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2 Bowel preparation improves the accuracy of the transvaginal ultrasound in the
3 diagnosis of rectosigmoid deep infiltrating endometriosis: a prospective study.

4

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20

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22

23 Keywords: deep infiltrating endometriosis, transvaginal ultrasound, bowel
24 endometriosis, bowel preparation, pelvic pain

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26

27

28 Precis
29 Bowel preparation improves the accuracy of the transvaginal ultrasound in the
30 diagnosis of rectosigmoid deep infiltrating endometriosis in patients with
31 suspected endometriosis and surgical criteria.

32
33 **Abstract**

34 **Study objective:** To compare the accuracy of transvaginal ultrasound (TVUS) with and
35 without bowel preparation (BP) to detect and describe intestinal nodules of deep
36 infiltrating endometriosis (DIE) with laparoscopic findings.

37 **Design:** prospective study of paired data.

38 **Design classification:** type II.1

39 **Setting:** tertiary university hospital from November 2014 to November 2015.

40 **Patients:** a cohort of women awaiting surgery for endometriosis.

41 **Interventions:** The wall of the rectum and lower sigmoid colon of the patients was
42 evaluated by 2 TVUS: the first ultrasound was performed without previous BP and the
43 second was done after a three-day low-residue diet and two 250 ml enemas 12h and
44 3h before TVUS.

45 **Measurements:** The presence or absence of rectosigmoid nodules visualized by
46 TVUS with and without BP were compared with laparoscopic results.

47 **Main results:** Forty patients with a mean age of 36.8 ± 5.0 years were included in the
48 study. On comparing the surgical findings histologically confirmed (presence or
49 absence of bowel nodules and localization) with those of the two TVUS with and
50 without BP, the sensitivity, specificity and Cohen's kappa (k) were 100%, 96% and
51 $k=0.95$; and 73%, 88% and $k=0.61$, respectively. Laparoscopy showed that up to
52 37.5% of patients (15/40) presented bowel involvement. Variables were clearly more
53 evaluable with than without BP.

54 **Conclusions:** TVUS with BP has a higher accuracy than TVUS without BP. BP allows
55 and facilitates the detection of more rectal nodules of DIE in patients with suspected
56 endometriosis and surgical criteria.

57

58 **Introduction**

59 Endometriosis may affect the rectosigmoid in 9% to 22% of all women with proven
60 endometriosis¹. Bowel endometriosis is believed to be the cause of chronic pelvic pain
61 and other gastrointestinal symptoms, including dyschezia, hematochezia, diarrhea and
62 constipation^{2,3}. This type of endometriosis can only be suspected in 40-68% of the
63 cases by physical examination^{4,7}. Even during laparoscopy, gynecologists might miss
64 deep infiltrating endometriosis (DIE) nodules infiltrating the rectum⁵. Therefore, a
65 precise pre-operative work-up with imaging methods is mandatory to decide the most
66 adequate surgical approach and to inform the patient about the possible risk of
67 complications⁶.

68 Several imaging techniques have been used to diagnose DIE nodules with rectal
69 involvement, including transvaginal ultrasound (TVUS)^{7,8,9}, transrectal
70 ultrasonography^{10,11}, endoscopic transrectal ultrasonography^{4,12}, magnetic
71 resonance^{7,13}, barium enema¹⁴ and multislice computed tomography¹⁵. The accuracy
72 of these techniques depends on the experience of the operator and the quality of the
73 equipment¹⁴, with the accessibility and the cost-effectiveness varying according to the
74 center.

75 TVUS offers important advantages compared with other imaging methods: it is a non-
76 invasive technique without radiation, it is cost-effective, anesthesia is not required,
77 gynecologists and radiologists are familiar with the technique, and it is well-accepted by
78 patients and presents excellent diagnostic accuracy⁹. It is currently considered the
79 first-line imaging procedure in women with suspected endometriosis^{8,16,17}. Some
80 authors have proposed the use of bowel preparation (BP)^{18,19,20}, water-contrast in the

81 rectal lumen²¹, saline solution²² or gel in the vagina²³ prior to TVUS in order to improve
82 the accuracy of the study. Nevertheless, few data are currently available about the role
83 of these substances in the diagnosis of intestinal DIE. To our knowledge, there are no
84 prospective studies comparing TVUS with and without BP in the diagnosis of bowel
85 endometriosis.

86 Therefore, the main objective of the present prospective study was to evaluate the
87 utility of BP prior to TVUS to detect and describe the characteristics of DIE nodules
88 infiltrating the rectosigmoid in women with suspected endometriosis, taking the surgical
89 findings confirmed histologically as a reference.

90

91 **Methods**

92 We performed a prospective preliminary study to compare TVUS with and without BP
93 for the diagnosis of bowel DIE with laparoscopy in a tertiary university hospital,
94 conducted from November 2014 to May 2015. A total of 185 consecutive patients
95 referred for the first time to our Endometriosis Unit for suspicion of DIE (based on pain
96 symptoms and/or physical examination) were selected for the study (Figure 1). After
97 being evaluated following our protocol, patients with surgical criteria were included (40
98 patients). Surgical criteria mainly included: pelvic pain unresponsive to medical
99 treatment, hydrosalpinx in infertile patients, ovarian endometriosis cysts >7 cm in size,
100 and rectosigmoid and/or ureteral stenosis. All the patients selected accepted to
101 participate. Patients who were virgins or in whom TVUS was not possible were
102 excluded.

103 All participants underwent 2 TVUS examinations within an interval of 2 weeks to 3
104 months. Any therapeutic change was performed between both TVUS examinations.
105 The first TVUS was performed without previous BP while the second procedure was
106 carried out following a three-day low-residue diet and two enemas of 250 ml (Figure 2).
107 The two rectal enemas were performed by the patients at home and consisted of 250
108 ml of sodium diphosphate: one on the eve of the examination, and the other within 1 to

109 3 hours prior to initiation of the second examination, in order to eliminate any rectal
110 residue and gases in the rectosigmoid. All the TVUS studies were performed by the
111 same trained gynecologist (CR), who was blinded to the clinical data and the results of
112 the first TVUS during the second examination with BP.

113 All the TVUS were carried out according to the Gonçalves method²⁴: a microconvex
114 endocavity probe (type RIC5-9, Voluson-V730 Expert, GE, Germany) was introduced
115 transvaginally, and the anterior rectal wall, rectosigmoid junction and lower sigmoid
116 colon were examined as far as possible. No other solution or transrectal gel was used.
117 Bowel involvement was suspected when a long, nodular, hypoechoic lesion
118 adhered to the anterior wall of the rectum was observed^{16,24,25}. Rectosigmoid DIE was
119 considered when the lesions affected at least the muscularis propria layer. When a
120 retrocervical, paracervical or torus uterinus lesion was adhered to the rectosigmoid,
121 affecting only the serosa layer of the bowel without compromising the muscularis
122 propria, the lesion was recorded as adhesions (Figure 3). If these variables could not
123 be visualized, they were recorded as non-evaluable. All examinations were interpreted
124 in real-time.

125 The following sonographic variables were analyzed: number of bowel nodules (on the
126 anterior rectum, rectosigmoid junction and lower sigmoid colon), measurements of the
127 nodules (longitudinal diameter measured curvilinear, anteroposterior and transversal
128 axes), the deepest layer of the rectum affected by the lesion, the percentage of the
129 circumference of the bowel affected and the distance between the most distal part of
130 the lower nodule and the anal verge (in cm) (Figure 4). This distance was calculated by
131 measuring the distance between the second curve of the rectum (8 cm from the anal
132 verge) and the bowel lesion²⁴. The quality of the BP used in the study was also
133 evaluated subjectively by the gynecologist, describing if the bowel was empty or not.

134 The appendix, terminal ileum and the upper segments of the sigmoid colon were not
135 evaluated due to the lack of an appropriate probe, and neither were DIE lesions outside
136 the rectosigmoid analyzed.

137 All participants started or remained on hormonal treatment while they were waiting for
138 surgery, following our current protocol. The surgical interventions were performed by
139 expert endometriotic surgeons. Lesions on the rectosigmoid suspected to be
140 endometriosis were removed. The decision of the technique was individualized,
141 managed by conservative laparoscopic procedures: shaving or disc excision or by
142 radical laparoscopic technique, including colorectal resection according to our clinical
143 protocols of management for DIE compromising the bowel based on previous surgical
144 algorithm published studies^{26,27}

145 Afterwards, the endometriotic tissue was histologically confirmed. Histologic evaluation
146 of the digestive specimens was performed by a single pathologist and all samples were
147 fixed in formalin and stained with hematoxylin-eosin. Bowel endometriosis implants
148 were defined by the presence of both endometriotic glands and stroma at microscopic
149 examination. We compared the results of TVUS (with and without BP) and those of
150 laparoscopy in the evaluation of two variables: presence or absence of adhesions or
151 nodules (histologically confirmed), and localization of nodules.

152 Statistical analysis was performed with the SPSS software package (version 19.0,
153 SPSS Inc, Chicago, IL, USA). Comparison between categorical variables was
154 performed with the Fisher's exact test. The Cohen's kappa (k) correlation was
155 computed to assess concordance between the presence/absence of nodules described
156 by TVUS and the surgical findings, histologically confirmed (gold standard). The value
157 of 1 indicated perfect agreement between ratings; 0.81–0.99, very good agreement;
158 0.61–0.80, good; 0.41– 0.60, moderate; 0.21–0.40 fair; and 0.20 or less, poor
159 agreement. Sensitivity, specificity, and predictive values were also calculated. Paired t-
160 test was performed to compare the characteristics of nodules measured by TVUS with
161 and without BP. Results were considered statistically significant with $p < 0.05$ (two-
162 sided). The sample size was arbitrarily set due to the preliminary nature of the study
163 and the lack of similar studies in the literature.

164 The Ethics Committee of the Hospital approved the study, and written informed
165 consent was obtained from all the participants.

166

167 **Results**

168 The demographic and clinical data of the 40 patients awaiting surgery for DIE included
169 in the study are shown in Table 1. Time lapse from the second TVUS to surgery was
170 3.6 ± 1.5 months. A total of 16 patients (40%) had a history of surgery for
171 endometriosis performed in other centers prior to inclusion in the present study. Up to 7
172 of these 16 patients (40%) presented rectosigmoid nodules in the TVUS performed for
173 the study. This fact is probably due to incomplete surgical resection performed in non-
174 referral centers, rather than DIE recurrence²⁸.

175 The accuracy of TVUS with and without BP was evaluated, being significantly better in
176 TVUS with BP ($p=0.02$). Table 2 shows the sensitivity, specificity, predictive values,
177 likelihood ratio and kappa correlation of transvaginal ultrasound (TVUS) with and
178 without bowel preparation (BP) taking the laparoscopic findings histologically confirmed
179 as a reference (presence or absence of nodules and localization). Cohen's k indicated
180 very good agreement ($k=0.95$) between TVUS with BP and laparoscopy, whereas good
181 agreement ($k=0.61$) was found with TVUS without BP.

182 Considering the results of the second TVUS after BP, 15 of the patients did not show
183 real nodules or adhesences in the rectosigmoid; 9 presented adhesences from the
184 posterior DIE to the serosa layer of the rectum, and nodules affecting the rectum or
185 lower sigmoid were detected in 16 patients. Two patients presented two nodules: one
186 on the rectum and one on the sigma. These results are in very good agreement with
187 the surgical findings, except for one patient in whom TVUS with BP showed a rectal
188 nodule not confirmed by laparoscopy (one false-positive). On comparing the results of
189 the laparoscopy with those of the TVUS without BP (Table 3), it was of note that 4
190 adhesences to the serosa layer were evaluated as real rectosigmoid nodules during

191 surgery (4 false-negatives), affecting at least the muscularis propria. Nodules on the
192 sigma were not visible without BP.

193 Regarding the detailed description of the rectosigmoid nodules, no statistically
194 significant differences were found between both techniques (Table 4). However,
195 precise measurements of the bowel nodules could not be possible in all cases using
196 TVUS without BP. The distance from the nodule to the anal verge was evaluable
197 without BP in 11 out of 18 nodules, and the transverse axis and the percentage of the
198 circumference of the bowel affected were determined in only 9 and 7 out of 18 nodules,
199 respectively (Table 4). Finally, BP was well-tolerated by all the participants.

200

201 **Discussion**

202 To our knowledge, this is the first prospective study demonstrating the usefulness of
203 TVUS with BP in the diagnosis of bowel DIE in patients with suspected endometriosis,
204 compared with laparoscopic findings.

205 Previous studies on TVUS with BP^{18,20} reported an excellent sensitivity and specificity
206 compared with laparoscopy (98% and 100%; 100% and 93%, respectively). This
207 accuracy for detecting rectosigmoid nodules is slightly higher than the results described
208 by other authors using TVUS without any substance in the rectum⁹: sensitivity 87%,
209 specificity 97%⁴, 67% and 92%²³, and 91% and 98%⁸. The sensitivity and specificity of
210 the present study are in concordance with other authors, showing better results with
211 TVUS with than without BP.

212 Some studies have described other methods to prepare the bowel which seem to
213 increase the accuracy of TVUS. Valenzano-Menada proposed the injection of saline
214 solution into the rectal lumen through a 6-mm catheter under ultrasonographic
215 control²¹. Although the accuracy of the technique was very high (sensitivity 97% and
216 specificity 100%), the intensity of pain reported was more intense than TVUS without
217 the water contrast. Moreover, this technique did not allow the diagnosis of DIE nodules

218 above the rectosigmoid junction (about 15 cm from the anal verge). The BP used in the
219 present study was similar to that described by Gonçalves et al²⁴ (an oral laxative and
220 two enemas) and is feasible for general application, being well tolerated and not
221 requiring hospitalization. Other authors prefer distension of the vagina to detect
222 intestinal nodules with TVUS. The introduction of a saline solution in the vagina has
223 demonstrated greater accuracy than TVUS alone for diagnosing rectovaginal
224 nodules²². However, only 3 patients presented rectal infiltration in this study, and the
225 effectiveness of this technique remains unclear. Guerriero also reported greater
226 accuracy with the introduction of 12 ml of ultrasound transmission gel in the probe
227 cover, describing this method as being “tenderness-guided”²³. Only 4 patients with
228 infiltration of the rectal wall were included in their study. Thus, the technique did not
229 allow evaluation of intestinal nodules.

230 Other types of BP have been used with other imaging techniques for the detection of
231 bowel endometriosis, such as double-contrast barium edema with endoscopic
232 transrectal ultrasonography¹⁴, or multislice computerized tomography (CT) enteroclysis¹⁵.
233 The main drawbacks of endoscopic transrectal ultrasonography are the need for
234 anesthesia, the reproducibility, the low accessibility and the cost. Therefore, with or
235 without enema in the rectum, this technique has currently been replaced by TVUS^{4,12}.
236 Multislice CT enteroclysis has shown excellent accuracy in identifying women with
237 bowel endometriosis¹⁵. Nevertheless, this technique requires a low-residue diet for
238 three days (as with our BP), hyoscine butylbromide to reduce bowel peristalsis,
239 intravenous contrast material (iopamidol) and, of course, exposure to radiation.
240 Therefore, despite the advantages of multislice CT enteroclysis compared with
241 magnetic resonance and its accuracy in identifying bowel endometriosis, this technique
242 is not as effective as TVUS with BP as a first-line imaging study.

243 Up to 37.5% (15/40) of our patients with suspected endometriosis showed rectosigmoid
244 involvement in the laparoscopy. Up to one third had been classified as adhesions
245 (without affecting muscularis propria) using TVUS without BP in the present study,

246 planning a wrong surgical approach⁶. Our percentage of bowel involvement are in
247 concordance with other studies, showing 42%¹⁸ and 44.7%¹² of rectosigmoid nodules
248 among the population of patients with DIE with surgical criteria.

249 Considering the sonographic parameters to describe and measure the rectosigmoid
250 nodules, comparison between both TVUS techniques was not assessable due to the
251 low number of nodules and evaluable variables without BP.

252 Finally, the present study has some strengths and limitations. One of the strengths is
253 that all the TVUS examinations were performed by the same trained gynecologist
254 within a short interval of time between the two procedures and blinded to the results of
255 the first study. With regard to the limitations of the present study, the aim of the present
256 study was to evaluate the utility of BP in the detection of rectosigmoid DIE nodules.
257 However, we did not assess whether this method also increases the detection of DIE
258 affecting the anterior compartment, uterosacral ligaments, the vagina wall or the
259 rectovaginal septum. The appendix, terminal ileum and the upper segments of the
260 sigmoid colon were not evaluated. Lastly, the sample included patients with surgical
261 criteria and, considering that this disease is currently being managed medically and
262 surgery can be avoided or delayed in a growing proportion of cases¹⁶, the results
263 cannot be extrapolated to the population without surgical endometriosis.

264 In conclusion, the use of TVUS with BP allows and facilitates the detection of more
265 rectal nodules of DIE in patients with suspected endometriosis suggesting the need to
266 include BP in TVUS procedures in order to improve the accuracy of the diagnosis of
267 DIE with rectosigmoid involvement. Other prospective studies including patients with
268 endometriosis, independently of the surgical approach, are needed.

269

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272

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367 **Figure legends**

368 Figure 1. Flow chart.

369 Figure 2. Rectum without deep infiltrating endometriosis visualized using transvaginal
370 ultrasound (TVUS) in the same patient A: without bowel preparation; B: with bowel
371 preparation.

372 Figure 3. A: adhesences between an endometriotic retrocervical nodule and the
373 anterior wall of the rectum, affecting only the serosa layer without compromising the
374 muscularis propia. Images obtained by transvaginal ultrasound (TVUS) with bowel
375 preparation.

376 Figure 4. Rectosigmoid nodule of endometriosis affecting muscularis propia layer
377 visualized using transvaginal ultrasound (TVUS) with bowel preparation A:
378 measurements of longitudinal and anteroposterior axis (sagittal plane); B:
379 measurement of transverse axis and the percentage of the circumference affected
380 (30%) (transverse plane).

381

382

383

384 **Table 1.** Demographic and clinical data of the 40 women included in the study.

Age* (Mean \pm SD) in years	36.8 \pm 5.0
Parity (Average \pm SD) Nulliparous N (%) 2 children N (%)	0.10 \pm 0.44 38 (95.0%) 2 (5.0%)
Patients with previous surgery for endometriosis. N (%)	16 (40.0%)
Infertile patients [†] N (%)	9 (22.5%)

385 *Age when the first TVUS was performed

386 [†]More than 1 year seeking pregnancy.

387 SD: standard deviation, N: number

388

389 **Table 2.** Sensitivity, specificity, predictive values, likelihood ratio and kappa correlation
 390 of transvaginal ultrasound (TVUS) with and without bowel preparation (BP) taking the
 391 laparoscopic findings histologically confirmed as a reference.

	TVUS without BP (n=40)	TVUS with BP (n=40)
Sensitivity	11/15 (73%)	15/15 (100%)
Specificity	22/25 (88%)	24/25 (96%)
Positive predictive value (Precision)	11/14 (79%)	15/16 (94%)
Negative predictive value	22/26 (85%)	24/24 (100%)
Positive Likelihood Ratio	6.08	25

Negative Likelihood Ratio	0.31	0
Accuracy	33/40 (82%)	39/40 (98%)
Cohen's kappa	0.61	0.95

392

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393 **Table 3.** Number of the visible adherences or rectosigmoid nodules of the patients
 394 included in the study. Comparison between transvaginal ultrasound (TVUS), with and
 395 without bowel preparation (BP), and surgical findings.

	Surgical findings		
	Without visible rectosigmoid endometriosis (n=15)	Visible adherences to the serous membrane of the rectum (n=9)	Visible rectosigmoid nodules (n=18)
TVUS without BP			
Without visible rectosigmoid endometriosis (n=16)	11 (69%)	3 (19%)	2 (12%)
Visible adherences to the serous membrane of the rectum (n=12)	3 (24%)	5 (42%)	4 (33%)

Visible rectosigmoid nodules (n=14)	2 (14%)	1 (7%)	11 (79%)
TVUS with BP			
Without visible rectosigmoid endometriosis (n=15)	15 (100%)	0 (0%)	0 (0%)
Visible adhesions to the serous membrane of the rectum (n=9)	0 (0%)	9 (100%)	0 (0%)
Visible rectosigmoid nodules (n=18)	1 (6%)	0 (0%)	17 (94%)

396

397 **Table 4.** Characteristics of the rectosigmoid nodules measured by transvaginal
 398 ultrasound (TVUS), with and without bowel preparation (BP).

Variables	Without BP*	With BP
Distance from anal verge in cm. $X \pm SD$ (N)	10.6 ± 3.4 (11)	10.3 ± 2.6 (18)
Longitudinal axis in mm. $X \pm SD$ (N)	29.9 ± 10.1 (11)	28.2 ± 11.3 (18)
Anteroposterior axis in mm. $X \pm SD$ (N)	9.2 ± 3.5 (10)	9.3 ± 4.0 (18)
Transverse axis in mm. $X \pm SD$ (N)	13.0 ± 5.2 (9)	12.9 ± 6.6 (18)
% Circumference of the bowel affected. $X \pm SD$ (N)	18.6 ± 3.8 (7)	26.5 ± 15.4 (18)

399 *Not all the parameters were evaluable by TVUS without BP.