Human Reproduction, Vol.29, No.6 pp. 1189–1198, 2014
Advanced Access publication on March 23, 2014 doi:10.1093/humrep/deu054

human reproduction

ORIGINAL ARTICLE ***Gynaecology***

Three-dimensional ultrasonography in the diagnosis of deep endometriosis

Stefano Guerriero[1,2,*], Luca Saba[3], Silvia Ajossa[1,2], Cristina Peddes[1,2], Marco Angiolucci[1,2], Maura Perniciano[1,2], Gian Benedetto Melis[1,2], and Juan Luis Alcázar[4]

[1]Department of Obstetrics and Gynecology, Blocco Q, Azienda Ospedaliero Universitaria, Polo di Monserrato s.s. 554, Monserrato 09045, Italy [2]University of Cagliari, Cagliari, Italy [3]Department of Radiology, Azienda Ospedaliero Universitaria, di Cagliari – Polo di Monserrato s.s. 554, Monserrato 09045, Italy [4]Department of Obstetrics and Gynecology, Clínica Universidad de Navarra, University of Navarra, Pamplona, Spain

*Corresponding author: gineca.sguerriero@tiscali.it

Submitted on November 19, 2013; resubmitted on February 18, 2014; accepted on February 24, 2014

STUDY QUESTION: In the use of 'tenderness-guided' transvaginal ultrasound, is the diagnostic accuracy of three-dimensional (3D) ultrasonography better than two-dimensional (2D) ultrasonography in the identification of deep endometriosis?

SUMMARY ANSWER: Three-dimensional ultrasonography has a significantly higher diagnostic accuracy in the diagnosis of posterior locations of deep endometriosis without intestinal involvement, such as the uterosacral ligaments, vaginal and rectovaginal endometriosis.

WHAT IS KNOWN ALREADY: The only previous study of the diagnosis of posterior compartment endometriosis reported an poor sensitivity of 3D ultrasonography for uterosacral and sigmoid colon involvement.

STUDY DESIGN, SIZE, DURATION: This diagnostic test study included 202 patients scheduled for surgery because of clinical suspicion of deep pelvic endometriosis and was carried out between January 2009 and September 2012.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Modified transvaginal ultrasonography was performed on all of the women by a single examiner. Two locations of deep endometriosis were considered: intestinal involvement and other posterior lesions (including vaginal location, rectovaginal septum and uterosacral ligaments). Once the 2D ultrasonography had been performed, the 3D acquisition was performed and the obtained volume was stored. To avoid the risk of recall bias, the same operator evaluated the 3D volumes 6 months after the last examination using virtual navigation to provide a presumptive diagnosis of the presence and localization of deep endometriosis. In addition, to evaluate the reproducibility of 3D, two operators with different levels of expertise performed a retrospective review of 3D volumes from a random sample of 35 patients, twice, 1 week apart to also assess intraobserver agreement. The diagnostic performance of both tests was expressed as area under the receiver-operating characteristics curve (AUC), sensitivity, specificity, positive and negative predictive values, positive (LR+) and negative (LR−) likelihood ratios, with their respective 95% confidence interval (CI). Reproducibility was evaluated using kappa statistics.

MAIN RESULTS AND THE ROLE OF CHANCE: Surgery revealed deep endometriosis in 129 patients. The AUCs for endometriosis of intestinal location were similar for both ultrasound techniques. The AUCs for endometriosis of other posterior locations were significantly different (0.891, 95% CI 0.839–0.943 for 3D versus 0.789, 95% CI 0.720–0.858 for 2D; $P = 0.0193$). For the intestinal involvement, the specificity, sensitivity, positive and negative predictive value, and LR+ and LR− were 93% (89−95%), 95% (88–98%), 89% (83–92%), 97% (93–99%), 13, and 0.06, respectively, for 2D ultrasound and 97% (93–99%), 91% (84–94%), 95% (88–98%), 95% (91–96%), 25, and 0.09, respectively, for 3D ultrasound. For other posterior locations, the specificity, sensitivity, positive and negative predictive value, and LR+ and LR− were 88% (82–93%), 71% (64–77%), 83% (75–90%), 79% (74–83%), 6.10, 0.32, respectively, for 2D ultrasound and 94% (89–97%), 87% (81–91%), 92% (86–96%), 90% (85–93%), 14.0, 0.14, respectively, for 3D ultrasound. Intraobserver agreement was substantial for both examiners (kappa 0.8754, for operator A and 0.7087, for operator B, respectively). Interobserver agreement was also substantial.

LIMITATIONS, REASONS FOR CAUTION: The disadvantages of 3D ultrasound to be considered are the necessity of newer ultrasonographic equipment and that fewer sonographers completely know the 3D technique. There are also some limitations within this study. First, an expert examiner performed the real-time ultrasound and 3D volume acquisitions. Second, the same operator also performed the 3D evaluations but at least 6 months after the last acquisition to avoid a possible recall bias.

WIDER IMPLICATIONS OF THE FINDINGS: The diagnostic performance obtained in the present study is superior to the accuracy reported in other studies of 3D ultrasonography, but not superior to all other published articles of 2D ultrasonography. The reported high diagnostic accuracy of 3D ultrasound could be widely generalizable because good reproducibility was demonstrated even with an operator with less expertise.

STUDY FUNDING/COMPETING INTEREST(S): This study was supported in part by the Regione Autonoma della Sardegna (project code CPR-24750).

Key words: endometriosis / ultrasonography / imaging / three-dimensional

Introduction

Endometriosis is a pathology that usually affects women of childbearing age and has an incidence rate estimated to be up to 10%. In particular, deep infiltrating endometriosis (DIE) may represent a serious condition because it can cause several symptoms such as dysmenorrhea, chronic pelvic pain, dyspareunia and dysuria (de Ziegler *et al.*, 2010), severely reducing the quality of life of the affected women.

The identification of endometriosis is important in order to select the correct therapeutic approach (Bulun, 2009; Giudice, 2010) and imaging techniques may help in the correct diagnosis. Identification of the endometriotic nodules and their correct localization may not only decrease the waiting time for a laparoscopy, but also, in some cases, avoid laparoscopy if it is too risky, as in the case of rectosigmoid involvement, and hence permit effective medical therapy based on the administration of low-cost drugs such as oral contraceptives (Bernardi and Pavone, 2013).

Currently, the two most frequently used techniques in the study of endometriosis are ultrasonography (US) (Bazot *et al.*, 2004a,b; Abrao *et al.*, 2007; Guerriero *et al.*, 2007, 2008; Piketty *et al.*, 2009; Hudelist *et al.*, 2011a,b) and magnetic resonance imaging (MRI) (Kinkel *et al.*, 1999; Bazot *et al.*, 2004b; Kataoka *et al.*, 2005; Saba *et al.*, 2011, 2012). US is considered the 'first-line' approach (Piketty *et al.*, 2009) whereas MRI may have a complementary role in the identification of recto-sigmoid endometriosis, depending on the site affected and whether the lesions are in the proximal sigmoid location or whether there are large pelvic masses (cysts or fibroids) (Saba *et al.*, 2012).

In the last 10 years, the ultrasonographic technique (Guerriero *et al.*, 2013a) has been dramatically improved with the introduction of modified approaches such as bowel preparation and/or rectal water contrast transvaginal ultrasonography, vaginosonography, the 'tenderness-guided' approach and, recently, the introduction of the three-dimensional (3D) probes that enable the acquisition of ultrasonographic volumetric data that can be assessed off-line (Guerriero *et al.*, 2009). Only a few recent studies have evaluated the potential role of 3D ultrasonography in the preoperative work-up of endometriosis (Guerriero *et al.*, 2009; Grasso *et al.*, 2010; Pascual *et al.*, 2010, 2013). The first was a study performed in only 33 patients by Grasso *et al.* (2010). These authors found an inexplicably poor sensitivity for uterosacral involvement (50%) and sigmoid colon endometriosis (33.3%). Other authors investigating the role of introital 3D ultrasonography only in the diagnosis of endometriosis of the rectovaginal septum found that the specificity and sensitivity were 94.7 and 89.5%, respectively (Pascual *et al.*, 2010, 2013).

To our knowledge, no previous study has compared two-dimensional (2D) ultrasonography with 3D ultrasonography. The aims of this study were to compare the diagnostic performance of 2D and 3D in detecting DIE in women with a clinical suspicion, and to assess the reproducibility of 3D ultrasonography.

Materials and Methods

Study population

This study was performed according to the STARD initiative (Rennie, 2003). The power of the study was calculated and to obtain an estimated sensitivity and a specificity of 90%, we found that at least 80 patients should be recruited, with a prevalence of endometriosis of ~40%. All premenopausal patients who were scheduled for surgery in our department (Department of Gynecology, Ospedale San Giovanni di Dio, University of Cagliari) from January 2009 to September 2012 and who had a clinical suspicion of deep endometriosis were prospectively included. The principal symptoms related by patients were dysmenorrhea, deep dyspareunia, acyclic pelvic pain, infertility and cyclic bowel and/or urinary symptoms. The physical examination was carried out by a different examiner (G.B.M.). The patients were consecutive. Patients may have previously undergone surgery but the operator did not know the results of the medical records.

Exclusion criteria were: (i) presence of an abdominal (uterine or ovarian) mass larger than 10 cm with subsequent distortion of the pelvic organs; (ii) emergency laparoscopy due to acute pain; (iii) either 2DUS or 3DUS not having been performed; (iv) insufficient description at surgery (v) pregnancy at the time of diagnosis; and (vi) surgery >30 days after the ultrasound evaluation.

Two-dimensional ultrasound technique

All patients underwent detailed ultrasonographic assessment within 1 month of surgery. Ultrasonography was performed by a single operator (with >20 years of experience in gynecological ultrasound) with the use of high-performance ultrasound equipment (Voluson I, General Electric, Milwaukee, WI, USA) with a 5–9 MHz frequency transvaginal probe.

The ultrasound techniques have been described in detail elsewhere (Guerriero *et al.*, 2007, 2008). Briefly, we performed transvaginal ultrasonography using an acoustic window between the transvaginal probe and the surrounding vaginal structures by increasing the amount of ultrasound gel inside the probe cover, coupled with an 'active' role of the patient, who indicated the site of any tenderness experienced during examination.

The diagnosis of deep pelvic endometriosis using 2DUS was based on criteria which varied in relation to the anatomical locations; these included abnormal thickening hypoechoic linear and nodules, with or without regular contours (Guerriero *et al.*, 2007, 2008; Bazot *et al.*, 2004a,b; Abrao *et al.*, 2007; Hudelist *et al.*, 2011a). The rectosigmoid colon was involved when it revealed an irregular hypoechoic nodule with or without hypo- or, rarely, hyperechoic foci (Fig. 1A). In this case, the normal appearance of the muscularis propria of the rectum sigma was replaced by a nodule of abnormal tissue with visible retraction and adhesions in some

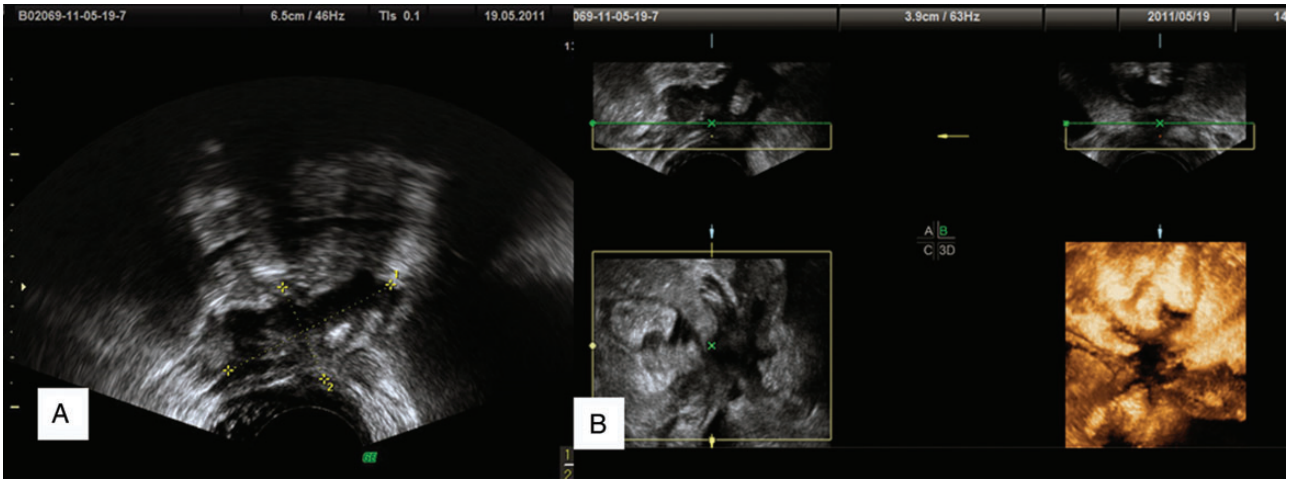

Figure 1 Rectosigmoid lesion as visualized using 2D (**A**) and 3D (**B**) ultrasound in the same patient. The 3D coronal rendering of rectosigmoid lesions showed typically spiculated lesions with retracting lines all around the nodule.

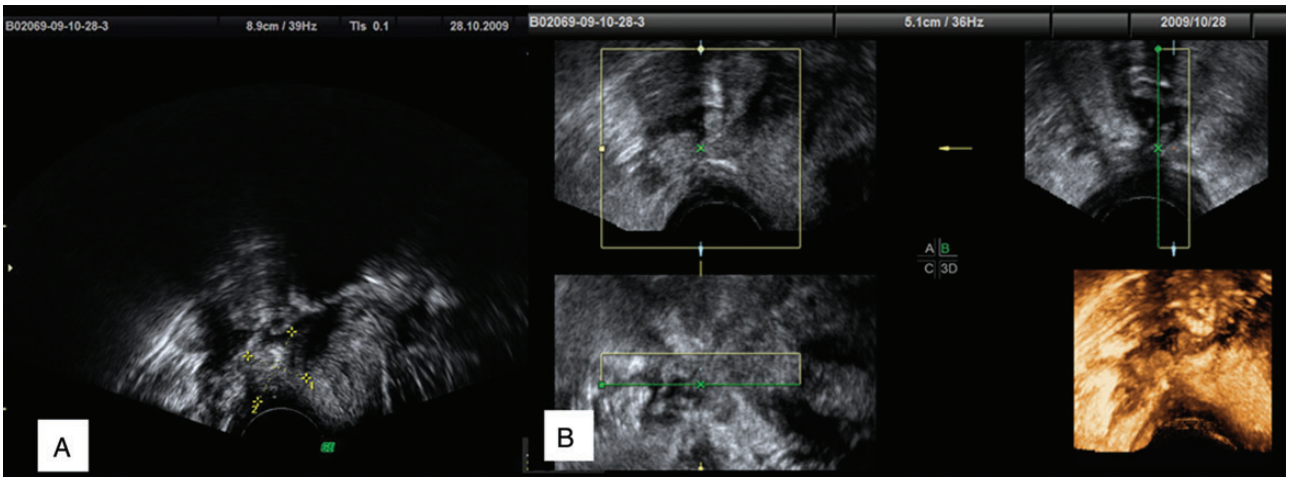

Figure 2 Vaginal forniceal lesion as visualized using 2D (**A**) and 3D (**B**) ultrasound in the same patient with extension toward the anterior rectal muscularis.

cases (Guerriero *et al.*, 2008). The involvement of the vagina was suspected when the posterior vaginal fornix was thickened, with or without cystic anechoic areas around it (Fig. 2A) (Guerriero *et al.*, 1998, 2007, 2008; Bazot *et al.*, 2004a,b; Abrao *et al.*, 2007; Hudelist *et al.*, 2011b). The involvement of the rectovaginal septum was suspected when the presence of a nodule below a horizontal plane passing along the lower margin of the posterior lip of the cervix under the peritoneum was observed (Bazot *et al.*, 2004a,b). The utero-sacral ligament was considered to be involved when a nodule was visible, with regular or irregular margins, and often, hyperechoic points in injury, or when a linear hypoechoic thickening with regular or irregular margins was detected (Fig. 3A). When the utero-sacral ligament was visible and was clearly delineated from adjacent structures, its thickening could be measured at the proximal insertion near the cervix. The typical images involving the bladder were characterized by the presence, in the context of its rear wall, and more frequently in the midline, of irregular, solid or mixed elongated or spherical lesions at the level of the dome or the base of bladder.

Three-dimensional ultrasound technique and analysis

After the 2DUS, patients underwent 3DUS acquisition. All acquisitions of 3D ultrasound images were performed in the sagittal plane using the same equipment as the 2DUS (Voluson I, General Electric). The obtained volume was stored on a hard disk and displayed later using dedicated software (4D View®, GE Healthcare Austria GmbH & Co OG). In order to eliminate the memory effect (recall bias), the volumes were analyzed off-line in a blinded fashion by means of the software 4D View by the same experienced operator 6 months after the last acquisition. Using a previously standardized approach to evaluate the presence of vaginal and rectovaginal endometriosis, we

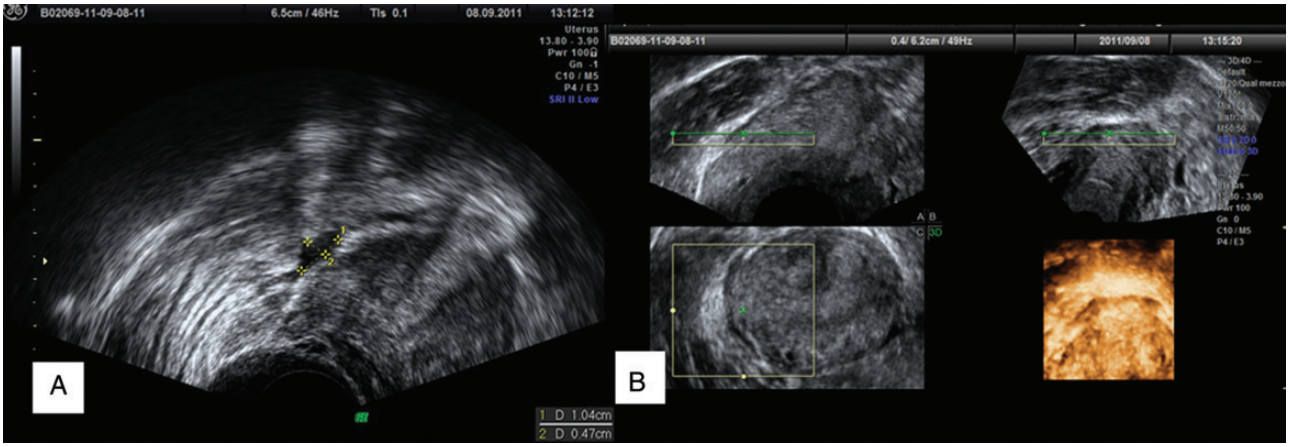

Figure 3 Utero-sacral lesions as visualized using 2D (**A**) and 3D (**B**) ultrasound in the same patient.

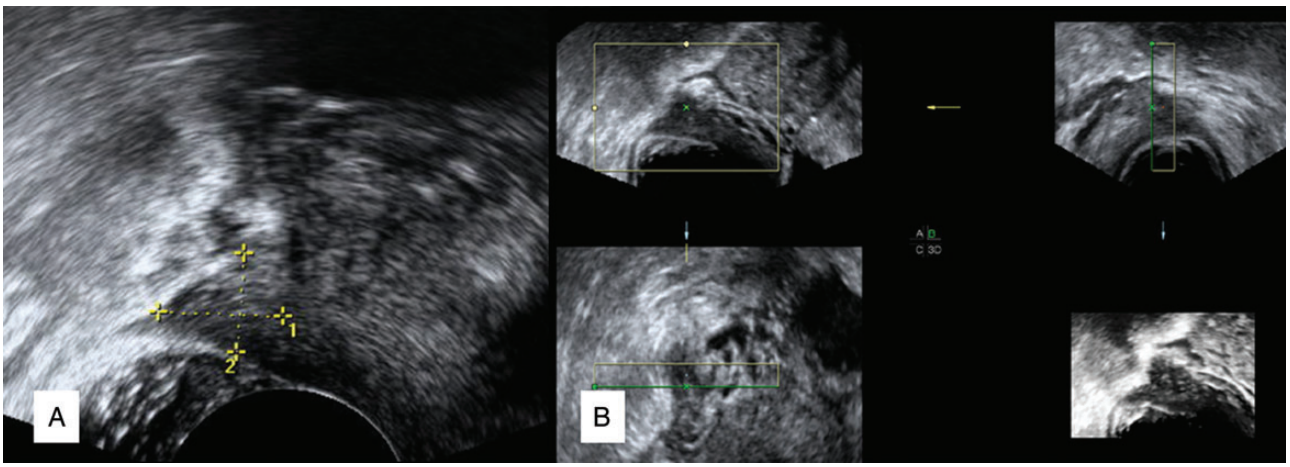

Figure 4 Vaginal forniceal lesion as visualized using 2D (**A**) and 3D (**B**) ultrasound in the same patient without involvement of recto-sigmoid tract.

performed a virtual navigation and a 3D evaluation using the plane B with the ROI line on the left side of the 3D box and the green line curved into the center of lesion (using a sagittal plane). Typically these lesions appear as small irregular nodules (Figs 2B and 4). On the contrary, to evaluate rectosigmoid lesions and utero-sacral ligaments, we evaluated plane A with the ROI line in the upper side of the 3D box and the green line curved into the lesion (coronal plane) (Guerriero *et al.*, 2010). On the 3D rendering, rectosigmoid lesions typically appear as spiculated lesions (Fig. 1B) with retracting lines all around the nodule, whereas the utero-sacral lesions showed a nodular or plaque shape laterally to the uterine torus (Figs 3B and 5).

Ultrasound (2D and 3D) analysis

For the purpose of this study, the lesions were grouped into two distinct locations: (i) intestinal, including lesions of the rectosigmoid region; and (ii) other posterior, including lesions at the level of the utero-sacral ligament, vaginal forniceal location and recto-vaginal septum. The diagnostic confidence for the presence or absence of endometriosis for each localization was graded using a 5-level classification: (i) surely present; (ii) probably present; (iii) uncertain; (iv) probably absent; and (v) definitely absent. Uncertainties in the dichotomous classification used to perform diagnostic accuracy were classified as absent disease.

To assess the reproducibility of 3DUS, the datasets of volumes from a random sample of 35 patients submitted to surgery, were reviewed a second time (2 weeks after the first evaluation) by the same operator who performed the scans in 2D and 3D (the operator with experience of 20 years in 2D and 10 years in 3D ultrasound) and by a second less experienced operator with a good knowledge of basic 2D and 3D imaging (with experience of 5 years in 2D and 2 years in 3D ultrasound). Both observers were blinded to the clinical data and the previous results.

Surgical evaluation

Surgical analysis was performed by the same group of surgeons of the same department, with at least 10 years of experience, and DIE was diagnosed according to Bazot *et al.* (2004a,b), by the presence of the following characteristics: (i) presence of endometrial tissue (stroma and endometrial glandular tissue) histologically or resection of a sub-peritoneal lesion; (ii)

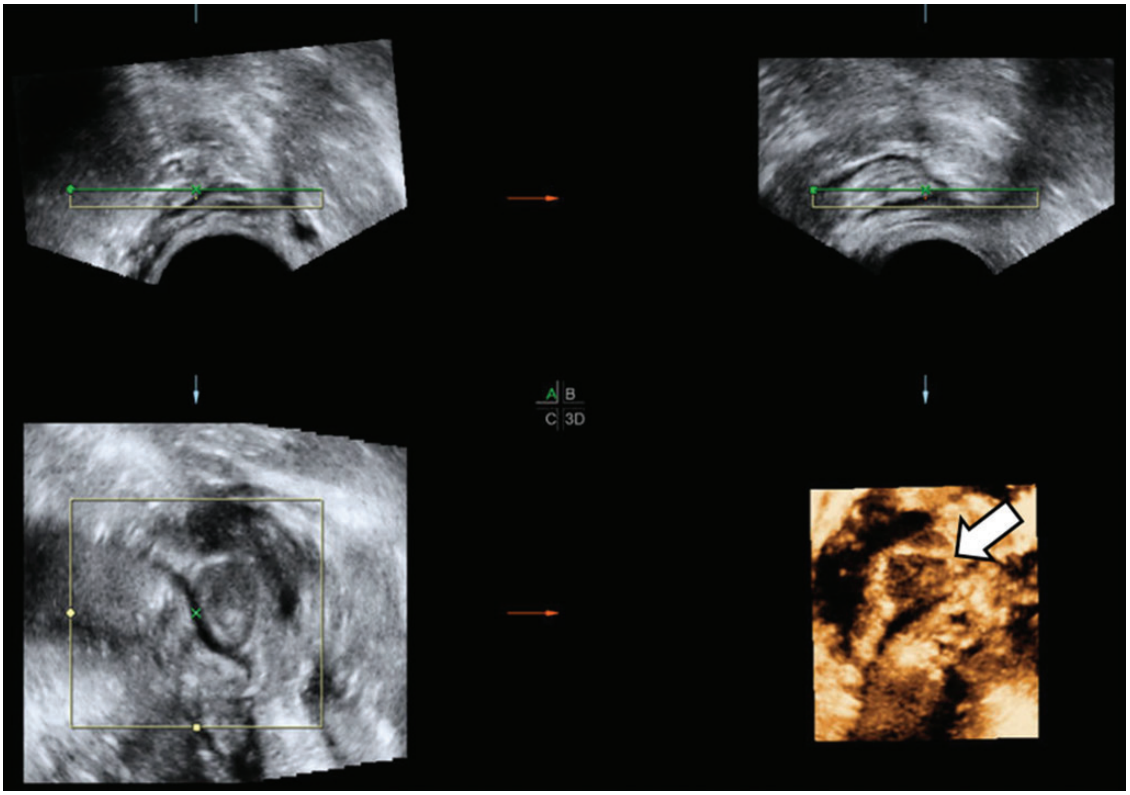

Figure 5 Coronal rendering of utero-sacral lesions by 3D ultrasound (missed using 2D ultrasound) showing a nodular shape laterally to the uterine torus.

direct visualization of the lesion attributable to deep endometriosis; or (iii) complete pouch of Douglas obliteration secondary to endometriosis with another localization of deep endometriosis (in this case, the tissue that caused the obliteration was unresectable because the surgeons considered it too risky or because the patient refused to undergo surgical removal of deep endometriosis). In these cases the nodules were investigated by rectal palpation during surgery.

Statistical analysis

Receiver-operating characteristics (ROC) curve analysis was performed and the area under the ROC (AUC) curves with their corresponding 95% confidence intervals (95% CI) was calculated. The sensitivity, specificity, positive (PPV) and negative (NPV) predictive values, positive (LR+) and negative (LR−) likelihood ratios with their corresponding 95% confidence intervals were calculated. In addition, the McNemar Chi square test was used to check equality of sensitivity and specificity of the two tests. The reproducibility of intra-operator and inter-operator was calculated using the weighted kappa index (weighted kappa) and a value between 0 and 0.2 was considered a poor agreement, 0.21 and 0.4 as fair agreement, 0.41 and 0.6 as moderate agreement, 0.61 and 0.8 as substantial agreement and 0.81 and 1 as almost perfect agreement (Brennan and Silman, 1992). A *P*-value of <0.05 was regarded to indicate statistical significance association and all values were calculated using a two-tailed significance level. Statistical analysis was performed with the SPSS 13.0 statistical package (SPSS, Inc., Chicago, IL, USA). Graphics were plotted with the MedCalc 8.0 software (MedCalc, Mariakerke, Belgium).

Results

Participants

The study included 202 patients (mean age ± SD: 34 years + 6; age range 18–52 years) who showed the following symptoms: (i) chronic pelvic pain, 101 patients (49%); (ii) dyspareunia, 51 patients (25%); and (iii) dysmenorrhea, 132 patients (65%). There were 38 patients who were not included in the study; 3 were excluded for the presence of an ovarian mass ≥10 cm; 3 had undergone emergency laparoscopy; 24 patients underwent only 2D evaluation; in 7 patients, the description of surgery was insufficient; and one patient was submitted to surgery 30 days after the ultrasound evaluation. Of the participants, 20 patients had undergone surgery previously. At the time of ultrasound examination, 37 patients were being treated with estrogen-progestin, while only 6 patients were using GnRH analogs. In 194 patients, a laparoscopic approach was performed; in 7 patients the laparotomy was performed and only one patient was submitted for mini-laparotomy. In 122 patients (60% of total), surgery showed severe adhesions.

The presence of deep endometriosis in various locations was reported by surgery in 129 patients (64% of the total). A single nodule of endometriosis was found in 75 patients (37% of the total patients operated) while 54 patients had endometriosis in more than one location (27% of the total of all patients operated). Only 17 women had a nodule localized in the anterior compartment (a prevalence of 8%) but in 10 of these women, there was an association with the presence of

deep endometriosis elsewhere. Surgical analysis showed that in 122 women, endometriosis was present in at least one posterior location. In 46 cases, there was an association between rectosigmoid endometriosis and another localization.

In 51 cases, surgery found pouch of Douglas obliteration. In 44 of these 51 cases, a complete exploration of the pouch of Douglas was still performed. In the other 7 patients, the presence of nodules was confirmed by palpation of the nodule in the rectal wall during surgery.

Test results

The presence of deep endometriosis in the recto-sigmoid colon was correctly suspected in 73 out of 77 patients by 2DUS, and in 70 out of 77 patients by 3DUS. On the contrary, the presence of deep endometriosis in other posterior locations was detected in 65 out of 91 patients with 2DUS and in 79 out of 91 patients with 3DUS. The ultrasonographic average diameters of the nodules in the different locations are summarized in Table I.

The diagnostic accuracy of the 2D and 3D ultrasound for the recto-sigmoid location is reported in Table II. There were no statistical differences in terms of sensitivity and specificity between the two approaches with overlap of 95% CI ($P = 0.375$ and 0.180, respectively). The diagnostic accuracy of 2D and 3D ultrasound for other posterior locations is reported in Table III. For these, there were statistical differences in terms of sensitivity, with absence of overlap of 95% CI ($P = 0.001$), but not in terms of specificity ($P = 0.146$). A detailed description of the false-positive and false-negative cases are reported in Table IV. For non-intestinal locations, the use of 3DUS reduced false negatives by 53% allowing the correct identification of 14 of the 26 false-negative lesions from 2DUS: at the level of the utero-sacral ligaments, false-negative cases decreased from 19 cases with 2DUS to 10 cases with 3DUS (47% reduction of false negatives with the use of 3D), at the level of the recto-vaginal septum, false negatives decreased from 4 cases with 2DUS to 1 case with 3DUS (75% reduction of false negatives using of 3D); at the level of the vaginal fornix, false negatives were

Table I The ultrasonographic average diameter of the nodules in the different locations.

Localization	Mean diameter ± standard deviation (mm)	Range (mm)
Rectum-sigmoid	17 ± 9	4–51
Vaginal	15 ± 7	3–37
Utero-sacral ligament	12 ± 5	5–23
Recto-vaginal Septum	13 ± 6	7–25

Table II Comparison of diagnostic performance of 2D and 3D ultrasound for endometriosis in the recto-sigmoid location.

	2D	3D
Specificity, % (*n*), 95% CI, %	93% (116/125) (89–95%)	97% (121/125) (93–99%)
Sensitivity, % (*n*), 95% CI, %	95% (73/77) (88–98%)	91% (70/77) (84–94%)
Positive predictive value % (*n*), 95% CI, %	89% (73/82) (83–92%)	95% (70/74) (88–98%)
Negative predictive value % (*n*), 95% CI, %	97% (116/120) (93–99%)	95% (121/128) (91–96%)
LR+ 95% CI	13 (7; 25)	25 (11; 75)
LR− 95% CI	0.06 (0.02, 0.15)	0.09 (0.05, 0.19)

Table III Comparison of diagnostic performance of 2D and 3D ultrasound for endometriosis in other posterior locations.

	2D	3D
Specificity, % (*n*), 95% CI, %	88% (98/111) (82–93%)	94% (104/111) (89–97%)
Sensitivity, % (*n*), 95% CI, %	71% (65/91) (64–77%)	87% (79/91) (81–91%)
Positive predictive value % (*n*), 95% CI, %	83% (65/78) (75–90%)	92% (79/86) (86–96%)
Negative predictive value % (*n*), 95% CI, %	79% (98/124) (74–83%)	90% (104/116) (85–93%)
LR+ 95% CI	6.10 (3.60, 10)	14 (6.69, 28)
LR− 95% CI	0.32 (0.23, 0.45)	0.14 (0.08, 0.24)

Table IV The false-positive and false-negative cases of both techniques in relationship with the presence of associated pelvic adhesions and other sites of endometriotic nodules as possible cause of misdiagnosis.

	Recto-sigmoid		Other posterior locations	
	2D-US	3D-US	2D-US	3D-US
False positive	9 (4, 44%) [9, 100%]	4 (0, 0%) [4, 100%]	13 (5, 38%) [7, 54%]	7 (4, 57%) [6, 85%]
False negative	4 (3, 75%) [3, 75%]	7 (5, 71%) [6, 86%]	26 (6, 23%) [10, 38%]	12 (1, 8%) [3, 25%]

Between round parentheses () are indicated the cases and the percentage where endometriosis was found in other locations.
Between brackets [] are indicated the cases and the percentage where severe adhesions were present.

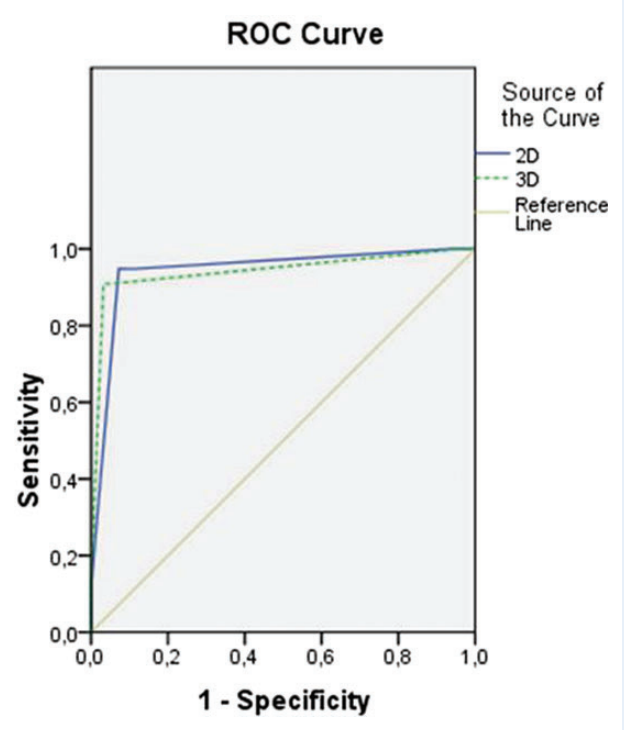

Figure 6 ROC curve analysis for endometriosis in the intestinal location.

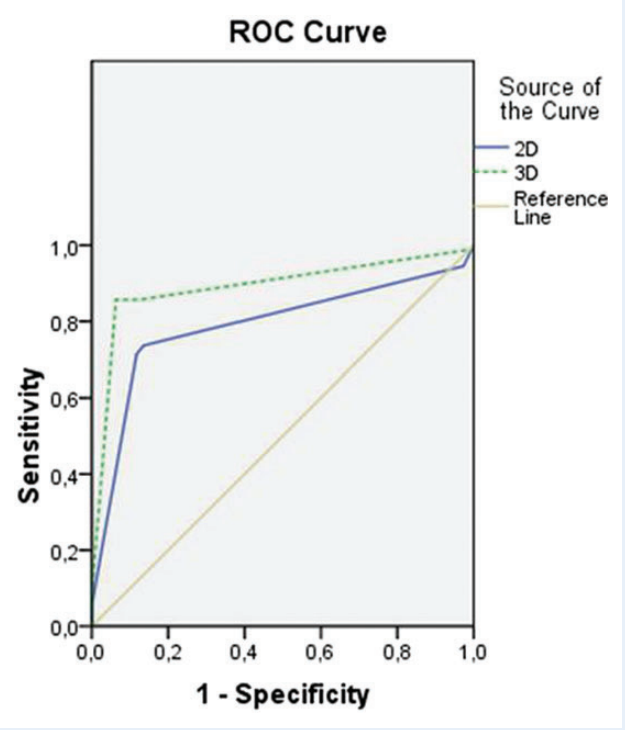

Figure 7 ROC curve analysis for endometriosis in other posterior locations.

reduced from 2 cases with 2DUS to 1 case with 3DUS (50% reduction of false negatives with the use of 3D).

The pre-test probability of rectosigmoid involvement was 38%, and this probability was increased up to 95% using 3D ultrasound when the test was positive and reduced to 5% when the test was negative (see Table II).

The pre-test probability of the involvement of other posterior locations was 45%, and this probability was increased up to 92% using 3D ultrasound when the test was positive and decreased to 10% when the test was negative (see Table III).

For the intestinal location, ROC curve analysis (Fig. 6) showed optimal results for both methods (2D and 3D ultrasound) (AUC = 0. 943, 95% CI 0.907–0.979 and AUC = 0.942, 95% CI 0.902–0.981, respectively; *P* value = 0.9704) and no statistically significant difference was found between the two methods. For the other posterior locations, the ROC curve analysis (Fig. 7) showed that the 3DUS had better performance compared with the 2DUS (AUC = 0.891, 95% CI 0.839–0.943 and 0.789, 95% CI 0.720–0.858; *P*-value = 0.0193).

The intra-observer agreement for the expert reader was 0.8754 (95% CI 0.7013–1), whereas for the less experienced reader it was 0.7087 (95% CI0.5002–0.9172). Kappa analysis showed that the inter-observer agreement was substantial with a value of 0.7094 (95% CI 0.5007–0.9181).

Discussion

Although some studies on the role of 3D ultrasound have been published in recent years (Guerriero *et al.*, 2009; Grasso *et al.*, 2010; Pascual *et al.*, 2010, 2013), to the best of our knowledge we are presenting the first prospective data on the comparison between 2D and 3D ultrasonography in all of the locations of the posterior compartment. Our study demonstrates that the 3D technique has a significantly higher diagnostic accuracy in the diagnosis of deep endometriosis in posterior locations other than the rectosigmoid colon, such as the uterosacral ligaments and vaginal endometriosis. The best AUC was obtained using the 3DUS with a value of 0.891, whereas using the 2DUS the AUC was 0.789, with a *P*-value = 0.0193 (Fig. 7).

Our data show better results in comparison with the study by Grasso *et al.* (2010) that reports poor accuracy of ultrasound for several locations such as utero-sacral ligament and recto-vaginal endometriosis. The reason for these differences is difficult to understand but in our study the imaging methodology is described in detail and the 2D and 3D ultrasounds are considered separately and not in conjunction as reported by Grasso *et al.* (2010). In comparison with the study of Abrao *et al.* (2007), performed using bowel preparations, our 3D ultrasound results showed a lower specificity and sensitivity for both locations. Otherwise several authors have failed to demonstrate a high sensitivity and specificity in other posterior locations such as the utero-sacral ligament vaginal location and rectovaginal septum (Hudelist *et al.*, 2011a; Saccardi *et al.*, 2012; Fratelli *et al.*, 2013; León *et al.*, 2014). Because the results are dependent on the examiner, it is difficult to make comparisons.

In clinical practice, the use of 3D ultrasound determines at least three possible advantages in comparison of 2D ultrasound (Downey *et al.*, 2000; Guerriero *et al.*, 2009). First, due to the good reproducibility demonstrated in the present study, with high values of kappa (ranging from 0.875 to 0.709), and the related reconstruction after a single

Figure 8 Lateral rendering of a rectosigmoid nodule by 3D ultrasound, where the image gives the impression of depth because more slides are represented than in 2D ultrasound.

sweep of the ultrasound beam across the target, we can correctly locate lesions in the pelvis evaluating the spatial relationship with other organs. Second, due to unrestricted access to an infinite number of viewing planes, we can evaluate the images even after the first acquisition to further study involvement of the ureter or bowel. In the case of rectosigmoid involvement (Fig. 8), we can also further study the relationship with the intestinal mucosa obtaining sharper contrast between different layers, as suggested by Egekvist *et al.* (2011). Third, because stored 3D volumes can be reassessed and compared by the same or different examiners over time, the effect of medical therapies can be evaluated more easily by looking at the same location.

Along with the demonstrated high diagnostic accuracy, it should be useful to store 3D datasets for a further evaluation of the same scan with slide by slide assessment of images, similar to the other imaging techniques such as the MR and CT. Also, the use of the coronal plane, which can be performed only using 3D, is a useful tool particularly for rectosigmoid and utero-sacral lesions.

An additional advantage is the possibility of introducing 3D off-line evaluations in teaching and training programs and in the learning curve of less expert operators in this field. In fact, some studies have demonstrated that this approach, in the differential diagnosis of adnexal lesions, is useful and would reduce the learning time by two-thirds (Alcázar *et al.*, 2012; Guerriero *et al.*, 2013b). Unfortunately, no studies about the use of stored 3D volumes for teaching purposes in the diagnosis of endometriosis are present in the literature and further studies should be performed in the future. A further advantage, recently published by our group, is the tissue characterization using mean gray value analysis (MGV) (Guerriero *et al.*, 2013c). The MGV was significantly higher in rectosigmoid nodules than in nodules with a rectovaginal location (23.863 versus 17.705; $P < 0.001$). Its clinical value in the diagnosis and assessment of distribution of deep endometriosis should be assessed in future studies.

Regarding other published studies of 2D ultrasound, we obtained comparable results in the detection of rectosigmoid endometriosis, for example, the meta-analysis recently published by Hudelist *et al.* (2011b). Apart from the work of Abrao *et al.* (2007), other published studies of 2D ultrasound in non-intestinal locations have reported similar results to ours in terms of sensitivity (Bazot *et al.*, 2004a,b; Guerriero *et al.*, 2008), although the specificity reported in the present study is lower.

To better explain the improvement of diagnostic accuracy reported by the use of 3D ultrasound, the false-positive and false-negative cases were analyzed in detail. In fact, this new tool showed a 50% reduction in false negatives (see Table IV), mostly due to a better diagnosis in USL lesions using the coronal plane. This is important because false negatives are frequently associated with severe adhesions.

Despite the advantages, there are a couple current disadvantages of 3D ultrasound to be considered. First, there is the necessity of newer ultrasonographic equipment and secondly, few sonographers so far are completely familiar with the 3D technique.

In our study there were also some weaknesses. First, an expert examiner performed real-time 2D ultrasound and then 3D volume acquisitions. This could affect the quality of the 3D volumes as the off-line assessment may have been easier. However several published studies have been performed using a similar protocol (Alcázar *et al.*, 2012; Guerriero *et al.*, 2013b). Second, the same operator also performed the 3D evaluations. To avoid a possible recall bias, the operator performed the evaluation at least 6 months after the last acquisition. In our opinion, this methodology further reduces the risk of bias. Third, this study illustrated the diagnostic accuracy of only one operator. The possible lack of generalization of data from a single individual could be a limitation of this study. However, we believe that this diagnostic accuracy could be widely generalizable because it showed good reproducibility with a less expert operator. Otherwise, in a multidisciplinary team involved in the management of deep endometriosis, the presence of an expert in ultrasonographic imaging is mandatory, as previously reported for MRI. It was demonstrated that a radiologist who is an expert in endometriosis improves the diagnostic accuracy in the preoperative assessment in comparison with a general radiologist (Saba *et al.*, 2011). Another bias in this study may have been the inability to perform a complete surgical exploration in case of some pouch of Douglas occlusions. In the present study, the number of women who did not undergo a complete exploration was very low and in all cases, we confirmed the presence of rectal nodules using rectal palpation during general anesthesia. The present study was performed in a high-risk population due to the presence of typical symptoms, and the prevalence of deep endometriosis was 64% (129 of 202), with 37% of the patients having only one localization involved, whereas 27% had two or more localizations involved. This prevalence was lower compared with that of Bazot *et al.* (2004a,b), but similar to that of Hudelist *et al.* (2011b) who demonstrated a prevalence of 63%.

In conclusion, although other studies are necessary to validate the advantages of 3D ultrasound, this study shows that 3D ultrasound is a useful new technique not only for the preoperative evaluation of deep infiltrating endometriosis, but also for the follow-up of expectant management or medical treatment.

Authors' roles

S.G.: substantial contributions to the study conception and design, acquisition of data, interpretation of data, drafting of the article and article revision and final approval of the version to be submitted. L.S.: substantial contributions to the study conception and design, interpretation of data, drafting of the article and article revision and final approval of the version to be submitted. S.A.: substantial contributions to data analysis, interpretation of data and article revision and final approval of the version to be submitted. C.P., M.A., M.P. and J.L.A.: substantial contributions to the acquisition of data and article revision and final approval of the version to be submitted. G.B.M: substantial contributions to article revision and final approval of the version to be submitted.

Funding

This study was supported in part by the Regione Autonoma della Sardegna (project code CPR-24750).

Conflict of interest

None declared.

References

Abrao MS, Goncalves MO, Dias JA Jr, Podgaec S, Chamie LP, Blasbalg R. Comparison between clinical examination, transvaginal sonography and magnetic resonance imaging for the diagnosis of deep endometriosis. *Hum Reprod* 2007;**22**:3092–3097.

Alcázar JL, Iturra A, Sedda F, Aubá M, Ajossa S, Guerriero S, Jurado M. Three-dimensional volume off-line analysis as compared to real-time ultrasound for assessing adnexal masses. *Eur J Obstet Gynecol Reprod Biol* 2012;**161**:92–95.

Bazot M, Thomassin I, Hourani R, Cortez A, Darai E. Diagnostic accuracy of transvaginal sonography for deep pelvic endometriosis. *Ultrasound Obstet Gynecol* 2004a;**24**:180–185.

Bazot M, Darai E, Hourani R, Thomassin I, Cortez A, Uzan S, Buy JN. Deep pelvic endometriosis: MR imaging for diagnosis and prediction of extension of disease. *Radiology* 2004b;**232**:379–389.

Bernardi LA, Pavone ME. Endometriosis: an update on management. *Womens Health (Lond Engl)* 2013;**9**:233–250.

Brennan P, Silman A. Statistical methods for assessing observer variability in clinical measures. *BMJ* 1992;**304**:1491–1494.

Bulun SE. Endometriosis. *N Engl J Med* 2009;**360**:268–279.

de Ziegler D, Borghese B, Chapron C. Endometriosis and infertility: pathophysiology and management. *Lancet* 2010;**376**:730–873.

Downey DB, Fenster A, Williams JC. Clinical utility of three-dimensional US. *Radiographics* 2000;**20**:559–571.

Egekvist AG, Forman A, Seyer-Hansen M. Three-dimensional ultrasound of deep infiltrating endometriosis involving the rectosigmoid colon. *Acta Obstet Gynecol Scand* 2011;**90**:122–125.

Fratelli N, Scioscia M, Bassi E, Musola M, Minelli L, Trivella G. Transvaginal sonography for preoperative assessment of deep endometriosis. *J Clin Ultrasound* 2013;**41**:69–75.

Giudice LC. Clinical practice. Endometriosis. *N Engl J Med* 2010; **362**:2389–2398.

Grasso RF, Di Giacomo V, Sedati P, Sizzi O, Florio G, Faiella E, Rossetti A, Del Vescovo R, Zobel BB. Diagnosis of deep infiltrating endometriosis: accuracy of magnetic resonance imaging and transvaginal 3D ultrasonography. *Abdom Imaging* 2010;**35**:716–725.

Guerriero S, Ajossa S, Gerada M, D'Aquila M, Piras B, Melis GB. 'Tenderness-guided' transvaginal ultrasonography: a new method for the detection of deep endometriosis in patients with chronic pelvic pain. *Fertil Steril* 2007;**88**:1293–1297.

Guerriero S, Ajossa S, Gerada M, Virgilio B, Angioni S, Melis GB. Diagnostic value of transvaginal 'tenderness-guided' ultrasonography for the prediction of location of deep endometriosis. *Hum Reprod* 2008; **23**:2452–2457.

Guerriero S, Alcázar JL, Ajossa S, Pilloni M, Melis GB. Three-dimensional sonographic characteristics of deep endometriosis. *J Ultrasound Med* 2009;**28**:1061–1066.

Guerriero S, Alcazar JL, Ajossa S, Pilloni M, Soggiu B, Paoletti AM, Melis GB. OP11.01: standardization of three dimensional ultrasonographic evaluation for the assessment of deep infiltrating endometriosis. *Ultrasound Obstet Gynecol* 2010;**36**(S1):82.

Guerriero S, Spiga S, Ajossa S, Peddes C, Perniciano M, Soggiu B, De Cecco CN, Laghi A, Melis GB, Saba L. Role of imaging in the management of endometriosis. *Minerva Ginecol* 2013a;**65**:143–166.

Guerriero S, Saba L, Ajossa S, Peddes C, Sedda F, Piras A, Olartecoechea B, Aubá M, Alcázar JL. Assessing the reproducibility of the IOTA simple

ultrasound rules for classifying adnexal masses as benign or malignant using stored 3D volumes. *Eur J Obstet Gynecol Reprod Biol* 2013b;**171**:157–160.

Guerriero S, Pilloni M, Alcazar JL, Sedda F, Ajossa S, Mais V, Melis GB, Saba L. Tissue characterization using mean gray value analysis in deep infiltrating endometriosis. *Ultrasound Obstet Gynecol* 2013c;**41**:459–464.

Hudelist G, Ballard K, English J, Wright J, Banerjee S, Mastoroudes H, Thomas A, Singer CF, Keckstein J. Transvaginal sonography vs. clinical examination in the preoperative diagnosis of deep infiltrating endometriosis. *Ultrasound Obstet Gynecol* 2011a;**37**:480–487.

Hudelist G, English J, Thomas AE, Tinelli A, Singer CF, Keckstein J. Diagnostic accuracy of transvaginal ultrasound for non-invasive diagnosis of bowel endometriosis: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2011b;**37**:257–263.

Kataoka ML, Togashi K, Yamaoka T, Koyama T, Ueda H, Kobayashi H, Rahman M, Higuchi T, Fujii S. Posterior cul-de-sac obliteration associated with endometriosis: MR imaging evaluation. *Radiology* 2005; **234**:815–823.

Kinkel K, Chapron C, Balleyguier C, Fritel X, Dubuisson JB, Moreau JF. Magnetic resonance imaging characteristics of deep endometriosis. *Hum Reprod* 1999;**14**:1080–1086.

León M, Vaccaro H, Alcázar JL, Martinez J, Gutierrez J, Amor F, Iturra A, Sovino H. Extended transvaginal sonography in deep infiltrating endometriosis: use of bowel preparation and an acoustic window with intravaginal gel: preliminary results. *J Ultrasound Med* 2014;**33**:315–321.

Pascual MA, Guerriero S, Hereter L, Barri-Soldevila P, Ajossa S, Graupera B, Rodriguez I. Diagnosis of endometriosis of the rectovaginal septum using introital three-dimensional ultrasonography. *Fertil Steril* 2010; **94**:2761–2765.

Pascual MA, Guerriero S, Hereter L, Barri-Soldevila P, Ajossa S, Graupera B, Rodriguez I. Three-dimensional sonography for diagnosis of rectovaginal septum endometriosis: interobserver agreement. *J Ultrasound Med* 2013; **32**:931–935.

Piketty M, Chopin N, Dousset B, Millischer-Bellaische AE, Roseau G, Leconte M, Borghese B, Chapron C. Preoperative work-up for patients with deeply infiltrating endometriosis: transvaginal ultrasonography must definitely be the first-line imaging examination. *Hum Reprod* 2009; **24**:602–607.

Rennie D. Improving reports of studies of diagnostic tests: the STARD initiative. *JAMA* 2003;**289**:89–90.

Saba L, Guerriero S, Sulis R, Pilloni M, Ajossa S, Melis G, Mallarini G. Learning curve in the detection of ovarian and deep endometriosis by using Magnetic Resonance: comparison with surgical results. *Eur J Radiol* 2011; **79**:237–244.

Saba L, Guerriero S, Sulcis R, Pilloni M, Ajossa S, Melis G, Mallarini G. MRI and 'tenderness guided' transvaginal ultrasonography in the diagnosis of recto-sigmoid endometriosis. *J Magn Reson Imaging* 2012;**35**: 352–360.

Saccardi C, Cosmi E, Borghero A, Tregnaghi A, Dessole S, Litta P. Comparison between transvaginal sonography, saline contrast sonovaginography and magnetic resonance imaging in the diagnosis of posterior deep infiltrating endometriosis. *Ultrasound Obstet Gynecol* 2012;**40**:464–469.