PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Rectal water contrast transvaginal ultrasound versus double-contrast barium enema in the diagnosis of bowel endometriosis
AUTHORS	Jiang, Jipeng; Liu, Ying; Wang, Kun; Wu, Xixiang; Tang, Ying

VERSION 1 - REVIEW

REVIEWER	Simone Ferrero IRCCS AOU San Martino - IST, DINOGMI, University of Genova, Italy
REVIEW RETURNED	13-Apr-2017

GENERAL COMMENTS	Major remarks 1) Page 7. Concerning the ultrasonographic description of recto-sigmoid endometriosis, the authors should refer to the IDEA consensus (Guerriero et al., 2016). Please add images to suppor the description 2) Page 7. The authors accurately describe how the depth of infiltration of endometriosis in the rectosigmoid wall is assessed. However, it would be useful to add images of RWC-TVS showing different degrees of infiltration. 3) Page 8. DCBE technique. In my experience, it may be difficult to estimate the depth of penetration of endometriosis in the intestinal wall using DCBE. Therefore, I believe that the authors should describe in details how DCBE was used to estimate the depth of penetration of endometriosis in the intestinal wall. Please clarify how you diagnose the infiltration of the muscularis propria, the submucosa and the mucosa. Please provide images to support your description. 4) Results. The authors describe the location of endometriotic nodules by using the terms: “sigmoid colon”, “rectum”, “rectosigmoid junction”. Accordingly to the IDEA consensus (Guerriero et al., 2016): lower anterior rectum, upper anterior rectum, rectosigmoid junction, anterior sigmoid. 5) Did the author assess the accuracy of the two techniques in estimating the distance between the lower margin of the lesion and the anal verge? 6) The author should provide information on the presence of multifocal disease (multiple nodules affecting the same intestinal segment). Furthermore, they should compare the accuracy of RWC-TVS and DCBE in diagnosing multifocal disease. Minor remarks 1) English revision is advisable 2) Page 12, please revised this sentence: It was necessary to Interruption the whole procedure is not necessary for all patients.

REVIEWER	Yixing Yuchi Harvard Medical School, USA
REVIEW RETURNED	23-Apr-2017

GENERAL COMMENTS	This paper aims to compare the accuracy between rectal water contrast transvaginal ultrasound and double-contrast barium enema in evaluating the bowel endometriosis presence as well as its extent. A quite large number of participants at reproductive age were enrolled.Their results indicate comparable accuracy in the bowel endometriosis diagnosis, but more tolerance for RWC-TVS was found when compared to those with DCBE. In general, this paper is of clinical significance and could be useful for clinical diagnosis. I have the following comments, which the authors may consider to revise their manuscript accordingly: 1. Some of the tables should be re-organized for better readability, for example, table entry in Figure 4. 2. Statistical analysis methods should be specified in each table legend. 3. I would like to see some discussion on the limitation of this study.

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer: 1
Major remarks
1) Page 7. Concerning the ultrasonographic description of recto-sigmoid endometriosis, the authors should refer to the IDEA consensus (Guerriero et al., 2016). Please add images to suppor the description.
Response: Thanks for reviewer's comments. According to reviewer's suggestion, we added new Figure 1 in the revised version, which supports the RWC-TVS description in the Materials and Methods.

2) Page 7. The authors accurately describe how the depth of infiltration of endometriosis in the rectosigmoid wall is assessed. However, it would be useful to add images of RWC-TVS showing different degrees of infiltration.
Response: Thanks for reviewer's comments. According to reviewer's suggestion, we added new Figure 2 in the revised version, which showed the infiltration of endometriosis in the rectosigmoid wall.

3) Page 8. DCBE technique. In my experience, it may be difficult to estimate the depth of penetration of endometriosis in the intestinal wall using DCBE. Therefore, I believe that the authors should describe in details how DCBE was used to estimate the depth of penetration of endometriosis in the intestinal wall. Please clarify how you diagnose the infiltration of the muscularis propria, the submucosa and the mucosa. Please provide images to support your description.
Response: Thanks for reviewer's comments. According to reviewer's suggestion, we have revised the description of DCBE in the revised version as follows: All procedures by DCBE were conducted by a motorized and tilting table to perform radiological and fluoroscopic examination. For preparation, patients kept low-residue diet in a 1-day period before the examination in order to keep enteric content fluid. Then examination was conducted after the intramuscular administration of 20 mg (1 ampoule) scopolamine to induce colonic hypotonia. The presence of bowel endometriosis was diagnosed on DCBE when the bowel lumen was narrowed at any level from the sigmoid to the anus (extrinsic mass effect) in association with crenulation of the mucosa and/or speculation of contour. Also, according to reviewer's suggestion, we added new Figure 3 to support the description.

4) Results. The authors describe the location of endometriotic nodules by using the terms: "sigmoid

colon", "rectum", "rectosigmoid junction". Accordingly to the IDEA consensus (Guerriero et al., 2016): lower anterior rectum, upper anterior rectum, rectosigmoid junction, anterior sigmoid.
Response: Thanks for reviewer's comments. According to reviewer's suggestion, we have read that paper and revised manuscript according to the IDEA consensus, as follows: The largest nodules of intestinal endometriosis were found located on anterior sigmoid of 53 patients, on upper anterior rectum of 30 patients, at rectosigmoid junction of 20 patients, on ileum of 5 patients and on caecum of 2 patients. Multifocal disease was found in 17 patients who had two nodules affecting the bowel. 15 cases were found to have those endometriosis lesions that only infiltrate intestinal serosa on anterior sigmoid, 5 cases were on rectum in and 3 cases were at rectosigmoid junction.

5) Did the author assess the accuracy of the two techniques in estimating the distance between the lower margin of the lesion and the anal verge?
Response: In the current study, we compared the accuracy of RWC-TVS and DCBE in determining the presence and extent of bowel endometriosis. We thank the reviewer for the insightful suggestion, and agree with the reviewer that it would be great to assess the accuracy of the two techniques in estimating the distance between the lower margin of the lesion and the anal verge. We would like to compare the accuracy of these two methods in estimating the distance between the lower margin of the lesion and the anal verge in our next study, which has been added in the discussion section as one of the limitations of the study.

6) The author should provide information on the presence of multifocal disease (multiple nodules affecting the same intestinal segment). Furthermore, they should compare the accuracy of RWC-TVS and DCBE in diagnosing multifocal disease.
Response: Thanks for reviewer's comments. In the current study, we compared the accuracy of RWC-TVS and DCBE in evaluating the presence and extent bowel endometriosis. For the extent evaluation, we compared the difference between size of the largest nodule determined by the imaging and histopathology. For the multifocal disease, we found in 17(15.5%) patients who had two endometriotic nodules affecting the bowel. Both of RWC-TVS and DCBE detected all of them, and have the same accuracy. We added the sentence in the Results as follows: "Multifocal disease was found in 17 patients who had two nodules affecting the bowel."

Minor remarks
1) English revision is advisable
Response: Thanks for reviewer's comments. We have engaged a native English speaking scientist to check and fix grammar errors and inappropriate words in revised version.

2) Page 12, please revised this sentence: It was necessary to Interruption the whole procedure is not necessary for all patients.
Response: Thanks for reviewer's comments. We have revised that sentence as follows: During both examinations, all patients were able to tolerate intestinal distension therefore no procedure interruption occurred.

Response to Reviewer: 2
This paper aims to compare the accuracy between rectal water contrast transvaginal ultrasound and double-contrast barium enema in evaluating the bowel endometriosis presence as well as its extent. A quite large number of participants at reproductive age were enrolled.Their results indicate comparable accuracy in the bowel endometriosis diagnosis, but more tolerance for RWC-TVS was found when compared to those with DCBE. In general, this paper is of clinical significance and could be useful for clinical diagnosis. I have the following comments, which the authors may consider to revise their manuscript accordingly:
1. Some of the tables should be re-organized for better readability, for example, table entry in Figure

4.
Response: Thanks for reviewer's comments. We revised the Figure 4 in revised version.

2. Statistical analysis methods should be specified in each table legend.
Response: Thanks for reviewer's comments. We have added the statistical analysis methods to the legend.

3. I would like to see some discussion on the limitation of this study.
Response: Thanks for reviewer's comments. We added the limitation and the future direction of the current study as follows:
The current study has several limitations. First, experience of ultrasonographer conducting RWC-TVS may affect the accuracy of the techniques in bowel endometriosis diagnosis. Second, the surgeons know the findings by RWC-TVS and DCBE. In an ideal study, surgeons should be blind to the findings of pre-operative investigations, but this theoretical design is unethical clinically, for diagnostic imaging would facilitate the nodule identification of intestinal endometriosis during surgery. Moreover, the knowledge of the pre-operative investigation findings only helps the surgeons to identify actually presenting endometriosis nodules. Third, DCBE and RWC-TVS didn't estimate the circumference percentage of intestinal wall that was infiltrated by the endometriosis, a criterion for choosing between bowel resection and nodulectomy. Hence, patients scheduling for nodulectomy based on the findings of RWC-TVS and DCBE should be aware of that the bowel resection may be required to excise the intestinal endometriosis completely. At last, the study was also limited in that we didn't assess the accuracy of the two techniques in estimating the distance between the lower margin of the lesion and the anal verge, which should be addressed in our follow up study. Future studies would also investigate whether RWC-TVS and DCBE can estimate the intestinal circumference percentage by endometriosis infiltration reliably. DCBE might still play a role for diagnosis workup in patients of suspicious bowel endometriosis. When RWC-TVS or TVS shows bowel muscular is infiltrated by big intestinal nodules, the bowel resection could probably be conducted without further examinations unless surgeons want to exclude the intestinal lesions close to sigmoid. When ultrasound shows one bowel nodule which might be removed by using nodulectomy, DCBE is better to be utilized to exclude other intestinal nodule presence in order to plan the operating procedure with colorectal surgeon as well as the patient adequately.

VERSION 2 – REVIEW

REVIEWER	Yixing Yuchi Harvard Medical School, U.S.
REVIEW RETURNED	04-Jun-2017

GENERAL COMMENTS	I thank the authors for addressing the comments properly, I do not have further comments.