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Ultrasonographic 'soft' markers for the detection of rectosigmoid endometriosis

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Abstract

Objectives: Due to the reported high sensitivity and specificity of ultrasound in the detection rate of rectosigmoid (RS) endometriosis when performed by an ultrasonographic (US) expert, this test should be considered a gold standard comparable to laparoscopy. No information is available regarding US soft markers in this disease. The aim of this study was to evaluate the use of US soft markers as “first level” examination in the suspicion of RS endometriosis.

Methods: We included in this prospective study **all** patients with clinical suspicion of deep endometriosis submitted to ultrasonographic evaluation in our academic center for ultrasonographic diagnosis of endometriosis at the Academic Department of Obstetrics and Gynecology, University of Cagliari, Policlinico Universitario Duilio Casula, Monserrato, Cagliari, Italy from January 2016 to February 2017. US performed by an expert was considered as gold standard for the presence of RS endometriosis. We evaluate the following soft markers as dependent variables using a logistic regression: presence of US signs of uterine adenomyosis, presence of an endometrioma, adhesions of the ovary to the uterus (“reduced ovarian mobility”), presence of “kissing ovaries” (KO), absence of sliding sign (SLS) for predicting the presence of RS involvement.

Results: Included in the present prospective observational study were 333 patients with clinical suspicion of deep endometriosis. One hundred six patients had an US diagnosis of RS endometriosis by an expert. The only significant variables found in the prediction model were the absence of SLS odd ratio (OR): 13.95 95%CI [7.7-25.3], the presence of “KO” OR: 22.5 95%CI [4.1-124] and the interaction between both variables OR: 0.03 95%CI [0.004-0.28]. According to the interaction of both variables, the RS endometriosis was observed when KO absent/ SLS present in 10% of cases (19/190), KO present / SLS present in 71.4% (5/7), KO absent/ SLS absent in 60.8% (76/125), KO presence / SLS absence in 54.5% (6/11). Thus, when the SLS was negative or KO was present, transvaginal US showed a specificity of 75% 95%CI [69%-80%] and a sensitivity of 82% 95%CI [73%-88%]. The pretest probability of RS endometriosis was 32%, and this

probability increased to 61% when at least one “soft marker” was present and fell to 10% when these ultrasonographic findings were absent.

Conclusions: Findings of absence of the SLS and/or the presence of KO are significant enough to screen patients with clinical suspicion of RS endometriosis to be referred to “second level” ultrasonography with a low rate of false negatives.

Introduction

A dedicated operator with specific knowledge is expected to have high predictive accuracy¹ in diagnosis of rectosigmoid (RS) deep infiltrating endometriosis (DIE). Due to the high sensitivity and specificity reported (higher than 90%)²⁻⁶, the detection rate of RS endometriosis by an ultrasonographic (US) evaluation of an expert has to be considered a gold standard comparable to laparoscopy⁷.

Additional indicators such as the so called “soft markers” has been proposed for the diagnosis of deep endometriosis. Reid et al⁸ observed a strong association between the absence of sliding sign (SLS) and the occlusion of the pouch of Douglas (POD) at laparoscopy with a sensitivity of 85% and a specificity of 96%. Hudelist et al⁹ observed a strong association between this sign and the presence rectosigmoid (RS) endometriosis with similar sensitivity and specificity. Menakya et al¹⁰ criticized this association suggesting that RS endometriosis can occur with or without POD obliteration and viceversa. These authors also stated the sliding sign is simple to demonstrate and does not require advanced sonologic skills while recognizing that the high diagnostic accuracy of US for RS is dependent on the experience of the operator^{10,11}. Other indirect signs of presence of DIE have been suggested by other authors, such as the presence of US signs of uterine adenomyosis¹², the presence of ovarian endometrioma^{13, 14}, adhesions of the ovary to the uterus (“reduced ovarian mobility”)^{15,16} and the presence of “kissing ovaries” (KO)¹⁷.

To our knowledge, there is no information in the literature regarding the use of all these soft markers alone or combined in the diagnosis of RS endometriosis. The aim of this study was to evaluate the use of US soft markers as “first level” examination in the suspicion of RS endometriosis.

Materials and Methods

This prospective study was performed according to the STARD initiative¹⁸. We included all patients with clinical suspicion of deep endometriosis submitted to ultrasonographic evaluation in our academic center for the ultrasonographic diagnosis of endometriosis at Department of Obstetrics and Gynecology, University of Cagliari, Policlinico Universitario Duilio Casula, Monserrato, Cagliari, Italy from January 2016 to February 2017.

Ultrasonography was performed by a single operator (with >20 years of experience in gynecological ultrasound) with the use of high-performance ultrasound equipment (Voluson E8, General Electric, Milwaukee, WI, USA) with a 5–9 MHz frequency transvaginal probe.

All the scans were performed using the four basic sonographic steps suggested by IDEA consensus¹⁹. First the operator examined the uterus and the adnexa. Sonographic signs of adenomyosis were recorded. The presence or absence of ovarian endometriomas was also noted.

The second step was to search for sonographic ‘soft markers’, as fixed ovaries. By applying pressure between the uterus and ovary, one can assess if the ovary is fixed to the uterus medially, to the pelvic side wall laterally or to the USLs (FIGURE 1). Also the presence of KO (defined as both ovaries joined together behind the uterus in the cul-de-sac) was noted (FIGURE 2).

The third step was to assess the status of the POD using the real-time TVS-based ‘sliding sign’. According with the IDEA consensus¹⁹, in order to assess the sliding sign when the uterus is anteverted, gentle pressure is placed against the cervix using the transvaginal probe, to establish whether the anterior rectum glides freely across the posterior aspect of the cervix (retrocervical region) and posterior vaginal wall. If the anterior rectal wall does so, the ‘sliding sign’ is considered positive for this location¹⁹. Demonstrating and describing the real-time ultrasound-based sliding sign in a retroverted uterus is different¹⁹. Gentle pressure is placed against the posterior upper uterine fundus with the transvaginal probe, to establish whether the anterior rectum glides freely

across the posterior upper uterine fundus. If the anterior rectum does so, the sliding sign is considered to be positive for this location.

The fourth step is to search for DIE nodules in the anterior and posterior compartments. The rectosigmoid colon was involved when it revealed an irregular hypoechoic nodule with or without hypo- or, rarely, hyperechoic foci (FIGURE 3). 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 cases ²⁰.

Additionally, we evaluated all the other possible locations of pelvic DIE. The involvement of the vagina was suspected when the posterior vaginal fornix was thickened, with or without cystic anechoic areas around it ²⁰⁻²⁴. 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 ²². 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. 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.

The following ultrasonographic findings was studied for predicting the presence of RS involvement and considered as dependent variables: 1. presence of US signs of uterine adenomyosis; 2. presence of an endometrioma; 3. adhesions of the ovary to the uterus (“reduced ovarian mobility”); 4. presence of “kissing ovaries”; 5. absence of SLS.

Final diagnosis of the US examination performed by an expert was considered as “gold standard” and the dependent variable for logistic regression analysis.

The influence of different sonographic findings was studied by stepwise forward logistic regression (Wald statistic) using the Statistical Package for the Social Sciences for Macintosh, version 6.1.1 (SPSS Inc., Chicago, IL, USA). The model of best fit that adequately described the data was chosen.

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.

Results

Three hundred thirty-three patients were included in the study (mean age \pm SD: 36.7 years \pm 8; age range 16–60 years). One hundred six patients had US diagnosis of RS endometriosis.

In table 1 the different kind of hormonal therapy of the patients are reported. Regarding the symptoms in 80 women (24.4%) a chronic pelvic pain was present; in 11 patients (3.4%) only dyspareunia; 36 patients (11%) only dysmenorrhea; in 37 patients (11%) dyspareunia and dysmenorrhea; in 30 patients (9%) sterility; 61 (18.3 %) women were oligosymptomatic. In the 33% of patients, a previous pelvic surgery was present in the history.

Regarding the ultrasonographic findings (Table 2), an ultrasonographic suspicion of adenomyosis was present in 67 women (20%) and at least one endometrioma was visualized in 79 women (23.7%). In 19 patients (5.7%) more than one endometrioma was present. In 41 patients (12%) one ovary showed a reduced mobility and in 32 (9.6%) both ovaries showed reduced mobility. The KO sign was present in 18 patients (5.4%) while the SLS was absent in 136 women (40.8%). Suspicion of endometriosis of the anterior compartment was present in 15 women (4.5%). Suspicion of endometriosis of the posterior compartment (including uterosacral ligaments, forniceal, rectovaginal septum and RS) was present in 50.8% of women.

The only significant variables for RS endometriosis which could be included in the prediction model were the absence of SLS with an odds ratio (OR) of 13.95 95%CI [7.7-25.3], the presence of KO with an OR of 22.5 95%CI [4.1-124] and the interaction between both variables with OR of 0.03 95%CI [0.004-0.28]. According to the interaction of both variables, RS endometriosis was observed when KO absent/ SLS present in 10% of cases (19/190), KO present / SLS present in 71.4% (5/7), KO absent/ SLS absent in 60.8% (76/125), KO presence / SLS absence in 54.5% (6/11). Thus, when the SLS was negative or KO was present (Table 3), transvaginal US showed a specificity of 75% 95%CI [69%-80%] and a sensitivity of 82% 95%CI [73%-88%] a PPV of 60%

95%CI [52%-69%] and a NPV of 90% 95%CI [85%-94%] . This combination of the soft markers have the higher kappa index indicating a moderate agreement.

The LR + was 3.33 [95% CI 2.61- 4.25] and the LR was 0.24 [95% CI 0.16 - 0.36]. The pretest probability of RS endometriosis was 32%, and this probability increased to 61% when at least one “soft marker” was present and fell to 10% when these ultrasonographic findings were absent.

Discussion

The present study suggests that the presence of at least of the absence of SLS and/or the presence of KO seems to be an efficient system to screen the patients with clinical suspicion of RS endometriosis to be referred to “second level” ultrasonography with a low rate of false negatives.

Some simple ultrasonographic findings, although associated with the presence of DIE have a relatively low diagnostic relevance for RS lesions. For example Exacoustos et al¹³ reported the absence of correlation with the dimension of endometrioma and presence of DIE. The association with endometrioma is demonstrated^{13,14} but our study suggest that this ovarian lesion is not directly correlated with the presence of RS endometriosis.

However, other US findings could be highlighted. In previous studies, some authors have evaluated the role of several findings correlated with the presence of DIE but not directly evaluating the role of these simple soft markers to screen the patient for RS endometriosis. SLS is one of those. Reid et al²⁵ investigate the optimal ultrasonographic screening method for rectal/rectosigmoid deep endometriosis but associating ultrasound SLS with the ultrasound direct visualization. In our study in the contrary we evaluated if some soft marker easy to perform can predict the presence of RS DIE.

The SLS is easy to learn. Tammaa et al¹¹ demonstrated that less experienced operators obtain competence after only 42 and 33 patients. Also the reproducibility of SLS was good^{10, 26}. For Menakaya et al¹⁰ non-specialist operators with 200 or more prior gynecological ultrasound examinations performed better than did those with less prior experience in the interpretation of offline videos of the sliding sign. In our study the absence of sliding sign seems to be more important than the presence of "kissing ovaries" as the latter has a very low sensitivity but with a very high specificity. The combination of both signs have the best Kappa value and OR. Based on obtained OR, the rectosigmoid involvement when at least one positive marker (kissing or sliding)

is present is thirteen times greater compared to the odds of the outcome occurring in the absence of at least one positive marker.

Also the evaluation of ovarian mobility showed a good reproducibility¹⁵ with good or very good intraobserver agreement for examiners with different degrees of experience (κ values ranging from 0.72 to 0.84) but unfortunately this soft marker is not significant in the prediction model that we found in the present study. Condous's group¹⁶ assessed the diagnostic accuracy of transvaginal sonographic (TVS) ovarian immobility in the detection of DIE in all location and obtained a sensitivity of 58.3% and a specificity of 74.1%. Unfortunately, a specific evaluation of RS DIE using ultrasonographic evaluation as gold standard was absent in Gerges's et al study.

In addition to the ultrasonographic findings, some clinical and imaging findings (as dysmenorrhea with VAS > 7, primary or secondary infertility, positive physical examination, at least one site of endometriosis seen at some imaging examination, pelvic adhesion process, etc.)^{24, 27-29} has been proposed to justify staging in advanced centers. Further studies should be performed to investigate if the association with these findings can improve the results of ultrasonographic soft markers used alone.

Some limitations should be considered in the present study. The main bias is that a single experienced operator performed the first three steps and after the evaluation of posterior and anterior compartment following the IDEA consensus suggestions. All the first three steps were performed initially and stored before the last step to reduce the risk of bias. Further studies will be performed to evaluate the diagnostic accuracy of less experienced operators. A particular attention should addressed in the next years to diffuse the "culture" that a detailed ultrasonographic scan can reduce the delay in the diagnosis of this disease creating specific courses and learning programs³⁰.

Another possible limitation is the impossibility to evaluate the real influence of other localizations of DIE on soft markers evaluated in the present study. In addition, in some patients with positive SLS the RS lesion was present. Further studies will be addressed to evaluate if the level of the

lesion can interfere with the diagnosis. At the moment no studies are present in the literature about this topic.

In conclusion the present study demonstrates that using detailed scanning protocol including dynamic ultrasonography, it is possible to screen patients for RS lesions in suspicious cases using SLS and KO as soft markers for further referral to a second level expert examination with a sufficient degree of accuracy.

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Legends of figures

Fig 1. An ovary is fixed to the uterus (U) laterally .

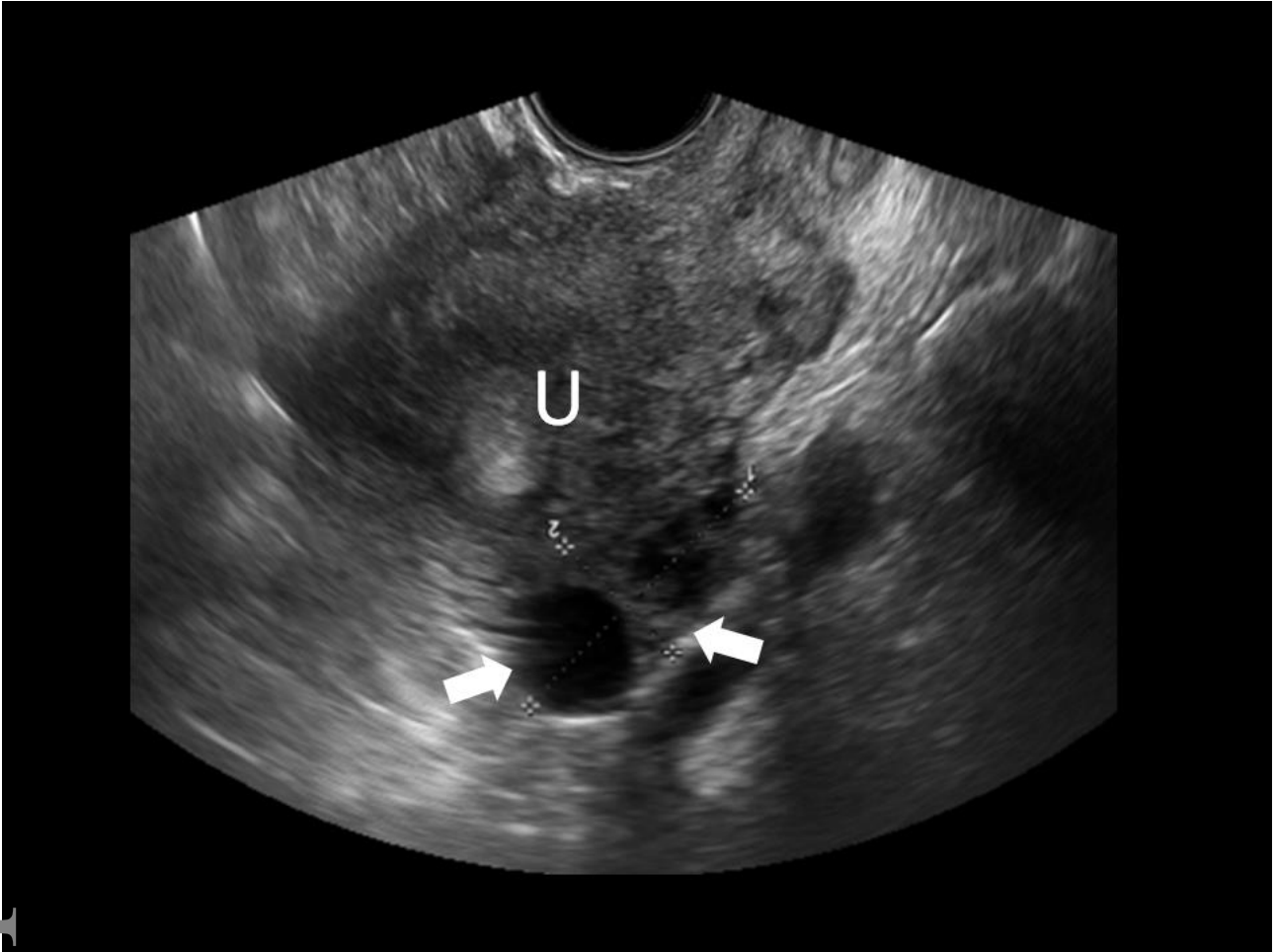
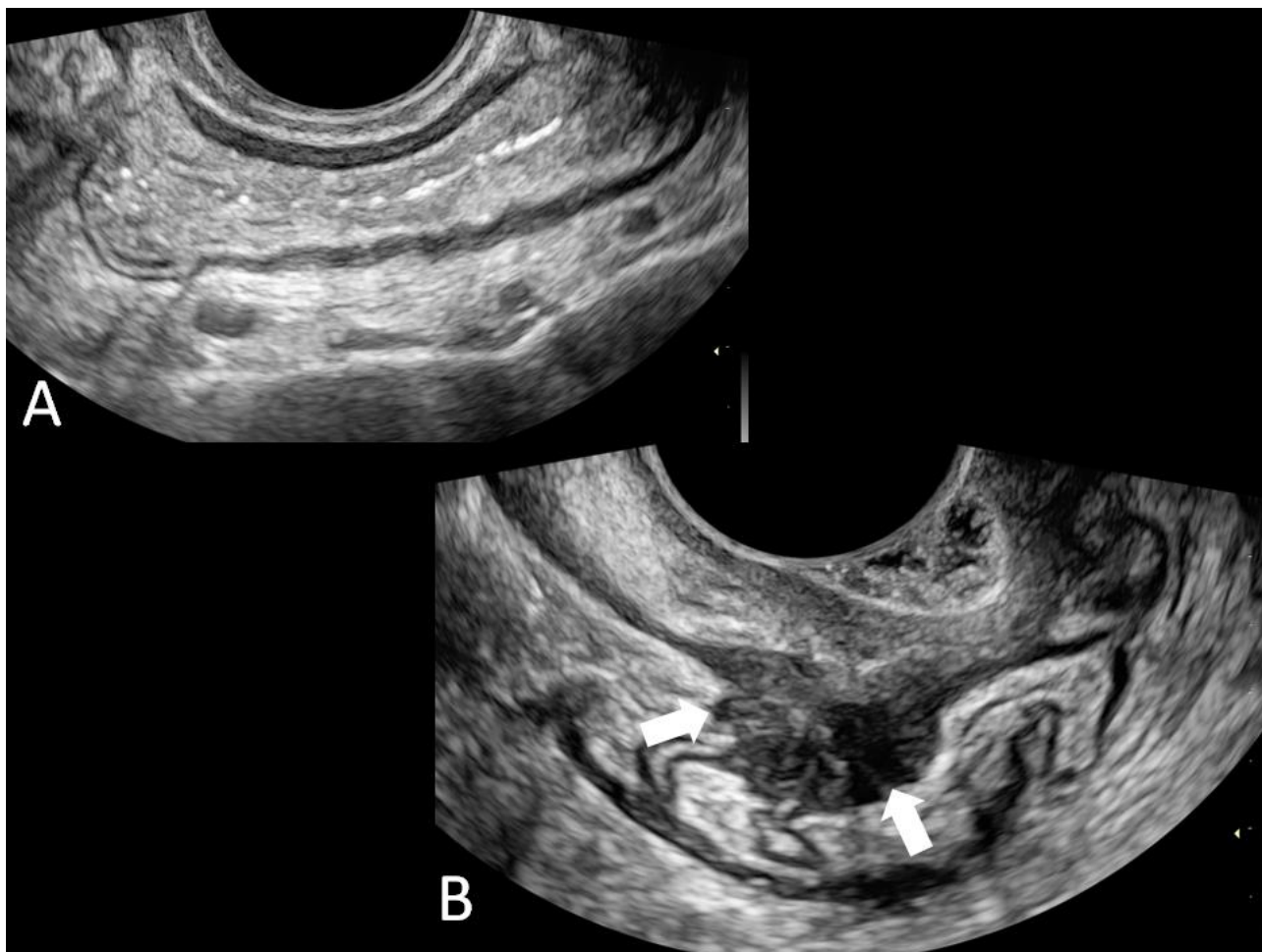


Fig 2. A presence of “kissing ovaries” defined as both ovaries joined together behind the uterus (U) in the cul-de-sac.



Fig 3. A normal rectosigmoid tract (A) and a rectosigmoid endometriotic lesion (B) visualized as an irregular hypoechoic nodule involving the muscular layer of the anterior wall of the bowel .



Tables:

Kind of hormonal therapy	Number of patients (%)
Estroprogestin	96(29%)
Progestin only	45(14%)
Levonorgestrel Intrauterine Device	1(0.3%)
Estroprogestin Ring	4(1.2%)
GnRH agonist	5(1.5%)
Menopause	11(3.3%)
Spontaneous cycles	169(51%)

Table 1 The different kind of hormonal therapy of the population included in the study

The ultrasonographic dependent variables:	Rectosigmoid involvement absent N=227 N(%)	Rectosigmoid involvement present N=106 N(%)	p
1. presence of US signs of uterine adenomyosis;	39(17.2%)	28(26.4%)	.057
2. presence of an endometrioma;	60(26.4%)	38(35.8%)	.093
3. adhesions of the ovary to the uterus (“reduced ovarian mobility”);	32(14.1%)	41(38.7%)	<0.001
4. presence of “kissing ovaries”;	7(3.1%)	11(10.4%)	.009
5. absence of sliding sign.	54(23.8%)	82(77.4%)	<0.001

Table 2. The ultrasonographic dependent variables in relationship with the presence or absence of endometriotic rectosigmoid lesions at ultrasound.

The ultrasonographic dependent variables:	Sensitivity	Specificity	PPV	NPV	Kappa	OR
1. presence of US signs of uterine adenomyosis;	26.4% (28/106)	82.8% (188/227)	41.8% (28/67)	70.7% (188/266)	.10	1.73 [.99-3.00]
2. presence of an endometrioma;	35.8% (38/106)	73.6% (167/227)	38.8% (38/98)	71.1% (167/235)	.09	1.55[0.94-2.56]
3. adhesions of the ovary to the uterus (“reduced ovarian mobility”);	38.7% (41/106)	85.9% (195/227)	56.2% (41/73)	75.0% (195/260)	.26	3.84[2.23-6.66]
4. presence of “kissing ovaries”;	10.4% (11/106)	96.9% (220/227)	61.1% (11/18)	69.8% (220/315)	.09	3.63[1.36-9.67]
5. absence of sliding sign.	77.4% (82/106)	76.2% (173/227)	60.3% (82/136)	87.8% (173/197)	.50	10.94[6.32-18.93]
6. At least one positive marker (kissing or sliding)	82.1% (87/106)	75.3% (171/227)	60.8% (87/143)	90.0% (171/190)	.53	13.848[7.57-26.34]

Table 3 Sensitivity, specificity, Positive predictive value (PPV), negative predictive value (NPV), Kappa value and Odds Ratio (OR) of ultrasonographic dependent variables in the suspicion of rectosigmoid endometriosis.