Author’s response to reviews

Title: Laparoscopic appendectomy versus open appendectomy for suspected appendicitis during pregnancy: A systematic review and updated meta-analysis

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Author’s response to reviews:

Editor Comments:

Further to referee 1’s comments, I’m afraid that further consideration of your manuscript will be dependent on your response regarding the novelty of your research over a previously published meta-analyses (https://www.ejog.org/article/S0301-2115(18)30166-0/fulltext).

Response:

Our study is more accurate, systematic, multifaceted, and logical than the study by Prodromidou et al. (EJOG 2018).

First, the five articles included in our study were all included in the search period of the study by Prodromidou et al. (EJOG 2018); however, these were not included in their analysis. Therefore, their study showed low reliability because of the limited literature search.

Second, the literature review process in the study by Prodromidou et al. (EJOG 2018) had errors. For example, the number of patients included in the analysis was incorrect.

Third, in the pooled studies, the negative appendectomy rate ranged from 3% to 42.9%. Therefore, it is correct to describe the selected subjects as pregnant women with “suspected appendicitis”. However, Prodromidou et al. (EJOG 2018) described the selected subjects as pregnant patients with “acute appendicitis,” which is inappropriate.

Fourth, we performed funnel plots and meta-regression analyses; these were not performed in the study by Prodromidou et al. (EJOG 2018).
Reviewer reports:

Turgut Donmez, M.D. (Reviewer 1):

The authors made a good study. But, a similar study and meta-analysis was reported in 2018 with the same findings of this study. (Prodromidou A. et. al. Outcomes after open and laparoscopic appendectomy during pregnancy: A meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2018 Jun;225:40-50 doi:10.1016/j.ejogrb.2018.04.010. Epub 2018 Apr 9. "Outcomes after open and laparoscopic appendectomy during pregnancy: A meta-analysis". Thus, in my opinion, the study should be rejected.

Sincerely Yours

Response 1:

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Second, the literature review process in the study by Prodromidou et al. (EJOG 2018) had errors. For example, the number of patients included in the analysis was incorrect.

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Fourth, we performed funnel plots and meta-regression analyses; these were not performed in the study by Prodromidou et al. (EJOG 2018).

1. Period of literature searching


2. Reliability of literature search

(1) BMC Surgery:

Included articles:

Miloudi et al. (2012)/ Khan et al. (2012)/ Jung et al. (2012)/ Upadhyay et al. (2007)/ Curet et al. (1996)

Response 1-1:

The above five articles included in our study are all included in the searching period of the study performed by Prodromidou A. et al. (EJOG); however, these are not included in the analysis. Therefore, the reliability of the literature search seems low.

(2) EJOG 2018:

(3) BJS 2012:

The following two studies included in our study are also included in the published paper by Wilasrusmee C. et al. (BJS):

Upadhyay et al. (2007)/ Curet et al. (1996)

3. Reliability of the literature review process (Outcome: fetal loss)

(1) BMC Surgery:

1) Afflek et al. (1999) : LA 0/19, OA 0/18
2) Kapan et al. (2013): LA 0/7, OA 0/10

(2) EJOG 2018:

1) Afflek et al. (1999) : LA 0/22, OA 0/18
2) Kapan et al. (2013) : LA 0/10, OA 0/10

(3) BJS 2012:

1) Afflek et al. (1999) : LA 0/19, OA 0/18
Response 1-2:

(1) In Afflek et al.'s study, 22 patients were initially enrolled in the laparoscopic appendectomy group, but only 19 patients were included in the analysis. Therefore, there is error in the process of the literature review in their study (Prodromidou A. et al. EJOG 2018).

(2) In Kapan et al.'s study, 10 patients were initially enrolled in the laparoscopic surgery group, but three patients underwent diagnostic laparoscopy, and did not have acute appendicitis. In addition, the three patients did not undergo appendectomy. It is correct that seven patients are included in the LA group. Therefore, there is an error in the process of the literature review in their study (Prodromidou A. et al. EJOG 2018).

4. Reliability of the literature review process (Outcome: preterm delivery)

(1) BMC Surgery:

1) Afflek et al. (1999) : LA 3/19, OA 2/18
2) Kirshtein et al. (2009): We did not include this study in the analysis for preterm delivery.

(2) EJOG 2018:

1) Afflek et al. (1999) : LA 3/22, OA 2/18
2) Kirshtein et al. (2009): Prodromidou A. et al. (EJOG 2018) included this study in the analysis for preterm delivery.

(3) BJS 2012:

1) Afflek et al. (1999) : LA 3/19, OA 2/18
2) Kirshtein et al. (2009): Wilasrusmee C. et al. (BJS 2012) also did not include this study in the analysis for preterm delivery.

Response 1-3:

In Afflek et al.’s study, 22 patients were initially enrolled in the laparoscopic appendectomy group, but only 19 patients were included in the analysis. Therefore, there is an error in the process of the literature review in their study (Prodromidou A. et al. EJOG 2018).
Response 1-4:

Our study and Prodromidou A. et al.'s study (EJOG) analyzed ‘preterm delivery’ as one of the outcomes. However, Kirshtein et al. (2009) analyzed ‘premature contraction’ as outcome, not preterm delivery. The two are different, apparently. Nevertheless, Prodromidou A. et al. (EJOG) included the study (Kirshtein et al. 2009) in the analysis for preterm delivery. It should not include the study by Kirshtein et al. (2009) in the analysis for preterm delivery. Therefore, there is an error in the process of the literature review in their study (Prodromidou A. et al. EJOG 2018).

5. Clarity of selected subjects

(1) BMC Surgery: For ‘suspected appendicitis’ during pregnancy
(2) EJOG 2018: For ‘acute appendicitis’ during pregnancy
(3) BJS 2012: For ‘suspected appendicitis’ during pregnancy

Response 1-5:

A negative appendectomy is an appendectomy done for presumed acute appendicitis that yields an appendix, that on pathology, is within normal limits. In pooled studies, the negative appendectomy rate ranged from 3% to 42.9%. Therefore, it is correct that the selected subject is described as pregnant women with “suspected appendicitis,” not “acute appendicitis.” However, Prodromidou A et al. (EJOG 2018) described the selected subject as pregnant patients with “acute appendicitis,” and it is not appropriate.

6. Fidelity of methods (statistical analysis)

(1) BMC Surgery:

Analytical techniques used in this study:
1) Forest plot
2) Sensitivity analysis
3) Funnel plots (publication bias)
4) Meta-regression analysis
(2) EJOG 2018:
Analytical techniques in used this study:
1) Forest plot
2) Sensitivity analysis

(3) BJS 2012:
Analytical techniques used in this study:
1) Forest plot
2) Funnel plots (publication bias)
3) Meta-regression analysis

Response 1-6:
The majority of previous studies focused on pregnancy (or obstetrical) (fetal loss and preterm delivery) and surgical (wound infection, intraabdominal abscess, operative time, hospital stay, etc.) outcomes as the study outcomes to evaluate the evidence regarding the safety of laparoscopic appendectomy (LA) versus open appendectomy (OA) for suspected appendicitis during pregnancy.

Surgical outcomes have been extensively studied in terms of the differences between LA and OA in the general population with suspected appendicitis. These studies generally show a common result for surgical outcomes. However, prospectively evaluating pregnancy outcomes (fetal loss and preterm delivery) in special populations, such as pregnancy, is difficult. Even in retrospective studies, the results are somewhat different. Therefore, further studies on pregnancy outcomes are needed in the future.

Our study, including both studies by Prodromidou A et al. (EJOG 2018) and Wlasrusmee C et al. (BJS 2012), which are the background of our study, showed that fetal loss was significantly higher in pregnant women who underwent LA compared with those who underwent OA. All three studies suggested that this finding was greatly influenced by the study undertaken by McGory et al. (2007). However, the three studies have different opinions regarding the safety of LA versus OA, especially the risk of fetal loss, in pregnancy with suspected appendicitis.

Wlasrusmee C et al. (BJS 2012) concluded that the available low-grade evidence suggests that LA in pregnant women might be associated with a greater risk of fetal loss.
Prodromidou A et al. (EJOG 2018) concluded that it is associated with a significantly increased rate of fetal loss. However, the author suggested that this finding must be interpreted with caution because fetal loss rates were comparable among the two groups (LA and OA) with the exclusion of an old high-bias study.

Our study, as an updated meta-analysis, concluded that it is not reasonable to conclude that LA in pregnant women might be associated with a greater risk of fetal loss. The sensitivity analysis of the studies comprising our meta-analysis showed that one study by McGory et al. (2007) had a disproportionately high influence on the findings from our meta-analysis, and that when this study was removed from the analysis, no significant difference was evident between LA and OA in relation to the risk of fetal loss. Thus, the findings from our systematic review and updated meta-analysis showed that it is not reasonable to accept without question the conclusions from previous systematic review and meta-analysis (Wilasrusmee C, et al. BJS 2012), which indicated that LA in pregnant women might be associated with a greater risk of fetal loss.

To obtain these results, we applied various analysis techniques that were not used in the study by Prodromidou A et al. (EJOG 2018). In other words, we performed the analysis in a more systematic, multifaceted, and logical way.

First, we performed the funnel plots for fetal loss and preterm delivery to evaluate the publication bias. However, the publication bias was not tested in the study by Prodromidou A et al. (EJOG 2018). This analysis is mostly included in the meta-analysis. Our results showed no evidence of publication bias.

Second, we conducted a sensitivity analysis and presented graphs to raise the visibility of the results. A sensitivity analysis, which involved repeating the sequential pooling outcomes while excluding each study in turn, was performed to evaluate whether the overall results were robust in relation to the excluded studies. Although Prodromidou A et al. (EJOG 2018) also performed a sensitivity analysis in their study, they did not clearly show the result graphs.

Third, meta-regression analyses were performed to examine whether the primary outcomes were associated with the other characteristics of the studies (e.g., publication year, complicated appendicitis, gestational age, pregnancy trimester, or a negative appendectomy). The meta-regression analyses showed trends toward a decreasing odds ratio (OR) for fetal loss in association with a more recent publication year and an increasing OR for fetal loss in association with a higher complicated appendicitis rate. However, Prodromidou A et al. (EJOG 2018) did not perform meta-regression analyses.

Medical technology has significantly improved in the last 10 years. Laparoscopic instruments have gradually evolved, contributing to the improvement of the quality and diversity of laparoscopic procedures. Among them, advances in energy devices and imaging are remarkable, and this progress is contributing to the deepening of anatomical knowledge and providing a safer and more stable technique. Therefore, it is not reasonable to accept without question the
conclusions determined by one study reported by McGory et al. in 2007. Although their study has the largest sample size among the pooled studies, our study suggests that further research is needed to evaluate whether the risk of fetal loss is associated with the severity of appendicitis (complicated appendicitis), and it might be necessary to analyze separately using only recent studies.

Zenon Pogorelic (Reviewer 2):
Overall nice study. No specific remarks.

Response 2:
Thank you for your thoughtful review.

Reviewer 2 (Reviewer 3):
Thank you for the opportunity to review this interesting manuscript. In my opinion, the work was well done, according to the purposes of the authors. The review of the literature was enough in terms of number and quality of articles. The statistics was correct and the interpretations of the data was adequate.

REQUESTED REVISIONS:
The authors did not respond in the topic Conclusion to the question of their objective. I recommend the publication of this article only after the authors include in Discussion comments based on their own experience and a very short conclusion (one or two sentences) responding to the title and objectives of this study.

Response 3:
Thank you for your valuable comment. I have added following sentences in the Discussion and Conclusion sections considering the reviewer's comments:
In the Discussion section (page 8, line 191)

“The present authors also prefer LA over OA for pregnant patients with presumed appendicitis because of its effectiveness in access to the appendix, visualization, and reduce surgical complications. Although our data are not yet enough to evaluate pregnancy outcomes in pregnant women who underwent LA, there was no complication such as fetal loss after LA.”

In the Conclusion section (page 12, line 273):

“Based on our results and recent literatures, we suggest that LA shows non-inferior safety with respect to pregnancy outcomes but superior with regard to surgical outcomes compared with OA in pregnant women with suspected appendicitis.”

I found some typos in the abstract and result section. The errors were corrected as follows.

(In the abstract section: page 2, line 40/ In the result section: page 6, line 142)

: preterm delivery (OR 0.75, 95% CI: 0.50–1.13) (before) → preterm delivery (OR 0.76, 95% CI: 0.51–1.15) (after)

In addition, I have corrected the figure numbering and uploaded the following corrected figure files:

“Fig. 3 → 4” and “Fig. 4 → 3”