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Original article

Comparison of rectal water contrast transvaginal ultrasound and double-contrast barium enema in assessing the presence and extent of bowel endometriosis

Running title: Comparison of RWC-TVS and DCBE

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Abstract

Objectives This study aims to compare the accuracy between rectal water contrast transvaginal ultrasound (RWC-TVS) and double-contrast barium enema (DCBE) in evaluating the bowel endometriosis presence as well as its extent.

Design & Setting 198 patients at reproductive age with suspicious bowel endometriosis were included. Physicians in two groups specialized at endometriosis performed RWC-TVS as well as DCBE before laparoscopy, and both groups were blinded to other groups' results. Findings from RWC-TVS or DCBE were compared to histological results. The severity of experienced pain severity through RWC-TVS or DCBE was assessed by an analog scale of 10 cm.

Results In total, 110 in 198 women were confirmed to have endometriosis nodules in the bowel by laparoscopy as well as histopathology. For bowel endometriosis diagnosis, DCBE and RWC-TVS demonstrated sensitivities of 96.4% and 88.2%, specificities of 100% and 97.3%, positive prediction values of 100% and 98.0%, negative prediction values of 98.0% and 88.0%, accuracies of 98.0% and 92.4% respectively. DCBE was related to more tolerance than RWC-TVS.

Conclusions RWC-TVS and DCBE demonstrate similar accuracies in the bowel endometriosis diagnosis, however, patients showed more tolerance for RWC-TVS than those with DCBE.

Keywords: bowel endometriosis; double-contrast barium enema; diagnosis; rectal water contrast transvaginal ultrasound

Strengths and limitations of this study

1. 110 in 198 women were confirmed to have endometriosis nodules in the bowel
2. DCBE was related to more tolerance than RWC-TVS
3. RWC-TVS and DCBE show similar accuracies in the bowel endometriosis diagnosis

Introduction

Bowel endometriosis influences 4-37% patients of endometriosis [1]. Lesions in intestinal endometriosis have variable sizes [2]. Endometriosis nodules of small sizes located in the bowel serosal surface hardly cause symptoms therefore treatments are not required [2]. Endometriosis nodules of larger sizes may infiltrate the wall of bowel and cause some gastrointestinal complaints such as diarrhea, dyschezia, constipation, intestinal cramping, and abdominal bloating [1 3]. The symptoms mimic acute bowel syndrome. The symptoms with bowel endometriosis mainly are nonspecific, usually causing misdiagnosis or diagnosis delay [4]. Physical examinations may suggest rectovaginal endometriosis presence. However, the accuracy is poor in identifying rectosigmoid nodules [5 6].

Until recently, endometriosis diagnosis ultrasound was limited to ovarian endometriosis patients. Other imaging methods were utilized for assessing bowel endometriosis, such as rectal endoscopic ultrasound, double-contrast barium enema (DCBE), transvaginal ultrasound (TVS), magnetic resonance imaging (MRI), virtual colonoscopy, and multidetector computerized tomography enema (MDCT-e) [7-10]. TVS, as a reliable and non-invasive method for assessing bowel endometriosis presence and extent [11]. Rectosigmoid nodules identification maybe facilitated by saline injection through a catheter going into the rectum through rectal-water contrast TVS (RWC-TVS), assessment of infiltration depth of endometriosis on intestinal wall as well as estimation of stenosis degree in the bowel lumen. Yet, no studies have compared the accurateness between DCBE and RWC-TVS in rectosigmoid endometriosis diagnosis [4 12 13].

The diagnosis of bowel endometriosis presence and extent before the surgery is necessary for making a decision on whether the operation is required as well as planning the operation procedure with colorectal surgeons [14]. Preoperational knowledge of intestinal endometriosis

nodules size, number, nodule infiltration depth on the wall of intestine, as well as bowel lumen stenosis degree allows for making best decision on whether the surgery is requisite and whether nodulectomy or bowel segmental resection should be chosen [15 16].

Additionally, preoperational determining of bowel endometriosis extent allows for that the surgeon informs the patient of the benefits as well as potential complications during the operation procedure to be performed. In fact, evolution or complications of the symptoms in digestive system postsurgery may be different for patients experiencing nodulectomy and segmental resection. In this study, we assessed and compared the diagnosis accuracy between DCBE and RWC-TVS for evaluating the bowel endometriosis presence and extent.

Materials and Methods

Study population

This study was conducted from May 2012 to Aug 2016. Patients at the reproductive ages with laparoscopy scheduled for intestinal endometriosis suspicious clinical examination or symptoms were recruited as participants in this study. During this period, it is required by imaging workup that DCBE as well as RWC-TVS were conducted in the patients with suspicious bowel endometriosis. Institutional review board of Tianjin First Center Hospital approved the protocols involved in this study before initialization of the study. All patients enrolled in this study signed the written consent form. Inclusion criteria of this study were: suspicious deep pelvic endometriosis, at reproductive age, gastrointestinal symptoms likely being caused by the bowel endometriosis, desire for complete surgical endometriosis excision. Exclusion criteria of this study were: precedent bilateral ovariectomy, radiological diagnosis of bowel endometriosis,

examination of barium radiology, colorectal surgery, hepatic or renal failure, suggestive intolerance for iodinated contrast medium, or refuse for DCBE or psychiatric disorders.

Symptoms were investigated systematically throughout the study and were documented in a database. The existence of deep dyspareunia, dysmenorrheal, dyschezia, and non-menstrual pelvic was examined and the symptom intensities were evaluated of all patients by a 10 cm visual analog scale (VAS), in which left edge indicated no pain and right extremity presented maximum pain. Whether the following gastrointestinal symptoms were presented was determined: irritable bowel syndrome of diarrhea-predominance, passage of the stool mucus, irritable bowel syndrome of constipation-predominance, abdominal bloating rectal bleeding, and intestinal cramping. A questionnaire of symptom analogue scale was utilized to estimate every gastrointestinal symptom severity.

The results of DCBE and RWC-TVS were compared to pathologic and surgical findings. The radiologists conducting DCBE as well as the gynecologists conducting TVS were both blinded to results of others. They were also blinded to clinical data, and only knew that the intestinal endometriosis presence was suspected. All the patients underwent laparoscopy, which was within one month after completion of investigations for diagnosis. Intestinal endometriosis disease was defined by the minimum infiltration of muscularis propria. Endometriosis foci on bowel serosa were peritoneal instead of bowel endometriosis. This study investigated the accurateness of RWC-TVS and DCBE in assessing the bowel endometriosis presence, evaluating the number and the size for nodules of bowel endometriosis as well as determining the existence of peritoneal endometriosis with only intestinal serosa being infiltrated.

Technique of rectal water contrast transvaginal ultrasound

Two physicians conducted all of the examinations in line with a standardized procedure. RWC-TVS was conducted by utilizing a Voluson E6 machine connected with a transvaginal transducer. Once the transducer was placed in the vagina, a 6-mm flexible catheter was inserted in rectal lumen with a distance of 15 cm to the anus through the anus. To facilitate of the catheter passage, a gel containing lidocaine was applied. A 50 mL syringe connected with the catheter and warm saline solution then was injected to the rectum as well as the sigmoid with ultrasonic control. The saline solution amount for showing the rectosigmoid varied from 100 to 350 mL, based on the intestinal wall dispensability. One hundred ml saline solution was slowly and continuously instilled at the procedure beginning, and the rest solution was instilled if requested by ultrasound. When the saline solution wasn't being infused during the ultrasound, Klemmer forceps attached to the catheter was placed to prevent backflow in the catheter. No significant saline solution leakage in the space was seen between catheter and anus. Before, during as well as after saline injection, images were taken. Bowel endometriosis was shown ultrasonographically as solid, hypoechoic, nodular lesions, adjacent to or penetrating the wall of the intestine. Hyperechoic foci sometimes may present inside the lesion. Intestinal distension permits defining the intestinal nodule limits and various layers within rectal wall in particular so as to estimate infiltration depth. The submucosa and intestinal serosa are hyperechoic. Two layers in muscularis propria were shown as strips with hypoechoic divided by a thin hyperechoic line. Muscularis mucosa appears hypoechoic, and interface connecting the lumen and mucosal layer appears hyperechoic. Infiltration of rectal endometriosis is verified by that hypoechoic nodules penetrate the wall of the intestine and in general muscularis mucosa was thickened by the hypoechoic nodules. Two different ultrasound signs are normally used to define this condition.

DCBE

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 so as to keep fluid of enteric content. Then examination was conducted after the intramuscular administration of Scopolamine at 20 mg (1 ampoule) dose so that colonic hypotonia was induced. The bowel endometriosis presence was diagnosed by DCBE if narrowed bowel lumen by any level was observed between the sigmoid and the anus related to the mucosa crenulation and/or speculated contour.

Examinations tolerability

Immediately after every examination, patients rated the level of discomfort experienced during DCBE as well as RWC-TVS using a 10 cm VAS. Mild pain was scored <2 by moderate pain was scored ≥2, and severe pain was scored >5.

Operation and histological assessment

The surgeons carefully examined the results and images by DCBE and RWC-TVS prior to the laparoscopy. Although the rectosigmoid endometriosis diagnosis and treatment were dependent on the laparoscopic findings, operational procedures were conducted through laparoscope evaluated by the team composed of colorectal as well as gynecological surgeons with lots of experience in the bowel endometriosis and pelvic treatment. At all cases, the rectum and sigmoid colon were examined systematically to confirm the endometriosis lesion presence after enough adhesiolysis. The lesions of bowel endometriosis were removed via intestinal resection, which happened in the cases of a single lesion with >3 cm diameter or infiltrating 50% or more of the intestinal wall circumference, or at least three lesions infiltrating muscular layer. In all the other bowel endometriosis cases, disk resection of partial-thickness or full-thickness was conducted. Excision by shaving was conducted for intestinal lesions with simply the serosal layer of bowel

wall infiltrated. All of the visible lesions that were suspicious endometriosis were removed and then sent for histology examination according to our clinical protocol.

The excised specimens were assessed by histology, and the infiltration depth of endometriosis nodules of bowel wall was assessed. In nodulectomy cases, specimens were oriented macroscopically along intestinal wall (from serosa to the mucosa) and cut to macro sections with two mm thickness. From every macrosection tissue, blocks at 1.5 cm length were attained in various numbers based on the lesion size, and sections at 5 μm were attained for microscopically evaluation from each tissue. In bowel resection cases specimens were longitudinally opened through their entire lengths. Two mm bowel wall longitudinal bands were dissected. The bands were embedded in the tissue blocks, and sections of 5 μm were attained for evaluation by microscopy.

Statistical analysis

Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) were assessed for both RWC-TVS and DCBE. Each test diagnostic value was also measured by negative likelihood ratio (LR-) and positive likelihood ratio (LR+). Efficacy parameters at 95% confidence intervals were calculated. McNemar's test using Yates continuity correction was utilized to compare accuracy of RWC-TVS and DCBE in the intestinal endometriosis diagnosis. McNemar's test was utilized to compare the patient number in which the rectosigmoid nodule numbers were identified by RWC-TVS and DCBE correctly. Accuracy of nodule size assessment with these imaging methods was evaluated by subtracting nodule size assessed by these methods from the nodule size assessed by histology. Nonparametric Mann-Whitney test was applied to compare pain intensity of patients with RWC-TVS or DCBE. Chi-square test was utilized to compare pain type (mild pain, moderate pain or severe pain). Spearman's rank correlation

coefficient was applied to define whether correlation between pain intensity of patients experiencing these two techniques exists. SPSS software was used for data analysis. $P< 0.05$ was considered as statistically significant.

Results

Study population

Totally, 198 patients participated in this study and all underwent surgeries were involved in the study (Figure 1). The major demographic characteristics in this study are displayed in Table 1. The pain intensities as well as gastrointestinal symptoms are shown in Table 2.

Surgery together with histology verified that bowel endometriosis nodules existed in 110 patients (55.6%). Endometriosis lesions infiltrated intestinal serosa among 28 patients. The remaining 82 patients carried pelvic endometriosis yet no evidence for intestinal lesions. The largest nodules of intestinal endometriosis were found located on sigmoid colon of 53 patients, on rectum of 30 patients, at rectosigmoid junction of 20 patients, on ileum of 5 patients and on caecum of 2 patients. 15 cases were found to have those endometriosis lesions that only infiltrate intestinal serosa on sigmoid colon, 5 cases was on rectum in and 3 cases were at rectosigmoid junction. The mean (±SD) lengths of bowel segments that were resected were 12.2 ± 3.6 cm. The endometriosis diagnosis was verified in all excised nodules by histology. Moreover, it showed that 62 patients (56.4 %) had deepest endometriosis nodules infiltrating the muscularis propria, 31 patients (28.2%) with the submucosa infiltrated and 17 patients (15.5%) with the mucosa infiltrated.

Accuracy of DCBE and RWC-TVS in the bowel endometriosis diagnosis

Table 3 described the accuracy, specificity, sensitivity, NPV, PPV, LR- and LR+ of RWC-TVS and DCBE in the bowel endometriosis diagnosis. DCBE identified 106 among 110 patients of bowel endometriosis (96.4%). 4 patients with the rectum muscularis propria infiltrated by endometriosis nodules were not defined, and the rectum muscularis propria were removed using partial-thickness nodulectomy. RWC-TVS identified 97 among 110 patients of intestinal endometriosis (88.2%). RWC-TVS was not able to identify 3 rectal nodules, 4 ileal lesions, 2 cecal lesions, and 4 sigmoid nodules infiltrating muscularis propria. Moreover, we found 4 of the patients with large and bilateral endometriosis in ovarian cysts, and they may hamper the intestinal nodules identification. There were 2 false positives of RWC-TVS, where endometriosis nodules in rectovagina were defined to infiltrate rectum muscularis.

Surgery verified the rectovaginal nodule presence but didn't reveal rectal muscularis infiltration. The specificity, sensitivity, NPV, PPV, LR-, LR+, as well as accuracy of these two techniques in the intestinal endometriosis diagnosis were presented in Table 3. McNemar's test displayed that no significant differences were found in accuracy of these two techniques for bowel endometriosis diagnosis (P=0.109). Histology examination showed that in 53 patients endometriosis infiltrated rectosigmoid colon submucosa or mucosa. DCBE correctly defined the infiltration depth in 27 of the patients (50.9%), while RWC-TVS correctly defined the infiltration depth in 20 of the patients (37.7%) (P=0.126). All other nodules infiltrated the mucosa or submucosa by histology was identified to only reach muscularis at RWC-TVS and DCBE. Both of these two techniques did not have false-positive cases of submucosal or mucosal infiltration diagnosis. Both RWC-TVS and DCBE underestimated the endometriosis nodules size. Nevertheless, underestimation was smaller for DCBE than for RWC-TVS (Table 4).

Additionally, in both techniques underestimation was larger for the nodules with the diameter ≥ 30 mm.

Tolerability of RWC-TVS and DCBE

DCBE was conducted safely in all patients. During both examinations all patients were able to tolerate intestinal distension. It was necessary to Interruption the whole procedure is not necessary for all patients. However, the pain intensity experienced in the course of DCBE was higher than that was experienced in the course of RWC-TVS (Table 5). A positive correlation was detected between the pain intensity experienced by patients throughout these two examinations (Spearman correlation coefficient=0.575, $p < 0.001$).

Discussion

This study is the first time to demonstrate that RWC-TVS and DCBE have comparable accuracy in bowel endometriosis diagnosis. Both DCBE and RWC-TVS underestimated the nodule size of bowel endometriosis, while underestimation was less for DCBE than for RWC-TVS, especially for the nodules with largest diameters ≥ 30 mm as shown in Table 4. Choosing ultrasonic technique often depends on the ultrasonographer experience rather than superiority evidence of one technique in comparison to others. In fact, TVS are required to be conducted by highly skillful professionals, and it was estimated recently that it requires conduction of about 40 cases [17] for the learning curve of an accurate deep pelvic endometriosis diagnosis by TVS. Consequently, it is kind of difficult to attain such extent of experience for the ultrasonographers in small hospitals. Main advantage for DCBE is that, with the entire colon retrograde distension, it provides the complete overview for the entire colon [18]. In this study, rectosigmoid was target of the distension for the aim in the current study was to compare to RWC-TVS and also right

colon endometriosis lesions are outside of the transvaginal approach field view. The reason that RWC-TVS was selected to compare to DCBE is because of the personal experience and the common bowel distension criterion with fluid. The authors subsequently confirmed usefulness of this technique in large series. Additionally, other authors have confirmed that opacification and intestinal distension with ultrasound gel are helpful for visualizing nodules of rectosigmoid endometriosis [19 20].

Previous studies suggested the reliability of TVS for rectosigmoid endometriosis diagnosis. The TVS sensitivity for rectosigmoid endometriosis detection is from 91 to 98%, the specificity is from 97 to 100%, the PPV is from 97 to 100% and the NPV is from 87 to 98% [21-24]. Recently, RWC-TVS was developed in order to facilitate intestinal lesion identification in patients of rectovaginal endometriosis as well as to determine endometriosis infiltration depth in intestinal wall [25]. TVS was utilized in patients of bowel endometriosis extensively recently, though little results are available for DCBE use of these patients. This study verified that RWC-TVS and DCBE have comparable accuracy in bowel endometriosis diagnosis. Both of these two techniques estimated the rectosigmoid nodule length precisely, while DCBE was even accurate than RWC-TVS for measuring the distance from the anal verge to the endometriosis nodule [9]. Visibly, the extensive experiences of the gynecologist and the radiologist in RWC-TVS and DCBE, may have affected the accurateness of the techniques in bowel endometriosis diagnosis [24 26]. The findings could be explained by that when conducting imaging techniques, especially RWC-TVS, it may be difficult to choose the plane where the irregular nodule of endometriosis has the longest diameter. Nevertheless, difference between the longest diameter and the estimated nodule size as assessed by histopathology was very small and also, most of the times it doesn't seem this difference influence the choice for bowel resection or nodulectomy as

treatment [27]. Importantly, the patients tolerated RWC-TVS better compared they did with DCBE. The findings are consistent with those previous studies indicating the accurateness of TVS for bowel endometriosis diagnosis and its comparison of TVS to the other techniques like rectal endoscopic ultrasound and MRI [11 28-30].

Researchers have questioned potential benefits by the introduction of aqueous contrast medium into rectum through TVS. TVS is dependent on the operator and it's possible that differences observed for the accurateness by the technique are caused by the ultrasonographer experience conducting the procedure [31]. However, application of intestinal aqueous contrast into TVS could facilitate the rectosigmoid lesion identification. Other methods have been suggested for improving the TVS accuracy in deep endometriosis detection, including using large amount transmission gel for ultrasound (12 mL) in probe cover or sonovaginography [32]. Till now, there is no study has demonstrated any ultrasonic technique better than others in deep endometriosis diagnosis.

TVS was suggested to be considered as the first investigation for patients of deep endometriosis and TVS allows for intestinal lesions diagnosis [24]. Other investigations including DCBE, MDCT-e, RWC-TVS, rectal endoscopic ultrasound and MRI should be utilized to determine intestinal endometriosis characteristics, such as the nodules size and number, the intestinal wall infiltration depth of nodules and the stenosis degree of bowel lumen [33-35]. RWC-TVS has some advantages over other techniques. For example, RWC-TVS is less expensive than MRI and MDCT-e and the required equipment for RWC-TVS is usually available to the gynecologists, who are typically involved in endometriosis patient management. Recently a study showed that RWC-TVS permit the stenosis degree estimation of intestinal lumen which is caused by the endometriosis [36]. Unfortunately, the current study did not

examine this parameter, which is a limitation in our investigation. Theoretically, RWC-TVS should also permit determination of the disease extent along longitudinal axis of the intestine. Apparently, RWC-TVS could not determine intestinal nodule presence located in the proximal of sigmoid because the lesions are outside of the view field in TVS.

The current study has several limitations. First, experience of ultrasonographer conducting RWC-TVS may affect the accurateness of the techniques in bowel endometriosis diagnosis. Second, the surgeons know the findings by RWC-TVS and DCBE. Though in an ideal study surgeons should not be aware of the findings by preoperative investigations, this theoretical design is unethical clinically, for diagnostic imaging would facilitate the nodule identification of intestinal endometriosis during surgery. Moreover, the knowledge of the preoperative 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. Future studies would 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 muscularis 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.

This study demonstrated RWC-TVS as a very reliable technique to determine the bowel endometriosis presence and extent and it has similar accuracy to that of DCBE. Nevertheless, RWC-TVS may underestimate multiple bowel nodule presence sometimes, and be conducted easily in the ambulatory setting; also it is easily tolerated by the patients. It is hypothesized to combine DCBE and TVS to attain a complete bowel preoperative assessment so as to provide adequate counseling to the patients and the most suitable surgical treatment in one step.

Data sharing statement

All data generated or analysed during this study are included in this published article. No additional unpublished data.

Author's contribution

Collected the data: Jipeng Jiang, Ying Liu, Kun Wang, Xixiang Wu; Designed the study and wrote the manuscript: Ying Tang; All authors approved the final submission.

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Conflict of interests

The authors declare no conflict of interests.

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Figure Legend

Fig.1 Flowchart of the study.

Table 1. Characteristics of study population

	n=198
Age (year)	32.7±4.9
BMI (kg/m^2)	23.4±2.4
Previous surgery for endometriosis	78 (39.4)
Previous live births	53 (26.8)
Hormonal therapy	
None	109 (55.1)
Sequential oral contraceptive	44 (22.2)
Norethisterone acetate	20 (10.1)
Continuous oral contraceptive	13 (6.6)
Norethisterone acetate and letrozole	12 (6.1)

Values were expressed as n (%) or mead ± SD. BMI: body mass index

Table 2. Intensity of pain and gastrointestinal symptoms of the study population (n=198)

	Patients with symptom n (%)	Intensity (mean ±SD)
Dysmenorrhea	171 (86.4)	6.9±1.6
Deep dyspareunia	127 (64.1)	5.5 ± 1.5
Non-menstrual pelvic pain	145 (73.2)	5.7 ± 1.2
Dyschezia	93 (47.0)	5.1 ± 1.9
Diarrhea-predominant IBS	63 (31.8)	7.1 ± 2.1
Constipation-predominant IBS	87 (43.9)	7.6 ± 1.9
Passage of mucus	42 (21.2)	6.1 ± 1.7
Rectal bleeding	19 (9.6)	5.3 ± 1.1
Intestinal cramping	98 (49.5)	6.8 ± 1.9
Abdominal bloating	119 (60.1)	6.5 ± 2.2

Values were expressed as n (%) or mead ± SD. Intensity of pain symptoms assessed using 10-cm visual analogue scale (VAS)

Table 3. Diagnostic performance of rectal Ewater contrast transvaginal ultrasonography (RWC-TVS) and double-contrast barium enema (DCBE) in the diagnosis of bowel and rectosigmoid endometriosis (n=198)

	DCBE	RWC-TVS
Bowel endometriosis		
Sensitivity	106/110 (96.4)	97/110 (88.2)
Specificity	97/97 (100)	95/97 (97.3)
PPV	106/106 (100)	97/99 (98.0)
NPV	97/101 (96.0)	95/108 (88.0)
LR+	N/A	41.67
LR-	0.04	0.13
Accuracy	194/198 (98.0)	183/198 (92.4)

Values were expressed as n (%). Bowel endometriosis defined as disease infiltrating at least the muscularis propria. LR+ could not be calculated because there was no false positive. LR+, positive likelihood ratio; LR−, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

Table 4. Difference between size of the largest nodule estimated by imaging techniques and that assessed on histopathology

	Largest diameter on histology (mm, mean ± SD)	DCBE		RWC-TVS	
		Mean difference (mm (95% CI))	Limits of agreement (mm)	Mean difference (mm (95% CI))	Limits of agreement (mm)
All nodules (n=110)	28.5 ±6.9	1.62 (0.98-2.23)	-4,32 to 7.43	2.27 (1.23-3.43)	-3.12 to 4.23
Nodules with diameter <30 mm (n= 77)	22.7 ± 4.1	0.73 (0.11-1.32)	-2.92 to 5.37	1.65 (0.81-2.76)	-2.32 to 3.78
Nodules with diameter ≥30 mm (n= 33)	35.9 ± 4.2	3.01 (1.96-4.15)	-5,56 to 8.34	3.91 (2.34-5.95)	-5.12 to 8.91

Mean difference calculated by subtracting size of nodule assessed by imaging technique from size of nodule assessed on histology. Limits of agreement calculated as mean difference ± 2 SDs of the difference. RWC-TVS, rectal water contrast transvaginal ultrasonography; DCBE, double-contrast barium enema.

Table 5. Intensity of pain experienced by 198 patients during rectal water contrast transvaginal ultrasonography (RWC-TVS) and double-contrast barium enema (DCBE) as assessed on a 10-cm visual analog scale (VAS)

Intensity of pain	RWC-TVS	DCBE	p value
Overall intensity of pain (mean ± SD)	3.9 ±1.8	4.9 ± 2.3	< 0.001
Categorical intensity of pain (n (%))			< 0.001
Mild pain (VAS score <2)	30 (15.2)	9 (4.5)	
Moderate pain (VAS score ≥ 2 and ≤ 5)	119 (60.1)	80 (40.4)	
Severe pain (VAS score > 5)	49 (24.7)	109 (55.1)	

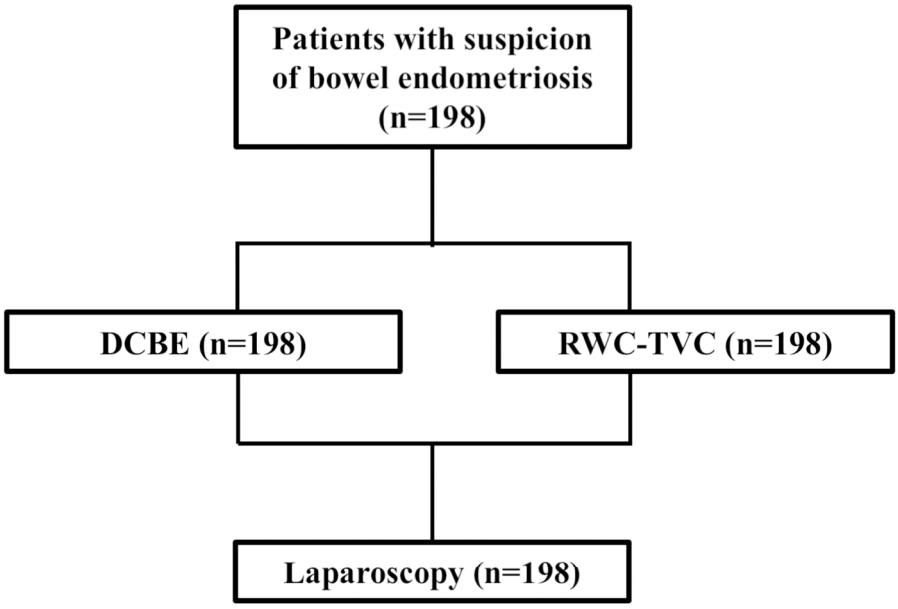

Fig.1

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Rectal water contrast transvaginal ultrasound versus double-contrast barium enema in the diagnosis of bowel endometriosis

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Original article

Rectal water contrast transvaginal ultrasound versus double-contrast barium enema in the diagnosis of bowel endometriosis

Running title: Comparison of RWC-TVS and DCBE

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Abstract

Objectives The aim of study was to compare the accuracy between rectal water contrast transvaginal ultrasound (RWC-TVS) and double-contrast barium enema (DCBE) in evaluating the bowel endometriosis presence as well as its extent.

Design & Setting 198 patients at reproductive age with suspicious bowel endometriosis were included. Physicians in two groups specialized at endometriosis performed RWC-TVS as well as DCBE before laparoscopy, and both groups were blinded to other groups' results. Findings from RWC-TVS or DCBE were compared to histological results. The severity of experienced pain severity through RWC-TVS or DCBE was assessed by an analog scale of 10 cm.

Results In total, 110 in 198 women were confirmed to have endometriosis nodules in the bowel by laparoscopy as well as histopathology. For bowel endometriosis diagnosis, DCBE and RWC-TVS demonstrated sensitivities of 96.4% and 88.2%, specificities of 100% and 97.3%, positive prediction values of 100% and 98.0%, negative prediction values of 98.0% and 88.0%, accuracies of 98.0% and 92.4% respectively. DCBE was related to more tolerance than RWC-TVS.

Conclusions RWC-TVS and DCBE demonstrated similar accuracies in the bowel endometriosis diagnosis, however, patients showed more tolerance for RWC-TVS than those with DCBE.

Keywords: bowel endometriosis; double-contrast barium enema; diagnosis; rectal water contrast transvaginal ultrasound

Strengths and limitations of this study

1. This is the first comparison of the accuracy between RWC-TVS and DCBE in the diagnosis of bowel endometriosis.
2. This study demonstrated RWC-TVS as a very reliable technique to determine the bowel endometriosis presence and extent and it has similar accuracy to that of DCBE.
3. We demonstrate DCBE is related to more tolerance than RWC-TVS.
4. This study requires a larger sample once suitable participants become available.

Introduction

Bowel endometriosis influences 4-37% patients of endometriosis [1]. Lesions in intestinal endometriosis have variable sizes [2]. Endometriosis nodules of small sizes locate in the bowel serosal surface hardly causing symptoms and treatments are not required [2]. Endometriosis nodules of larger sizes may infiltrate the wall of bowel and cause some gastrointestinal complaints such as diarrhea, dyschezia, constipation, intestinal cramping, and abdominal bloating [1 3]. The symptoms mimic acute bowel syndrome. The symptoms with bowel endometriosis mainly are nonspecific, usually causing misdiagnosis or diagnosis delay [4]. Physical examinations may suggest rectovaginal endometriosis presence. However, the accuracy is poor in identifying rectosigmoid nodules [5 6].

Until recently, endometriosis diagnosis ultrasound was limited to ovarian endometriosis patients. Other imaging methods were utilized for assessing bowel endometriosis, such as rectal endoscopic ultrasound, double-contrast barium enema (DCBE), transvaginal ultrasound (TVS), magnetic resonance imaging (MRI), virtual colonoscopy, and multidetector computerized tomography enema (MDCT-e) [7-10]. TVS, as a reliable and non-invasive method for assessing bowel endometriosis presence and extent [11]. Rectosigmoid nodules identification maybe facilitated by saline injection through a catheter going into the rectum through rectal-water contrast TVS (RWC-TVS), assessment of infiltration depth of endometriosis on intestinal wall as well as estimation of stenosis degree in the bowel lumen. Yet, no studies have compared the accurateness between DCBE and RWC-TVS in rectosigmoid endometriosis diagnosis [4 12 13].

The diagnosis of bowel endometriosis presence and extent before the surgery is necessary for making a decision on whether the operation is required as well as planning the operation procedure with colorectal surgeons [14]. Preoperational knowledge of intestinal endometriosis

nodules size, number, nodule infiltration depth on the wall of intestine, as well as bowel lumen stenosis degree allows for making best decision on whether the surgery is requisite and whether nodulectomy or bowel segmental resection should be chosen [15 16].

Additionally, preoperational determining of bowel endometriosis extent allows for that the surgeon informs the patient of the benefits as well as potential complications during the operation procedure to be performed. In fact, evolution or complications of the symptoms in digestive system post-surgery may be different for patients experiencing nodulectomy and segmental resection. In this study, we assessed and compared the diagnosis accuracy between DCBE and RWC-TVS for evaluating the bowel endometriosis presence and extent.

Materials and Methods

Study population

This study was conducted from May 2012 to Aug 2016. Patients at the reproductive ages with laparoscopy scheduled for intestinal endometriosis suspicious clinical examination or symptoms were recruited as participants in this study. During this period, it is required by imaging workup that DCBE as well as RWC-TVS were conducted in the patients with suspicious bowel endometriosis. Institutional review board of Tianjin First Center Hospital approved the protocols involved in this study before initialization of the study. All patients enrolled in this study signed the written consent form. Inclusion criteria of this study were: suspicious deep pelvic endometriosis, at reproductive age, gastrointestinal symptoms likely being caused by the bowel endometriosis, desire for complete surgical endometriosis excision. Exclusion criteria of this study were: precedent bilateral ovariectomy, radiological diagnosis of bowel endometriosis,

examination of barium radiology, colorectal surgery, hepatic or renal failure, suggestive intolerance for iodinated contrast medium, or refuse for DCBE or psychiatric disorders.

Symptoms were investigated systematically throughout the study and were documented in a database. The existence of deep dyspareunia, dysmenorrheal, dyschezia, and non-menstrual pelvic was examined and the symptom intensities were evaluated of all patients by a 10 cm visual analog scale (VAS), in which left edge indicated no pain and right extremity presented maximum pain. Whether the following gastrointestinal symptoms were presented was determined: irritable bowel syndrome of diarrhea-predominance, passage of the stool mucus, irritable bowel syndrome of constipation-predominance, abdominal bloating rectal bleeding, and intestinal cramping. A questionnaire of symptom analogue scale was utilized to estimate every gastrointestinal symptom severity.

The results of DCBE and RWC-TVS were compared to pathologic and surgical findings. The radiologists conducting DCBE as well as the gynecologists conducting TVS were both blinded to results of others. They were also blinded to clinical data, and only knew that the intestinal endometriosis presence was suspected. All the patients underwent laparoscopy, which was within one month after completion of investigations for diagnosis. Intestinal endometriosis disease was defined by the minimum infiltration of muscularis propria. Endometriosis foci on bowel serosa were peritoneal instead of bowel endometriosis. This study investigated the accurateness of RWC-TVS and DCBE in assessing the bowel endometriosis presence, evaluating the number and the size for nodules of bowel endometriosis as well as determining the existence of peritoneal endometriosis with only intestinal serosa being infiltrated.

Technique of rectal water contrast transvaginal ultrasound

Two physicians conducted all of the examinations in line with a standardized procedure[10]. RWC-TVS was conducted by utilizing a Voluson E6 machine connected with a transvaginal transducer. Once the transducer was placed in the vagina, a 6-mm flexible catheter was inserted in rectal lumen with a distance of 15 cm to the anus through the anus. To facilitate of the catheter passage, a gel containing lidocaine was applied. A 50 mL syringe connected with the catheter and warm saline solution then was injected to the rectum as well as the sigmoid with ultrasonic control. The saline solution amount for showing the rectosigmoid varied from 100 to 350 mL, based on the intestinal wall dispensability. One hundred ml saline solution was slowly and continuously instilled at the procedure beginning, and the rest solution was instilled if requested by ultrasound. When the saline solution wasn't being infused during the ultrasound, Klemmer forceps attached to the catheter was placed to prevent backflow in the catheter. No significant saline solution leakage in the space was seen between catheter and anus. Before, during as well as after saline injection, images were taken. Bowel endometriosis was shown ultrasonographically as solid, hypoechoic, nodular lesions, adjacent to or penetrating the wall of the intestine. Hyperechoic foci sometimes may present inside the lesion. Intestinal distension permits defining the intestinal nodule limits and various layers within rectal wall in particular so as to estimate infiltration depth. The submucosa and intestinal serosa are hyperechoic. Two layers in muscularis propria were shown as strips with hypoechoic divided by a thin hyperechoic line. Muscularis mucosa appears hypoechoic, and interface connecting the lumen and mucosal layer appears hyperechoic (Figure 1). Infiltration of rectal endometriosis was verified by that hypoechoic nodules penetrate the wall of the intestine and in general muscularis mucosa was thickened by the hypoechoic nodules. Two different ultrasound signs were normally used to define this condition (Figure 2).

DCBE

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 (Figure 3).**Examinations tolerability**

Immediately after every examination, patients rated the level of discomfort experienced during DCBE as well as RWC-TVS using a 10 cm VAS. Mild pain was scored <2 by moderate pain was scored ≥2, and severe pain was scored >5.

Operation and histological assessment

The surgeons carefully examined the results and images by DCBE and RWC-TVS prior to the laparoscopy. Although the rectosigmoid endometriosis diagnosis and treatment were dependent on the laparoscopic findings, operational procedures were conducted through laparoscope evaluated by the team composed of colorectal as well as gynecological surgeons with lots of experience in the bowel endometriosis and pelvic treatment. At all cases, the rectum and sigmoid colon were examined systematically to confirm the endometriosis lesion presence after enough adhesiolysis. The lesions of bowel endometriosis were removed via intestinal resection, which happened in the cases of a single lesion with >3 cm diameter or infiltrating 50% or more of the intestinal wall circumference, or at least three lesions infiltrating muscular layer. In all the other bowel endometriosis cases, disk resection of partial-thickness or full-thickness was conducted. Excision by shaving was conducted for intestinal lesions with simply the serosal layer of bowel

wall infiltrated. All of the visible lesions that were suspicious endometriosis were removed and then sent for histology examination according to our clinical protocol.

The excised specimens were assessed by histology, and the infiltration depth of endometriosis nodules of bowel wall was assessed. In nodulectomy cases, specimens were oriented macroscopically along intestinal wall (from serosa to the mucosa) and cut to macro sections with two mm thickness. From every macrosection tissue, blocks at 1.5 cm length were attained in various numbers based on the lesion size, and sections at 5 μm were attained for microscopically evaluation from each tissue. In bowel resection cases specimens were longitudinally opened through their entire lengths. Two mm bowel wall longitudinal bands were dissected. The bands were embedded in the tissue blocks, and sections of 5 μm were attained for evaluation by microscopy.

Statistical analysis

Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) were assessed for both RWC-TVS and DCBE. Each test diagnostic value was also measured by negative likelihood ratio (LR-) and positive likelihood ratio (LR+). Efficacy parameters at 95% confidence intervals were calculated. McNemar's test using Yates continuity correction was utilized to compare accuracy of RWC-TVS and DCBE in the intestinal endometriosis diagnosis. McNemar's test was utilized to compare the patient number in which the rectosigmoid nodule numbers were identified by RWC-TVS and DCBE correctly. Accuracy of nodule size assessment with these imaging methods was evaluated by subtracting nodule size assessed by these methods from the nodule size assessed by histology. Nonparametric Mann-Whitney test was applied to compare pain intensity of patients with RWC-TVS or DCBE. Chi-square test was utilized to compare pain type (mild pain, moderate pain or severe pain). Spearman's rank correlation

coefficient was applied to define whether correlation between pain intensity of patients experiencing these two techniques exists. SPSS software was used for data analysis. $P< 0.05$ was considered as statistically significant.

Results

Study population

Totally, 198 patients participated in this study and all underwent surgeries were involved in the study (Figure 4). The major demographic characteristics in this study were displayed in Table 1. The pain intensities as well as gastrointestinal symptoms were shown in Table 2.

Surgery together with histology verified that bowel endometriosis nodules existed in 110 patients (55.6%). Endometriosis lesions infiltrated intestinal serosa among 28 patients. The remaining 82 patients carried pelvic endometriosis yet no evidence for intestinal lesions. 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. The mean (±SD) lengths of bowel segments that were resected were 12.2 ± 3.6 cm. The endometriosis diagnosis was verified in all excised nodules by histology. Moreover, it showed that 62 patients (56.4 %) had deepest endometriosis nodules infiltrating the muscularis propria, 31 patients (28.2%) with the submucosa infiltrated and 17 patients (15.5%) with the mucosa infiltrated.

Accuracy of DCBE and RWC-TVS in the bowel endometriosis diagnosis

Table 3 described the accuracy, specificity, sensitivity, NPV, PPV, LR- and LR+ of RWC-TVS and DCBE in the bowel endometriosis diagnosis. DCBE identified 106 among 110 patients of bowel endometriosis (96.4%). 4 patients with the rectum muscularis propria infiltrated by endometriosis nodules were not defined, and the rectum muscularis propria were removed using partial-thickness nodulectomy. RWC-TVS identified 97 among 110 patients of intestinal endometriosis (88.2%). RWC-TVS was not able to identify 3 rectal nodules, 4 ileal lesions, 2 cecal lesions, and 4 sigmoid nodules infiltrating muscularis propria. Moreover, we found 4 of the patients with large and bilateral endometriosis in ovarian cysts, and they may hamper the intestinal nodules identification. There were 2 false positives of RWC-TVS, where endometriosis nodules in rectovagina were defined to infiltrate rectum muscularis.

Surgery verified the rectovaginal nodule presence but didn't reveal rectal muscularis infiltration. The specificity, sensitivity, NPV, PPV, LR-, LR+, as well as accuracy of these two techniques in the intestinal endometriosis diagnosis were presented in Table 3. McNemar's test displayed that no significant differences were found in accuracy of these two techniques for bowel endometriosis diagnosis (P=0.109). Histology examination showed that in 53 patients endometriosis infiltrated rectosigmoid colon submucosa or mucosa. DCBE correctly defined the infiltration depth in 27 of the patients (50.9%), while RWC-TVS correctly defined the infiltration depth in 20 of the patients (37.7%) (P=0.126). All other nodules infiltrated the mucosa or submucosa by histology was identified to only reach muscularis at RWC-TVS and DCBE. Both of these two techniques did not have false-positive cases of submucosal or mucosal infiltration diagnosis. Both RWC-TVS and DCBE underestimated the endometriosis nodules size. Nevertheless, underestimation was smaller for DCBE than for RWC-TVS (Table 4).

Additionally, in both techniques underestimation was larger for the nodules with the diameter ≥ 30 mm.

Tolerability of RWC-TVS and DCBE

DCBE was conducted safely in all patients. During both examinations, all patients were able to tolerate intestinal distension therefore no procedure interruption occurred. However, the pain intensity experienced in the course of DCBE was higher than that was experienced in the course of RWC-TVS (Table 5). A positive correlation was detected between the pain intensity experienced by patients throughout these two examinations (Spearman correlation coefficient=0.575, $p < 0.001$).

Discussion

This study is the first time to demonstrate that RWC-TVS and DCBE have comparable accuracy in bowel endometriosis diagnosis. Both DCBE and RWC-TVS underestimated the nodule size of bowel endometriosis, while underestimation was less for DCBE than for RWC-TVS, especially for the nodules with largest diameters ≥ 30 mm as shown in Table 4. Choosing ultrasonic technique often depends on the ultrasonographer experience rather than superiority evidence of one technique in comparison to others. In fact, TVS are required to be conducted by highly skillful professionals, and it was estimated recently that it requires conduction of about 40 cases [17] for the learning curve of an accurate deep pelvic endometriosis diagnosis by TVS. Consequently, it is kind of difficult to attain such extent of experience for the ultrasonographers in small hospitals. Main advantage for DCBE is that, with the entire colon retrograde distension, it provides the complete overview for the entire colon [18]. The aim in the current study was to compare to RWC-TVS and also right colon endometriosis lesions are outside of the transvaginal

approach field view. The reason that RWC-TVS was selected to compare to DCBE was because of the personal experience and the common bowel distension criterion with fluid. The authors subsequently confirmed usefulness of this technique in large series. Additionally, other authors have confirmed that opacification and intestinal distension with ultrasound gel are helpful for visualizing nodules of rectosigmoid endometriosis [19 20].

Previous studies suggested the reliability of TVS for rectosigmoid endometriosis diagnosis. The TVS sensitivity for rectosigmoid endometriosis detection is from 91 to 98%, the specificity is from 97 to 100%, the PPV is from 97 to 100% and the NPV is from 87 to 98% [21-24]. Recently, RWC-TVS was developed in order to facilitate intestinal lesion identification in patients of rectovaginal endometriosis as well as to determine endometriosis infiltration depth in intestinal wall [25]. TVS was utilized in patients of bowel endometriosis extensively recently, though little results are available for DCBE use of these patients. This study verified that RWC-TVS and DCBE have comparable accuracy in bowel endometriosis diagnosis. Both of these two techniques estimated the rectosigmoid nodule length precisely, while DCBE was even accurate than RWC-TVS for measuring the distance from the anal verge to the endometriosis nodule [9]. Visibly, the extensive experiences of the gynecologist and the radiologist in RWC-TVS and DCBE, may have affected the accurateness of the techniques in bowel endometriosis diagnosis [24 26]. The findings could be explained by that when conducting imaging techniques, especially RWC-TVS, it may be difficult to choose the plane where the irregular nodule of endometriosis has the longest diameter. Nevertheless, difference between the longest diameter and the estimated nodule size as assessed by histopathology was very small and also, most of the times it doesn't seem this difference influence the choice for bowel resection or nodulectomy as treatment [27]. Importantly, the patients tolerated RWC-TVS better compared they did with DCBE.

The findings are consistent with those previous studies indicating the accurateness of TVS for bowel endometriosis diagnosis and its comparison of TVS to the other techniques like rectal endoscopic ultrasound and MRI [11 28-30].

Researchers have questioned potential benefits by the introduction of aqueous contrast medium into rectum through TVS. TVS is dependent on the operator and it's possible that differences observed for the accurateness by the technique are caused by the ultrasonographer experience conducting the procedure [31]. However, application of intestinal aqueous contrast into TVS could facilitate the rectosigmoid lesion identification. Other methods have been suggested for improving the TVS accuracy in deep endometriosis detection, including using large amount transmission gel for ultrasound (12 mL) in probe cover or sonovaginography [32]. Till now, there is no study has demonstrated any ultrasonic technique better than others in deep endometriosis diagnosis.

TVS was suggested to be considered as the first investigation for patients of deep endometriosis and TVS allows for intestinal lesions diagnosis [24]. Other investigations including DCBE, MDCT-e, RWC-TVS, rectal endoscopic ultrasound and MRI should be utilized to determine intestinal endometriosis characteristics, such as the nodules size and number, the intestinal wall infiltration depth of nodules and the stenosis degree of bowel lumen [33-35]. RWC-TVS has some advantages over other techniques. For example, RWC-TVS is less expensive than MRI and MDCT-e and the required equipment for RWC-TVS is usually available to the gynecologists, who are typically involved in endometriosis patient management. Recently a study showed that RWC-TVS permit the stenosis degree estimation of intestinal lumen which is caused by the endometriosis [36]. Unfortunately, the current study did not examine this parameter, which is a limitation in our investigation. Theoretically, RWC-TVS should also permit

determination of the disease extent along longitudinal axis of the intestine. Apparently, RWC-TVS could not determine intestinal nodule presence located in the proximal of sigmoid because the lesions are outside of the view field in TVS.

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.

This study demonstrated RWC-TVS as a very reliable technique to determine the bowel endometriosis presence and extent and it has similar accuracy to that of DCBE. Nevertheless, RWC-TVS may underestimate multiple bowel nodule presence sometimes, and be conducted easily in the ambulatory setting; also it is easily tolerated by the patients. It is hypothesized to combine DCBE and TVS to attain a complete bowel preoperative assessment so as to provide adequate counseling to the patients and the most suitable surgical treatment in one step.

Data sharing statement

All data generated or analyzed during this study are included in this published article. No additional unpublished data.

Author's contribution

Collected the data: Jipeng Jiang, Ying Liu, Kun Wang, Xixiang Wu; Designed the study and wrote the manuscript: Ying Tang; All authors approved the final submission.

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Conflict of interests

The authors declare no conflict of interests.

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Figure Legends

Fig. 1 RWC-TVS image showing a rectal endometriotic nodule thickening the muscularis mucosa (arrowhead). The rectal lumen is distended by saline solution (WC).

Fig. 2 RWC-TVC image showing a rectal endometriotic nodule (arrow) with largest longitudinal diameter of 2.7 infiltrating the intestinal submucosa.

Fig. 3 DCBE showing the effect of a large endometriotic nodule on the surface of the sigmoid colon.

Fig. 4 Flow chart of the study.

Table 1. Characteristics of study population

	n=198
Age (year)	32.7 ± 4.9
BMI (kg/m^2)	23.4 ± 2.4
Previous surgery for endometriosis	78 (39.4)
Previous live births	53 (26.8)
Hormonal therapy	
None	109 (55.1)
Sequential oral contraceptive	44 (22.2)
Norethisterone acetate	20 (10.1)
Continuous oral contraceptive	13 (6.6)
Norethisterone acetate and letrozole	12 (6.1)

Values were expressed as n (%) or mean ± SD. BMI: body mass index

Table 2. Intensity of pain and gastrointestinal symptoms of the study population (n=198)

	Patients with symptom n (%)	Intensity (mean ± SD)
Dysmenorrhea	171 (86.4)	6.9 ± 1.6
Deep dyspareunia	127 (64.1)	5.5 ± 1.5
Non-menstrual pelvic pain	145 (73.2)	5.7 ± 1.2
Dyschezia	93 (47.0)	5.1 ± 1.9
Diarrhea-predominant IBS	63 (31.8)	7.1 ± 2.1
Constipation-predominant IBS	87 (43.9)	7.6 ± 1.9
Passage of mucus	42 (21.2)	6.1 ± 1.7
Rectal bleeding	19 (9.6)	5.3 ± 1.1
Intestinal cramping	98 (49.5)	6.8 ± 1.9
Abdominal bloating	119 (60.1)	6.5 ± 2.2

Values were expressed as n (%) or mean ± SD. Intensity of pain symptoms assessed using 10-cm visual analogue scale (VAS)

Table 3. Diagnostic performance of rectal Ewater contrast transvaginal ultrasonography (RWC-TVS) and double-contrast barium enema (DCBE) in the diagnosis of bowel and rectosigmoid endometriosis (n=198)

	DCBE	RWC-TVS
Bowel endometriosis		
Sensitivity	106/110 (96.4)	97/110 (88.2)
Specificity	97/97 (100)	95/97 (97.3)
PPV	106/106 (100)	97/99 (98.0)
NPV	97/101 (96.0)	95/108 (88.0)
LR+	N/A	41.67
LR-	0.04	0.13
Accuracy	194/198 (98.0)	183/198 (92.4)

Values were expressed as n (%). Bowel endometriosis defined as disease infiltrating at least the muscularis propria. LR+ could not be calculated because there was no false positive. LR+, positive likelihood ratio; LR-, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

McNemar's test with Yates continuity correction was used to compare the accuracy of DCBE and RWC-TVC.

Table 4. Difference between size of the largest nodule estimated by imaging techniques and that measured on histopathology

	Largest diameter on histology (mm, mean ± SD)	DCBE Mean difference (mm, 95% CI)[a]	DCBE Limits of agreement (mm)[b]	RWC-TVS Mean difference (mm, 95% CI)[a]	RWC-TVS Limits of agreement (mm)[b]
All nodules (n=110)	28.5 ±6.9	1.62 (0.98-2.23)	−4.32 to 7.43	2.27 (1.23-3.43)	−3.12 to 4.23
Nodules with diameter <30 mm (n= 77)	22.7 ± 4.1	0.73 (0.11-1.32)	−2.92 to 5.37	1.65 (0.81-2.76)	-2.32 to 3.78
Nodules with diameter ⩾30 mm (n= 33)	35.9 ± 4.2	3.01 (1.96-4.15)	−5.56 to 8.34	3.91 (2.34-5.95)	-5.12 to 8.91

RWC-TVS, rectal water contrast transvaginal ultrasonography; DCBE, double-contrast barium enema. **a**. Mean difference calculated by subtracting size of size of nodule by imaging technique from size of nodule measured on histology**. b**. Limits of agreement calculated as mean difference ± 2 SDs of the difference.

Table 5. Intensity of pain experienced by 198 patients during rectal water contrast transvaginal ultrasonography (RWC-TVS) and double-contrast barium enema (DCBE) as assessed on a 10-cm visual analog scale (VAS)

Intensity of pain	RWC-TVS	DCBE	p value
Overall intensity of pain (mean ± SD)	3.9 ±1.8	4.9 ± 2.3	< 0.001
Categorical intensity of pain (n (%))			< 0.001
Mild pain (VAS score < 2)	30 (15.2)	9 (4.5)	
Moderate pain (VAS score ≥ 2 and ≤ 5)	119 (60.1)	80 (40.4)	
Severe pain (VAS score > 5)	49 (24.7)	109 (55.1)	

The Mann-Whitney test was used to compare the intensity of pain. The chi-square test was used to compare the type of pain.

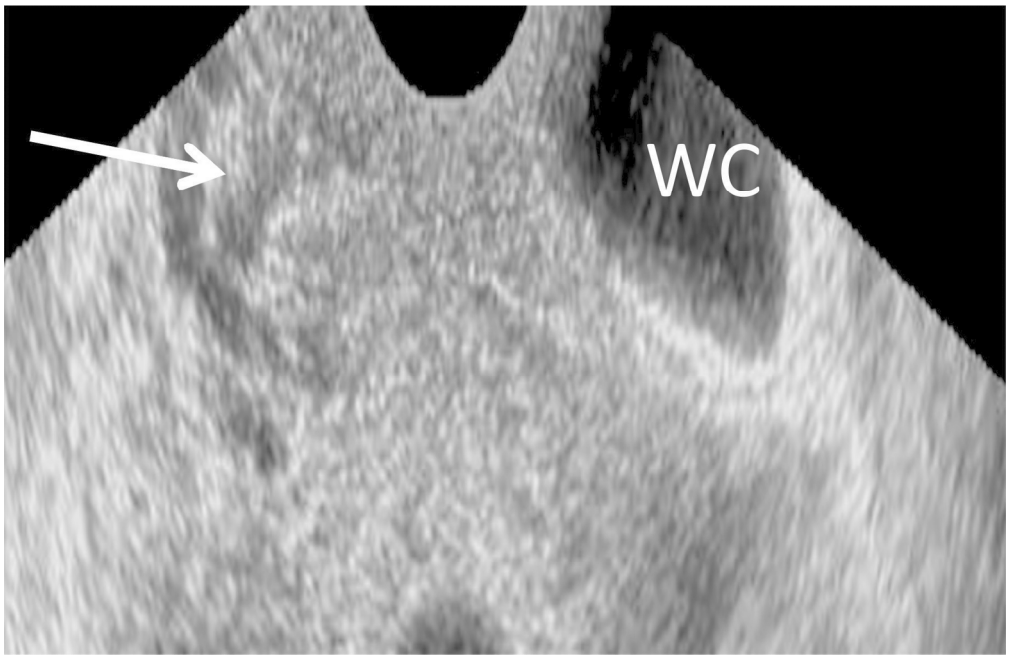

Figure 1

154x100mm (300 x 300 DPI)

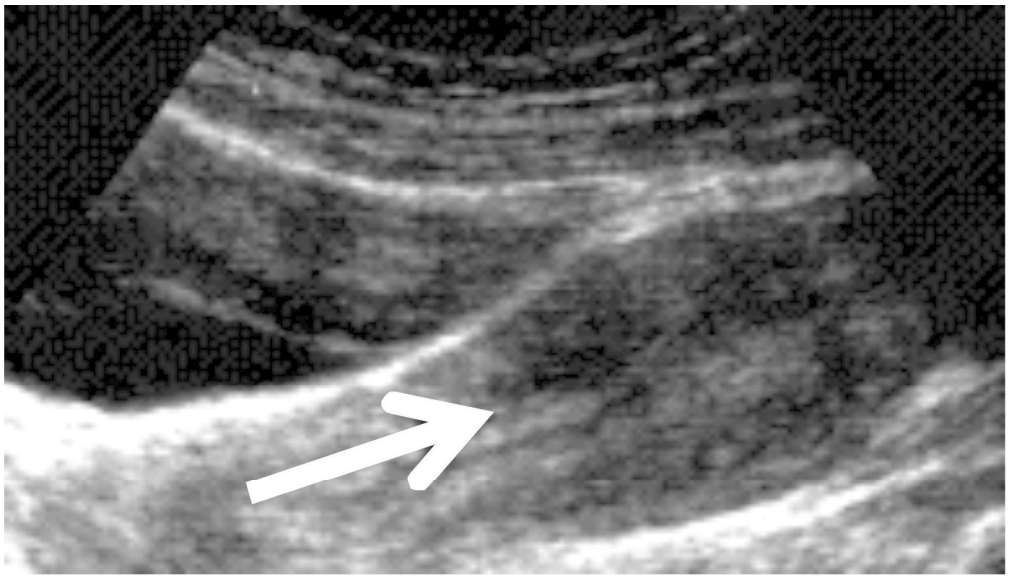

Figure 2

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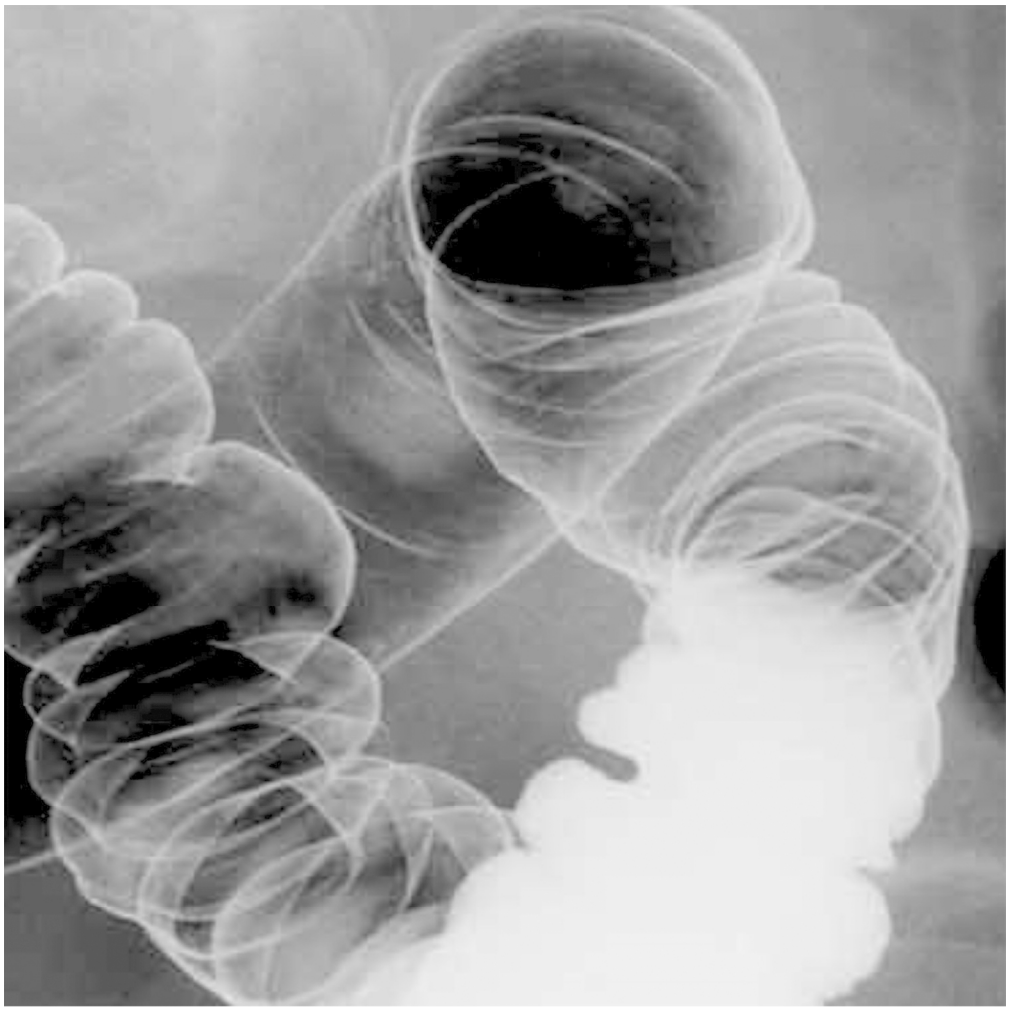

Figure 3

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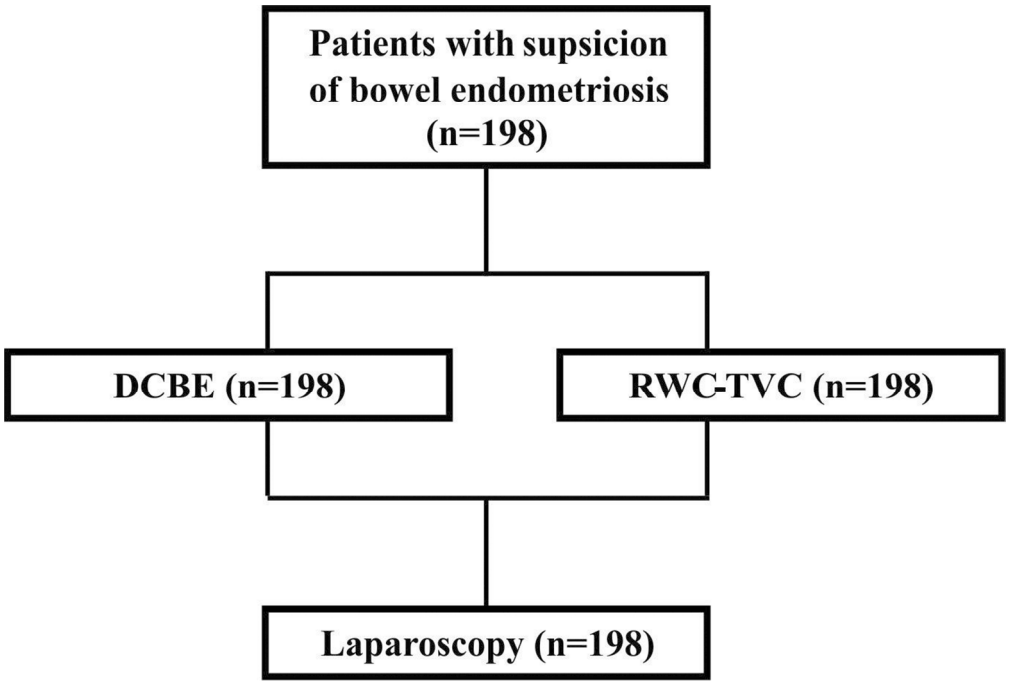

Figure 4

115x77mm (300 x 300 DPI)

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	1
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	4
	4	Study objectives and hypotheses	5
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	5
Participants	**6**	Eligibility criteria	5
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	
	8	Where and when potentially eligible participants were identified (setting, location and dates)	
	9	Whether participants formed a consecutive, random or convenience series	
Test methods	**10a**	Index test, in sufficient detail to allow replication	6
	10b	Reference standard, in sufficient detail to allow replication	
	11	Rationale for choosing the reference standard (if alternatives exist)	
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	9
	15	How indeterminate index test or reference standard results were handled	
	16	How missing data on the index test and reference standard were handled	
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	
	18	Intended sample size and how it was determined	
RESULTS			
Participants	**19**	Flow of participants, using a diagram	10
	20	Baseline demographic and clinical characteristics of participants	
	21a	Distribution of severity of disease in those with the target condition	
	21b	Distribution of alternative diagnoses in those without the target condition	
	22	Time interval and any clinical interventions between index test and reference standard	
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	10
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	
	25	Any adverse events from performing the index test or the reference standard	
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	12
	27	Implications for practice, including the intended use and clinical role of the index test	
OTHER INFORMATION			
	28	Registration number and name of registry	
	29	Where the full study protocol can be accessed	
	30	Sources of funding and other support; role of funders	

STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.