TITLE PAGE

Full Title: Correlation between ultrasound findings and laparoscopy in prediction of Deep Infiltrating Endometriosis (DIE)

Short Title: Ultrasound findings of DIE and laparoscopy

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ABSTRACT

Background: Detailed pre-operative description of endometriotic lesions by non-invasive methods is an important tool for accurate diagnosis and effective treatment of the disease. TVUS is a sensitive method for diagnosis of DIE however is highly operator dependent and consistent results require adequately trained and experienced clinicians.

Aims: The aim of the study is to assess the accuracy of TVUS in predicting DIE by comparing it with laparoscopic findings. We also compared US done in the community by general radiologists with examinations done by specialist gynaecologists.

Materials and Methods: A retrospective cohort study of patients who underwent laparoscopy for excision of possible endometriosis between July 2014 to February 2019 who had a TVUS prior to laparoscopy.

Results: A total of 119 patients were included. TVUS was shown to be useful in detecting all but bladder DIE. Community TVUS was no better than chance at identifying most DIE (AUC of 0.48-0.60) except in the detection of ovarian endometriomas and adhesions (AUC= 0.84). Specialist TVUS correctly identified most DIE with greatest utility for DIE in rectosigmoid (AU = 0.85, $p<0.000$), followed by pouch of Douglas/pouch of Douglas adhesions (AUC= 0.82, $p<0.000$), ovarian endometriomas/ovarian adhesions (AUC=0.79, $p<0.000$), uterosacral ligaments (AUC = 0.75, $p<0.000$) and rectovaginal septum (AUC= 0.69, $p<0.05$).

Conclusion: Specialist TVUS is informative in examining the presence of DIE particularly in posterior compartments which may increase surgical complexity. Community TVUS is significantly less beneficial however more accessible to the general public. This adds to the argument that increasing access to DIE-TVUS appears favourable.

INTRODUCTION

Endometriosis affects 10-15% of women and can result in significant deterioration in quality of life^{1,2,3,4}. Deep infiltrating endometriosis (DIE) is the term used when endometrial implants, fibrosis and muscular hyperplasia are present below the peritoneum (>5mm) and involve, in descending order of frequency, the uterosacral ligaments, the rectosigmoid colon, the vagina and the bladder^{5,6,7,8}. It can alter the normal pelvic anatomy and be associated with significant

adhesions in the pelvis which may make surgical removal quite complex. The location and extent of the DIE is essential for adequate pre-operative work-up of these patients.

Detailed description of endometriosis with ultrasound is quickly becoming a very valuable instrument for pre-operative diagnosis of endometriosis. However, the appropriate skills and training pathway required for competency are less clear.

The diagnosis of DIE using non-invasive means has most commonly consisted of Transrectal Ultrasonography (TRUS), Magnetic Resonance Imaging (MRI) and TVUS. The current literature demonstrates varying degrees of accuracy for these methods. Overall, it appears that MRI and TVUS are the most accurate, sensitive and specific forms of non-invasive imaging for the detection of DIE⁹. MRI however is a costly modality and thus due to low cost and easy access, it has long been argued that TVUS should be the first examination for the diagnosis of DIE in those with clinical suspicion.

TVUS is however highly operator dependent and good diagnostic results may only be achieved by an adequately trained and experienced medical team¹⁰. Pre-operative ultrasounds performed by less experienced physicians (residents in training with 12–24 months of experience in gynaecological ultrasound) as compared to experienced physicians (gynaecologist specialised in gynaecologic ultrasound with more than 10 years' experience) had a significantly reduced accuracy (80.9% vs 88.1%) and sensitivity (45.3% vs 77.1%)¹¹.

Interestingly however, it has been shown that sonographers are able to attain a skill level matched to that in expert centres within 38 scans if trained appropriately.¹² This adds further to the argument therefore that DIE-TVUS should become a part of standard ultrasound training or that only centres with a special interest and further training in endometriosis ultrasound should offer the service.

Aims

The aim of our study is to examine the correlation between transvaginal ultrasound findings and laparoscopy in the prediction of deep infiltrating endometriosis. In particular, we seek to

assess the accuracy of TVUS in predicting DIE and to quantify the differences seen between community ultrasound and those performed by subspecialists in gynaecological ultrasound.

MATERIALS AND METHODS

This was a retrospective cohort study of patients who underwent laparoscopy for treatment of possible endometriosis between July 2014 to February 2019 by a single surgeon in the private sector (Frances Perry House/ Agora Specialist Centre, Epworth Hospital) . Inclusion criteria included all patients who underwent a laparoscopy for possible resection of endometriosis. Patients were excluded if they: had incomplete information (i.e. no USS report) or were undergoing laparoscopy for another indication i.e. transabdominal cerclage. Both symptomatic and asymptomatic patients were included.

Information was collected from online medical records. Information collected included patient demographics, presence of symptoms (defined as dysmenorrhoea, dyspareunia, dyschezia dysuria or chronic pelvic pain), previous endometriosis treatment, presence of subfertility, previous subfertility treatments, USS location (community/specialist), bowel preparation prior to USS, USS findings and laparoscopy findings.

Specialist USS was defined as those performed by clinicians with a Certification in Obstetric and Gynaecological Ultrasound (COGU), a 3 year training programme in advanced Obstetric and Gynaecological Ultrasound offered in Australia. Specialist ultrasound refers to those which were both performed and reported by a COGU clinician. USS and laparoscopy findings that were relevant were chosen based on previous studies.^{5, 24} These included the presence of: ovarian endometriomas/ovarian adhesions, pouch of Douglas DIE/pouch of Douglas adhesions, bladder and uterovesical (UV) fold DIE, rectosigmoid DIE, rectovaginal septum DIE and uterosacral ligament DIE. The documented presence of DIE on laparoscopy was confirmed on histology (defined as both the presence of endometriosis and depth of >5mm).

The key measures examined included the area under the curve (AUC; the ability of the test to correctly identify normal versus abnormal), sensitivity (the proportion of patients in whom the TVUS correctly identified would have DIE on laparoscopy), specificity (the proportion of patients in whom the TVUS correctly identified would have no DIE on laparoscopy), positive predictive value (PPV; the proportion of patients for whom the TVUS did detect DIE and for

whom DIE was found) and negative predictive values (NPV; the proportion of patients for whom the TVUS did not detect DIE and laparoscopy did not find DIE).

The study was approved by the Royal Women's Hospital Human Research Ethics Committee (Reference AQA19/30).

RESULTS

A total of 195 patients were identified as having a laparoscopy by this single surgeon during July 2014 to February 2019. Of these, 36 were excluded for incomplete information (No ultrasound), 40 were excluded as the laparoscopies were primarily performed for other indications and not for possible endometriosis (Transabdominal cerclage/removal of complex ovarian cyst). This left a total of 119 patients with complete information for analysis (Table 1). Of these, the majority received specialist TVUS ($n = 75$, 63%) and the remaining received community TVUS ($n = 44$, 37%).

Ultrasound (overall) has value in the diagnosis of most DIE, aside from bladder/UV fold

Overall, we found that TVUS in the diagnosis of DIE is useful in most cases of DIE (Table 2). Greatest utility was found for the detection of ovarian endometriomas and ovarian adhesions (AUC = 0.83, $p < 0.000$), followed by rectosigmoid colon DIE (AUC = 0.80, $p < 0.000$), pouch of Douglas DIE and pouch of Douglas adhesions (AUC = 0.76, $p < 0.000$), rectovaginal septum DIE (AUC = 0.66, $p < 0.05$) and then uterosacral ligaments DIE (AUC = 0.64, $p < 0.05$). The ability of TVUS in detecting bladder/utero-vesical fold DIE however was poor (AUC = 0.49, $p = 0.93$). Sensitivity appeared low (ranging from 0% to 85%).

Community ultrasound is no better than chance at identifying most DIE

We found that community USS performs with poor sensitivity (ranging from 0% to 69%) and an AUC of 0.48-0.60 for diagnosis of DIE in the pouch of Douglas, UV fold, rectosigmoid, rectovaginal septum and uterosacral ligaments (Table 3). Community USS does have value in the detection of ovarian endometriomas and adhesions with an AUC of 0.84. The PPV is difficult to interpret in the context of small numbers however the NPV ranged from 51-91%.

Specialist ultrasound is better than chance at identifying most DIE

We found that specialist ultrasound was better than chance at identifying most DIE (Table 3). Greatest utility was found for the detection of rectosigmoid DIE (AUC = 0.85, $p < 0.000$), followed by pouch of Douglas DIE (AUC = 0.82, $p < 0.000$), ovarian endometriomas and ovarian adhesions (AUC = 0.79, $p < 0.000$), uterosacral ligaments DIE (AUC = 0.75, $p < 0.000$) and rectovaginal septum DIE (AUC = 0.69, $p < 0.05$). As similar to previous findings, specialist ultrasound was not very useful in detecting bladder/UV fold DIE (AUC = 0.49, $p = 0.92$). The PPV of specialist ultrasound ranged from 79-94% except for bladder/UV fold DIE and the NPV ranged from 70-90%.

Specialist ultrasound is superior to community in the detection of DIE in the pouch of Douglas, rectosigmoid and uterosacral ligaments

Specialist ultrasound is significantly better in the detection of DIE in pouch of Douglas, rectosigmoid and uterosacral ligaments as compared to community ultrasound (Table 3)

Specialist ultrasound is still superior to community in the detection of DIE in symptomatic individuals

We found that for those patients who were symptomatic and received a community USS ($n = 27$), the AUC ranged from 0.50 – 0.61, except for the detection of ovarian endometriomas and ovarian adhesions (AUC = 0.88, $p < 0.05$) (Table 4). Sensitivity for the use of community USS in symptomatic individuals was also low (ranging from 0% - 22%) except for ovarian endometriomas and adhesions (sensitivity – 75%). Even in symptomatic patients, specialist ultrasound was significantly better in the detection of DIE in uterosacral ligaments (Table 4). There was greater utility in the use of specialist TVUS for rectosigmoid and POD DIE as compared to community ultrasound, however this finding was not significant in symptomatic individuals.

DISCUSSION

While many studies have assessed the usefulness of TVUS in the diagnosis of DIE, few have compared community to specialist TVUS to laparoscopic findings in the Australian setting.

This study demonstrates that the use of TVUS is better than chance at diagnosing cases of DIE in most areas of the pelvis.

On the assumption that specialist TVUS usually requires more training to be performed, we expected that specialist TVUS would be more useful than community TVUS at identifying most cases of DIE. Our study found this to be the case when identifying DIE in the POD, rectosigmoid colon and uterosacral ligaments. Although community TVUS is less beneficial, it is more accessible to the general public. This study therefore advocates for either incorporation of DIE-TVUS training into standard ultrasound education or a specialisation program for community sonographers.

These results are in keeping with previous studies. It has been demonstrated that when TVUS is performed by adequately trained personnel, the sensitivity, specificity, positive and negative predictive values are significantly higher¹². Furthermore, previous studies have shown an overall high sensitivity and specificity for TVUS in detecting DIE in the posterior compartments^{4,7}.

Interestingly, although non-significant, community TVUS showed a greater AUC than specialist TVUS in detecting ovarian endometriomas and ovarian adhesions. This finding was more pronounced, although still non-significant, in symptomatic individuals. The sensitivity however of specialist TVUS in detection of ovarian endometriomas and ovarian adhesions was higher than for community in the study population and symptomatic individuals. Ovarian endometriomas and adhesions may present more acutely in the clinical setting and may result in a more timely ultrasound. Given that community TVUS is more accessible this may result in a greater finding of ovarian endometriomas and adhesions. To further investigate this, timing of TVUS may be useful in future studies.

Furthermore, it appeared that TVUS was not useful in either community or specialist settings at detecting bladder/UV fold DIE. In our study, only one patient had DIE of the bladder/UV fold identified on TVUS however 25% had bladder/UV fold DIE on laparoscopy. This appears to contradict earlier studies which have found that sensitivity using TVUS was best for DIE involving bladder disease¹³. The incidence of bladder/UV fold DIE in our study is much higher than the general population. As a specialist centre in advanced laparoscopic gynaecological surgery, it may be that the incidence of more challenging cases of

endometriosis, specifically deep infiltrating endometriosis, is over-represented in our patient population.

Strengths and Limitations

Some strengths of our study included that the study design was in keeping with previously cited methods. Furthermore, that all cases of suspected laparoscopic DIE were confirmed on histological findings.

In regards to limitations, we combined subgroups of DIE. This was the case for ovarian endometrioma and ovarian adhesions along with POD DIE and POD adhesions. This choice was made due to ambiguities in interpreting ultrasound reports as they may represent DIE in the same area and are more open to subjective interpretation. We did not find a significant difference between community and specialist TVUS in the diagnosis of DIE for POD/POD adhesions or ovarian endometriomas/ovarian adhesions in symptomatic individuals. This may rather reflect the smaller subgroup of patients in this category and highlight the need for analysis with a larger population.

Furthermore, the values of sensitivity, specificity, PPV and NPV must be interpreted with caution. Our study found that specialist TVUS was more sensitive than community TVUS but less specific in all areas of DIE detection. This was due to a large percentage of negative findings on community TVUS.

It is important to note that the observed use of bowel preparation, although collected in our study, may not be a realistic depiction of actual use. We relied on documentation of bowel prep use and no documentation was met with the assumption that it was unknown/not used. It is known that particular specialist ultrasound clinics routinely use bowel preparation. We did not control for the use of bowel-preparation in our study which may be useful when assessing the usefulness of TVUS in the diagnosis of rectosigmoid colon DIE.

Future directions

We used symptomatic and asymptomatic patients for our study group. As the presence and extent of DIE may not correlate with patient symptoms, it remains unclear how and to what degree preoperative TVUS findings should influence the decision to perform surgery or the type of intervention to take²¹.

Increased surgical complexity can occur when there is DIE in the posterior compartments, in particular POD and rectosigmoid colon, which specialist TVUS was significantly more useful at detecting. Despite this finding however, we did not assess whether this resulted in any improvement in clinical care or outcomes. For example, the involvement of colorectal surgeons in anticipated cases of difficult DIE involving the rectosigmoid colon was not assessed and may be useful to assess in future studies. Patient outcomes such as length of stay and pain rating may be a future point of interest and aid in developing a cost/benefit analysis of introducing compulsory training in DIE-TVUS.

Another utility for compulsory training in DIE-TVUS is greater uptake amongst patients, which would be primarily achieved by education of primary healthcare providers around the advantages of accurate pre-operative imaging. As suggested by Guerriero et al. TVUS could be used also for the follow-up of patients with ultrasound diagnosis of DIE but with good symptom relief from treatment²⁰.

Conclusion

Overall, the findings of this study support specialist ultrasounds in the diagnosis of DIE. Improving access to specialist-level ultrasound, be it through upskilling of community sonographers to enable the development of specialised centres or education of general practitioners as to where to refer patients for a more accurate scan, certainly seems favourable.

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Tables and Figures

Table 2: Diagnostic Performance of TVUS in the Diagnosis of Endometriosis with Laparoscopy as the Gold Standard

n = 119

	AUC ^a (95% CI)	<i>p</i> =	Sensitivity (%)	Specificity (%)
Ovarian endometriomas and Ovarian Adhesions	0.83 (0.75-0.91)	<i>p</i> < 0.000	84 (49/59)	60 (50/60)
Pouch of Douglas and Pouch of Douglas Adhesions DIE	0.76 (0.67-0.85)	<i>p</i> < 0.000	56 (31/55)	97 (61/63)
Bladder/UV Fold DIE	0.49 (0.38-0.61)	<i>p</i> = 0.93	0 (0/30)	99 (88/89)
Rectosigmoid colon DIE	0.80 (0.67-0.92)	<i>p</i> < 0.000	60 (15/25)	99 (93/94)
Rectovaginal septum DIE	0.66 (0.53-0.79)	<i>p</i> < 0.05	34 (10/29)	98 (88/90)
Uterosacral ligaments DIE	0.64 (0.54-0.74)	<i>p</i> < 0.05	34 (18/53)	94 (62/66)

^a The area under the curve is related to the overall ability of the test to correctly identify normal versus abnormal. If the test were perfect, the AUC would equal 1; if it was worthless (no better at identifying normal versus abnormal than chance), the AUC would be 0.5.

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Table 3: Diagnostic performance of Community and Specialist TVUS in the Diagnosis of Endometriosis with Laparoscopy as the Gold Standard

	Community TVUS						Specialist TVUS						Comparison	
	<i>n</i> = 44						<i>n</i> = 75						N = 119	
	AUC (95% CI)	<i>p</i> =	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC (95% CI)	<i>p</i> =	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Difference AUC	<i>p</i> =
Ovarian endometriomas and Ovarian Adhesions	0.84 (0.70-0.99)	<i>p</i> < 0.000	69 (11/16)	100 (28/28)	100 (11/11)	85 (28/33)	0.79 (0.68-0.87)	<i>p</i> < 0.000	88 (38/43)	69 (22/32)	79 (38/48)	81 (22/27)	0.06 (-0.12-0.24)	<i>p</i> = 0.53
Pouch of Douglas and Pouch of Douglas Adhesions DIE	0.57 (0.38-0.76)	<i>p</i> = 0.45	15 (2/13)	100 (31/31)	100 (2/2)	74 (31/42)	0.82 (0.72-0.92)	<i>p</i> < 0.000	69 (29/42)	94 (31/33)	94 (29/31)	70 (31/44)	-0.24 (-0.46 - -0.03)	<i>p</i> < 0.05
Bladder/UV Fold DIE	0.50 (0.32-0.69)	<i>p</i> = 1.00	0 (0/14)	100 (30/30)	0 (0/0)	68 (30/11)	0.49 (0.33-0.65)	<i>p</i> = 0.92	0 (0/16)	98 (58/59)	0 (0/1)	78 (58/74)	0.008 (-0.24-0.25)	<i>p</i> = 0.95
Rectosigmoid colon DIE	0.50 (0.20-0.80)	<i>p</i> = 1.00	0 (0/4)	100 (40/40)	0 (0/0)	91 (40/44)	0.85 (0.73-0.97)	<i>p</i> < 0.000	71 (15/21)	98 (53/54)	94 (15/16)	90 (53/59)	-0.35 (-0.67 - -0.03)	<i>p</i> < 0.05
Rectovaginal septum DIE	0.60	<i>p</i> = 0.34	20 (2/10)	100 (34/34)	100 (2/2)	81 (34/42)	0.69	<i>p</i> < 0.05	42 (8/19)	96 (54/56)	80 (8/10)	83 (54/65)	-0.09	<i>p</i> = 0.50

	(0.38-						(0.54-						(-0.36 -	
	0.82)						0.85)						0.18)	
Uterosacral	0.48	$p = 0.81$	0	96	0	51	0.75	$p <$	56	93	86	74	-0.27	$p < 0.05$
ligaments DIE	(0.31-		(0/21)	(22/23)	(0/1)	(22/43)	(0.63-	0.000	(18/32)	(40/43)	(18/21)	(40/54)	(-0.48 -	
	0.65)						0.87)						0.06)	

Table 4: Diagnostic performance of Community and Specialist TVUS in the Diagnosis of Endometriosis with Laparoscopy as the Gold Standard in Symptomatic Individuals

	Community TVUS <i>n</i> = 27						Specialist TVUS <i>n</i> = 60						Comparison N = 87	
	AUC (95% CI)	<i>p</i> =	Sensitivity (%) (9/12)	Specificity (%) (15/15)	PPV (%) (9/9)	NPV (%) (15/18)	AUC (95% CI)	<i>p</i> =	Sensitivity (%) (31/35)	Specificity (%) (17/25)	PPV (%) (31/39)	NPV (%) (17/21)	Difference AUC (-0.12-0.29)	<i>p</i> =
Ovarian endometriomas and Ovarian Adhesions	0.88 (0.72-1.00)	<i>p</i> = 0.001	75 (9/12)	100 (15/15)	100 (9/9)	83 (15/18)	0.78 (0.66-0.91)	<i>p</i> < 0.000	89 (31/35)	68 (17/25)	79 (31/39)	81 (17/21)	0.09 (-0.12-0.29)	<i>p</i> = 0.37
Pouch of Douglas and Pouch of Douglas Adhesions DIE	0.61 (0.37-0.85)	<i>p</i> = 0.36	22 (2/9)	100 (18/18)	7 (2/29)	58 (18/31)	0.83 (0.73-0.94)	<i>p</i> < 0.000	75 (27/36)	92 (22/24)	93 (27/29)	71 (22/31)	0.22 (-0.49-0.04)	<i>p</i> = 0.10
Bladder/UV Fold DIE	0.50 (0.27-0.73)	<i>p</i> = 1.00	0 (0/10)	100 (17/17)	0 (0/0)	63 (17/27)	0.50 (0.33-0.67)	<i>p</i> = 1.00	0 (0/16)	100 (44/44)	0 (0/0)	73 (44/60)	0.00 (0.00-0.00)	<i>p</i> = 1.00
Rectosigmoid colon DIE	0.50 (0.15-0.85)	<i>p</i> = 1.00	0 (0/3)	100 (24/24)	0 (0/0)	89 (24/27)	0.86 (0.73-0.98)	<i>p</i> < 0.000	74 (14/19)	98 (40/41)	93 (14/15)	89 (40/45)	0.36 (-0.73-0.02)	<i>p</i> = 0.06
Rectovaginal septum DIE	0.61	<i>p</i> = 0.36	22 (2/9)	100 (18/18)	100 (2/2)	72 (18/25)	0.70	<i>p</i> < 0.05	44 (8/18)	95 (40/42)	80 (40/50)	80 (8/10)	0.09	<i>p</i> = 0.56

Uterosacral ligaments DIE	(0.37- 0.85)						(0.54- 0.86)						(-0.38- 0.20)	
	0.50	$p = 1.00$	0	100	0	33	0.78	$p <$	60	97	95	71	0.28	$p < 0.05$
	(0.27- 0.74)		(0/18)	(9/9)	(0/0)	(9/27)	(0.66- 0.91)	0.000	(18/30)	(29/30)	(18/19)	(29/41)	(-0.55- -0.02)	

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