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Original Article

# Ultrasonographic Findings Indirectly Predicting Parametrial Involvement in Patients with Deep Endometriosis: The ULTRA-PARAMETRENDO I Study

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**ABSTRACT** **Study Objective:** To evaluate ultrasonographic findings as a first-line imaging tool to indirectly predict the presence of parametrial endometriosis (PE) in women with suspected deep endometriosis (DE) undergoing surgery.

**Design:** Retrospective analysis of a prospectively collected database (ULTRA-PARAMETRENDO I study; NCT05239871).

**Setting:** Referral center for DE.

**Patients:** Consecutive patients undergoing laparoscopic surgery for DE.

**Interventions:** Preoperative transvaginal ultrasonography was done according to the International Deep Endometriosis Analysis consensus statement. A stepwise forward regression analysis was performed considering the simultaneous presence of DE nodules and the following ultrasonographic indirect signs of DE: diffuse adenomyosis, endometriomas, ovary fixed to the lateral pelvic wall or the uterine wall, absence of anterior/posterior sliding sign, and hydronephrosis. The gold standard for the presence of PE was surgery with histologic confirmation.

**Measurements and Main Results:** Of 1079 patients, 212 had a surgical diagnosis of PE (left: 18.5%; right: 17.0%; bilateral: 15.9%). The obtained prediction model ($\chi^2$ = 222.530; p <.001) for PE included, as independent indirect DE signs presence of hydronephrosis (odds ratio [OR] = 14.5; p = .002), complete absence of posterior sliding sign (OR = 3.3; p <.001), presence of multiple endometriomas per ovary (OR = 3.0; p = .001), and ovary fixation to the uterine wall (OR = 2.4; p <.001); as independent concomitant DE nodules, presence of uterosacral nodules with the largest diameter >10 mm (OR = 3.2; p <.001), presence of rectal endometriosis with the largest diameter >25 mm (OR = 2.3; p = .004), and rectovaginal septum infiltration (OR = 2.3; p = .003). The optimal diagnostic balance was obtained considering at least 2 concomitant DE nodules and at least 1 indirect DE sign (area under the curve 0.75; 95% confidence interval, 0.72−0.79).

**Conclusion:** Specific indirect ultrasonographic findings should raise suspicion of PE in women undergoing preoperative assessment for DE. The suspicion of parametrial invasion may be critical to address patients to expert leading centers, where proper diagnosis and surgical treatment for PE can be performed. Journal of Minimally Invasive Gynecology (2022) 00, 1−12. © 2022 AAGL. All rights reserved.

*Keywords:* Deep endometriosis; Endometriosis; Laparoscopy; Parametrial endometriosis; Ultrasound

The authors declare that they have no conflict of interest.

The preliminary results of the study ULTRA-PARAMETRENDO I have been presented at Royal College of Obstetricians and Gynaecologists World Congress 2022, 13-15 June 2022, London (UK), being awarded as "Best in Session Oral Presentation."

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Endometriosis is an estrogen-dependent, chronic gynecologic disorder characterized by ectopic endometrium-like epithelium and/or stroma, usually with an associated inflammatory process [1]. This benign chronic disease affects up to 18% of women of reproductive age, increasing to 31% and 42% in the case of patients with infertility and pelvic pain, respectively [2]. Three main phenotypes of pelvic endometriosis have been identified: peritoneal, ovarian, and deep endometriosis (DE) [1].

DE consists of endometrium-like tissue lesions in the abdomen, extending under the peritoneal surface; these lesions are usually nodular, invade adjacent structures, and are associated with fibrosis and disruption of normal anatomy. DE is thought to affect 20% of women with pelvic endometriosis, and it has been associated with severe pain and infertility. Many pelvic structures can be affected by DE, including the uterosacral ligaments, vagina, rectosigmoid colon, bladder, and parametrial ligaments [1,3].

Parametrium is the subperitoneal connective areolar tissue that extends from the cervix and the vagina to the pelvic sidewall; this bilateral anatomical structure includes uterine vessels, part of the ureteral course, lymphatic structures, and pelvic autonomic nerves [4,5]. Parametrial involvement by endometriosis represents a severe form of DE, whose surgical treatment exposes patients to the risk of severe intra- and postoperative complications [6]. Therefore, preoperative detection of patients with suspected parametrial endometriosis (PE) is relevant for accurately planning the surgical procedures in the hands of expert surgeons in dedicated centers.

Transvaginal sonography (TVS) is the first-line imaging technique for ruling out DE nodules in patients with suspected endometriosis [7]. In 2016, the International Deep Endometriosis Analysis (IDEA) group published a consensus to standardize the nomenclature of ultrasonographic pelvic evaluation in women with suspected endometriosis [8]; in the IDEA criteria, PE has not been recognized and classified.

The accuracy of TVS for detecting the presence of PE has been investigated in a few studies characterized by heterogenous methodology and small populations [9−13]; in addition, a standardized description of PE has not been published yet. Recently, Guerriero et al performed a systematic review with meta-analysis (4 studies included), showing that TVS has a pooled limited sensitivity of 31% (95% confidence interval [CI], 10%−64%) for PE. These authors stated the need to standardize an exploratory technique with adequate reproducibility for detecting PE and establish a common terminology for describing the parametrial ultrasonographic anatomy [14].

Some indirect ultrasonographic signs have been correlated to DE presence, such as the ultrasonographic presence of uterine adenomyosis [15] and ovarian endometriomas [16], eventually with the "kissing ovaries" sign [17,18], and the fixation of the ovary to the uterus or pelvic wall [19].

The absence of sliding sign has been strongly associated with pouch of Douglas (POD) obliteration at laparoscopy [20]; subsequently, a high prevalence of rectosigmoid endometriosis has been found in women with the absence of a posterior sliding sign [21]. The International Deep Endometriosis Analysis group (IDEA) consensus included all these indirect DE signs in the first, second, and third basic ultrasonographic steps, which should be performed when evaluating patients with suspected DE [8]. Notably, previous studies reported a higher prevalence of some of these signs in patients with PE [9,10]; therefore, detecting specific indirect DE signs could help predict the presence of PE, for which TVS has, as highlighted above, limited diagnostic parameters.

Previous evidence also showed that patients with PE often have concomitant large DE nodules localized in other pelvic localizations, such as in the rectovaginal septum, vagina, and rectum [6,9,10]; subsequently, preoperatively ruling out the presence of specific DE nodules at ultrasound may trigger the suspicion of parametrial involvement.

Considering the above, this study aims to identify ultrasonographic findings and, subsequently, to build a preoperative model for indirectly predicting the presence of PE during surgery in women with suspected DE requiring laparoscopy.

## Materials and Methods

This was a retrospective analysis (ULTRA-PARAMETRENDO I study) of a prospectively collected database, including consecutive patients with clinical suspicion of DE who underwent a preoperative ultrasonographic approach at a referral institution for endometriosis (Department of Obstetrics and Gynecology, Gynecologic Oncology and Minimally-Invasive Pelvic Surgery, International School of Surgical Anatomy, IRCCS "Sacro Cuore-Don Calabria" Hospital, Negrar, Verona, Italy) between January 2021 and December 2021.

The primary objective of this study was to evaluate the use of ultrasonographic findings as a first-line imaging tool for indirectly predicting PE in women with suspected DE requiring surgery. The secondary aim of this study is to study the best prediction model for indirectly diagnosing PE at the preoperative ultrasound.

Exclusion criteria for this study were previous surgical diagnosis of PE, previous radiological assessment of endometriosis by magnetic resonance (MR), previous bilateral ovariectomy, and the impossibility of performing TVS for any technical reason.

Before the ultrasonographic exam, clinical data were obtained by collecting age, parity, body mass index, ongoing medical treatments, and reported symptoms, either relating to pain (dysmenorrhea, dyspareunia, chronic pelvic pain, dyschezia, and dysuria) or associated with functional impairment of defecation and bladder voiding.

All the patients included in this study underwent ultrasonographic evaluation by 4 operators (C.Z., M.A., A.S., and

P.DM.) with more than 5 years of experience in diagnosing endometriosis (each operator performs over 1500 transvaginal sonograms/year for DE). Within 15 days from ultrasonographic exams, patients underwent operative laparoscopy. Surgical and histologic findings were compared with the preoperative ultrasonographic diagnosis.

### *Ultrasound*

The ultrasonographic examinations were done using 2 high-performance machines (Samsung Ultrasound System HS60 and WS80; Samsung Medison, Seoul, South Korea) equipped with a 5- to 9-MHz transvaginal probe and a 3.5- to 5-MHz transabdominal probe.

Evaluation of concomitant DE nodules was done according to the IDEA consensus statement [8]. The following anatomic localizations were assessed: uterosacral ligaments (identifying torus involvement), rectovaginal septum, vagina, rectosigmoid (anterior lower and upper rectum, rectosigmoid junction, and sigmoid colon), and bladder. Number, size (3 diameters), and localization of DE nodules were collected.

At TVS, rectosigmoid endometriosis often consists of hypoechoic thickening of bowel muscularis propria, eventually characterized by hyperechoic foci with blurred margins (Figs. 1A, 2A, 3A and 4A) [8]; rectosigmoid nodules can even replace the typical appearance of the intestinal muscularis propria; retraction and/or adhesions can be concomitantly present [8,22]. DE nodules in the uterosacral ligaments are characterized by regular or irregular margins and often hyperechoic points or linear hypoechoic thickening with regular or irregular margins (Figs. 1B, 2B, 3B and 4B). DE nodules in the rectovaginal septum appear as lesions below a horizontal plane that passes along the lower margin of the posterior lip of the cervix under the peritoneum (Figs. 1A and 3A). Vaginal DE nodules can be suspected when the posterior vaginal fornix is thickened, with or without surrounding cystic anechoic areas. Contiguous DE lesions involving more than 1 pelvic structure have been considered separately in multiple localizations; that is, nodules of the vagina and/or rectum extending to the rectovaginal septum were also regarded as rectovaginal nodules [23].

At the ultrasound, the presence of indirect DE signs was systematically investigated by following the first 3 steps of the IDEA consensus [8]: (1) evaluation of uterus and adnexa, researching ultrasonographic signs of adenomyosis and the presence of endometriomas; (2) evaluation of "soft markers"; (3) assessment of POD status by evaluating real-time ultrasound-based "sliding sign."

The ultrasonographic signs of focal or diffuse adenomyosis were recorded, following the Morphological Uterus Sonographic Assessment (MUSA) criteria [24], as well as the eventual presence of unilateral or bilateral ovarian endometriomas, which appear as a unilocular cyst with ground-glass echogenicity of the cyst fluid (Figs. 1C and 2C) [25]. The evaluation of ultrasonographic "soft markers" included the assessment of ovarian mobility by applying pressure between this organ and the uterus and ovary, as described by other

**Fig. 1**

(A) Ultrasonographic findings: large low rectal DE nodule (maximum diameter 41 mm) infiltrating the rectovaginal septum; (B) large right uterosacral ligament DE nodule (maximum diameter 13 mm); (C) two endometriomas of the left ovary; (D) left hydroureteronephrosis detected by evaluating the appearance of renal calyces (transabdominally). (E) "Frozen pelvis" with endometriosis involving different pelvic viscera at the beginning of the surgical approach. Starting from the pelvic brim, ureterolysis is performed along the ureteral course on the pelvic sidewall until healthy tissue is reached. (F) After extensive left ureterolysis, a dilated ureter running into the lateral left pathologic parametrium (hatched area) infiltrated by endometriosis can be observed. C = cervix; DE = deep endometriosis; EC = endometriotic cyst; EN = endometriotic nodule; LPRS = lateral pararectal space; MPRS = medial pararectal space; MR = mesorectum; OUA = obliterated umbilical artery; OV = ovary; R = rectum; RP = renal pelvis; RVS = rectovaginal septum; Ur = ureter; UsL = uterosacral ligament; Ut = uterus; V = vagina.

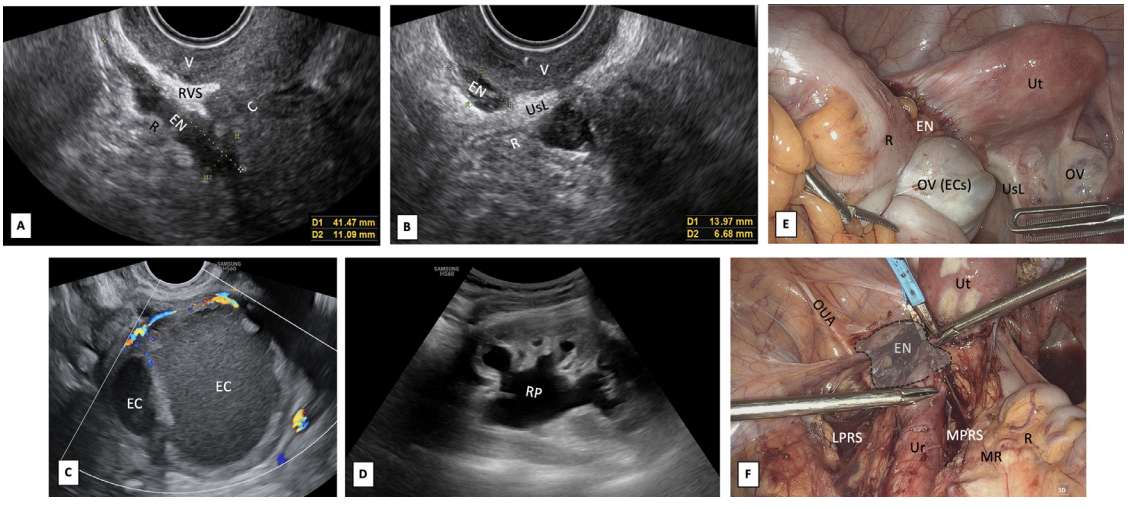
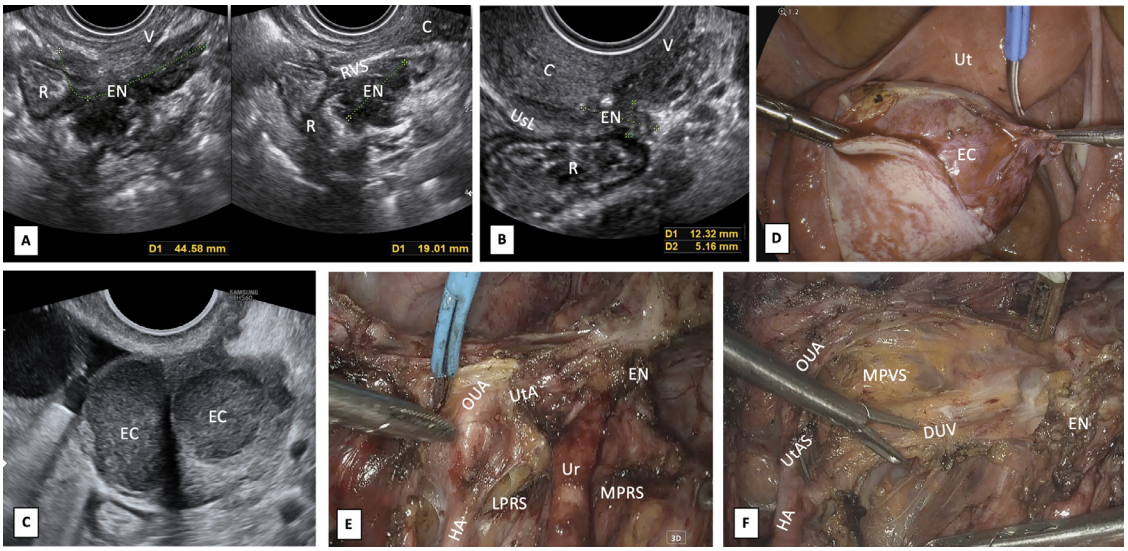


**Fig. 2**

(A) Ultrasonographic findings: large low rectal DE nodule (maximum diameter 44 mm); (B) large right uterosacral ligament DE nodule (maximum diameter 13 mm); (C) 2 endometriomas of the left ovary (the "crescent sign" is detectable). (D) Enucleation of left endometriomas at the beginning of the surgical approach; dissection of parametrial planes, isolation of left ureteral course, lateral parametrectomy. (E–F) When possible, isolating and sparing the uterine vessels at the intersection with the ureter is performed; when the cardinal ligament is infiltrated by endometriotic tissue and fibrotic retraction, sacrificing the uterine artery may be necessary. C = cervix; DE = deep endometriosis; DUV = deep uterine vein; EC = endometriotic cyst; EN = endometriotic nodule; HA = hypogastric artery; LPRS = lateral pararectal space; MPRS = medial pararectal space; MPVS = medial paravesical space; OUA = obliterated umbilical artery; R = rectum; RVS = rectovaginal septum; Ur = ureter; UsL = uterosacral ligament; UtA = uterine artery; UtAS = uterine artery stump; V = vagina.




authors [26]; the ovary was classified as hypomobile/fixed if it did not glide smoothly against the uterus (including uterosacral ligaments; medial fixation) and/or pelvic sidewall (lateral fixation) (Fig. 4C). The presence of "kissing ovaries," defined as both ovaries joined together behind the uterus in the POD, was also investigated [18]. In addition to the previously mentioned "soft markers," any evidence of ureteric dilatation of the third distal of both ureters was checked, as previously reported (Fig. 3D) [27]. This assessment was systematically complemented by abdominal ultrasonography to identify the presence of hydronephrosis by assessing the appearance of calyces and renal pelvis and renal parenchyma thickness (Figs. 1D and 3C).

The posterior sliding sign was investigated by applying the same technique employed for evaluating ovarian mobility; in the case of immobility of the rectum against the uterus and the posterior cervix/vaginal fornix, a negative posterior sliding sign (or absence of sliding sign) was described, reflecting possible adhesion and endometriotic involvement of these structures with POD obliteration [20]. Similarly, anterior vesical-uterine plica obliteration was investigated by performing a real-time transvaginal ultrasonographic sliding sign assessment between the anterior uterine and bladder wall.

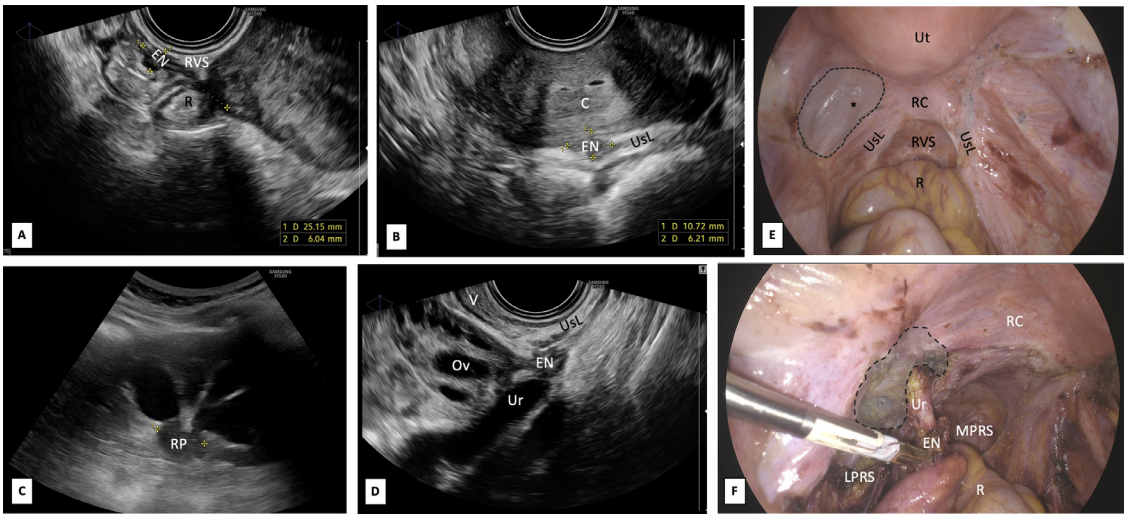
### *Surgery*

Before laparoscopy, the surgeons evaluated the reports and the images from diagnostic ultrasonography. Surgical procedures were performed by a team of gynecologic, urological, and colorectal surgeons with extensive experience in the surgical treatment of DE (more than 1200 laparoscopic procedures/year for suspected DE).

At our institution, the nerve-sparing laparoscopic excision of DE is performed by following the "Negrar method" [28,29], which includes 6 progressive steps: step 0—adhesiolysis, ovarian surgery, and removal of the involved peritoneal tissues; step 1—opening of presacral space, development of avascular spaces, and identification and preservation of pelvic sympathetic fibers of the inferior mesenteric plexus, superior hypogastric plexus, upper hypogastric nerves, and lumbosacral sympathetic trunk and ganglia; step 2—dissection of parametrial planes, isolation of ureteral course, and, when intraoperatively suspected lateral parametrial involvement, lateral parametrectomy with preservation of sympathetic fibers of posterolateral parametrium and lower mesorectum (the lower hypogastric nerves and proximal part of the inferior hypogastric plexus or pelvic plexus; Figs. 1F, 2F, 3F and 4D); step 3—when intraoperatively suspected posterior parametrial involvement, posterior parametrectomy by identifying deep uterine vein and preserving parasympathetic pelvic splanchnic nerves and cranial and middle part of mixed inferior hypogastric plexus; step 4—preservation of the caudad part of the inferior hypogastric plexus in posterolateral parametrial ligaments; step 5—preserving the caudad part of the inferior hypogastric plexus in paravaginal planes; and step 6—

**Fig. 3**

(A) Ultrasonographic findings: rectovaginal septum DE nodule infiltrating low rectum; (B) large right uterosacral ligament DE nodule (maximum diameter 11 mm); (C) left hydroureteronephrosis detected by evaluating the severe renal pyelectasis (transabdominally) and (D) the prevesical ureteral dilatation. (E) At surgery, retraction of left posterolateral parametrium (*; lateral parametrium: hatched area). After extensive left ureterolysis, development of lateral and medial pararectal spaces (Latzko's and Okabayashi's), and (F) posterior parametrectomy, an extrinsic parametrial EN causing hydroureteronephrosis can be observed. C = cervix; DE = deep endometriosis; EN = endometriotic nodule; LPRS = lateral pararectal space; MPRS = medial pararectal space; Ov = ovary; R = rectum; RC = retrocervix (uterine torus); RP = renal pelvis; RVS = rectovaginal septum; Ur = ureter; UsL = uterosacral ligament; V = vagina.




when intraoperatively suspected rectosigmoid involvement, rectal shaving or discoid or segmental resection with colorectal anastomosis, as previously indicated [29−31].

The presence of PE was described in the case of intraoperative evidence of DE nodules in anterior, lateral, and posterior parametrium, which eventually required a partial or total radical parametrectomy [28,29]. The posterior parametrium is defined after the surgical development of the rectovaginal septum and the pararectal spaces, being represented by the condensation of the uterosacral, rectovaginal, and lateral rectal ligaments together with their neurovascular and lymphatic structures. The lateral parametrium is visualized after the surgical opening of the medial and lateral paravesical and pararectal spaces. This area is split into cranial and medial portions and into lateral and caudad portions by the course of the ureter, which respectively correspond to the cardinal ligament (or Mackenrodt ligament) and the paracervix. The anterior parametrium is identified after surgical development of the vesicouterine septum and the medial and lateral paravesical spaces. This area is split into cranial and medial portions and into lateral and caudad portions by the ureter, which respectively correspond to the vesicouterine ligament and the lateral ligament of the bladder [4,5].

The diagnosis of DE nodules was confirmed by the pathological analysis of nodules excised at the surgery. Endometriosis was identified by the presence of endometrial−like epithelium and stroma. The maximal length of each DE nodule was calculated during pathological assessment. The severity of the disease was classified according to the revised American Society for Reproductive Medicine staging.

### *Statistical Analysis*

In the analysis, ultrasonographic findings were conventionally categorized into two groups: DE nodules and indirect DE signs. Ultrasonographic findings expressed as continuous variables were dichotomized using the Youden index. The chi-square test was used to explore the associations between the presence of PE and all the ultrasonographic findings considered. Only the ultrasonographic findings significantly associated (p values <.05) with the presence of PE were used as predictors in a multivariable logistic regression model. Using a stepwise forward selection approach, the final model was estimated. Nagelkerke $R^2$ and the percentage of correctly classified cases were calculated for the final model. To explore the predictive power of the ultrasonographic findings selected in the final multivariable model, sensitivity and specificity were calculated for each predictor and for a combination of them. In particular, sensitivity, specificity, and area under the curve (AUC) were calculated along with their 95% CIs when at least 1 concomitant DE nodule, at least 1 indirect DE sign, at least 1 concomitant DE nodule and 1 indirect DE sign, at least 2 concomitant DE nodules and 1 indirect DE sign, at least 1 concomitant DE nodule and 2 indirect DE signs, and at least 2 concomitant DE nodules and 2 indirect DE signs

were present. AUC were compared by using the DeLong test.

Data were collected by a dedicated software (EGES software v.3.0.10; Mitcom, Mantua, Italy) and were analyzed using the SPSS software version 26.0 (SPSS Science, Chicago, IL).

### *Ethical Approval*

The local ethics committee approved the study protocol (CE Prog. 3705CESC − Comitato etico AOVR; approval 09-03-2022). Patients participating in the study provided written informed consent. This study was registered in Clinicaltrial.gov (NCT05239871). This study followed the STARD stands for "Standards for Reporting Diagnostic accuracy studies"[32].

## Results

### *Demographic Characteristics*

During the period considered, 1183 consecutive patients were referred to our institution with clinical suspicion of DE requiring a surgical approach. Considering the exclusion criteria of the study, the definitive analysis was done on 1079 patients. The study flow is available in Fig. 5. The patients' mean (± standard deviation) age was 35.3 ± 4.7 years. At the study time, 804 women (74.5%; 95 CI, 71.9%−77.2%) were using hormonal therapies. Table 1 reports the other demographic characteristics of the study population.

**Table 1**

Demographic characteristics of the study population

| Demographic variable | N = 1079 |
|---|---|
| Age, yrs, mean ± SD | 35.3 ± 4.7 |
| Body mass index, kg/m$^2$, mean ± SD | 22.9 ± 3.5 |
| Smokers, n (%) | 144 (13.3) |
| Race, n (%) | |
| Caucasian | 1065 (98.7) |
| African | 8 (0.8) |
| Asiatic | 6 (0.5) |
| Parous women, n (%) | 336 (31.1) |
| Previous surgery for endometriosis, n (%) | 295 (27.5) |
| Use of hormonal therapies at the time of study inclusion, n (%) | 804 (74.6) |
| Oral estroprogestin pill | 263 (32.7) |
| Contraceptive vaginal ring | 58 (7.2) |
| Desogestrel | 91 (11.3) |
| Norethindrone acetate | 72 (9.0) |
| Dienogest | 237 (29.5) |
| Etonogestrel-releasing implant | 28 (3.5) |
| Levonorgestrel-releasing intrauterine device | 41 (5.1) |
| Gonadotropin-releasing hormone analog | 14 (1.7) |
| Symptoms, n (%) | |
| Dysmenorrhea | 432/494* (87.4) |
| Deep dyspareunia | 893/996† (89.7) |
| Nonmenstrual pelvic pain | 931 (86.4) |
| Dyschezia | 473 (43.9) |
| Diarrhea | 154 (14.3) |
| Constipation | 178 (16.5) |
| Abdominal bloating | 204 (18.9) |
| Intestinal cramping | 170 (15.8) |
| Passage of mucus | 137 (12.7%) |
| r-ASRM classification at surgery, n (%) | |
| Stage I | 102 (9.5) |
| Stage II | 134 (12.4) |
| Stage III | 178 (16.5) |
| Stage IV | 664 (61.6) |

r-ASRM = revised American Society for Reproductive Medicine; SD = standard deviation.

* All the other patients were using hormonal therapies causing amenorrhea.

† Eighty-two patients were not sexually active.

### *Ultrasonographic Findings*

At the ultrasound, 1483 DE nodules were observed (1.4 ± 0.4 nodules per patient). Uterosacral ligament DE nodules were detected in 445 patients (659 nodules; right: 49.6%; left: 50.4%), with bilateral involvement in 214 of them (48.1%). Rectosigmoid localization was reported in 296 women (92 rectal, 160 rectosigmoid junction, and 59 sigmoid nodules). Forty-one patients (3.8%) had evidence of bladder endometriosis. Ovarian endometriomas were observed at ultrasound in 329 patients (471 cysts; right: 49.6%; left: 50.4%); in 82 patients (7.6%) and 51 patients (4.7%) of them, respectively, there was evidence of bilateral ovarian involvement and 2 or more endometriomas per ovary. A total of 762 women (70.6%) had ultrasonographic features that suggested diffuse uterine adenomyosis. At least 1 ovary was fixed to uterine (medial) and pelvic (lateral) walls in 315 women (29.2%) and 325 women (30.1%) cases, respectively. The "kissing ovaries" sign was present in 42 women (3.8%), and the posterior sliding sign was completely absent in 202 women (18.7%).

### *Surgical Findings*

At laparoscopic surgery, complete eradication of visible endometriosis was obtained in 96.5% of cases (n = 1041). A colorectal shaving was performed in 36.7% (n = 396) cases, a discoid excision in 11.3% (n = 123) cases, and a segmental colorectal resection in 15.3% (n = 165) cases. Ureterolysis was performed in 523 cases (right: 46.3%; left: 53.7%); 33 patients (3.1%) underwent a ureteroneocystostomy. In 197 women (18.3%), a combined hysterectomy was also performed; in this subgroup, a radical hysterectomy was done in 146 cases (74.1%).

A total of 212 patients had a surgical diagnosis of PE (left: 18.5%; right: 17.0%; bilateral: 15.9%).

### *Ultrasonographic Findings Predicting Parametrial Involvement*

Table 2 reports the prevalence of ultrasonographic findings that resulted to be significantly different in patients

**Table 2**

Ultrasonographic findings (classified in concomitant DE nodules and indirect DE signs) with a significant difference in prevalence (p <.05) in patients with or without parametrial endometriosis (any side) at the surgery

| Ultrasonographic finding | Parametrial endometriosis at surgery, (n = 212) | No parametrial endometriosis at surgery, (n = 866) |
|---|---|---|
| Number (%) of patients with: | | |
| DE nodules | | |
| Rectosigmoid | 99 (46.7) | 197 (22.7) |
| Upper/lower rectum | 37 (17.5) | 52 (6.0) |
| Rectosigmoid junction | 45 (21.2) | 112 (12.9) |
| Sigmoid | 17 (8.0) | 33 (3.8) |
| Utero-sacral ligaments | 120 (56.6) | 325 (37.5) |
| Bilateral involvement | 59 (27.8) | 155 (17.9) |
| Torus involvement | 84 (39.6) | 229 (26.4) |
| Rectovaginal septum | 48 (22.6) | 40 (4.6) |
| Vagina | 26 (12.3) | 40 (4.6) |
| Indirect DE signs | | |
| Endometriomas | 96 (45.3) | 233 (26.9) |
| Multiple endometriomas per ovary | 25 (11.8) | 26 (3.0) |
| Ovarian fixation to pelvic wall (lateral fixation) | 87 (41.0) | 238 (27.5) |
| Ovarian fixation to uterine wall/uterosacral ligaments (medial fixation) | 124 (58.5) | 191 (22.0) |
| Absence of anterior sliding sign | 51 (24.1) | 110 (12.7) |
| Absence of posterior sliding sign | 98 (46.2) | 104 (12.0) |
| Kissing ovaries | 22 (10.4) | 20 (2.3) |
| Hydronephrosis | 7 (3.3) | 2 (0.2) |

DE = deep endometriosis.

with and without the surgical presence of PE. In patients with PE, DE nodules were most commonly localized in the uterosacral ligaments (n = 120, 56.6%) and in the rectum (n = 37, 17.7%); in particular, a largest nodule diameter of >10 mm and >25 mm, respectively, for uterosacral and rectal nodules were identified as the best cutoff values for discriminating with the presence of PE (p <.05). Similarly, a completely absent posterior sliding sign was the most common indirect DE sign associated with the presence of PE (n = 98; 46.2%).

Regression analysis led to a statistically significant prediction model ($\chi^2$ = 222.530; p <.001), explaining 29.4% (Nagelkerke $R^2$) of the variance in surgical parametrium (any side) and correctly classifying 82.9% of cases (Figs. 1−4). This model included, as independent indirect DE signs, presence of hydronephrosis (odds ratio [OR], 14.5; 95% CI, 2.7−78.3; p = .002), complete absence of posterior sliding sign (OR, 3.3; 95% CI, 2.2−5.0; p <.001), presence of multiple endometriomas per ovary (OR, 3.0; 95% CI, 1.6−5.7; p = .001), and ovary fixation to uterine wall (OR, 2.4; 95% CI, 1.6−3.5; p <.001), and as indirect independent concomitant DE nodules, presence of uterosacral nodules with largest diameter >10 mm (OR, 3.2; 95% CI, 2.0−5.0; p <.001), presence of rectal endometriosis with largest diameter >25 mm (OR, 2.3; 95% CI, 1.3−4.3; p = .004), and rectovaginal septum infiltration (OR, 2.3; 95% CI, 1.3−3.8; p = .003).

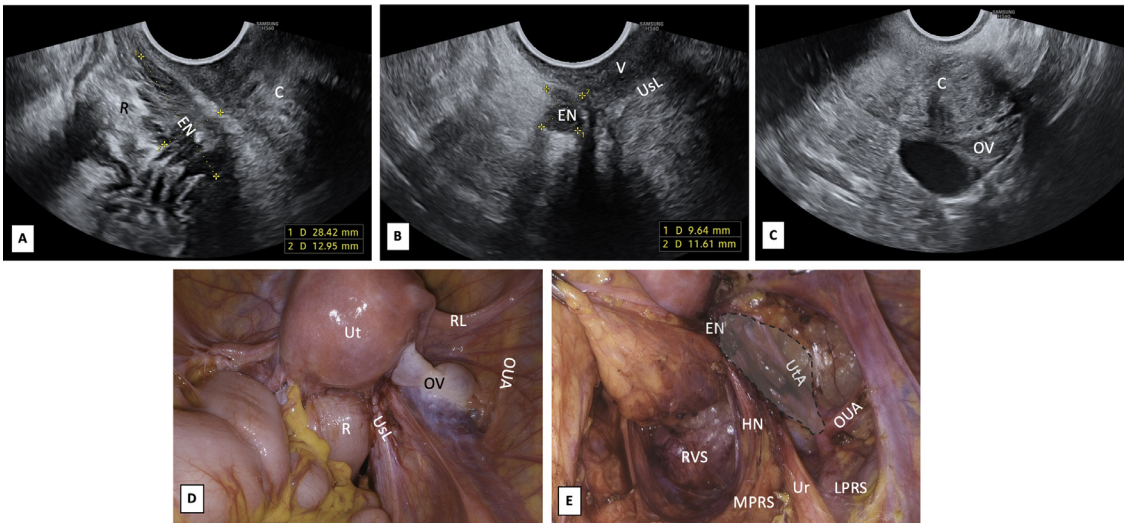
Overall, none of the ultrasonographic findings selected in the final model, when considered singularly, demonstrated a relevant sensitivity for predicting the presence of PE (Table 3 and Supplemental Table 1). Sensitivity and specificity were, respectively, 49.5% and 74.5% when at least 1 significant concomitant DE nodule was present; 75.0% and 74.3% when at least 1 significant indirect DE sign was present; and 84.0% and 59.7% when at least 1 concomitant DE nodule and 1 indirect DE sign were present. The optimal diagnostic balance was obtained considering at least 2 concomitant DE nodules and at least 1 indirect DE sign (AUC 0.75; 95% CI, 0.72−0.79). This model had significantly higher accuracy in comparison with the previous combination of indirect DE signs and concomitant DE nodules (p = .002), demonstrating a sensitivity of 78.8% (95% CI, 72.7%−84.1%) and a specificity of 72.3% (95% CI, 69.2%−75.3%) for the presence of PE (Supplemental Tables 2 and 3). Fig. 6 shows the receiver operating characteristic (ROC) curves related to the different prediction models evaluated in the study.

## Discussion

Until now, the performance of ultrasound in detecting the presence of PE has been investigated in few trials characterized by limited sample size and heterogenous methodology [9−13]; moreover, most of these diagnostic accuracy

**Fig. 4**

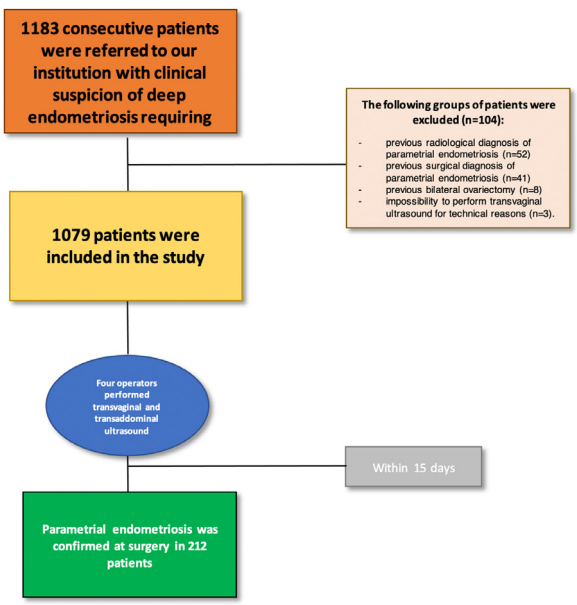
(A) Ultrasonographic findings: large low rectal DE nodule (maximum diameter 28 mm) infiltrating the rectovaginal septum; (B) large right uterosacral ligament DE nodule (maximum diameter 12 mm); (C) right ovary fixed to the uterine wall. (D) "Frozen pelvis" with endometriosis involving different pelvic viscera at the beginning of the surgical approach. (E) Extensive right ureterolysis, development of lateral and medial pararectal spaces (Latzko's and Okabayashi's); dissection of the rectovaginal septum. The endometriotic nodule of the uterine right uterosacral ligament infiltrates the lateral parametrium (hatched area). C = cervix; DE = deep endometriosis; EN = endometriotic nodule; HN = hypogastric nerve; LPRS = lateral pararectal space; MPRS = medial pararectal space; OUA = obliterated umbilical artery; OV = ovary; R = rectum; RL = round ligament; RVS = rectovaginal septum; Ur = ureter; UsL = uterosacral ligament; UtA = uterine artery; V = vagina.




studies evaluate DE in multiple pelvic localizations, and therefore, they are not specifically focused on parametrial involvement by endometriosis [11−13]. A recent systematic review with meta-analysis performed by Guerriero et al showed that TVS has a pooled sensitivity of 31%, a specificity of 98%, a positive likelihood ratio of 18.5, and a negative likelihood ratio of 0.70 for PE, obtaining diagnostic odds ratio of 26 (95% CI, 10−68); nevertheless, the heterogeneity of these studies was high for both sensitivity ($I^2$ = 90.44%) and specificity ($I^2$ = 86.39%). In several centers, MR is used widely as an alternative to ultrasound examination. Limited data reported that MR might be a suitable diagnostic tool for detecting the presence of PE [33]; in particular, the use of thin-section oblique 2D-T2W imaging (sagittal and axial) seems to be helpful for evaluating parametrial involvement by endometriosis [34]. However, TVS should be considered a first-line imaging technique for evaluating patients with suspected endometriosis because of its similar diagnostic accuracy for DE nodules and better cost-effectiveness [7].

**Fig. 5**

Flowchart of the study




Previous evidence showed that patients with PE complain of having a more severe intensity of dysmenorrhea, more frequent voiding symptoms, and more constipation than patients with DE, but no parametrial involvement [6]. Although the surgical approach for PE leads to an improvement in patient's symptoms [29,35], it may cause severe iatrogenic pelvic organ dysfunctions, owing to accidental injury of pelvic nerves, particularly in the case of bilateral parametrial infiltration when performed by unskilled surgical operators [36]. Over time, the principles of nerve-sparing surgery have been incorporated into the surgical treatment for DE to minimize such iatrogenic damages and potentially reduce the risk of functional complications

**Table 3**

Diagnostic parameters of concomitant DE nodules and indirect DE signs (considered singularly) included in the prediction model for parametrial endometriosis (any side) at surgery

| Ultrasonographic presence of: | SE | SP | PPV | NPV | LR+ | LR− | ACC |
|---|---|---|---|---|---|---|---|
| | | | DE nodules | | | | |
| Rectal nodule >25 mm of largest diameter | 15.6 (11.0−21.2) | 96.7 (94.4−97.2) | 48.4 (37.5−59.7) | 82.3 (81.4−83.1) | 3.9 (2.5−6.1) | 0.9 (0.8−0.9) | 80.2 (77.7−82.5) |
| Rectovaginal septum infiltration | 22.6 (17.2−28.9) | 95.9 (94.4−97.2) | 57.8 (47.7−67.4) | 83.5 (82.4−84.5) | 5.6 (3.7−8.4) | 0.8 (0.8−0.9) | 81.5 (79.0−83.4) |
| Uterosacral ligament nodule >10 mm of largest diameter | 24.5 (18.9−30.9) | 92.9 (90.9−94.5) | 45.6 (37.5−54.1) | 83.4 (82.3−84.5) | 3.4 (2.5−4.8) | 0.8 (0.8−0.9) | 79.4 (76.9−81.8) |
| | | | Indirect DE signs | | | | |
| Hydronephrosis | 3.3 (1.3−6.7) | 99.8 (99.2−100.0) | 77.8 (42.3−94.4) | 80.4 (80.5−81.2) | 14.3 (3.0−68.4) | 1.0 (0.9−1.0) | 80.8 (78.3−83.1) |
| Ovarian fixation to uterine wall/uterosacral ligaments (medial fixity) | 58.5 (51.5−65.2) | 78.0 (75.1−80.7) | 39.4 (35.4−43.5) | 88.5 (86.7−90.1) | 2.7 (2.2−3.1) | 0.5 (0.5−0.6) | 74.1 (71.4−76.7) |
| Complete absence of posterior sliding sign | 46.2 (39.4−53.2) | 88.0 (85.7−90.1) | 48.5 (42.8−54.3) | 87.0 (85.5−88.4) | 3.9 (3.1−4.9) | 0.6 (0.5−0.7) | 79.8 (77.3−82.2) |
| Multiple endometriomas per ovary | 11.8 (7.8−16.9) | 97.0 (95.6−98.0) | 49.0 (36.2−62.0) | 81.8 (81.0−82.3) | 3.9 (2.3−6.7) | 0.9 (0.9−1.0) | 80.3 (77.8−82.6) |

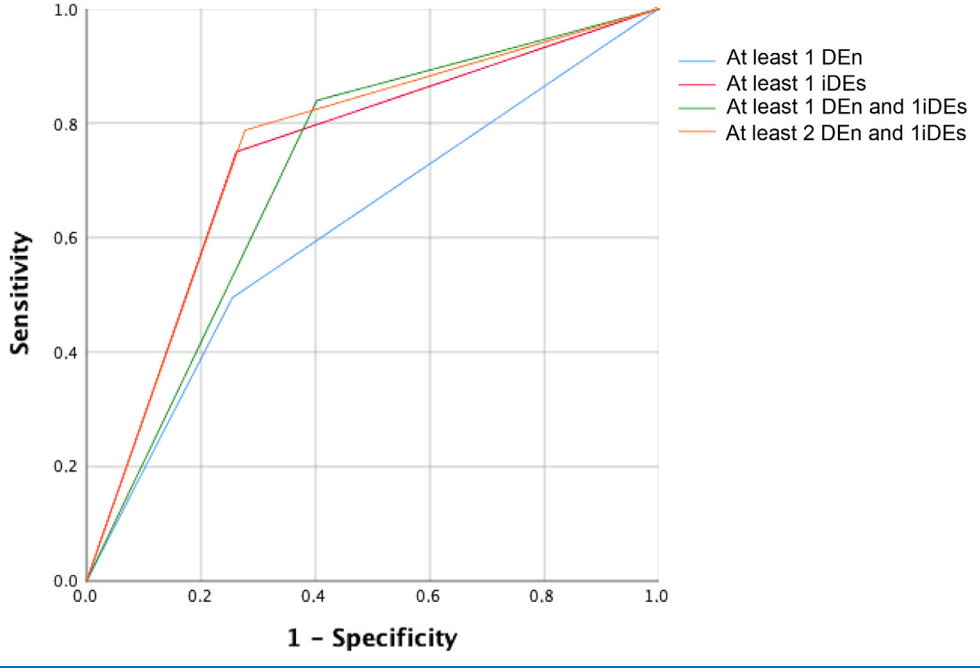
SE, SP, PPV, NPV, and ACC are presented as % (95% CI). LR+ and LR- are presented as n (95% CI).
ACC = accuracy; DE = deep endometriosis; LR+ = positive likelihood ratio; LR− = negative likelihood ratio; NPV = negative predictive value; PPV = positive predictive value; SE = sensitivity; SP = specificity.

[28,29,37]. Therefore, the preoperative detection of parametrial involvement by endometriosis lying in the proximity of urinary, vascular, and nervous structures is crucial and should be followed by accurate operative management of patients within dedicated multispecialty surgical teams belonging to centers dedicated to DE.

Considering the limited results published in the current literature about the direct PE assessment at the ultrasound, alternative strategies for detecting parametrial involvement by endometriosis are demanding. The results of our study show that the possibility of predicting parametrial invasion by recognizing specific DE nodules and indirect DE signs

**Fig. 6**

Receiver operating characteristic curves related to the combination of concomitant DE nodules and in direct DE signs included in the prediction model for the presence of parametrial endometriosis (any side) at surgery. DEn = deep endometriosis nodule; iDEs = indirect DE signs.



may be useful for less expert operators (sonographers/radiologists/surgeons) to refer patients to expert leading centers, where proper diagnosis and surgical treatment for PE can be performed. Our data demonstrated that large rectal and uterosacral ligament nodules and infiltration of the rectovaginal septum might predict a higher risk of finding PE at surgery; in fact, it can be hypothesized that parametrial involvement by endometriosis can be because of infiltration from large posterior compartment nodules. These results are in line with previous studies showing a significantly higher prevalence of posterior DE in women with PE [6,9,10]. Specifically, in our analysis, a maximum diameter cutoff of 10 mm for uterosacral DE had the best discriminative performance for detecting PE; these findings are similar to those of a previous French study by Bazot et al [9] for uterosacral nodules potentially associated with PE. In contrast, different indirect DE signs, such as the ovarian fixation to the uterine wall, the complete absence of posterior sliding sign, and hydronephrosis significantly predicted the presence of PE. Similar to our findings, an Italian retrospective case-series study describing the characteristics of 26 parametrial lesions reported a correlation between ipsilateral reduced/absent ovarian mobility and PE [10]. In fact, the ovarian fixation to the uterine wall may be subsequent to the presence of large uterosacral nodules and severe posterior uterine adenomyosis, which superficially infiltrates the homolateral ovary with medialization of its pelvic position; this tends to be concomitant to a relevant spread of the disease to the parametrium. The absence of the posterior sliding sign, an indirect sign of POD obliteration [20], can be related to the presence of large posterior pelvic compartment DE, which may extend to posterolateral parametrium, leading in the most severe cases to the surgical condition of "frozen pelvis" (Figs. 1E and 4D). Importantly, patients with PE are more likely to also have hydroureteronephrosis [38], which may derive from the extrinsic involvement of the ureter in its pelvic parametrial course [39]. As shown in our study, hydroureteronephrosis has an elevated specificity (99.8%) but low sensitivity (3.3%) for predicting the presence of PE; in fact, in most cases, patients with PE do not present ureteral dilatation; this is also supported by a recent study by Arena et al [40] demonstrating that PE can carry out a 4-fold higher risk of ureteral endometriosis, even in the absence of ureteral dilatation or hydronephrosis. In light of the above, finding, hydronephrosis in a patient of reproductive age with suspected DE is highly suggestive of PE. Overall, abdominal ultrasonography should be considered complementary to transvaginal ureteral assessment for evaluating the appearance of calyces and renal pelvis and renal parenchyma thickness; in the case of extrinsic endometriotic involvement because of posterolateral parametrium, ureteral dilatation tends to characterize its proximal pelvic segment, which can only be indirectly visualized by evaluating kidneys at transabdominal ultrasound; dilatation of the prevesical ureter, which can be assessed by TVS, is more commonly subsequent to the presence of large trigonal bladder nodules infiltrating the vesical intramural ureter, but it may be more rarely concomitant to anterior parametrial lesions (Fig. 3D) [38,41].

In our study, despite being part of the predictive model, none of the abovementioned concomitant DE nodules and indirect DE signs singularly predicted the presence of PE with high sensitivity (3.3%−58.5%) in our cohort of women. Otherwise, the optimal diagnostic balance for PE was obtained when considering them together; among different combinations (Supplemental Table 2), the presence of at least 2 concomitant DE nodules and at least 1 indirect DE sign showed a sensitivity and specificity of 78.8% and 72.3%, respectively (Fig. 6).

The presence of PE has been considered by the new #Enzian classification [42], which has been applied in the preoperative evaluation of patients with suspected DE by ultrasound [43−45]. However, until now, a standardized exploratory technique providing an accurate visualization of PE has not been introduced in clinical practice, and reliable reproducibility of sonographic evaluation of this area is demanding. Recently, some Italian authors proposed for the first time some anatomic landmarks for describing the presence of DE nodules in lateral and dorsal parametrial areas [46]. The presence of anterior, lateral, and posterior parametrium should be distinguished for each hemipelvis for their relevant implication in radical pelvic surgery [4]. In fact, parametrial areas include the visceral pelvic ligaments (also defined as "pillars") together with vascular, lymphatic, and neural structures enveloped in a double layer of visceral pelvic fascia [47,48]. We deem that ultrasonographic landmarks, such as the ureter, uterine artery, and lateral vesical ligaments, could be further investigated for distinguishing the different topographic parametrial areas, thus providing a standardized classification; nevertheless, future studies are necessary to draw a conclusion on this topic.

The retrospective design is a theoretical limitation of the study; however, the database was prospectively collected, including all the consecutive patients who underwent ultrasound exams and surgical treatment at the same institution in a relatively limited time (1 year). Although 4 operators did the ultrasonographic exams, they all had dedicated training and extensive experience in diagnosing DE.

Although its exact prevalence has been estimated with heterogeneous results, previous studies showed that PE is not a rare finding in patients with DE undergoing surgery (14.5%−75%) [33,49,50]. Our results demonstrated that PE lesions were located more often in the left hemipelvis (18.5% vs 17.0%), in aggrement with other previous manuscripts on this topic [6,10,33]. The relatively high prevalence of PE in our study might be explained because our institution is a referral center for severe DE, which surgically manages approximately 1200 patients with suspected DE per year. In addition, the population selected in our study may also explain a higher diagnostic rate of DE. However, the systematic surgical evaluation of parametrium allowed for obtaining reliable data on the prevalence of PE.

In the future, it would be interesting to perform this analysis on a larger scale to confirm its validity further. In addition, evaluating specific preoperative risk factors by a mathematical model could help physicians better plan the surgical approach and perform accurate preoperative counseling about benefits and risks characterizing surgical options in the case of a high risk of parametrial involvement. Considering the above, an ongoing study, defined as the ULTRA-PARAMETRENDO II study, is determining a preoperative score for predicting the risk of PE.

## Conclusion

Specific ultrasonographic findings in women with DE are associated with the presence of PE involvement at surgery. The possibility to indirectly suspect parametrial invasion may be relevant to address patients to expert leading centers, where proper diagnosis and surgical treatment for PE can be performed.

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## Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.jmig.2022.10.008.

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