission and its complement, discharge to home, each have too few adverse events to allow for multivariable adjustment (the counts were $n \sim 14$ and $n \sim 9$), vs 7 adjusting covariates.
6. Tables 3 and 4: Should include a column of unadjusted mean differences (or median) or RRs to contrast with the adjusted differences.

Associate Editor's Comments:

Please throughout your revision frame your findings in terms of association rather than causality (e.g., "altered" is causal)

EDITORIAL OFFICE COMMENTS:

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

2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Any author agreement forms previously submitted will be superseded by the eCTA. During the resubmission process, you are welcome to remove these PDFs from EM. However, if you prefer, we can remove them for you after submission.

3. All submissions that are considered for potential publication are run through CrossCheck for originality. The following lines of text match too closely to previously published works. Variance is needed in the following sections:

- a. Methods Section: Please cite your previous publication (JAMA Surg. 2017;152(7):e1711032.) here, and note that these methods have been described previously.
- b. Variance needed: Lines 300-02 ("As a highly integrated...improvement methodology").

4. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at <https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize>. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

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

6. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

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

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

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

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

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

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

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

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 Journal's Production Editor had the following to say about the figures in your manuscript:

"-Figure 1: author needs to upload as separate file in EM"

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce.

14. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at <http://links.lww.com/LWW-ES/A48>. The cost for publishing an article as open access can be found at <http://edmgr.ovid.com/acd/accounts/ifauth.htm>.

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

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 and that each author has given approval to the final form of the revision.

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by May 02, 2019, 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

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

May 9, 2019
The Editor, Obstetrics and Gynecology

Dear Editor,

Thank you for giving us the opportunity to re-submit the manuscript now entitled **“Enhanced recovery after surgery to change process measures and reduce opioid use in cesarean deliveries: A Quality Improvement Initiative.”** (MS# ONG-19-461 by Hedderson et al.). We appreciated the thoughtful comments from the reviewers and have tried to address all of their concerns. The reviewers clearly spent a great deal of time with our paper and we feel the paper is greatly improved. We have also addressed the editor’s comments and revised the manuscript accordingly. We have attached a detailed response to the reviewer’s and editor’s comments. If the editor requires any additional changes, please let us know.

[REDACTED]

The other authors and I look forward to hearing from you.

Sincerely,

Monique Hedderson

Dr. Monique Hedderson

Enhanced recovery after surgery implementation in elective cesarean deliveries within an integrated healthcare delivery system

REVIEWER COMMENTS:

Reviewer #1: The authors present the outcomes of having implemented an obstetrical enhanced recovery system within an health system in California aimed at improving outcomes after elective cesarean delivery. This is important work, especially given the unacceptable rate of maternal morbidity and mortality in the United States as compared to other western nations. The authors should be commended for their work. However, there are several issues that the manuscript needs to address.

General comments:

1* The manuscript contains lots of jargon terms that are not clearly defined. Readers of the manuscript are most likely not used to terms such as "process metrics" and "regional dashboards".

We revised the manuscript to more clearly define terms used.

"Process metrics" *We now use the term "process measures" and we define it in the manuscript. See lines 80-81*

"We designed this pre-post study to assess changes in process measures (defined as clinical care measures clinicians do to maintain or improve the health of their patients)¹⁵ and outcomes among patients undergoing elective cesarean deliveries during the 12 months before and 12 months after implementation of the ERAS program."

"Regional dashboards" - *We now define the term "regional dashboard", See lines 152-153*

"Regional performance dashboards created to provide a performance report to review the process measures and outcomes at each of the 15 medical centers and for the KPNC region overall were developed to display and track process and outcome measures based on the EHR data and were provided on a weekly basis to local teams."

2* While the authors attempt to look at multiple aspects of post-elective cesarean delivery, the scope of the manuscript strongly focuses on administration of opioids vs non-opioid analgesia and patients' pain scores. This is not clear when the authors express the objective of the study (Lines 29-31). The use of non-opioid pain medication should be a primary focus of the paper and others made secondary (Lines 88-89).

We revised the manuscript and the objectives to first focus on the pain management process measure changes relating to increased use of non-opioid analgesia component of the ERAS program, the other ERAS process measures and outcomes examined are described as secondary outcomes. We also updated the title to reflect the focus on reducing exposure to opioids. We also added additional measures of opioid use to address other reviewer comments.

3* The authors should refer to a recently published quality improvement study by Holland et al from January 2019 published in Obstetrics & Gynecology titled "Evaluation of a Quality Improvement

Intervention That Eliminated Routine Use of Opioids After Cesarean Delivery" that performed similar work. The authors should review this paper in the context of their work.

We appreciated the reviewer directing us to this publication we now discuss this reference in the revised discussion. See lines 302-311.

"A recent quality improvement intervention designed to eliminate routine use of oral opioids for analgesia postcesarean delivery, also reduced the use of oral opioids in-hospital from 68% to 40%, with no impact on patient satisfaction or pain relief and also decreased opioid prescriptions at hospital discharge²⁶. We also found a decrease in outpatient opioids dispensed at hospital discharge, this is consistent with a recent study of opioid use following cesarean delivery that found greater in-hospital opioid use was associated with greater opioid use post-discharge.²⁷ In the context of the current opioid epidemic, our findings contribute to a growing body of evidence that is possible to implement quality improvement programs to reduce inpatient and outpatient opioid exposure without negatively impacting pain relief.

Specific comments:

4* Line 68: "...postoperative phrases" should read "postoperative phases".

We appreciate the reviewer catching that typo.

5* Line 85: "...other stakeholders". Who are these other stakeholders? These are never defined.

We deleted the term other stakeholders as we realized we had previously described all the stakeholders involved earlier in that sentence.

6* Lines 98-99, 149-150: The study regimen for non-opioid analgesia should be clearly defined.

We added the following details highlighted in italics below. See lines 95-96.

For pain management, patients routinely received intrathecal opioids followed by acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) every 6 hours, or 4 times daily. *Patients received scheduled 24 hours of IV acetaminophen followed by PO if patient was taking pills.* Oral oxycodone was available for breakthrough pain. Inpatient pain management was directed towards decoupling opioid administration from that of other pain medications (e.g., NSAIDs and acetaminophen). A similar practice was implemented for default discharge decoupled pain medication prescriptions (defined as separate prescriptions for opioids, acetaminophen and NSAIDs as opposed to combination products).

We also added this, see lines 100-104.

Pre-ERAS cohort, the order sets included the option for Norco or Percocet and the default number was 30 tablets. Post-ERAS, we adopted the decoupled medications (Tylenol, motrin, oxycodone). There was still the option for norco, but most providers elected to use the former combination. The number of tablets of oxycodone was reduced to 20 tablets. In addition, patients received scheduled 24 hours of IV acetaminophen followed by PO if patient was taking pills.

7* Line 105: Which EHR was used? Is this consistent throughout all hospitals?

See lines 149-151 in the revised manuscript.

“KPNC’s EHR system is designed by Epic Corporation® and customized for the needs of Kaiser Permanente and has been renamed KP HealthConnect. All medical centers and hospitals in KPNC use the same KP HealthConnect system.”

8* Line 115: What are regional performance dashboards?

See line 133-134 in the revised manuscript.

We now define the term “regional dashboard”, which is a performance report designed to review the process measures and outcomes at each of the 15 medical centers and for the region overall.

9* Line 118: What is the role of nurse consultant mentors?

We now define the nurse consultant mentors role. See line 136-139 in the revised manuscript:

“Regional support was also provided through biweekly teleconferencing and frequent communication with nurse consultant mentors, ¹⁶ who were experts in performance improvement deployed to each medical facility to keep ERAS implementation on track and to identify and provide solutions for any barriers.”

10* Lines 124-127: Are the hospitals treating different patient populations? Were language barriers considered when analyzing data?

Each hospital does treat different patient populations. We attempted to control for differences in patient populations between hospitals by controlling for patient factors during the two study periods in the adjusted analyses: age at delivery, race-ethnicity pre-pregnancy BMI, parity and preterm birth. We did not initially examine differences in language barriers. However, we have information on the percent of patients who required an interpreter. Only approximately 4.0% of patients required an interpreter and there were no differences in the pre and post implementation periods. We ran models further adjusted for language barriers, but we found it did not change our point estimates, therefore we did not update the adjusted models presented. The language barrier variable is highly correlated with the race-ethnicity variable since 95% of the women who required an interpreter were Asian or Hispanic. We now present the percent of patients needing an interpreter in Table 2.

ERAS Elective Cesarean Section Patients		
Pre	Post	P-value
(n = 4,689)	(n = 4,624)	

Language interpreter required	195 (4.2)	183 (4.0)	0.66
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11* Line 139: "process of care metrics". Define these.

See response #1, we now use the term process measures and define that term the first time we use it.

12* Lines 150-153: Do the authors have information on pain scores from day 2 or day 3, as it is known that post -cesarean patients have worsening of pain at that juncture.

We do have information on pain scores from day 2 and day 3. The reviewer is correct and we did observe that pain scores worsened at day 2 both pre and post ERAS implementation. However, when we ran the multivariate analysis separately for day 2 and day 3 we found similar results, with patients in the post-ERAS period reporting more improvements in pain score (See Table below). In the interest of brevity, we did not add this to the revised manuscript. We did add the following brief sentence to results see line 245-247.

"We examined average delta pain scores separately by postoperative day (0 to 3) and the average delta pain scores at or below patient pain tolerance were significantly higher in the post-ERAS implementation period for all days (data not shown)."

Model for pain scores reported at Day 2 and Day 3-separately

	<u>Adjusted mean difference or risk ratios</u>	<u>p-value</u>
Average delta pain score Post-Op day 2	-0.35 (-0.44, -0.26)	<0.001
Average delta pain score at or below patient pain tolerance Post-Op day 2	1.07 (1.05-1.10)	<0.001
Average delta pain score Post-Op day 3	-0.37 (-0.50, -0.25)	<0.001
Average delta pain score at or below patient pain tolerance Post-Op day 3	1.09 (1.05-1.14)	<0.001
Overall average delta pain score days 0-3	-0.28 (-0.36, -0.21)	<0.001
Average delta pain score at or below patient pain tolerance Post-Op day 0-3	1.06 (1.04-1.08)	<0.001

13* Lines 179-181, 239: It is unclear as to why depression was evaluated as an outcome. Clarify this, as currently it does not appear relevant to ERAS evaluation.

We initially included postpartum depression because we thought that the decrease in opioid exposure might impact postpartum mood and thus depression. However, we recognize that it is unlikely for the ERAS program to have impacted postpartum depression, it was not something the program was designed to impact, therefore, we have removed it as an outcome in the revised manuscript.

14* Lines 240-241: What were the authors using pre-ERAS for surgical site infection prophylaxis? Was the ERAS designed to evaluate a practice change?

Pre-ERAS surgical site infection prophylaxis included preoperative antibiotics and a chlorhexidine gluconate abdominal cleaner during surgical prep. Post-ERAS implementation chlorhexidine wipes were given to patients to use at home. ERAS was designed to evaluate this practice change. A description of this practice change was added to the manuscript see lines 111-113 and Table 1.

15* Lines 297-298: "...opioid safety initiative". No information is provided regarding what this initiative exactly is.

We now elaborate on the opioid safety initiative that was implemented in Kaiser Permanente Northern California, See Line 330-333 in the revised discussion.

"...initiative implemented local guidelines and provider training around screening for opioid misuse, implementing signed opioid agreements, increasing urine drug screening, and reducing high dose prescribing as appropriate."

16* Table 1: In the preoperative section for patient education, verbal counseling and written brochures are mentioned, but this is not enumerated in the text. How are patients counseled? Is there uniformity between hospitals?

All hospitals received the same staff training regarding how to educate their patients, however, we have no ability to directly measure whether it was delivered uniformly across hospitals. See revised text line 115-118.

"Patient education was provided during a preoperative visit where patients received an ERAS kit that included a brochure explaining ERAS and what to expect before, during and after their surgery, the carbohydrate drink with instructions on when to consume it and instructions on the use of the chlorhexidine wipes".

Reviewer #2: To evaluate implementation of an Enhanced Recovery After Surgery (ERAS) program for patients undergoing elective cesarean deliveries by comparing process and outcome measures before and after implementation. ERAS program was implemented among elective cesarean delivery patients in 2016 within the Kaiser Permanente Northern California integrated healthcare delivery system. pre-post study of ERAS implementation to compare changes in process and outcome measures during the 12 months before (Pre: n = 4,689) and 12 months after (Post: n= 4,624) implementation.

Objective is well defined

Abstract: well done

We appreciate the positive comments.

Materials and Methods: What did your standard order set look like pre ERAS for NPO after MN or eating before cesarean? How about eating and ambulation and removal of foley and pain meds? From Figure 1 it looks like multi-modal pain management and pre-op nutrition and early ambulation were new goals. This is important to understand the differences between pre and post op metrics. How did you measure time to first ambulation retrospectively. Was this written or checked by nurses. This would seem to me a difficult calculation and very resource heavy. Given that ambulation wasn't mandated as it was post ERAS and that ambulation is dependent on many factors (nursing time, breastfeeding, pain control).

Pre-ERAS NPO after midnight was recommended but this was not standardized and patients were recommended to ambulate and eat as tolerated and the removal of foley occurred when ambulating. This is now described in the paper see line 104-110.

We now added the following explanation regarding documentation which was standard practice for nurses both pre and post ERAS implementation. See lines 193-195.

“Time to first ambulation was documented by nurses and recorded in flowsheets in the EHR both pre and post ERAS implementation”.

Instead of comparing groups before and after (really an impossible task because the groups are so different) why don't you simply report on the percent of women that achieved each metric after ERAS implementation. The comparison before and after ERAS seems like an artificial comparison for some of the metrics because the process was completely different. Granted it does show the change that was needed and gives some perspective.

We appreciate the reviewer's suggestion of reporting just the data after implementation. However, we do think it is helpful to demonstrate that our data suggests that there were in fact practice changes that occurred post ERAS implementation. While these changes were expected due to the change in process, we wanted to demonstrate that the practice changes were in fact accomplished.

Figure 1 is excellent

We appreciated the positive comment and we think Figure 1 demonstrates how effectively the ERAS program was implemented in practice.

Was all the data present in the EHR for the retrospective data? Was a percent of data missing?

Yes, all the data was present in the EHR retrospective data. Missing data on the process and outcome measures is noted in a footnote in Tables 3 and 4 that explains if the n's do not add up to the total at the top it is due to missing data. In general, we had very little missing data.

Did the patients have to buy their own special drink or could they simply drink apple juice? please explain

Patients were given an ERAS kit that included the apple juice for them to drink. See response # 16 to reviewer 1.

IV Acetaminophen is expensive and some hospitals discourage its use, please comment

Our decision to use IV Acetaminophen was based on 2015 pharmacokinetic data that showed that patients who received IV or intrathecal opioids had delayed gastric emptying which would have impaired uptake of oral acetaminophen, thus IV acetaminophen was preferred. The implementation of the ERAS program was a quality improvement initiative and therefore cost was not a main consideration.

Did you increase any resources (personnel) for implementation at any of the 15 hospitals or simply reorganized.

We did not increase personnel for the ERAS implementation instead we reorganized existing staff. We add a brief sentence with this information to line 129-131.

“Nursing and physician leads at each site were supported by local quality and multidisciplinary clinical teams that led ERAS pathway implementation. Thus, existing staff was used to implement the ERAS program.”

One of the process items was avoid exteriorization of the uterus / was this accomplished? data pre and post ERAS?

Unfortunately we did not collect data on exteriorization of the uterus so we are unable to look at changes in this process measure.

Discussion: could you describe challenges and obstacles in implementation ? This is both a change management and an Implementation. Was there a steady change over time. When did they reach a steady state in implementation. Was there much heterogeneity between hospitals? What did those scorecards look like.

It is challenging for clinicians and hospital staff to adopt changes to clinical practice and to agree to follow a pathway to standardize care that removes some of the autonomy in the decision making process. To overcome these challenges the ERAS program was presented at each medical facility 2 months before the facility was expected to go live with the program to socialize the upcoming changes with clinical staff. It was critical to present evidence supporting the proposed changes and to educate the staff regarding the safety of the changes. For example, there was initially concern regarding the safety of the shortened fasting period and concerns it may increase aspiration, but prior to implementation the ERAS performance improvement staff presented data on the safety of the proposed change. Other concerns included potential increases in workload in the pre-operative clinics receiving patients and post-operatively to achieve early ambulation. However, all changes were successfully implemented with existing clinical staff. We now discuss some of these challenges in the discussion. See lines 333-338.

Was there much heterogeneity between hospitals?

There was heterogeneity between hospitals but that was true both before and after implementation of the ERAS program. We now adjust our multivariate models for medical center, but medical center was not a confounder in our analyses and our results are essentially unchanged. We updated all the data in Tables 3 and 4 with the models adjusted for medical center.

Was there a steady change over time?

Since the ERAS program was presented at each medical center two months before the center was expected to go live with the changes, it is expected that we started to see changes in the two months before implementation. Figure 1 shows the data on process metrics on a monthly basis 12- months before and after implementation. It demonstrates that the changes were sustained over the 12- month period. We now added the following to the discussion line 339-341.

‘Since the ERAS program was presented at each medical center two months before the center was expected to go live with the changes, we believe that the changes in the process measures two months before implementation were likely due to the ERAS program.’

Comment on patient satisfaction / sustainability and any changes that you made to teams after 3 ,6,9,12 months after implementation.

We did not actively make changes to the teams during the 12- month period. We used existing teams at

each medical center to implement and sustain the ERAS program. Unfortunately, we did not have information on patient satisfaction, we added that to the limitation section. Again Figure 1 demonstrates the sustained changes over time.

Do you have any plans to extend this in a modified/streamlined approach for unscheduled cesareans.?

Yes, we have extended this approach for unscheduled cesareans and we hope to evaluate that population in a future analysis.

Reviewer #3: Very timely study in the era of opioid overuse/abuse.

We appreciate the positive comment.

1. Please clarify (line 134) operating room tables? I assume that this was a query in the OR scheduling data base tables in the EHR?

We appreciate the reviewer catching this confusing term, the reviewer is correct it was a query in the operating room scheduling database table in the EHR, we revised the sentence accordingly.

2. Were there any interfacility differences in the outcome data?

Our results are averages over all of the facilities. We know that within KPNC there are interfacility differences in process and outcome data, both pre and post ERAS implementation. We re-ran our analyses adjusting for medical facility and medical facility was not a significant confounder, but we updated all the models in Tables 3 and 4 with models adjusted for facility.

3. What were the exclusion criteria?

We included all women who underwent an elective cesarean section during the study period, we did not have any exclusion criteria. A small percentage of women were missing data on outcome variables and they were excluded from those analyses. See response to reviewer 2 above.

4. Were there any outcome differences between nulliparous and multiparous patients or between patients with no previous cesarean sections compared to prior cesarean sections?

To address this comment, we examined interaction terms between these variables and the outcome variables. We found no significant interaction term suggesting results were similar across these groups.

5. Did intraoperative or postpartum hemorrhage / anemia affect the any of the outcome or process measures?

We calculated the interaction terms for post-ERAS implementation by postpartum hemorrhage and anemia and below we present the stratified analyses for the process measures with significant interaction terms. There were not significant differences in outcome measures. Hours to first ambulation and early nutrition within 12 hours changed less post ERAS among women with postpartum hemorrhage, this would be expected given the medical condition of hemorrhage. Similarly for women with Anemia, we observed some differences in the magnitude of the effect size but we stil saw changes in women with

and without anemia. We did not add this new data to the manuscript, but we can if the editor requests this additional data.

Postpartum Hemorrhage

	POSTPARTUM_HEMORRHAGE=1		POSTPARTUM_HEMORRHAGE=0	
Hours to first ambulation	-1.51 (-3.26, 0.24)	0.091	-2.85 (-3.18, -2.51)	<0.001
Early nutrition within 12 hours	6.61 (4.59 - 9.51)	<0.001	4.46 (4.15 - 4.80)	<0.001

Postpartum Anemia

	POSTPARTUM_ANEMIA=1		POSTPARTUM_ANEMIA=0	
Hours to first ambulation	-1.56 (-2.60, -0.51)	0.004	-2.92 (-3.27, -2.56)	<0.001
Hours to first nutrition	-13.03 (-14.39, -11.67)	<0.001	-11.08 (-11.50, -10.65)	<0.001
Morphine equivalents, average rate per day, mg	-7.85 (-8.98, -6.72)	<0.001	-5.78 (-6.20, -5.36)	<0.001
Met Multi-modal Analgesic	6.26 (4.95 - 7.92)	<0.001	9.63 (8.71 - 10.6)	<0.001
Met IV acetaminophen	5.87 (4.71 - 7.31)	<0.001	8.55 (7.81 - 9.37)	<0.001
Filled Opioid Prescription at Discharge	0.90 (0.85 - 0.96)	0.001	0.97 (0.95 - 0.98)	<0.001

6. In table 3, early ambulation was 60.9% in the post-ERAS cohort, but the mean hours to first ambulation was 13.82 hours, please elaborate.

In table 3, the mean hours to first ambulation of 13.82 hour in the post-ERAS is the adjusted mean from the generalized linear model (GLM) model. We confirmed and this data is correct and it is also correct that the early ambulation was 60.9%.

7. Please clarify the use of acetaminophen, was IV acetaminophen scheduled or was it only given as an IV if oral acetaminophen was not effective?

The orderset included a scheduled IV acetaminophen every 6 hours after delivery in the operating room for 24 hours then postoperative it converted to PO if patient was taking pills. This is now described in lines 106-107.

8. What was the duration of time patients received scheduled non-narcotic medications intravenous? First 24 hours, first 48 hours?

Patients received scheduled 24 hours of IV acetaminophen followed by PO if patient was taking pills. We now describe that on 95-96.

9. What percentage of patients did not require any narcotics?

All patients received intrathecal opioids as part of the epidural. 21.4% in post-ERAS compared to 8.3% in pre-ERAS didn't require any opioids postoperatively. We added this data to Table 3 and results line 97.

10. How was it determined how many tablets of narcotics to prescribe in the pre-and post-ERAS cohorts? Was there a change in the prescription recommendation or standards?

Pre-ERAS cohort, the order sets included the option for Norco or Percocet and the default number was 30 tablets. Post-ERAS, we adopted the decoupled medications (Tylenol, motrin, oxycodone). There was still the option for norco, but most providers elected to use the former combination. The number of tablets of narcotics was reduced to 20 tablets. See this addition line 100-104.

11. What percentage of patients requested a refill of narcotics after discharge?

Pre-ERAS 17.1% requested a refill of the opioid prescription and Post-ERAS that decreased slightly to 15.3% within 6 months of hospital discharge (p-value<0.011). This is among the patients who had filled opioid at the discharge.

12. Were you able to determine if the number of narcotic refills changed between the two cohorts?

There is no significant difference between the number of refills between the two cohorts.

Analysis Variable : OPIOID_REFILL_DISDT_UPTO6M_COUNT

GROUP	N	Obs	Mean	Std Dev	Minimum	25th Pctl	Median	75th Pctl	Maximum
A:Pre	4689		1.8	2.2	1.0	1.0	2.0	22.0	
B:Post	4624		1.9	2.2	1.0	1.0	2.0	27.0	

12. Were you able to determine if the number of narcotic refills changed between the two cohorts?
See response number 11 above, the number of refills did not change between the two cohorts.

13. Were there any racial/ethnic differences in narcotic use?

We looked at the difference in mean morphine equivalent in the post-ERAS period by race ethnicity and did find significant differences by race/ethnicity. It was 5.6 Hispanics, 4.5 Asians, 7.4 Blacks and 6.3 Whites (<0.001). While interesting we think it is beyond the scope of this paper to discuss disparities in opioid use. However, if the editor prefers we can add this data and discuss it.

14. Were you able to calculate any cost benefit from the ERAS implementation?

This was a quality improvement initiative not designed to be cost-savings. Therefore, we did not collect the required cost data that is needed to perform a cost-benefit analysis.

STATISTICAL EDITOR'S COMMENTS:

1. lines 108-111, 122-127 and Fig 1: First, the Fig needs a legend to explain for the reader the meaning of the time scale along the x-axis, (ie, that the calendar times may be different for the transition for individual centers and whether the 2 pilot centers were/were not included in the analysis.) It appears from Fig 1 that there were changes in each metric that preceded month "0". Was there communication among the centers or crossover by providers that could have affected the transition. Another aspect that may be confusing for the reader is that the graphs display monthly metrics (presumably mean or

median values for each month), but the graphs imply a continuous change. For example, time zero was excluded from analysis (lines 126-127) , but the crossover at time zero is shown in all the graphs. Should change format to individual indicators for each month (excluding time zero). The early ambulation and early nutrition metrics appear to be changing at -2 months.

We added a legend to better explain the time scale along the x-axis and changed the format of the figure so as not to imply a continuous change. We now explain that the ERAS program was presented at each medical center two months before the center was expected to go live with the changes, therefore it is not unexpected that we started to see changes in early ambulation and early nutrition in the two months before implementation. Figure 1 is standardized to each medical center's go live date and pilot sites are included.

2. Table 2: Need units for BMI.

The BMI units were added to Table 1.

3. Table 3: Need to address issues cited above re: Fig 1. Might have been better addressed with time series analysis.

We appreciate the editor's comment and suggestion regarding time series analysis. We note that there were no trends over time prior to the time when the ERAS intervention was implemented at each site. Since the ERAS training started during the two month prior to go live implementation we expect these changes were due ERAS implementation and not to other time trends.

4. The morphine equivalents are cited as "average" values, but Fig 1 cites as median and the column headings in Table 3 refer to mean and adjusted mean values. If median was the more appropriate descriptor for the distributions, then should consistently cite and analyze as medians.

Yes, it is correct that in figure 1 ME rate per day is presented as a median, that is because the data in the figure is descriptive and ME rate was not normally distributed. In table 3 and table 4, all continuous metrics were presented as LS-means from GLM model.

5. Table 4: The counts of 30-day ICU admission and its complement, discharge to home, each have too few adverse events to allow for multivariable adjustment (the counts were $n \sim 14$ and $n \sim 9$), vs 7 adjusting covariates.

We had a footnote next to the risk ratio for 30-day ICU admission specifying that we presented the crude model because a multivariate model would not converge. We now also present the crude model for discharge to home even though that model did converge. However, if the editor prefers we could remove the RR estimate entirely for these two rare outcomes.

6. Tables 3 and 4: Should include a column of unadjusted mean differences (or median) or RRs to contrast with the adjusted differences.

We added a column of the unadjusted mean differences to tables 3 and 4.

Associate Editor's Comments:

Please throughout your revision frame your findings in terms of association rather than causality (e.g., "altered" is causal)

We removed the use of “altered” and made other revision to frame the findings in terms of associations.

EDITORIAL OFFICE COMMENTS:

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

YES

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

2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Any author agreement forms previously submitted will be superseded by the eCTA. During the resubmission process, you are welcome to remove these PDFs from EM. However, if you prefer, we can remove them for you after submission.

Please remove them for me.

3. All submissions that are considered for potential publication are run through CrossCheck for originality. The following lines of text match too closely to previously published works. Variance is needed in the following sections:

a. Methods Section: Please cite your previous publication (JAMA Surg. 2017;152(7):e171032.) here, and note that these methods have been described previously.

We now cite our previous publication and note that these methods have been described previously. See line 94.

b. Variance needed: Lines 300-02 (“As a highly integrated...improvement methodology”).

We revised the sentence in line 300.

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

[Improvement/reVITALize](#). If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

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

We meet these guidelines.

6. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

We meet these guidelines for the title limit and we added the appropriate subtitle.

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

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

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

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

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

We meet these guidelines. This work was presented at the following meetings, we are unclear where to note that in the manuscript.

--American Society for Enhanced Recovery (ASER) poster presentation 4/25/19 in Washington DC

--Society for Academic Specialists in OB/GYN (SASGOG) podium presentation 5/2/19 in Nashville, TN

--Accepted: ACS Quality and Safety meeting podium presentation 7/21/19 in Washington DC

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

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

We meet these guidelines and provide the word count on the title page.

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

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

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

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13. The Journal's Production Editor had the following to say about the figures in your manuscript:

"-Figure 1: author needs to upload as separate file in EM"

We know include the figure as a separate file.

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