Ultrasound Obstet Gynecol 2015; **46**: 534–545
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.15667

Accuracy of transvaginal ultrasound for diagnosis of deep endometriosis in uterosacral ligaments, rectovaginal septum, vagina and bladder: systematic review and meta-analysis

S. GUERRIERO*, S. AJOSSA*, J. A. MINGUEZ†, M. JURADO†, V. MAIS*, G. B. MELIS* and J. L. ALCAZAR†

**Department of Obstetrics and Gynecology, University of Cagliari, Policlinico Universitario Duilio Casula, Monserrato, Cagliari, Italy; †Department of Obstetrics and Gynecology, Clínica Universidad de Navarra, School of Medicine, University of Navarra, Pamplona, Spain*

KEYWORDS: bladder endometriosis; deep endometriosis; meta-analysis; rectovaginal septum; systematic review; transvaginal ultrasound; uterosacral ligaments; vaginal endometriosis

ABSTRACT

Objective *To review the diagnostic accuracy of transvaginal ultrasound (TVS) in the preoperative detection of endometriosis in the uterosacral ligaments (USL), rectovaginal septum (RVS), vagina and bladder in patients with clinical suspicion of deep infiltrating endometriosis (DIE).*

Methods *An extensive search was performed in MEDLINE (PubMed) and EMBASE for studies published between January 1989 and December 2014. Studies were considered eligible if they reported on the use of TVS for the preoperative detection of endometriosis in the USL, RVS, vagina and bladder in women with clinical suspicion of DIE using the surgical data as a reference standard. Study quality was assessed using the PRISMA guidelines and QUADAS-2 tool.*

Results *Of the 801 citations identified, 11 studies (*n = *1583) were considered eligible and were included in the meta-analysis. For detection of endometriosis in the USL, the overall pooled sensitivity and specificity of TVS were 53% (95%CI, 35–70%) and 93% (95%CI, 83–97%), respectively. The pretest probability of USL endometriosis was 54%, which increased to 90% when suspicion of endometriosis was present after TVS examination. For detection of endometriosis in the RVS, the overall pooled sensitivity and specificity were 49% (95%CI, 36–62%) and 98% (95%CI, 95–99%), respectively. The pretest probability of RVS endometriosis was 24%, which increased to 89% when suspicion of endometriosis was present after TVS examination. For detection of vaginal endometriosis, the overall pooled sensitivity and specificity were 58% (95%CI, 40–74%) and 96% (95%CI, 87–99%), respectively. The pretest probability of vaginal endometriosis was 17%, which increased to 76% when suspicion of endometriosis was present after TVS assessment. Substantial heterogeneity was found for sensitivity and specificity for all these locations. For detection of bladder endometriosis, the overall pooled sensitivity and specificity were 62% (95%CI, 40–80%) and 100% (95%CI, 97–100%), respectively. Moderate heterogeneity was found for sensitivity and specificity for bladder endometriosis. The pretest probability of bladder endometriosis was 5%, which increased to 92% when suspicion of endometriosis was present after TVS assessment.*

Conclusion *Overall diagnostic performance of TVS for detecting DIE in uterosacral ligaments, rectovaginal septum, vagina and bladder is fair with high specificity.* *Copyright © 2015 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Deep infiltrating endometriosis (DIE) is defined as the subperitoneal infiltration of endometrial implants of ≥ 5mm, not only in the rectosigmoid but also in the uterosacral ligaments (USL), rectovaginal septum (RVS), vagina and bladder[1]. Although the majority of these lesions cause several symptoms related to their location, such as subfertility, dysmenorrhea, dyspareunia, dysuria, dyschezia, chronic pelvic pain, hematochezia and hematuria, a delay between the onset of first symptoms and clinical diagnosis of endometriosis has been reported with an interval of about 7–10 years[2,3]. In the last 10 years non-invasive diagnostic methods such

Correspondence to: Prof. S. Guerriero, Department of Obstetrics and Gynecology, University of Cagliari, Policlinico Universitario Duilio Casula, Monserrato, Blocco Q, SS 554, Bivio di Sestu, Monserrato, 09042 Cagliari, Italy (e-mail gineca.sguerriero@tiscali.it)

Accepted: 3 August 2015

Table 1 Characteristics of studies included according to PICOS (Patients, Intervention, Comparator, Outcomes, Study design) criteria

Reference	*Setting*	n	*Method of TVS*	*Observers*	*Reference standard†*	*Cases with DIE (n)*
Bazot (2004)[42]	Single center	142	Non-enhanced	Single	Surgery and histopathology following Bazot's criteria	USL (71), RVS (8), vagina (17), bladder (7)
Guerriero (2008)[43]	Single center	88	Non-enhanced (tenderness-guided)	Single	Surgery and histopathology following Bazot's criteria	USL (24), RVS (46), vagina (34), bladder (4)
Bazot (2009)[44]	Single center	92	Non-enhanced	Single	Surgery and histopathology following Bazot's criteria	USL (83), RVS (11), vagina (30)
Hudelist (2011)[45]	Multicenter	155	Non-enhanced	Single	Surgery and histopathology	USL (30), RVS (9), vagina (11), bladder (4)
Vimercati (2012)[46]	Single center	90	Non-enhanced	Single	Surgery and histopathology	USL (112)*, RVS (18), vagina (4), bladder (6)
Saccardi (2012)[47]	Single center	54	Enhanced (saline contrast SVG)	Single	Surgery and histopathology	USL (9), RVS (36), vagina (19)
Holland (2013)[48]	Single center	198	Non-enhanced	Two	Surgery	USL (40), RVS (32), bladder (5)
Fratelli (2013)[49]	Single center	420	Non-enhanced	Three	Surgery and histopathology following Bazot's criteria	USL (247), RVS (132), bladder (25)
Exacoustos (2014)[50]	Multicenter	104	Non-enhanced	Single	Surgery in all and histopathology in some	USL (176)*, RVS (46), vagina (29), bladder (8)
León (2014)[51]	Single center	51	Enhanced (gel contrast SVG)	Single	Surgery and histopathology	Vagina (5), bladder (5)
Reid (2014)[52]	Multicenter	189	Enhanced (gel contrast SVG)	Two	Surgery and histopathology following Bazot's criteria	USL (10), RVS (11), vagina (11)

Only the first author of each study is given. All studies were prospective and included women with clinical suspicion of deep infiltrating endometriosis (DIE). In all studies, the index test was transvaginal ultrasound (TVS). *Findings for each uterosacral ligament (USL) given separately. †Bazot's criteria are those described in reference 42. RVS, rectovaginal septum; SVG, sonovaginography.

as magnetic resonance imaging (MRI) and transvaginal ultrasound (TVS) have been proposed for use in daily clinical practice[4], and, currently, TVS is the first-line technique[4] for the diagnosis of DIE in locations other than the rectosigmoid. As suggested by Exacoustos *et al.*[4], the ultrasonographic diagnosis of DIE has inconsistent results with a wide range of accuracies described between studies, which may reflect variations in the examination technique, quality of ultrasound equipment and experience of the operators. As no systematic review has yet been published in the literature, the purpose of this one was to evaluate the diagnostic accuracy of TVS in the preoperative detection of endometriosis in the USL, RVS, vagina and bladder in patients with clinical suspicion of DIE, using surgical data as a reference standard.

METHODS

Protocol and registration

We performed this systematic review and meta-analysis according to the PRISMA statement (http://www.prisma-statement.org/). All methods for inclusion/exclusion criteria, data extraction and quality assessment were specified in advance. The protocol was not registered.

Data sources and searches

Studies published between 1989 and December 2014 were screened by one author (S.G.) using two electronic databases (PubMed/MEDLINE and EMBASE) to identify potentially eligible studies. We did not use methodological filters in database searches to avoid possible omission of relevant studies, according to recommendations of Leeflang *et al.*[5]. The search terms included and captured the concepts of 'endometriosis', 'transvaginal', 'ultrasound', 'sonography', 'infiltrating' and 'deep'. There were no language restrictions in the search.

Study selection and data collection

One author (S.G.) screened the titles and abstracts identified by the searches to exclude obviously irrelevant articles, i.e. those not strictly related to the topic under review. Full-text articles were obtained to identify potentially eligible studies, and three authors (S.G., S.A. and J.L.A.) independently applied the following inclusion criteria: (1) prospective or retrospective cohort study with ≥ 50 patients; (2) participants aged over 18 years with clinical suspicion of DIE based on clinical complaints and/or physical examination; (3) presurgical detection of DIE; (4) TVS as the index test; (5) surgical assessment of the presence of endometrial tissue in the USL, RVS, vagina and bladder as the reference standard; (6) presence of results sufficient to construct a 2×2 table of diagnostic performance as minimum data requirement.

To avoid inclusion of duplicate cohorts in the meta-analyses, in the case of two studies from the same authors, the period of each study was examined; if dates overlapped we chose the latest study according to the publication date, considering that patients from the first study were also included in the latest one. We excluded studies that focused only on the diagnosis of DIE affecting the rectosigmoid and bowel.

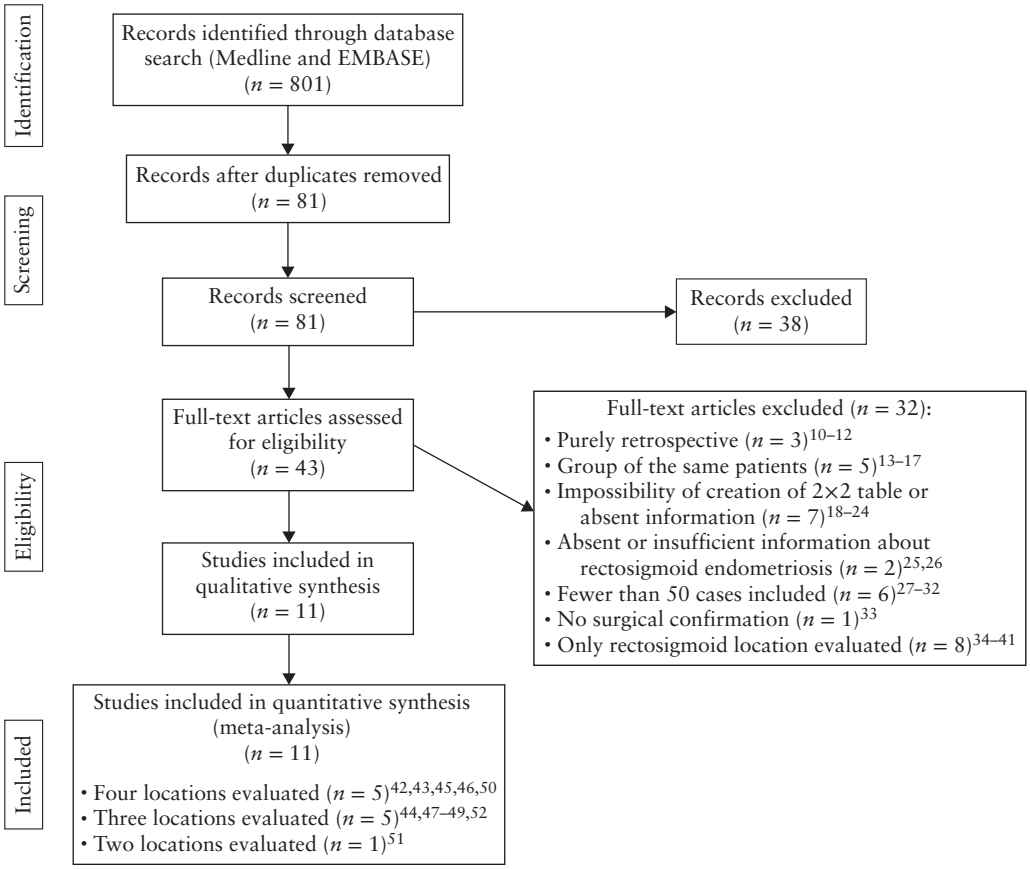

Figure 1 Flowchart showing literature identification and selection.

PICOS (Patients, Intervention, Comparator, Outcomes, Study design) criteria used for inclusion and exclusion of studies are shown in Table 1. Diagnostic accuracy results and additional useful information on patients and procedures were retrieved from the selected primary studies independently by the same authors (S.G., S.A. and J.L.A.). Disagreements arising during the process of study selection and data collection were resolved by consensus among them.

Risk of bias in individual studies

Quality assessment was conducted, adapting the tool provided by the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2)[6]. The QUADAS-2 format includes four domains: (1) patient selection, (2) index test, (3) reference standard, and (4) flow and timing. For each domain, the risk of bias and concerns about applicability (the latter not applying to the domain of flow and timing) were analyzed and rated as low, high or unclear risk. The results of quality assessment were used for descriptive purposes to provide an evaluation of the overall quality of the included studies and to investigate potential sources of heterogeneity.

Three authors (S.G., S.A. and J.L.A.) evaluated independently the methodological quality, using a standard form with quality assessment criteria and a flow diagram; they resolved disagreements by discussion.

Statistical analysis

We extracted or derived information on diagnostic performance of TVS. A random-effects model was used to determine overall pooled sensitivity, specificity, positive likelihood ratio (LR+) and negative likelihood ratio (LR−). Positive and negative likelihood ratios (LRs) were used to characterize the clinical utility of a test and to estimate the post-test probability of disease. An LR of 0.2–5.0 provides weak evidence for either ruling out or confirming the disease. An LR of 5.0–10.0 and 0.1–0.2 provides moderate evidence to either confirm or rule out the disease. An LR > 10 or < 0.1 provides strong evidence to either confirm or rule out the disease[7]. Using the mean prevalence of DIE (pretest probability) in each subset, depending upon the method and LRs, post-test probabilities were calculated and plotted on Fagan nomograms.

We assessed the presence of heterogeneity for sensitivity and specificity using the Cochran's Q test and the I^2 index[8]. A P-value < 0.1 indicates heterogeneity. The I^2 index describes the percentage of total variation across studies that is due to heterogeneity rather than chance. According to Higgins *et al.*[8], I^2 values of 25%, 50% and 75% would be considered to indicate low, moderate and high heterogeneity, respectively[8]. Forest plots of sensitivity and specificity of all the included studies were produced.

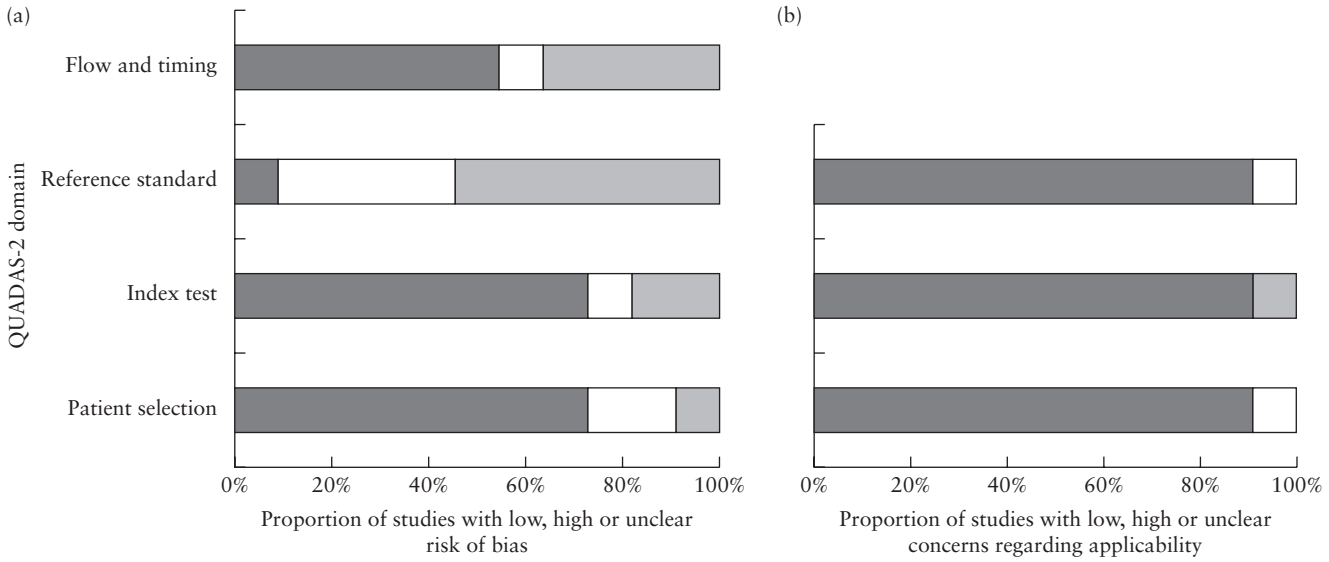

Figure 2 Quality evaluation of all 11 studies included in the meta-analysis, according to QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) criteria[6], with respect to risk of bias (a) and concerns regarding applicability (b). ■, low; □, high; ▩, unclear.

Summary receiver–operating characteristics (sROC) curves were plotted to illustrate the relationship between sensitivity and specificity. We did not discriminate between non-enhanced TVS (plain TVS) and enhanced TVS (TVS with some type of enhancing technique such as gel vaginosonography) due to the small number of studies that used enhanced TVS, preventing meaningful comparisons being drawn.

If heterogeneity existed, meta-regression was used to assess covariates that could explain it. The covariates analyzed were sample size, prevalence, study design (prospective/retrospective), median patient age and number of observers (single/multiple), except if all studies were prospective or the series was always consecutive. This depended on the studies included for the analysis of each pelvic location. Publication bias was assessed by a regression of diagnostic log odds ratio against $1/\sqrt{}$(effective sample size), weighted by effective sample size, with a $P < 0.10$ for the slope coefficient indicating significant asymmetry[9]. A funnel plot was created. All analyses were performed using MIDAS (Meta-analytical Integration of Diagnostic Accuracy Studies) and METANDI commands in STATA version 12.0 for Windows (Stata Corporation, College Station, TX, USA). A P-value < 0.05 was considered as statistically significant.

RESULTS

Search results

The electronic search provided a total of 801 citations but after removal of 720 duplicate records, 81 citations were left. Of these, 38 were excluded because it was clear from the title or abstract that they were not relevant to the review. We examined the full text of the remaining 43 articles. Finally, 32 studies[10–41] were discarded because they did not meet the inclusion criteria or focused on the diagnosis of DIE with only rectosigmoid/bowel involvement. The remaining 11 studies published between August 2004 and December 2014 were included in the review and meta-analysis[42–52]. No additional relevant studies were found from references cited in the papers included in the review. A flowchart summarizing literature identification and selection is given in Figure 1.

Characteristics of included studies

For the detection of USL endometriosis, a total of 1482 patients were included in the final analyses. The studies of Exacoustos *et al.*[50] and Vimercati *et al.*[46] reported separately the findings in each USL. Among these women, DIE was detected in 802 USLs. Mean prevalence was 54%, ranging from 5%[52] to 90%[44]. Mean prevalence was considered as the pretest probability (Table 1). For detection of RVS endometriosis, a total of 1482 patients were included in the final analyses. Among these women, 349 had DIE affecting the RVS. Mean prevalence was 24%, ranging from 6%[42] to 67%[47]. For the detection of vaginal endometriosis, a total of 965 patients were included in the final analyses. Among these women, 160 had DIE affecting the vagina. Mean prevalence was 17%, ranging from 4%[46] to 39%[43]. For detection of bladder endometriosis, a total of 1248 patients were included in the final analyses. Among these women, 64 had DIE affecting the bladder. Mean prevalence was 5%, ranging from 3%[45] to 10%[51].

Methodological quality of included studies

A graphical display of the evaluation of the risk of bias and concerns regarding applicability of the selected studies is shown in Figure 2. Regarding risk of bias

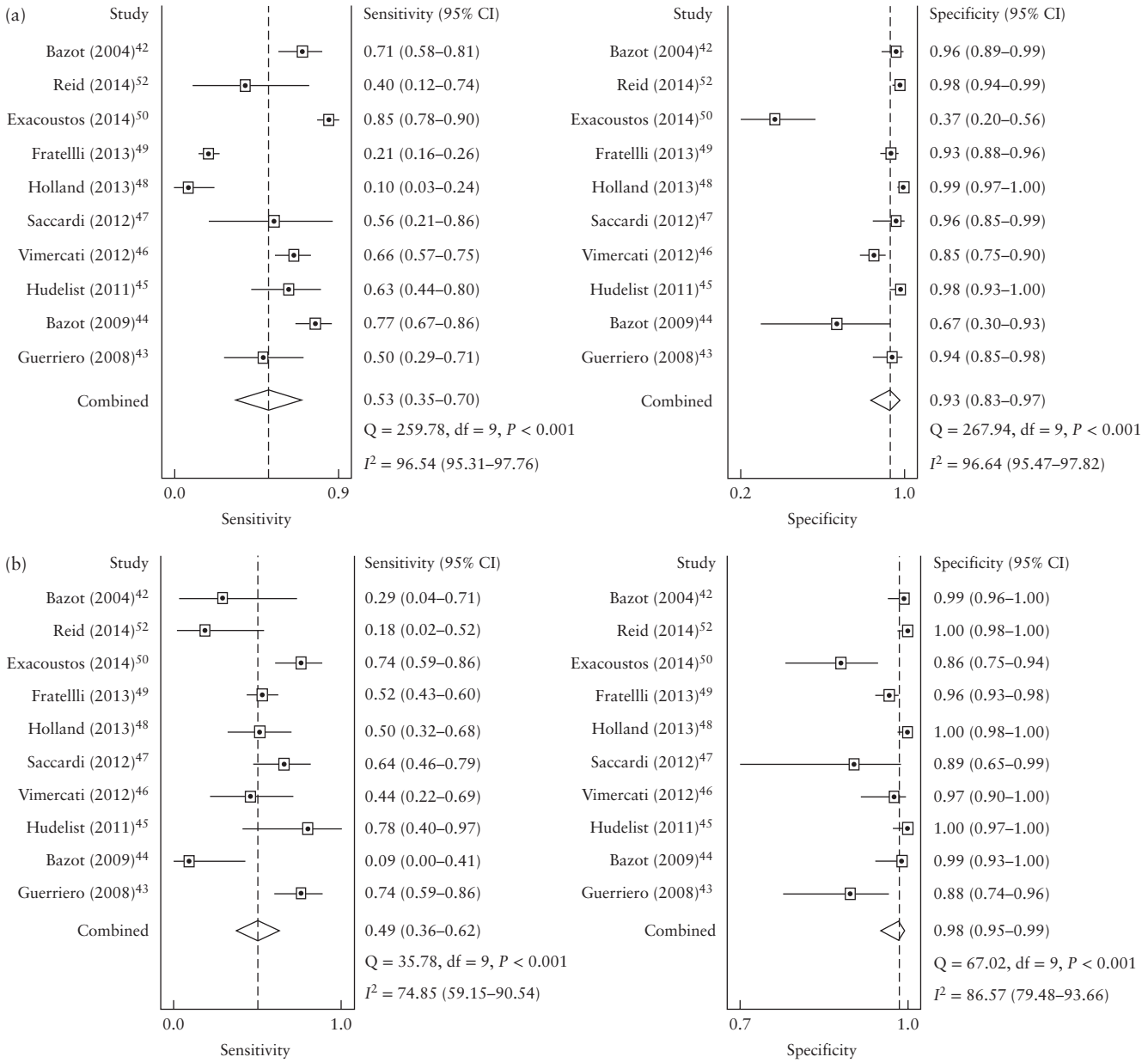

Figure 3 Forest plots of studies evaluated for detection of deep infiltrating endometriosis involving uterosacral ligaments (a) and rectovaginal septum (b), as well as vagina (c) and bladder (d) (next page), using transvaginal ultrasound. Summary sensitivity and specificity as well as heterogeneity statistics (Cochran's Q and I^2) are shown.

and the domain patient selection, three studies did not report explicitly or were not clear regarding patient inclusion criteria[47,48,52]. Concerning the domain index test, eight of the 11 studies described adequately how index test was conducted and interpreted[42–45,48,49,51,52]. Concerning flow and timing domain, the time elapsed between the index test and reference standard was unclear in four studies[44,45,47,51] and the risk of bias was high in one[52]. Concerning the domain reference standard, all studies were likely to classify the target condition correctly by the reference standard. However, in most it was unclear if reference standard results were interpreted without knowledge of the results of the index test and, in some studies, laparoscopic findings, and not histological data alone, were also considered as reference standard.

Regarding applicability, for the domain patient selection, all but one study[44] were deemed to include patients that matched the review question. For the domain index test, most studies were considered as having low concerns for applicability since the index test was described well enough for study replication, as was the reference standard domain.

Diagnostic performance of TVS for detection of DIE involving uterosacral ligaments

Overall, pooled sensitivity, specificity, LR+ and LR− of TVS in detecting DIE in the USL were 53% (95%CI, 35–70%), 93% (95%CI, 83–97%), 7.8 (95%CI, 3.7–16.4) and 0.51 (95%CI, 0.36–0.71), respectively. Heterogeneity was significant for sensitivity (I^2, 96.5%;

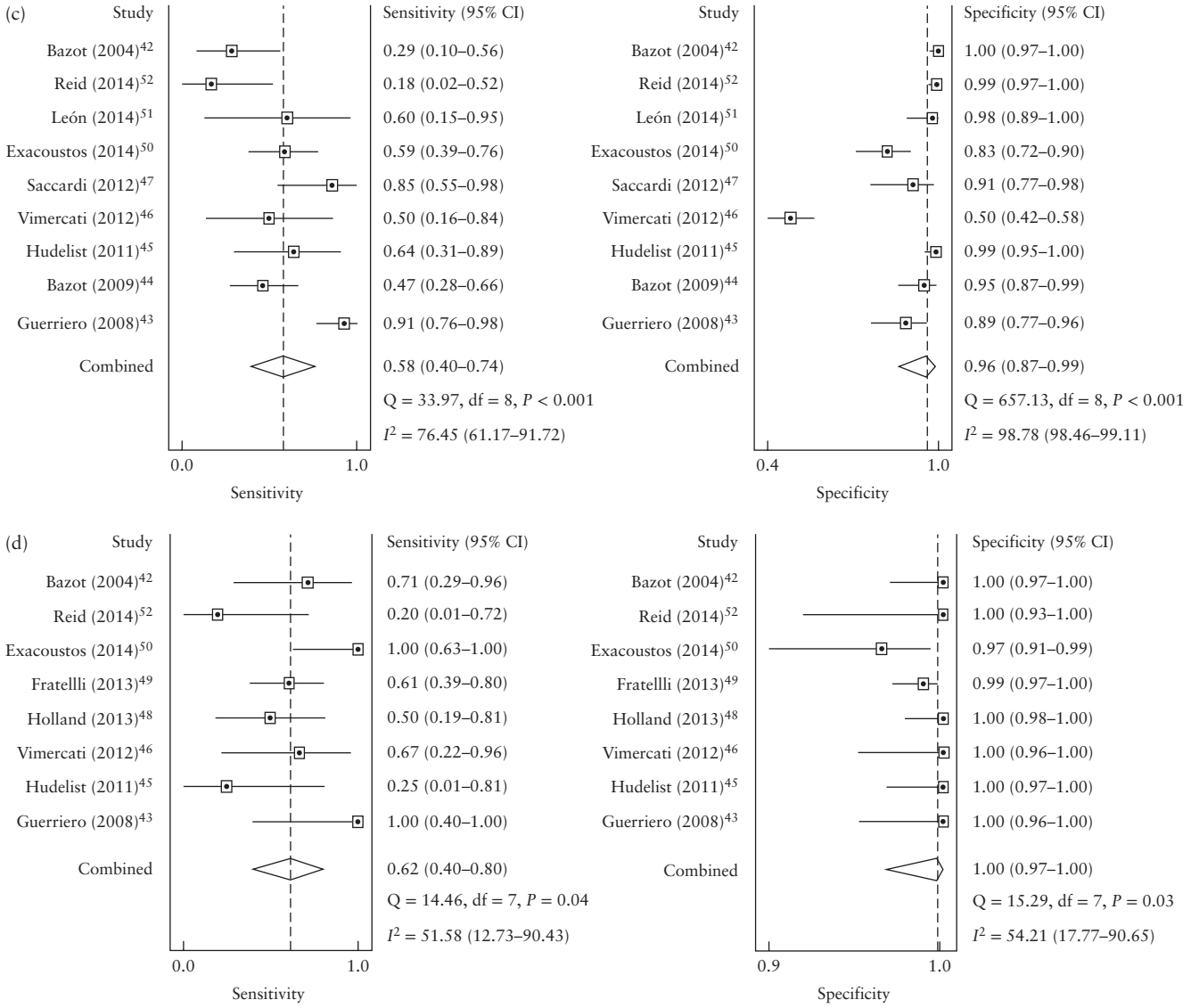

Figure 3 *Continued.*

Cochran Q, 259.8; $P < 0.001$) and specificity (I^2, 96.6%; Cochran Q, 267.9; $P < 0.001$) (Figure 3). sROC curves are shown in Figure 4. Fagan nomograms show that a positive test increases significantly the pretest probability of DIE involving the USL, from 54% to 90%, while a negative test decreases significantly the pretest probability, from 54% to 37% (Figure 5). Meta-regression showed that more than one observer during the TVS examination ($P < 0.001$) explained the heterogeneity in sensitivity (Figure 6), and prevalence ($P < 0.001$) explained the heterogeneity observed in specificity (Figure 6).

Diagnostic performance of TVS for detection of DIE involving rectovaginal septum

Overall, pooled sensitivity, specificity, LR+ and LR− of TVS detecting DIE in the RVS was 49% (95%CI, 36–62%), 98% (95%CI, 95–99%), 26.9 (95%CI, 10.2–71.3) and 0.52 (95%CI, 0.40–0.67), respectively. Heterogeneity was significant for sensitivity (I^2, 74.9%; Cochran Q, 35.8; $P < 0.001$) and specificity (I^2, 86.6%; Cochran Q, 67.0; $P < 0.001$) (Figure 3). sROC curves are shown in Figure 4. Fagan nomograms show that a positive test increases significantly the pretest probability of DIE involving the RVS, from 24% to 89%, while a negative test decreases significantly the pretest probability, from 24% to 14% (Figure 5). Meta-regression showed that prevalence ($P < 0.01$) explained the heterogeneity in both sensitivity and specificity (Figure 6).

Diagnostic performance of TVS for detection of DIE involving the vagina

Overall, pooled sensitivity, specificity, LR+ and LR− of TVS in detecting DIE in the vagina was 58% (95%CI, 40–74%), 96% (95%CI, 87–99%), 15.3 (95%CI, 4.6–51.3) and 0.44 (95%CI, 0.29–0.66), respectively. Heterogeneity was significant for sensitivity (I^2, 76.5%; Cochran Q, 34.0; $P < 0.001$) and specificity (I^2, 98.8%; Cochran Q, 657.1; $P < 0.001$) (Figure 3). sROC curves

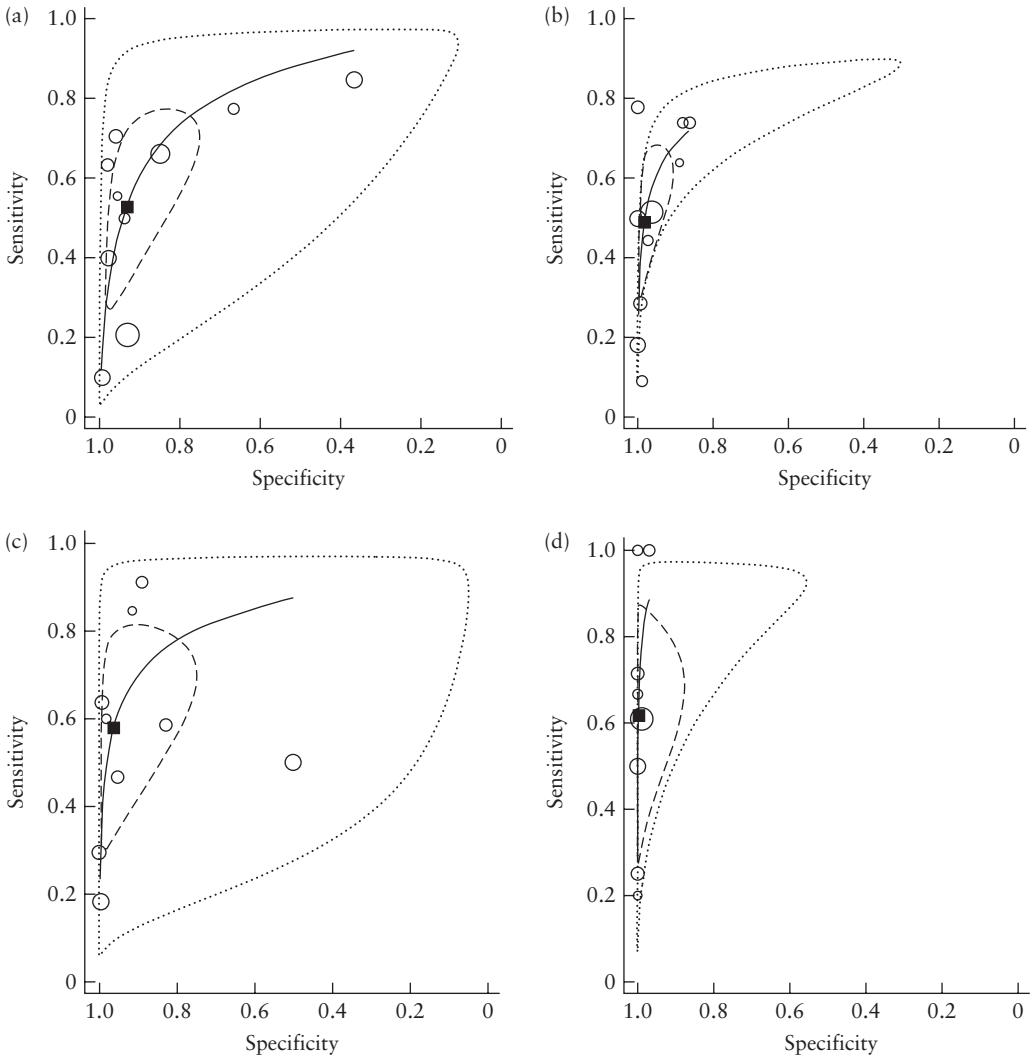

Figure 4 Summary receiver–operating characteristics (sROC) curves (——) for detection of deep infiltrating endometriosis involving the uterosacral ligaments (a), rectovaginal septum (b), vagina (c) and bladder (d), using transvaginal ultrasound. ○, Study estimate; ■, summary point; – – –, 95% confidence region; ....., 95% prediction region.

are shown in Figure 4. Fagan nomograms show that a positive test increases significantly the pretest probability of DIE involving the vagina, from 17% to 76%, while a negative test decreases significantly the pretest probability, from 17% to 8% (Figure 5). Meta-regression showed that more than one observer at the TVS examination ($P < 0.001$) explained the heterogeneity in sensitivity and specificity (Figure 6) and prevalence ($P < 0.001$) explained the heterogeneity in sensitivity (Figure 6).

Diagnostic performance of TVS for detection of DIE involving the bladder

Overall, pooled sensitivity, specificity, LR+ and LR– of TVS for detecting DIE in the bladder was 62% (95%CI, 40–80%), 100% (95%CI, 97–100%), 208.4 (95%CI, 21.0–2066.0) and 0.38 (95%CI, 0.22–0.66), respectively. Moderate heterogeneity was found for sensitivity (I^2, 51.6%; Cochran Q, 14.5; $P = 0.04$) and specificity (I^2, 54.2%; Cochran Q, 15.3; $P = 0.03$) (Figure 3). sROC curves are shown in Figure 4. Fagan nomograms show that a positive test increases significantly the pretest probability of DIE involving the bladder, from 5% to 92%, while a negative test decreases significantly the pretest probability, from 5% to 2% (Figure 5). Meta-regression showed that more than one observer ($P < 0.01$) and consecutive series ($P < 0.01$) explained the heterogeneity observed in specificity (Figure 6).

No publication bias for all locations considered in the review was present (Figure 7).

DISCUSSION

The ultrasonographic findings of endometriosis involving the USL, RVS, vagina and bladder are completely different from those of rectosigmoid endometriosis, characterized by replacement of normal muscularis propria of the rectosigmoid by a nodule of abnormal tissue[42–52]. Lesions in the USL are characterized by nodules with regular or irregular margins, and often hyperechoic points, or a linear hypoechoic thickening with regular or irregular margins. Nodules in the RVS are described as lesions below a

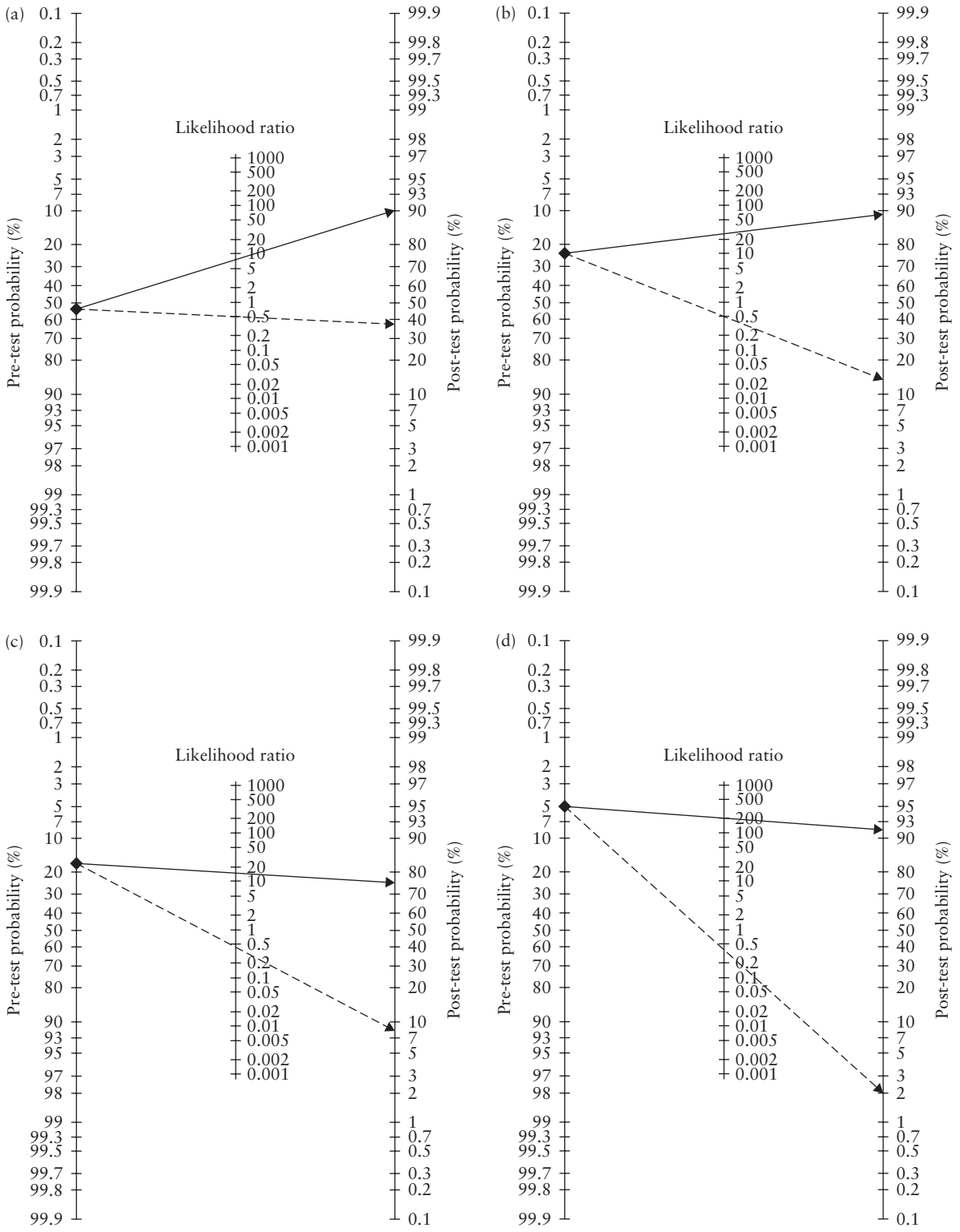

Figure 5 Fagan nomograms for detection of deep infiltrating endometriosis involving the uterosacral ligaments (a), rectovaginal septum (b), vagina (c) and bladder (d), using transvaginal ultrasound. Pretest probability (◆) and effect of a positive test result (⟶) and a negative test result (– – ▸) are indicated.

horizontal plane that passes along the lower margin of the posterior lip of the cervix, under the peritoneum[42]. Lesions in the vagina should be suspected when the posterior vaginal fornix is thickened, with or without surrounding cystic anechoic areas[42]. Endometriosis of the bladder is characterized by the presence of hypoechoic elongated or spherical lesions involving the posterior bladder wall, more frequently in the midline[42], at the level of the dome or base of the bladder.

The results of the present meta-analysis suggest that TVS is a fair imaging method for diagnosis of endometriosis involving the USL, RVS, vagina and bladder with

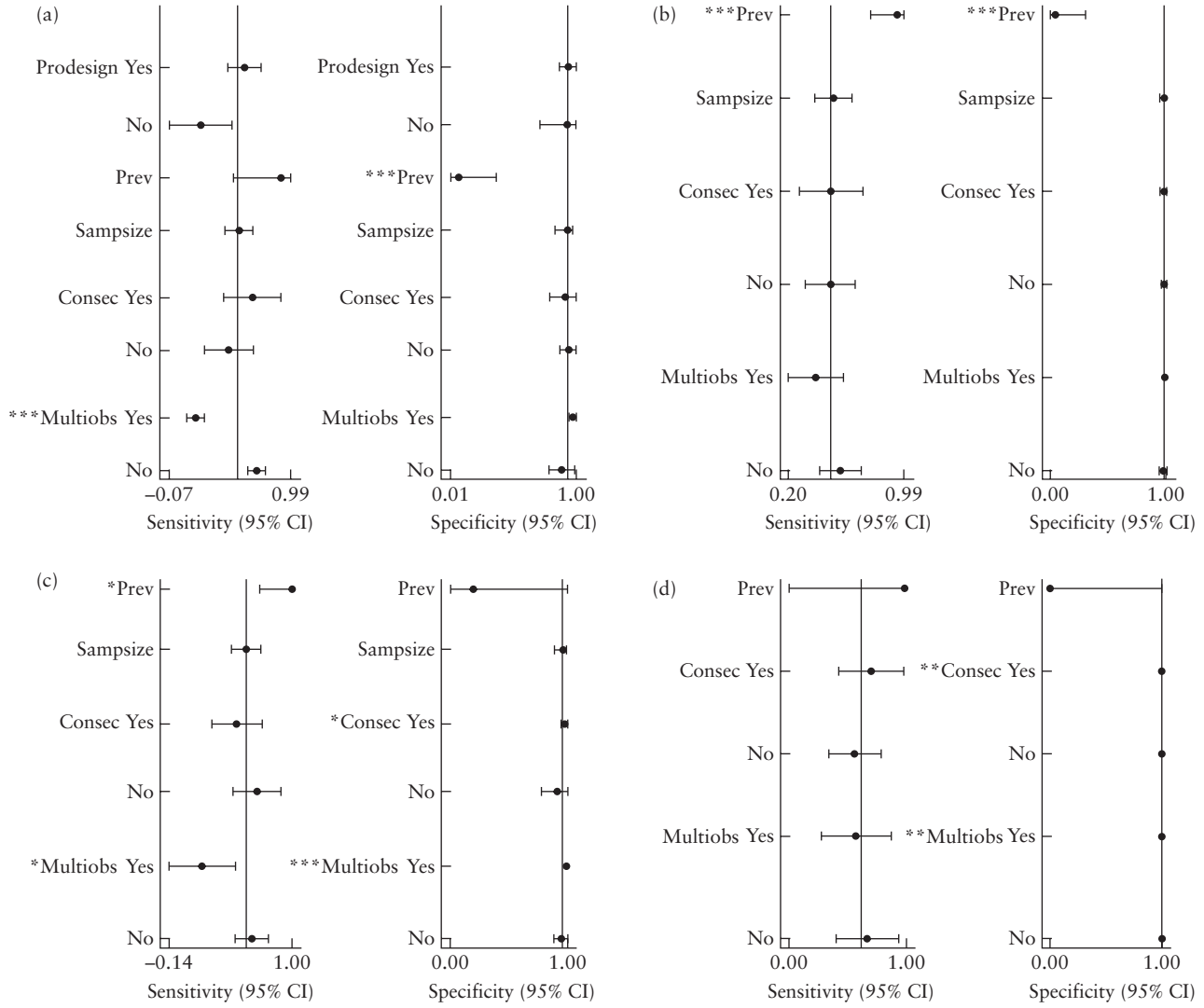

Figure 6 Meta-regression plot for univariate analysis. Prevalence (Prev) and multiobservers (Multiobs) are statistically significant covariates that explain heterogeneity in sensitivity or specificity for uterosacral ligaments (a). Prevalence is a significant covariate that explains heterogeneity in sensitivity and specificity for rectovaginal septum (b). Prevalence, multiobservers and consecutive series (Consec) are statistically significant covariates that explain heterogeneity in sensitivity or specificity for vagina (c). Multiobservers and consecutive series are covariates that explain heterogeneity in specificity for bladder (d). $*P < 0.05$, $**P < 0.01$, $***P < 0.001$. Prodesign, prospective study design; Sampsize, sample size.

respective sensitivities and specificities of 53% and 93%, 49% and 98%, 58% and 96%, and 62% and 100%. From a clinical perspective, TVS seems a useful first-line method for diagnosis. From a pretest probability for USL endometriosis of 54%, this probability increased to 90% when suspicion of DIE was present at TVS examination, and fell to 37% when ultrasonographic findings in the USL were absent. For RVS endometriosis, the pretest probability was 24%, which increased to 89% when suspicion of DIE was present at TVS examination and fell to 14% when no ultrasonographic findings in the RVS were found. The pretest probability of vaginal endometriosis was 17%, which increased to 76% when suspicion of DIE was present after TVS examination and fell to 8% when ultrasonographic findings in the vagina were absent. For bladder endometriosis, the pretest probability was 5%, which increased to 92% when suspicion of DIE was present after TVS examination and fell to 2% when no ultrasonographic findings in the bladder were found. The high specificity of TVS would make it a useful test for confirming DIE. In particular, an ultrasonographic diagnosis of DIE could be used to reduce the need for diagnostic laparoscopy due to its reliability and because laparoscopy, in the case of advanced extension of DIE, is a difficult procedure to perform with a high rate of complications[4]. Medical treatment seems to be the preferred approach for these cases of DIE, and TVS could be recommended in patients with well-controlled pain and absence of evidence of intestinal stenosis or ureteral involvement. TVS could also be used for the follow-up of patients with ultrasonographic diagnosis of DIE but with good remission of symptoms during medical treatment, or for those seeking to become pregnant.

Based on the results of our meta-analysis, in cases with negative findings, and depending on the symptoms,

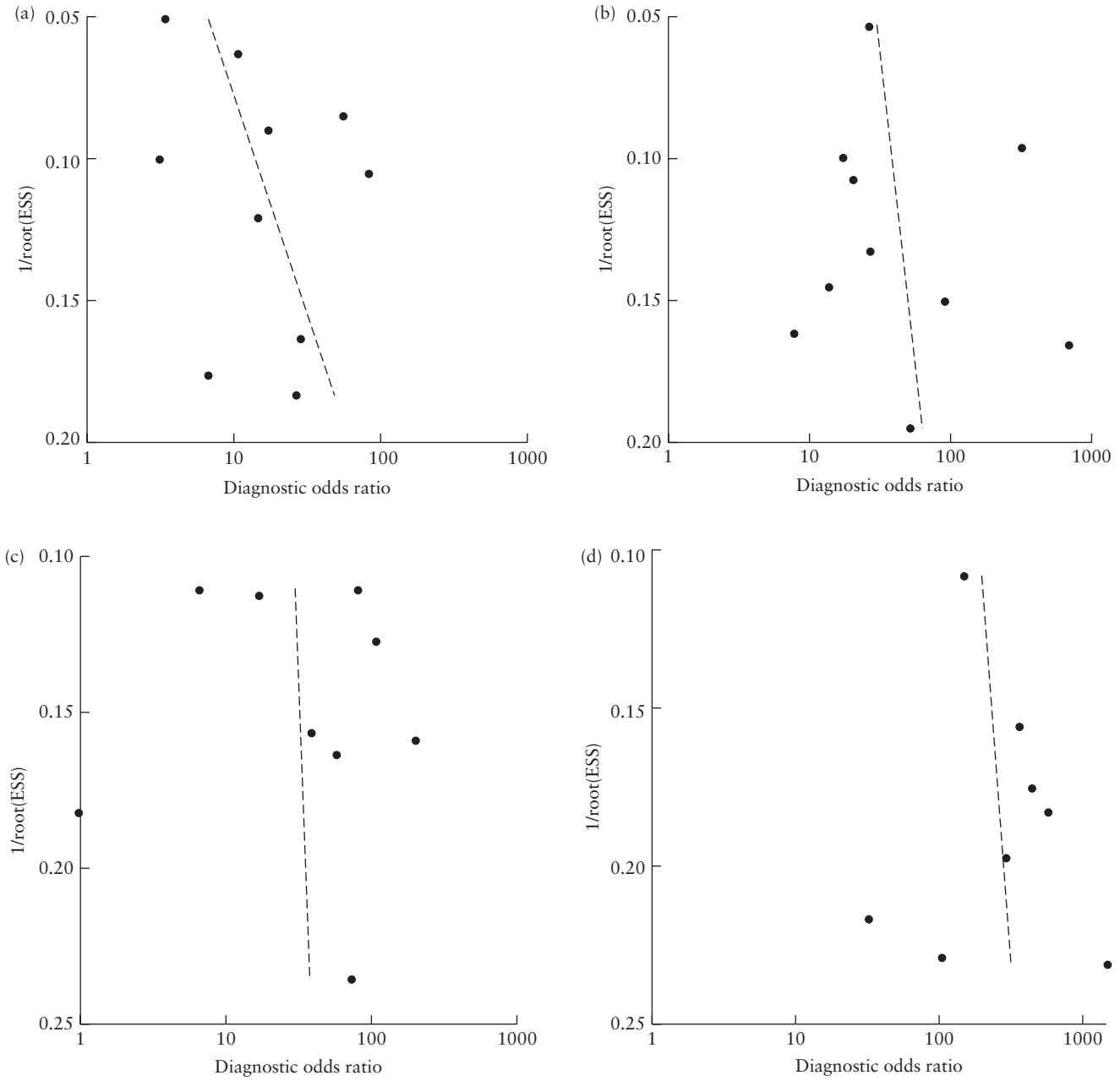

Figure 7 Deek's funnel plots showing that no publication bias exists for studies reporting on detection of deep infiltrating endometriosis in the uterosacral ligaments (a), rectovaginal septum (b), vagina (c) and bladder (d). Individual studies (●) and regression lines (- – – -) are shown. Deeks' funnel plot asymmetry test *P*-values = (a) 0.17, (b) 0.60, (c) 0.91 and (d) 0.65. ESS, effective sample size.

further investigation using MRI[17,27,29,32,34,44,46,47] or three-dimensional sonography[41] could be recommended.

Although it failed to investigate heterogeneity, a recent meta-analysis evaluated the diagnostic imaging of DIE by MRI[53]. In comparison with TVS, higher pooled sensitivities for detection of DIE in the USL, RVS and vagina (85%, 77% and 82%, respectively) were reported. In contrast, lower pooled specificities for detection of DIE (80% for USL, 95% for RVS and 90% for vagina) were described compared to that of TVS. Regarding detection of DIE in the bladder, similar sensitivities and specificities are reported for both techniques. As demonstrated previously for the rectosigmoid[17], these two imaging techniques may be used in a complementary approach due to the different specificity and sensitivity found in patients with a negative result on TVS examination but high clinical suspicion of DIE.

Among the weaknesses of the review, it must be mentioned that we did not search all databases (MEDLINE and EMBASE only), and articles were not searched independently by two different authors. For USL, vagina and bladder, a source of heterogeneity in three studies[48,49,52] was the presence of more than one observer. A recent study[54] suggests the importance of this factor to be decreased, showing that, at least in the same population of well-trained staff, reproducibility is good. A source of heterogeneity in cases of USL, RVS and vaginal endometriosis is their prevalence. In fact, prevalence of

USL endometriosis ranged from 5%[52] to 90%[44] in the included studies while prevalence of RVS and vaginal endometriosis ranged from 6%[42] to 67%[47] and 4%[46] to 39%[43], respectively. Possible explanations for the heterogeneity in prevalence could be different methodology used during surgery and different surgeons involved in each study[45,48,51], but also the modality of determination of the endometriotic lesion. In fact, although the reference standard was surgery in all included studies, in some cases complete obliteration of the cul-de-sac and absence of appropriate consensus for radical surgery reduces the possibility of a histopathological diagnosis, and in five studies[42–44,49,52] Bazot's criteria of diagnosis was used. In these studies DIE was diagnosed if at least one of the following characteristics were present: (1) presence of endometrial tissue; (2) direct visualization of the lesion attributable to DIE; or (3) complete obliteration of the pouch of Douglas secondary to endometriosis, with another location of DIE. Although application of this approach can explain partially the difference in prevalence described in the different studies, the prevalence of DIE in the USL reported in the two studies that used Bazot's criteria were 5%[52] and 90%[44], respectively. In contrast, for RVS and vaginal endometriosis of which prevalence ranged from 6%[42] to 67%[47] and from 4%[46] to 39%[43], respectively, the studies that used Bazot's criteria had the lowest prevalence for RVS[42] and the highest[43] for vaginal endometriosis. No matter what the source of different disease prevalence is, its existence has been shown to affect test performance, most likely due to an increased familiarity of examiners with abnormal findings as prevalence increases. Furthermore, the different definitions of some lesions, such as RVS[50], or less detailed descriptions presented in some studies[48,49,51] can interfere with this prevalence. Due to this observed heterogeneity, the need for an international consensus is essential to create future prospective multicenter studies and improve further the methodology.

REFERENCES

1. Koninckx PR, Meuleman C, Demeyere S, Lesaffre E, Cornillie FJ. Suggestive evidence that pelvic endometriosis is a progressive disease, whereas deeply infiltrating endometriosis is associated with pelvic pain. *Fertil Steril* 1991; **55**: 759–765.
2. Matsuzaki S, Canis M, Pouly JL, Rabischong B, Botchorishvili R, Mage G. Relationship between delay of surgical diagnosis and severity of disease in patients with symptomatic deep infiltrating endometriosis. *Fertil Steril* 2006; **86**: 1314–1316.
3. Hudelist G, Fritzer N, Thomas A, Niehues C, Oppelt P, Haas D, Tammaa A, Salzer H. Diagnostic delay for endometriosis in Austria and Germany: causes and possible consequences. *Hum Reprod* 2012; **27**: 3412–3416.
4. Exacoustos C, Manganaro L, Zupi E. Imaging for the evaluation of endometriosis and adenomyosis. *Best Pract Res Clin Obstet Gynaecol* 2014; **28**: 655–681.
5. Leeflang MMG, Scholten RJPM, Rutjes AWS, Reitsma JB, Bossuyt PMM. Use of methodological search filters to identify diagnostic accuracy studies can lead to the omission of relevant studies. *J Clin Epidemiol* 2006; **59**: 234–240.
6. Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM, QUADAS-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011; **155**: 529–536.
7. EUnetHTA Guideline: *Meta-analysis of Diagnostic Test Accuracy Studies*. European Network for Health Technology Assessment. 2014.
8. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557–560.
9. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. *J Clin Epidemiol* 2005; **58**: 882–893.
10. Balleyguier C, Chapron C, Dubuisson JB, Kinkel K, Fauconnier A, Vieira M, Helenon O, Menu Y. Comparison of magnetic resonance imaging and transvaginal ultrasonography in diagnosing bladder endometriosis. *J Am Assoc Gynecol Laparosc* 2002; **9**: 15–23.
11. Hensen JH, Puylaert JB. Endometriosis of the posterior cul de-sac: clinical presentation and findings at transvaginal ultrasound. *AJR Am J Roentgenol* 2009; **192**: 1618–1624.
12. Koga K, Osuga Y, Yano T, Momoeda M, Yoshino O, Hirota Y, Kugu K, Nishii O, Tsutsumi O, Taketani Y. Characteristic images of deeply infiltrating rectosigmoid endometriosis on transvaginal and transrectal ultrasonography. *Hum Reprod* 2003; **18**: 1328–1333.
13. Bazot M, Malzy P, Cortez A, Roseau G, Amouyal P, Darai E. Accuracy of transvaginal sonography and rectal endoscopic sonography in the diagnosis of deep infiltrating endometriosis. *Ultrasound Obstet Gynecol* 2007; **30**: 994–1001.
14. Hudelist G, Oberwinkler KH, Singer CF, Tuttlies F, Rauter G, Ritter O, Keckstein J. Combination of transvaginal sonography and clinical examination for preoperative diagnosis of pelvic endometriosis. *Hum Reprod* 2009; **24**: 1018–1024.
15. 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.
16. Menada MV, Remorgida V, Abbamonte LH, Fulcheri E, Ragni N, Ferrero S. Transvaginal ultrasonography combined with water-contrast in the rectum in the diagnosis of rectovaginal endometriosis infiltrating the bowel. *Fertil Steril* 2008; **89**: 699–700.
17. 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.
18. Eskenazi B, Warner M, Bonsignore L, Olive D, Samuels S, Vercellini P. Validation study of nonsurgical diagnosis of endometriosis. *Fertil Steril* 2001; **76**: 929–935.
19. Okaro E, Condous G, Khalid A, Timmerman D, Ameye L, Huffel SV, Bourne T. The use of ultrasound-based 'soft markers' for the prediction of pelvic pathology in women with chronic pelvic pain – can we reduce the need for laparoscopy? *BJOG* 2006; **113**: 251–256.
20. Savelli L, Manuzzi L, Pollastri P, Mabrouk M, Seracchioli R, Venturoli S. Diagnostic accuracy and potential limitations of transvaginal sonography for bladder endometriosis. *Ultrasound Obstet Gynecol* 2009; **34**: 595–600.
21. Valenzano Menada M, Remorgida V, Abbamonte LH, Nicoletti A, Ragni N, Ferrero S. Does transvaginal ultrasonography combined with water-contrast in the rectum aid in the diagnosis of rectovaginal endometriosis infiltrating the bowel? *Hum Reprod* 2008; **23**: 1069–1075.
22. Yazbek J, Helmy S, Ben-Nagi J, Holland T, Sawyer E, Jurkovic D. Value of preoperative ultrasound examination in the selection of women with adnexal masses for laparoscopic surgery. *Ultrasound Obstet Gynecol* 2007; **30**: 883–888.
23. Piessens S, Healey M, Maher P, Tsaltas J, Rombauts L. Can anyone screen for deep infiltrating endometriosis with transvaginal ultrasound? *Aust N Z J Obstet Gynaecol* 2014; **54**: 462–468.
24. Mangler M, Medrano N, Bartley J, Mechsner S, Speiser D, Schneider A, Köhler C. Value of diagnostic procedures in rectovaginal endometriosis. *Aust N Z J Obstet Gynaecol* 2013; **53**: 389–394.
25. Holland TK, Yazbek J, Cutner A, Saridogan E, Hoo WL, Jurkovic D. Value of transvaginal ultrasound in assessing the severity of pelvic endometriosis. *Ultrasound Obstet Gynecol* 2010; **36**: 241–248.
26. Marasinghe JP, Senanayake H, Saravanabhava N, Arambepola C, Condous G, Greenwood P. History, pelvic examination findings and mobility of ovaries as a sonographic marker to detect pelvic adhesions with fixed ovaries. *J Obstet Gynaecol Res* 2014; **40**: 785–790.
27. Grasso RF, DiGiacomo 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* 2009; **35**: 716–725.
28. Bazot M, Detchev R, Cortez A, Amouyal P, Uzan S, Darai E. Transvaginal sonography and rectal endoscopic sonography for the assessment of pelvic endometriosis: a preliminary comparison. *Hum Reprod* 2003; **18**: 1686–1692.
29. Carbognin G, Girardi V, Pinali L, Raffaelli R, Bergamini V, Pozzi Mucelli R. Assessment of pelvic endometriosis: correlation of US and MRI with laparoscopic findings. *Radiol Med* 2006; **111**: 687–701.
30. Fraser MA, Agarwal S, Chen I, Singh SS. Routine vs. expert-guided transvaginal ultrasound in the diagnosis of endometriosis: A retrospective review. *Abdom Imaging* 2015; **40**: 587–594.
31. Holland TK, Hoo WL, Mavrelos D, Saridogan E, Cutner A, Jurkovic D. Reproducibility of assessment of severity of pelvic endometriosis using transvaginal ultrasound. *Ultrasound Obstet Gynecol* 2013; **41**: 210–215.
32. Gauche Cazalis C, Koskas M, Martin B, Palazzo L, Madelenat P, Yazbeck C. [Preoperative imaging of deeply infiltrating endometriosis in: Transvaginal sonography, rectal endoscopic sonography and magnetic resonance imaging]. [Article in French] *Gynecol Obstet Fertil* 2012; **40**: 634–641.
33. Tammaa A, Fritzer N, Strunk G, Krell A, Salzer H, Hudelist G. Learning curve for the detection of pouch of Douglas obliteration and deep infiltrating endometriosis of the rectum. *Hum Reprod* 2014; **29**: 1199–1204.
34. 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.
35. Valenzano Menada M, Remorgida V, Abbamonte LH, Nicoletti A, Ragni N, Ferrero S. Does transvaginal ultrasonography combined with water-contrast in the rectum aid in the diagnosis of rectovaginal endometriosis infiltrating the bowel? *Hum Reprod* 2008; **23**: 1069–1075.
36. 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.
37. Hudelist G, Tuttlies F, Rauter G, Pucher S, Keckstein J. Can transvaginal sonography predict infiltration depth in patients with deep infiltrating endometriosis of the rectum? *Hum Reprod* 2009; **24**: 1012–1017.
38. Goncalves MO, Podgaec S, Dias JA Jr, Gonzalez M, Abrao MS. Transvaginal ultrasonography with bowel preparation is able to predict the number of lesions and rectosigmoid layers affected in cases of deep endometriosis, defining surgical strategy. *Hum Reprod* 2010; **25**: 665–671.
39. Ferrero S, Biscaldi E, Morotti M, Venturini PL, Remorgida V, Rollandi GA, Valenzano Menada M. Multidetector computerized tomography enteroclysis vs. rectal water contrast transvaginal ultrasonography in determining the presence and extent of bowel endometriosis. *Ultrasound Obstet Gynecol* 2011; **37**: 603–613.
40. Savelli L, Manuzzi L, Coe M, Mabrouk M, Di Donato N, Venturoli S, Seracchioli R. Comparison of transvaginal sonography and double-contrast barium enema for diagnosing deep infiltrating endometriosis of the posterior compartment. *Ultrasound Obstet Gynecol* 2011; **38**: 466–471.
41. Guerriero S, Saba L, Ajossa S, Peddes C, Angiolucci M, Perniciano M, Melis GB, Alcázar JL. Three-dimensional ultrasonography in the diagnosis of deep endometriosis *Hum Reprod* 2014; **29**: 1189–1198.
42. Bazot M, Thomassin I, Hourani R, Cortez A, Darai E. Diagnostic accuracy of transvaginal sonography for deep pelvic endometriosis. *Ultrasound Obstet Gynecol* 2004; **24**: 180–185.
43. 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.
44. Bazot M, Lafont C, Rouzier R, Roseau G, Thomassin-Naggara I, Darai E. Diagnostic accuracy of physical examination, transvaginal sonography, rectal endoscopic sonography, and magnetic resonance imaging to diagnose deep infiltrating endometriosis. *Fertil Steril* 2009; **92**: 1825–1833.
45. 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* 2011; **37**: 480–487.
46. Vimercati A, Achilarre MT, Scardapane A, Lorusso F, Ceci O, Mangiatordi G, Angelelli G, Van Herendael B, Selvaggi L, Bettocchi S. Accuracy of transvaginal sonography and contrast-enhanced magnetic resonance-colonography for the presurgical staging of deep infiltrating endometriosis. *Ultrasound Obstet Gynecol* 2012; **40**: 592–603.
47. 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.
48. Holland TK, Cutner A, Saridogan E, Mavrelos D, Pateman K, Jurkovic D. Ultrasound mapping of pelvic endometriosis: does the location and number of lesions affect the diagnostic accuracy? A multicentre diagnostic accuracy study. *BMC Womens Health* 2013; **13**: 43.
49. 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.
50. Exacoustos C, Malzoni M, Di Giovanni A, Lazzeri L, Tosti C, Petraglia F, Zupi E. Ultrasound mapping system for the surgical management of deep infiltrating endometriosis. *Fertil Steril* 2014; **102**: 143–150.
51. 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.
52. Reid S, Lu C, Hardy N, Casikar I, Reid G, Cario G, Chou D, Almashat D, Condous G. Office gel sonovaginography for the prediction of posterior deep infiltrating endometriosis: a multicenter prospective observational study. *Ultrasound Obstet Gynecol* 2014; **44**: 710–718.
53. Medeiros LR, Rosa MI, Silva BR, Reis ME, Simon CS, Dondossola ER, da Cunha Filho JS. Accuracy of magnetic resonance in deeply infiltrating endometriosis: a systematic review and meta-analysis. *Arch Gynecol Obstet* 2015; **291**: 611–621.
54. Tammaa A, Fritzer N, Lozano P, Krell A, Salzer H, Salama M, Hudelist G. Interobserver agreement of non-invasive diagnosis of endometriosis by transvaginal sonography (TVS) *Ultrasound Obstet Gynecol* (in press). DOI: 10.1002/uog.14843.

