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Science Editor
World Journal of Gastroenterology

Paris, January 7, 2018

Dear Science Editor,

Please find enclosed our revised manuscript entitled "**Endometriosis Nodule Thickness on Preoperative Rectosigmoid Endoscopic Ultrasonography Predicts the Need for Bowel Resection versus Shaving Technique**" by Desplats at al. re-submitted as an original article to the *World Journal of Gastroenterology.*

We would like to thank the reviewers for their constructive comments, which helped to guide the revisions of the manuscript.

Please find the following response to the reviewers' comments.
Please note that all the modifications are highlighted in yellow in the manuscript.

1. **Comment 1 from Reviewer #1: "The Authors should provide more details regarding the US technique used: type of probe, frequency, patient position, normal anatomy of the rectal wall, ultrasonographic pattern of endometriosis, technique of measurement"**

We do agree with the reviewer and added more details about US technique probe as below:

"The patients were in lateral decubitus position whenever it was possible. The first step involved endoscopic evaluation of the mucosae and the digestive lumen. The second step involved an ultrasonographic evaluation of the digestive wall. The device used was a flexible Pentax (Argenteuil, France) echoendoscope with radial probe. The normal rectosigmoid anatomy appears as follows on ultrasound (from the lumen to the serosa): hyperechoic mucosa and submucosa are separated by the hypoechoic muscularis mucosa, the two layers of the smooth muscle, internal and external, are hypoechoic and separated by an hyperechoic line, then there is an external hyperechoic line which is the interface between the muscular layer and the serosa. Rectosigmoid endometriosis appears as an hypoechoic nodule infiltrating the muscular layer. Mucosal or submucosal invasion are characterized by an interruption of their hypoechogenic line."

2. **Comment 2 from Reviewer#1: "Moreover, why did they not use 3D, elastography, contrast medium or Doppler? If not, in the DISCUSSION, they should comment if these new technologies could provide further advantages or not."**

The comment is very interesting and we added new data about 3D Ultrasound and

Transvaginal sonography with water contrast such as follows:

"Other ultrasound techniques were also evaluated for the diagnosis of deep infiltrating endometriosis. Guerriero et al. studied compared the diagnostic accuracy of 2-Dimensions ultrasound (DUS) and 3-DUS in patients with deep infiltrating endometriosis confirmed surgically (*Guerriero et al. Deep Infiltrating Endometriosis -ComparisonBetween 2-DimensionalUltrasonography (US), 3-DimensionalUS, and MagneticResonance Imaging, J Ultrasound Med, 2018*). They showed no significant difference regarding sensitivity, specificity, NPV and PPV between techniques for the intestinal location. Nevertheless, they used transvaginal ultrasound and, to our knowledge, there is no such study comparing the diagnostic accuracy of 2D and 3D RS-EUS. This could be the subject of further researches.

Another interesting study by Bergamini et al. compared the diagnostic accuracy of RS-EUS with Transvaginal Sonography with Water-Contrast in the Rectum (RWC-TVS) in the diagnosis of rectosigmoid endometriosis, confirmed by surgical and pathological findings (*Bergamini et al. Preoperative assessment of intestinal endometriosis: A comparison of transvaginal sonography with water-contrast in the rectum, transrectal sonography, and barium enema, Abdom Imaging, 2010*). In this study RWC-TVS appeared to have better diagnostic performance than RS-EUS but the difference wasn't significant with sensitivity, specificity, PPV and NPV of 96%, 90%, 98% and 81.8% and 88.2%, 80%, 95.7% and 57.1% respectively. However, this time again, they only studied the diagnostic accuracy of the exam and not its performance as a pretherapeutic test as we decided to do in our study. As the same maneer, this could be an interesting subject for further investigations.

Many other ultrasound techniques have also been studied in the diagnosis of intestinal endometriosis such as elastosonography [15] but none of them has been evaluated as a pretherapeutic test."

3. **Comment 3 from Reviewer#1: "It is also not clear to me, if the surgeon who performed the operations was blind to the preoperative US findings. If not this could represent a huge bias for the study."**

In our study, regarding its retrospective design, the surgeon wasn't blind to the preoperative RS-EUS findings and these findings took part in the decision of the surgical procedure. This is surely one of the limitations of the study.

Nevertheless, as our study is, to our knowledge, the first one evaluating not the diagnostic performance of RS-EUS but which of nodules characteristics could help to choose the surgical procedure, the surgeon didn't know that the thickness of the nodule might be a predictor.

4. **Comment 4 from Reviewer #1: "We recommend Authors also to add a few images of normal US anatomy and not-infiltrating endometriosis nodule."**

We thank the reviewer for this comment. We added an image of an normal view of the rectal wall in rectosigmoid endoscopic ultrasonography with this text added in *Material and Methods* : The patients were in lateral decubitus position whenever it was possible. The first step involved endoscopic evaluation of the mucosae and the digestive lumen. The second step involved an ultrasonographic evaluation of the digestive wall. The device used was a flexible

Pentax (Argenteuil, France) echoendoscope with radial probe. The normal rectosigmoid anatomy appears as follows on ultrasound 7,5 MHz (from the lumen to the serosa): hypoechoic mucosa, hyperechoic submucosa, and hypoechoic muscular layer *(Figure 1)*. Rectosigmoid endometriosis appears as an hypoechoic nodule infiltrating the muscular layer. Mucosal or submucosal invasion are characterized by an interruption of their hypoechogenic line *(Figure 2)*.
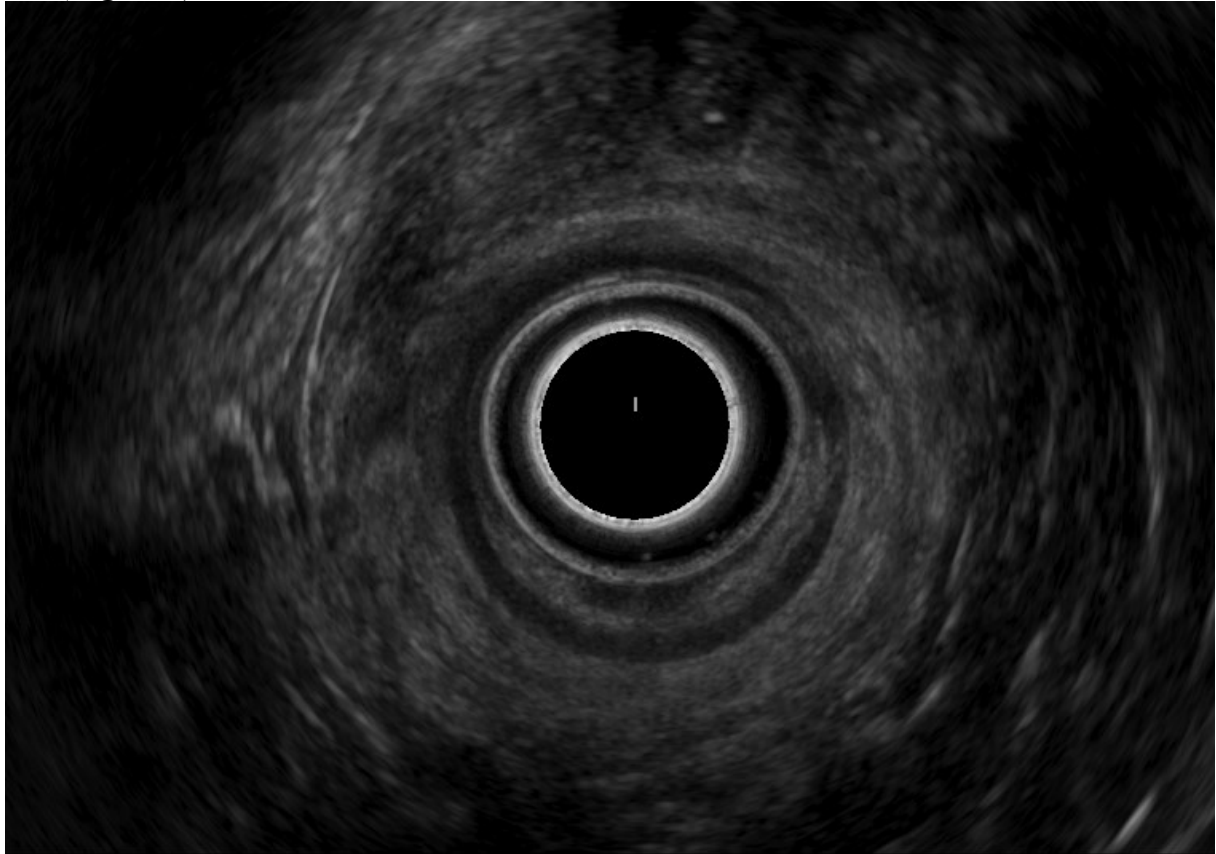

Figure 1. Normal view of the rectal wall with a radial probe in Rectosigmoid Endoscopic Ultrasonography.
Arrow: mucosae. Star: submucosa. Disc : muscular layer
Device: PENTAX EG-3670 URK ultrasound video-endoscope 7.5 MHz

5. **Comment from Reviewer #2 : "I suggest some discussion on other ultrasound findings that may also be useful such as uterosacral ligament thickness, thickened pericolic fat, ovarian mobility and focal tenderness which is discussed in the literature and how this relates to what you decided to use instead"**

We read this comment with a lot of interest. It is true that those ultrasound findings were discussed in the literature and could be studied as predictors for bowel resection. In fact, the criteria mentioned by the reviewer were studied in a study by Chowdary et al. (*Chowdary et. al, Multicentre retrospective study to assess diagnostic accuracy of ultrasound for superficial endometriosis— Are we any closer?, Aust N Z J Obstet Gynaecol 2018),* assessing the diagnostic accuracy of transvaginal sonography in diagnosing superficial endometriosis. Nevertheless, in our study, we decided to focus on the RS-EUS findings and its role in the pre-operative management of rectosigmoid endometriosis, which is part of deep

endometriosis.

6. Comment from Reviewer #3: "However it would be useful to compare the resets obtained by EUS with colonoscopy and RMN. Furthermore the discussion should be modified including the manuscript describing the prediction rate of other procedures".

We do agree with the reviewer and had more precise data in our study.
We now can read the third paragraph in the discussion as below:

"Other technics were also evaluated in detecting and characterizing deep infiltrating endometriosis nodules such as transvaginal ultrasonography, MRI and colonoscopy.
Nowadays, transvaginal ultrasonography has been well studied and experiences great performance in detecting and characterizing rectosigmoid endometriosis nodules and their digestive wall infiltration. In a study par Goncalves et al. this exam showed indeed sensitivity and a specificity of 97% and 100% respectively [4]. Although, performance drops when detecting an infiltration of the submucosae with sensitivity between 62% to 83%, [4][12] maybe explaining why it has never been studied as a predictive factor for the surgery needed such as we did for RS-EUS. […] Colonoscopy has also been studied but cannot be routinely performed for the diagnosis of intestinal endometriosis, giving poor outcomes to this exam with a sensitivity of 7% and a specificity of 85%, due to the paucity of lesions affecting the intestinal mucosa [13]. […] Regarding MRI, our study completes the recent findings concerning MRI measures of stenosis and long axis to predict the need for bowel resection. In this study, a nodule's short axis of 11mm or more was predictor for bowel resection with a sensitivity and specificity of 93% and 99% respectively. Similarly, a bowel stenosis of 30% or more experienced a sensitivity of 95% and a specificity of 99% in predicting the need for a bowel resection [9]. Nevertheless, MRI colonography was a required parameter of this study, and this technique is only available in a limited number of centers. In comparison, RS-EUS is a common, easily accessible exam and is currently well evaluated in staging of deep infiltrating endometriosis with better sensitivity and negative predictive value compared with MRI [11]; this finding indicates that MRI exams do not detect nodules that are detectable by RS-EUS. More precisely, RS-EUS experiences better sensitivity (79% vs. 47%) and negative predictive value (71% vs. 63%) than MRI when detecting a mucosal or submucosal involvement [15]. Therefore, RS-EUS appears to be more adequate in the preoperative evaluation of rectosigmoid endometriosis"

[4]   *Goncalves MO da C, Podgaec S, Dias JA, Gonzalez M, Abrao MS. Transvaginal ultrasonography with bowel preparation is able to predict the number of lesions and rectosigmoid layers affected in cases of deep endometriosis, defining surgical strategy. Hum Reprod 2010; 25: 665–671*
[9]   *Scardapane A, Lorusso F, Francavilla M, Bettocchi S, Fascilla FD, Angelelli G, Scioscia M. Magnetic Resonance Colonography May Predict the Need for Bowel Resection in Colorectal Endometriosis. BioMed Res Int 2017; 2017 Im Internet: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5632851/*
[11]   *Delpy R, Barthet M, Gasmi M, Berdah S, Shojai R, Desjeux A, Boubli L, Grimaud J-C. Value of Endorectal Ultrasonography for Diagnosing Rectovaginal Septal Endometriosis Infiltrating the Rectum. Endoscopy 2005; 37: 357–361*
[12]   *Hudelist G, Tuttlies F, Rauter G, Pucher S, Keckstein J. Can transvaginal sonography*

predict infiltration depth in patients with deep infiltrating endometriosis of the rectum? Hum Reprod 2009; 24: 1012–1017

[13]   *Milone M, Mollo A, Musella M, Maietta P, Fernandez LMS, Shatalova O, Conforti A, Barone G, Placido GD, Milone F. Role of colonoscopy in the diagnostic work-up of bowel endometriosis. World J Gastroenterol 2015; 21: 4997–5001*

[15]   *Kim A, Fernandez P, Martin B, Palazzo L, Ribeiro-Parenti L, Walker F, Bucau M, Collinot H, Luton D, Koskas M. Magnetic Resonance Imaging Compared with Rectal Endoscopic Sonography for the Prediction of Infiltration Depth in Colorectal Endometriosis. J Minim Invasive Gynecol 2017; 24: 1218–1226*

7.   Comment from Rewiewer #4: "However, as the authors said, the study has some limitations. The biggest is it is a retrospective study. If there were some new cases the conclusion must be persuasive. Therefore, the conclusion need be used more uncertain sentences"

It is certain that our study, as we mentioned it, suffers from its retrospective design and small number of patients. Therefore we changed some sentences with a conditional language such as follows :
- In the abstract: "The presence of a rectosigmoid nodule of endometriosis greater than 5.20 mm thick on RS-EUS **might predict** the need for bowel resection"
- In the conclusion: "In our retrospective study, we found that an endometriosis nodule greater than 5.20 mm thick **might predict** the need for bowel resection in rectosigmoid endometriosis"

We hope that the revised manuscript will fulfill your standards for publication, and we would be grateful if you would reconsider its publication in the *World Journal of Gatroenterology*

Sincerely yours,

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