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Transvaginal ultrasound for the diagnosis of adenomyosis: systematic review and meta-analysis

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Precis: Systematic review and meta-analysis of studies in the last 10 years on use of 2D- and 3D-transvaginal ultrasound for diagnosis of adenomyosis show good accuracy.

Abstract

Adenomyosis is characterized by the presence of ectopic foci of endometrial glandular tissue and/or stroma within the myometrium. The diagnosis of adenomyosis is made traditionally through histological evaluation of the post-surgical specimen. More recently, imaging with transvaginal ultrasound (TVUS) has been used for the pre-operative diagnosis of adenomyosis. As yet, there is no consensus regarding the best imaging feature or combination thereof for the non-surgical diagnosis of adenomyosis. This study systematically evaluates the literature in the last 10 years to determine the accuracy of TVUS 2D, different imaging features, enhancing methods such as TVUS 3D, elastography and color Doppler in the non-surgical diagnosis of adenomyosis. A total of 8 studies were included. Pooled sensitivity and specificity for TVUS 2D for the diagnosis of adenomyosis for all combined imaging characteristics was 83.8% and 63.9%, respectively. Pooled sensitivity for 355 total patients with use of imaging feature of heterogeneous myometrium with TVUS 2D was highest (86.0%), and pooled specificity for 283 total patients with use of globular uterus was highest (78.1%). After including the "question mark" sign with other TVUS features, higher sensitivity and specificity, of 92% and 88%, respectively, were noted. For TVUS 3D, pooled sensitivity and specificity for all combined imaging characteristics was 88.9% and was 56.0%. Poor definition of junctional zone showed the highest pooled sensitivity (86%) and the highest pooled specificity (56.0%) for the diagnosis of adenomyosis with TVUS 3D**.** There was no improvement in overall accuracy in TVUS 3D compared to TVUS 2D. Preliminary results of TVUS with color Doppler showed a high sensitivity and specificity for the differentiation between adenomyosis and myomas (95.6% and 93.4%). Also, TVUS elastography in one study showed an improvement in specificity (82.9%) compared to TVUS 2D (63.9%), though with comparable sensitivity. Larger studies are needed to advance our understanding of the different types of adenomyosis and their clinical impact.

Introduction

Adenomyosis is characterized by the presence of ectopic foci of endometrial glands and/or stroma within the myometrium, which may be diffusely distributed (diffuse adenomyosis) or circumscribed as a nodular lesion (focal adenomyosis or adenomyoma).[1 2] The gold standard for the diagnosis of adenomyosis is histopathological confirmation of the presence of ectopic endometrium

within the myometrium.[3-6] The absence of standardization for the histological diagnosis of adenomyosis is reflected in the varying prevalence reported, ranging from 5 to 70% worldwide.[7]

Patients with adenomyosis may be asymptomatic or present with pain and abnormal bleeding symptoms.[8] Because adenomyosis lesions can be difficult to identify during surgery and their complete excision is challenging, hysterectomy often remains the definitive treatment. Accurate non-invasive diagnosis of the disease with imaging becomes essential, therefore, for medical therapy or surgical planning particularly in patients wishing to retain their fertility.[9]

Magnetic resonance imaging (MRI) and transvaginal ultrasonography (TVUS) have been used as pre-operative imaging tools for adenomyosis and have been shown to have similar diagnostic accuracy.[10] Though TVUS has the advantage of incurring less costs, it is operator-dependent.[11] [12] Various ultrasonographic criteria have been utilized for the diagnosis of adenomyosis. These sonographic criteria include the presence of heterogeneous myometrial areas, findings of anechoic areas of 1 to 3 mm in diameter in the myometrium (known as myometrial cysts), and asymmetry of anterior and posterior uterine wall thickness.[12] Other sonographic markers of adenomyosis include the presence of echogenic striations in the sub-endometrium, sub-endometrial echogenic nodules, nodular endometrial-myometrial interface and poor definition of junctional zone.[9] [13-20] At present, there is no consensus regarding the most accurate imaging feature or combination of features for the ultrasound diagnosis of adenomyosis.[9] [13-20] Improved imaging recognition of adenomyosis could facilitate better understanding of the natural progression of the disease and advance its clinical treatment options outside of surgery.

The main objective of this paper is to conduct a systematic review of the literature in the last 10 years regarding the accuracy of TVUS in the preoperative diagnosis of adenomyosis. We aim to also evaluate the accuracy of the specific imaging features utilized and the role and efficacy of enhancing techniques such as power Doppler, 3D imaging and elastography available with ultrasound.

Material and Methods

Search Strategy

A thorough search of PubMed/MEDLINE for all available current literature in English published in the last 10 years was performed and a review based on PRISMA guidelines was conducted.[21] The quality of the individual studies was judged using the QUADAS (Quality Assessment of Diagnostic Accuracy Studies) criteria, a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews.[22]

We used the search terms “adenomyosis” and "ultrasound" and “adenomyosis”, as well as “adenomyosis” and "imaging" as key words to recover all possible publications using the PubMed database. MeSH terms used included: (("diagnostic imaging"[Subheading] OR ("diagnostic"[All Fields] AND "imaging"[All Fields]) OR "diagnostic imaging"[All Fields] OR "ultrasound"[All Fields] OR "ultrasonography"[MeSH Terms] OR "ultrasonography"[All Fields] OR "ultrasound"[All Fields] OR "ultrasonics"[MeSH Terms] OR "ultrasonics"[All Fields]) OR ("diagnostic imaging"[Subheading] OR ("diagnostic"[All Fields] AND "imaging"[All Fields]) OR "diagnostic imaging"[All Fields] OR "ultrasonography"[All Fields] OR "ultrasonography"[MeSH Terms]) OR ("ultrasonics"[MeSH Terms] OR "ultrasonics"[All Fields]) OR ("diagnostic imaging"[Subheading] OR ("diagnostic"[All Fields] AND "imaging"[All Fields]) OR "diagnostic imaging"[All Fields] OR "diagnostic imaging"[MeSH Terms] OR ("diagnostic"[All Fields] AND "imaging"[All Fields])) AND ("adenomyosis"[MeSH Terms] OR "adenomyosis"[All Fields]).

Selection criteria / eligibility

Included in this study are both retrospective and prospective studies that assessed the accuracy of TVUS (considered here as the index test) with or without enhancing techniques (3D, color Doppler, elastography) as a diagnostic tool. All included studies used histopathologic examination (considered as the gold standard) for confirmation of adenomyosis. We excluded single case reports and review articles.

Data extraction

Two authors (MPA and JR) abstracted the data into tables and another author (GMB) separately confirmed accuracy. In cases of conflict, resolution was achieved by discussion with the senior authors (EB, RMK and MSA). References of articles were also manually reviewed for other relevant papers. Data obtained from the studies include first author, publication year, sample size, study design, imaging tool, imaging characteristics or features, types of tumors and stage, There were 7 main imaging characteristics/criteria/features assessed in this study to include: myometrial cysts, heterogeneous myometrial areas, myometrial hypoechoic linear striations, globular-appearing uterus, asymmetry of the myometrial wall, poor definition of the endometrial–myometrial junction, and “question mark” sign (Figures 1 and 2). “Question mark” sign is defined with ultrasound when the uterine corpus was flexed backward, the fundus of the uterus faced the posterior pelvic compartment and the cervix was directed anteriorly towards the urinary bladder.

Statistical analysis

Data was extracted to construct 2x2 contingency tables of diagnostic performance (numbers of true positive, false negative, false positive and true negative test results). Meta-analysis was performed using the Meta-Disc (Clinical Biostatistics Unit, Ramon y Cajal Hospital, Madrid, Spain), a Windows-based software for meta-analysis of test accuracy data.[23] Summary estimates of sensitivity and specificity with 95% confidence interval were calculated using the Der Simonian and Laird random-effects model.

Results

From 648 initial papers obtained from the primary computerized search, 595 studies were excluded (Figure 3). All reviews, studies not written in English, and studies not published in the last 10 years were excluded. The abstracts of the 53 remaining studies were read and, using the inclusion/exclusion criteria, 21 were selected to be read in full-text. A total of 8 papers, were included in the final systematic review for qualitative synthesis [9 13-19], of which 7[9 13-18] were included for quantitative analysis (meta-analysis).

With regards to the imaging tools and number of patients included in this review, 5 of the papers assessed TVUS with 2D (TVUS 2D), 3 assessed TVUS with 3D (TVUS 3D), and 1 evaluated TVUS with elastography (TVUS elastography) (Table 1). All studies were case series evaluating the accuracy of TVUS imaging tool confirmed by histopathological evaluation. All of the studies included patients submitted to hysterectomy due to dysmenorrhea, menometrorrhagia or suspected adenomyosis.[9 13-19] Only one included also patients submitted to myomectomy.[16] The prevalence of histologically confirmed adenomyosis and fibroids in the included studies ranged from 34.0% to 73.6% and 23.6% to 94.3%, respectively.

Quality Assessment

Three[13-15] of included papers were of good quality and five[9 16-19] were of fair quality using QUADAS scoring (Table 1). In three studies rated as good[13-15], pathologists were blinded to the imaging results. All other studies rated as fair included evaluators who were not blinded for both the standard and index tests, which may have created a review bias. Also, only one study[15] reported the uninterpretable/ intermediate results which were excluded while, in all other studies, this information was not reported.

Transvaginal ultrasound 2D (TVUS 2D)

Five studies for a total of 568 patients addressed the accuracy of TVUS 2D in the diagnosis of adenomyosis and were included for quantitative analysis.[13-17] Three studies[13 14 17] considered the diagnosis of adenomyosis when at least one sonographic criteria was present and two studies [15 16] when two

sonographic criteria were present. The reported sensitivity and specificity of TVUS 2D in these separate studies varied greatly, ranging from 75% to 85% and 43% to 90% (Figure 4). Meta-analysis was performed and the overall pooled sensitivity and specificity of all combined imaging characteristics of TVUS 2D evaluation of adenomyosis were 83.8% and 63.9%, respectively. (Figure 4).

Multiple TVUS 2D imaging characteristics were utilized in these studies. Asymmetry of myometrial wall, myometrial cysts, hypoechoic linear striations, and heterogeneous myometrium were evaluated in 3 studies; globular-appearing uterus and poor definition of the endometrial–myometrial zone were evaluated in 2; and "question mark" sign evaluated in only 1 study (Table 2).

The sensitivity and specificity of each TVUS 2D characteristic reported in the 5 studies varied greatly. For presence of myometrial cysts, sensitivity ranged from 53.1% to 82.4% and specificity from 45.3% to 97.5%. For hypoechoic linear striations, sensitivity ranged from 30.8% to 91.8% and specificity from 71.1% to 95.5%. Asymmetry of the myometrial wall was found to have sensitivity ranging from 46.9% to 61.5% and specificity from 63.6% to 80% (Table 2). A meta-analysis was performed for each of the ultrasound characteristics (summarized in Table 2). The overall pooled sensitivity for a total of 355 patients for heterogeneous myometrium with TVUS 2D was highest (86.0%), while the overall pooled specificity for a total of 283 patients was highest for globular uterus (78.1%).

The efficacy of the use of the sonographic sign called "question mark" for the presence of adenomyosis was first reported in a 2015 study.[17] This study reported that the overall sensitivity and specificity of TVUS 2D was 83% and 88%, respectively. After including the "question mark" sign with other ultrasound features in the imaging diagnosis, higher sensitivity and specificity, 92% and 88%, respectively, were noted.

Transvaginal ultrasound 3D (TVUS 3D)

Three studies that included a total of 214 patients addressed the accuracy of TVUS 3D in the diagnosis of adenomyosis.[9 15 18] The diagnosis of adenomyosis was defined by the presence of one sonographic feature in one study[9] and two features in two studies[15 18]. The sensitivity was similar between TVUS 3D studies, ranging from 86.7% to 91.7%. However, specificity of TVUS 3D varied greatly, ranging from 44.4% to 86.7%. When all 3 studies were subjected for quantitative analysis, the overall pooled sensitivity and specificity of all combined imaging characteristics of TVUS 3D evaluation of adenomyosis were 84.7% and 81.0% (Figure 5).

The imaging characteristics evaluated in all the TVUS 3D studies were presence of myometrial cysts, heterogeneous myometrial areas, asymmetry of the myometrial wall, and poor definition of the endometrial–myometrial junction. Poor definition of junctional zone was noted when the sonographer was unable to visualize a clear distinction between the endometrial-myometrial layers. This last criterion showed the highest pooled sensitivity (86%) and the highest pooled specificity (56.0%) for the diagnosis of adenomyosis with TVUS 3D. However, its specificity varied greatly among the studies from 22.5% to 82.8%. Similarly, accuracy of the use of myometrial cysts varied greatly between studies, with sensitivity ranging from 33.3% to 83.3% and specificity from 5% to 88.9%. Hypoechoic linear striations was evaluated by only 1 paper [18], showing a sensitivity and specificity of 52.8% and 61.1%.

Transvaginal ultrasound with color Doppler

One study[9] compared 100 patients with adenomyosis to patients with myoma using TVUS with color Doppler. The lesions were evaluated for morphology, vascularity, pulsatility Index (PI), resistive Index (RI) and maximum velocity (Vmax).

For adenomyosis lesions, a central vascular pattern was observed in 93% of cases compared to a peripheric vascular pattern in 89% of patients with myoma. Doppler PI (09.0 ± 0.20 vs 1.5 ± 0.20), RI (0.50 ± 0.15 vs 0.9 ± 0.15) and Vmax (12.0 ± 2.5 vs 7.0 ± 2.5 cm/sec) were significantly different between adenomyosis and myoma groups. Using a cut-off value of PI > 1.2 and RI > 0.7, sensitivity for the diagnosis of adenomyosis with TVUS with color Doppler was 95.6%, specificity was 93.4%, positive predictive value was 88.6% and negative predictive value was 97.6%. This study suggested benefit to the use of TVUS with color Doppler in differentiating adenomyosis from myomas with an overall diagnostic accuracy of the use of TVUS with color Doppler for adenomyosis of 93.8%.

Transvaginal ultrasound elastography

Acar *et al*. evaluated 53 patients submitted to hysterectomy for menorrhagia with TVUS elastography.[19] Adenomyosis was confirmed in 39 cases. Color and numerical values of Young's modulus in the areas of maximum myometrial stiffness was measured. TVUS elastography imaging (color window) with adenomyosis was characterized by red, green and yellow colors (showing predominately heterogeneous staining due to high stiffness), while unremarkable myometrium was mapped by blue color. Comparing the mean value of Young's modulus in patients with and without adenomyosis, significant difference was noted (72.7 kPA IC: 22.6–274.2 vs 28.3 kPA IC:12.7–59.5; $p < .05$). Also, when the Young's modulus value higher than 34.6 kPa was utilized as the threshold, the

sensitivity and specificity of TVUS elastography in adenomyosis diagnosis were 89.7% and 82.9%, respectively.

Discussion

The prevalence of adenomyosis is considerable in women in reproductive age, ranging from 20-35%. The prevalence of adenomyosis is likely underestimated because of the lack of standardized criteria in both imaging and histological confirmation.[7] To illustrate, it has been estimated that histological confirmation of adenomyosis ranges from 5-70% of patients who undergo hysterectomy.[12]

The availability of better imaging tools and determination of the best diagnostic feature(s) for adenomyosis would provide greater understanding of the disease. Studies evaluating multiple TVUS imaging characteristics have suggested different types of adenomyosis to be associated with other conditions and with varying clinical presentations. [11] To illustrate, external adenomyosis has been associated with deep endometriosis in 49-60% of cases.[24] Diffuse adenomyosis was noted to be more frequently associated with menorrhagia compared to nodular adenomyosis (84% versus 37%; p = .001).[10] Indeed, recent findings showed that the presence of more ultrasound features of adenomyosis in the patient was positively associated with more severe menstrual pain scores.[25 26]

In the present systematic review, 8 qualified studies showed that overall, TVUS 2D and TVUS 3D are effective methods for diagnosis of adenomyosis with pooled sensitivity of 84% and 89%, and pooled specificity of 64% and 56%, respectively. Improved diagnostic performance was noted when the "question mark" sign was used in addition to the other imaging characteristics. For all other imaging characteristics, accuracy varied greatly between studies, with the greatest variability observed in presence of myometrial cysts and hypoechoic linear striations for both TVUS 2D and TVUS 3D studies. This finding highlights the fact that further studies comparing each of these features for diagnosis performed by larger and multiple centers would be helpful. Future studies should also determine if characterization of the extent of disease (such as depth of myometrial infiltration, amount of myometrial cysts, or even amount of discrepancy between anterior and posterior myometrial thickness) may improve upon diagnostic performance.

In this review, specificity of TVUS 2D for adenomyosis was significantly enhanced with the use of TVUS 3D (64% vs 81%, respectively), while the sensitivity was not affected (84% vs 85%). Also, the pooled sensitivity and specificity for each of the imaging characteristics used in TVUS 3D were similar to those used in TVUS 2D with the exception of the use of poor definition of junctional zone where greater

sensitivity was noted when used in TVUS 3D compared to TVUS 2D (sensitivity 87.8% vs 58.6%, specificity 56.0% vs 71.5%, respectively).

The use of color Doppler to differentiate adenomyosis from malignancies and uterine leiomyoma has been suggested previously. [9 13] In this review, one study has been conducted showing the potential of use of color Doppler in identifying the vascular pattern of adenomyomas has a high accuracy in differentiating these lesions from myomas. Because only one study has shown a difference in vascular pattern compared to myomas, larger comparative studies are needed in order to further delineate the role of the use of TVUS with color Doppler and other enhancement tools such as TVUS elastography for the differentiation between myomas and adenomyosis.

This systematic review confirms that TVUS 2D is effective and should be considered as the first line ultrasound imaging method for the diagnosis of adenomyosis. Enhancing tools such as TVUS 3D improved upon sensitivity when used with poor definition of junctional zone,, while no improvement was noted in the overall sensitivity compared to TVUS 2D. There remains a lack of consensus in the imaging criteria used for non-histologic confirmation of adenomyosis. More robust comparative studies are needed to advance our understanding of the disease and ultimately, expand the non-surgical treatment options for patients with adenomyosis.

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Figure 1. Two-dimensional ultrasound imaging of a uterus in a longitudinal section with the sonographic signs associated with presence of adenomyosis.

A: represents diffuse adenomyosis with heterogeneous myometrium, asymmetry of posterior myometrial wall, hypoechoic linear striations, poor definition junctional zone, and "question mark" sign. B: represents globular uterus and heterogeneous myometrium. C: arrows indicate myometrial cysts.

Figure 2. Two-dimensional ultrasound imaging of a uterus in a longitudinal section with the sonographic signs associated with presence of adenomyosis.

A: represents diffuse adenomyosis with heterogeneous myometrium, arrows indicate myometrial cysts, poor definition junctional zone

B: represents globular uterus, heterogeneous myometrium, and asymmetry of posterior myometrial wall

Figure 3. Flow diagram showing selection of articles for systematic review.

Figure 4. Pooled sensitivity and specificity off all combined imaging characteristics of TVUS 2D evaluation of adenomyosis

Figure 5. Pooled sensitivity and specificity off all combined imaging characteristics of TVUS 3D evaluation of adenomyosis

Table 1: Included studies on TVUS imaging tools to access adenomyosis in the last 10 years

TVUS type	Study	Standard test	Total (n)	Adenomyosis n (%)	Fibroids n (%)	
2D	Kepkep, 2007[12]	Hysterectomy	70	26 (37.1)	20 (28.6)	Good
2D	Sun, 2010[13]	Hysterectomy	213	85 (39.9)	93 (43.7)	Good
2D	Hanafi, 2013[15]	Hysterectomy (130) Myomectomy (33)	163	110 (67.5)	134 (82.2)	Fair
2D	Di Donato, 2015[16]	Hysterectomy	50	24 (48.0)	NR	Fair

2D /3D	Exacoustos, 2011[14]	Hysterectomy	72	32 (44.4)	17 (23.6)	Good
3D	Luciano, 2013[17]	Hysterectomy	54	36 (66.7)	NR	Fair
3D/ Color Doppler	Sharma, 2015[9]	Hysterectomy	88	30 (34.0)	53 (60.2)	Fair
Elastography	Acar, 2016[18]	Hysterectomy	53	39 (73.6)	50 (94.3)	Fair

TVUS: transvaginal ultrasound. Quality of included studies evaluated using QUADAS scoring for included studies and evaluated imaging tools. NR: not reported. All included studies were accuracy studies

Table 2 - Meta-analysis of transvaginal ultrasound 2D and 3D characteristics for the diagnosis of adenomyosis

TVUS characteristics	**TVUS 2D**								**TVUS 3D**							
	Study	**n**	**Sens**	**Spec**	**TP**	**FP**	**FN**	**TN**	**Study**	**n**	**Sens**	**Spec**	**TP**	**FP**	**FN**	**TN**
Asymmetry myometrial wall	Kepkep, 2007	70	61.5	63.6	16	16	10	28	Exacoustos, 2011	50	58.3	72.2	21	5	15	13
	Sun, 2010	213	58.8	75.0	50	32	35	96	Luciano, 2013	73	59.4	27.5	19	29	13	11
	Exacoustos, 2011	72	46.9	80.0	15	8	17	32	Sharma, 2015	88	60.0	65.5	18	20	12	38
	Pooled	**355**	**57.2**	**71.9**					**Pooled**	**215**	**59.2**	**53.4**				
Myometrial cysts	Kepkep, 2007	70	61.5	81.8	16	8	10	36	Exacoustos, 2011	50	33.3	88.9	12	2	24	16
	Sun, 2010	213	82.4	45.3	70	70	15	58	Luciano, 2013	73	62.5	5.0	20	38	12	2
	Exacoustos, 2011	72	53.1	97.5	17	1	15	39	Sharma, 2015	88	83.3	77.6	25	13	5	45
	Pooled	**355**	**72.0**	**62.7**					**Pooled**	**215**	**58.2**	**54.3**				
Hypoechoic linear striations	Kepkep, 2007	70	30.8	95.5	8	2	18	42	Luciano, 2013	73	52.8	61.1	19	7	17	11
	Sun, 2010	213	91.8	71.1	78	37	7	91								
	Exacoustos, 2011	72	50.0	90.0	16	4	16	36								
	Pooled	**355**	**71.3**	**79.7**												
Heterogeneous myometrium	Kepkep, 2007	70	80.8	61.5	21	17	5	27	Exacoustos, 2011	50	83.3	50.0	30	9	6	9
	Sun, 2010	213	87.1	60.2	74	51	11	77	Luciano, 2013	73	90.6	47.5	29	21	3	19

	Exacoustos, 2011	72	87.5	65.0	28	14	4	26	Sharma, 2015	88	73.3	34.5	22	38	8	20
	Pooled	**355**	**86.0**	**61.3**					**Pooled**	**215**	**82.7**	**41.4**				
	Kepkep, 2007	70	46.2	81.8	12	8	14	36	Exacoustos, 2011	50	88.9	44.4	32	10	4	8
Poor definition	Sun, 2010	213	62.4	68.0	53	41	32	87	Luciano, 2013	73	87.5	22.5	28	31	4	9
junctional zone									Sharma, 2015	88	86.7	82.8	26	10	4	48
	Pooled	**283**	**58.6**	**71.5**					**Pooled**	**215**	**87.8**	**56.0**				
	Kepkep, 2007	70	69.2	86.4	18	6	8	38								
Globular uterus	Sun, 2010	213	50.6	78.1	43	28	42	100								
	Pooled	**283**	**55.0**	**80.2**												
Question mark sign	Di Donato, 2015	50	75.0	92.3	18	2	6	24								

TVUS: transvaginal ultrasonography; Spec: specificity (%); Sens: sensitivity (%); TP: true-positive; FP: false-positive; TN: true-negative; FN: false-negative.

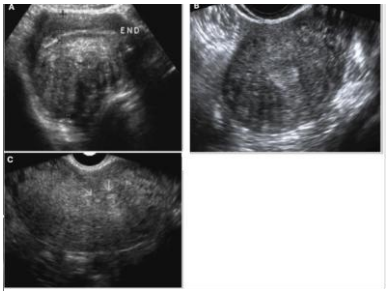

Figure 1.tiff

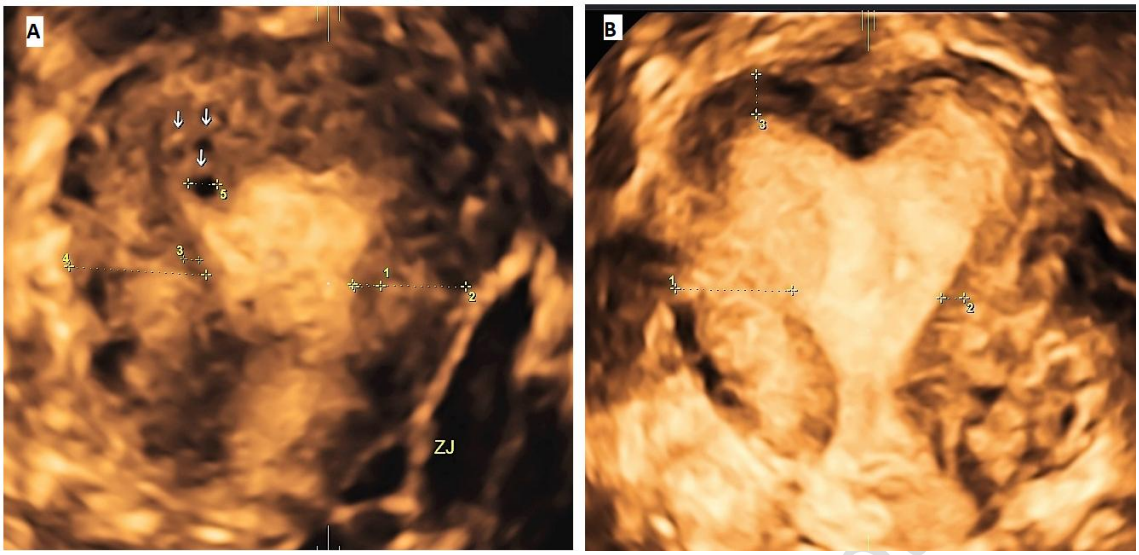

Figure 2.tif

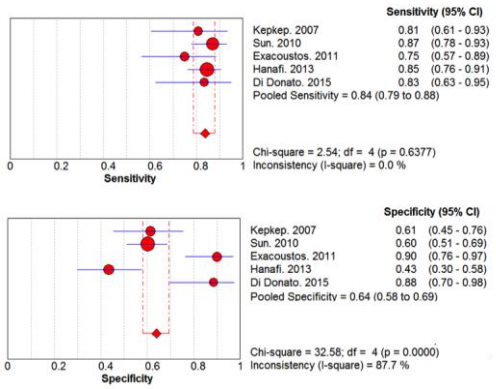

Figure 3.tiff

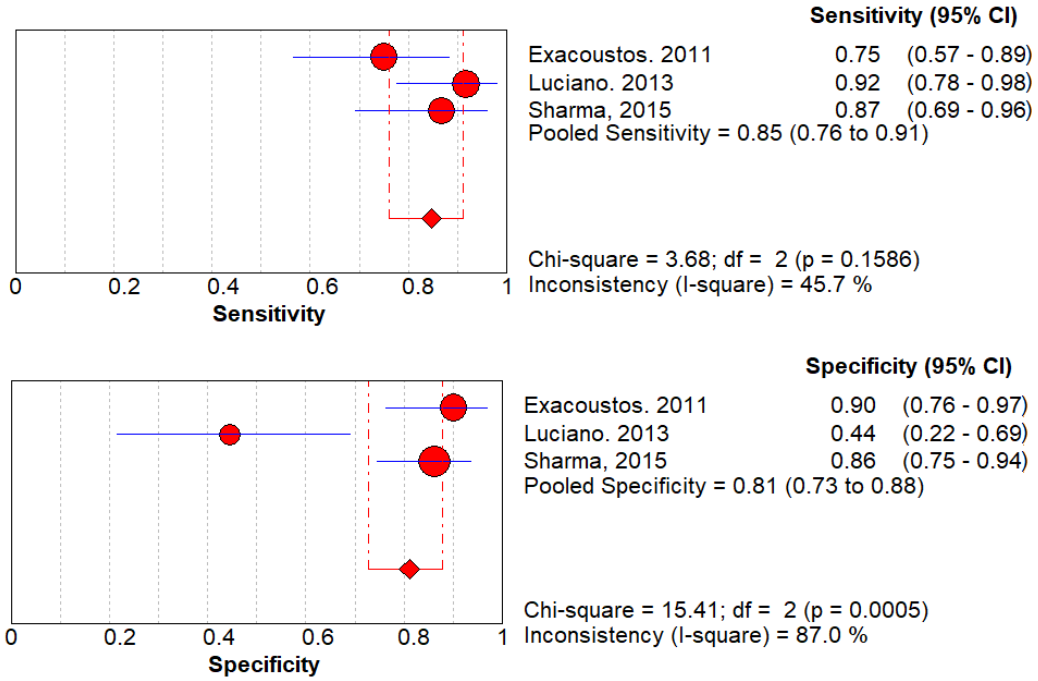

Figure 4.tiff