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The association between ultrasound-based 'soft markers' and endometriosis type/location: A prospective observational study

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ABSTRACT

Objective: Evaluate whether symptoms and/or transvaginal ultrasound (TVS) 'soft markers' (ovarian immobility and/or site-specific tenderness (SST)) are associated with endometriosis type/location.
Study design: Multicenter prospective observational study (January 2009 to February 2013) in tertiary centers for women with chronic pelvic pain who underwent detailed history, specialized TVS, and laparoscopy. Chart findings were collated into a study database. Outcome measures included correlation between symptoms, ovarian immobility or SST on TVS and endometriosis type and/or location. The performance of ovarian immobility to predict ipsilateral SE was evaluated in terms of accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).
Results: A total of 189 participants were included. Ovarian immobility on TVS was significantly associated with: ipsilateral pelvic pain, uterosacral ligament (USL) and pelvic sidewall superficial endometriosis (SE), endometrioma, posterior compartment deep endometriosis (DE), pouch of Douglas (POD) obliteration, and need for bowel surgery (all $p < 0.05$). For women with isolated SE (i.e.no endometrioma, DE, or POD obliteration), left ovarian immobility was significantly associated with left USL SE ($p = 0.01$) and left adnexal SST corresponded to left pelvic sidewall SE ($p = 0.03$). The accuracy, sensitivity, specificity, PPV and NPV for ovarian immobility at TVS and the presence of ipsilateral pelvic sidewall SE for the left ovary was: 71%, 16%, 87%, 27% and 78%, respectively; and for the right ovary was: 82%, 7.0%, 94%, 14% and 87%, respectively.
Conclusion: Ovarian immobility on TVS was significantly associated with ipsilateral pelvic pain, USL/pelvic sidewall SE, endometrioma, posterior compartment DE, and POD obliteration. The diagnostic accuracy of ovarian immobility for disease location in women with isolated SE showed a high specificity and NPV, but poor sensitivity and PPV, suggesting that ipsilateral pelvic sidewall SE is less likely to be present in women with a mobile ovary (in the absence of endometrioma or DE). Larger studies are required to further evaluate the usefulness of soft markers for the localization of isolated SE.

Introduction

A recent Cochrane Review on the non-invasive diagnosis of endometriosis highlighted the utility of transvaginal ultrasound (TVS) as a highly specific test for endometriomas and deep endometriosis (DE) of the posterior compartment anatomic sites [1]. However, no imaging technique achieved levels of sensitivity or specificity to replace surgery and histopathology as gold standard for the diagnosis of superficial endometriosis (SE) [1]. The inability to rule in, and possibly more importantly, rule out SE yields a hugely problematic scenario for women, healthcare providers, and those responsible for funding healthcare. This uncertainty may result in women being exposed to the risks and costs of diagnostic surgery. As such, all stakeholders should be interested in diagnosing SE in a non-invasive manner.

To address this, two possible useful ultrasound-based 'soft markers' have been evaluated: 1) ovarian immobility and 2) site-specific tenderness (SST). Ovarian immobility on TVS is associated with endometriosis at surgery [2], presence of endometriomas [3], and pouch of Douglas (POD) obliteration [4,5]. The combination of

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symptoms, physical examination, and ovarian immobility on TVS was able to demonstrate a sensitivity and specificity of 92% and 61%, respectively, for the detection of endometriosis at laparoscopy [6]. Other studies support and encourage the inclusion of ovarian mobility assessment on TVS in women with suspected endometriosis [7–10].

Knowledge of ovarian immobility may improve our understanding of endometriosis severity preoperatively, allowing more thorough surgical planning. The ability to predict an increased risk of pelvic sidewall SE could help identify those likely to require pelvic sidewall dissection and ureterolysis, both advanced skills. To date, studies evaluating the association between ovarian mobility and SE are scarce.

Furthermore, the relation between endometriosis and SST is a potentially valuable component of the TVS examination that warrants further investigation. Yong et al. attempted to predict the presence of SE based on tenderness elicited during physical and TVS examination, but found SST yielded a high false positive rate and was not useful in locating SE [11]. Conversely, when focusing on posterior compartment DE, SST reliably predicted specific locations of DE [12,13].

Our presented study aimed to determine whether symptoms and/or TVS-based 'soft markers' are associated with endometriosis type (SE, endometrioma, and DE) and location in women referred to tertiary care centres with suspected endometriosis.

Materials and methods

A multicenter prospective observational study was performed from January 2009 to February 2013 at nine tertiary care centres in Sydney, Australia. Ethics approval for this study was obtained by the local ethics committee (#06/049). Data on the 189 women included in this study have been published in two other studies [5,14].

An information sheet was given to eligible women and verbal informed consent was obtained. Inclusion criteria included: postmenarchal and premenopausal status, history of chronic pelvic pain [2] and/or endometriosis, and scheduled for laparoscopy. Exclusion criteria were pregnancy and current or previous history of gynaecological malignancy.

All participants underwent a detailed history, physical examination and preoperative TVS including assessment of POD obliteration, DE, and 'soft markers' [15]. Operators were provided definitions of ovarian mobility status and instructions on how to assess this prior to their assessments. The normal, mobile state was defined as an ovary that moves freely against the adjacent pelvic sidewall and uterus (Supplementary Video 1). The abnormal, immobile state was defined as an ovary that does not move freely against the adjacent pelvic sidewall and/or uterus (Supplementary Video 2).

In order to assess for SST during the TVS, the examiner placed gentle pressure with the transvaginal probe against the right and left adnexa, right and left USLs, and anterior and posterior vaginal fornices. A verbal Numerical Rating Scale (vNRS) (0 (no pain) to 10 (worst pain imaginable)) was used to quantify SST. In this study, SST was performed prior to the assessment for visible disease.

Participants then underwent laparoscopy, in which a systematic inspection for pathology was done. When superficial, peritoneal plaque-like lesions (red, black, brown, or white in color) were identified and ablated/excised, SE was documented. A visual diagnosis of SE was accepted in the absence of a histopathology specimen (that is, in the context of ablation) [16,17]. The remainder of disease was managed as deemed appropriate by the surgeon. Operative reports were reviewed by the authors and the surgical findings were recorded in the Excel database.

Univariate analysis of the data was used to investigate the distribution of variables in participants included in this study. For continuous variables, descriptive statistics are reported including the mean, standard deviation and range, with p-values calculated using ANOVA tests. For categorical variables, the frequency of different categories and the percentages are listed for the various surgical findings associated with TVS finding of ovarian immobility using Fisher's exact test. The vNRS scores for SST were analyzed for significance between participants with and without endometriosis using Fisher's exact test. A p-value <0.05 was considered statistically significant. The associations between symptoms, ovarian mobility and endometriosis type and location was analyzed and p-values were obtained using Fisher's exact test. Subgroup analysis for symptoms, ovarian mobility and SST with relation to endometriosis type and location was also performed for participants without endometrioma ($n = 43$) and participants without endometrioma or DE ($n = 112$). Benjamini-Hochberg adjusted p-values have been computed to indicate the false discovery (or significance) rate due to multiple comparisons. The performance of ovarian immobility to predict ipsilateral SE in women without endometrioma/POD obliteration/DE was evaluated in terms of accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) using Fisher's exact test. Women with missing values for any of the variables studied were excluded from the analysis.

Power analysis was done with Fisher's exact tests using a dataset of internal pilot project with 56 women, with an interest to detect a significant association between the ovarian fixation at TVS with the presence of DE or SE at surgery. Assuming the rate of ovarian fixation for the group with DE present and absent is 0.68 and 0.29, respectively, and the DE prevalence 0.34, with a two-sided significance of 0.05 and a power of 0.8, total 60–80 women will be required detecting an overall association for DE; whilst similarly, 150–180 women will be required for SE.

Statistical computing software R Version 3.4.0 (www.r-project.org) was used for analysis.

Results

Two hundred and twenty consecutive women were recruited. Of these, 189 participants with preoperative TVS ultimately underwent laparoscopy and were included in the final analysis (Fig. 1). The mean age was 32.2+/-7.46 years and 92/189 (48.7%) had a history of endometriosis. The prevalence of endometriosis was 146/189 (77.2%).

Regarding participant symptomatology and endometriosis type and location, the statistically significant associations are outlined in Tables 1A (symptoms associated with presence of endometrioma) and 1B (symptoms associated with DE). The only symptom significantly associated with the SE was diarrhea (present, 34.8% versus absent, 17.4%; $p = 0.031$).

Superficial endometriosis

SE was present in 122/189 (64.6%) participants. Distribution of disease location is outlined in Table 2. Isolated disease with no evidence of endometrioma/DE was present in 66/122 (54.1%). Histopathology was available for 75/122 (61.4%) participants with SE. For the women with isolated SE, 32/66 (48.0%) participants had histopathology confirmed. There was no difference in the historical variables between participants with and without isolated SE.

Ovarian endometrioma

Endometriomas were present in 46/189 (24.3%) participants; 16/189 (8.5%) had bilateral lesions, whereas 15/189 (7.9%) had only

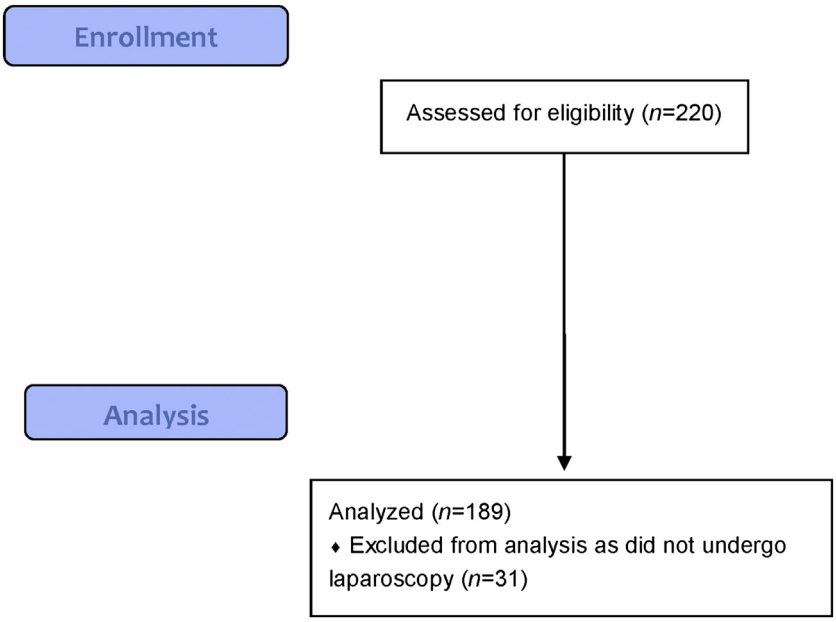

Fig. 1. Flow chart of patient enrollment and study eligibility.

a right endometrioma and 15/189 (7.9%) had only a left endometrioma. The presence of endometrioma at surgery was significantly associated with posterior compartment DE (60.9% versus 19.1% without endometrioma, $p < 0.001$) and more specifically anterior rectal/rectosigmoid DE (50.0% versus 12.8%, $p < 0.001$). Table 1A displays the symptoms significantly associated with endometrioma presence and location.

Posterior compartment deep endometriosis

Posterior compartment DE was visualized in 57/189 (30.2%) participants and 47/189 (24.9%) participants had POD obliteration. Table 1B displays the symptoms significantly associated with DE location. Posterior compartment DE was confirmed in 44/47 (93.6%) participants with POD obliteration who underwent complete surgical dissection. Three participants did not undergo POD dissection with resection of disease; therefore, no histopathological diagnosis was achieved. However, for all three of these participants, rectal DE was visualized at preoperative TVS.

Ovarian mobility

Symptoms significantly associated with ovarian immobility on TVS for women with unilateral and bilateral endometrioma(s) included: dyschezia, dysmenorrhea, rectal bleeding, right or left lower abdominal pain and tenesmus (all p-values <0.05). Table 3 outlines the symptoms significantly associated with ovarian immobility for women without endometrioma(s). Unilateral ovarian fixation on TVS was identified in 68/189 (36.0%) participants, while 31/189 (16.4%) had bilateral ovarian immobility. The left ovary was immobile in more participants than then right ($n = 55$, 29.1% versus $n = 44$, 23.3%). Amongst participants without an endometrioma ($n = 143$), the left ovary was immobile in 19.0%, right ovary immobile in 12.5% and both ovaries immobile in 5.6%.

Table 4 displays the association between ovarian immobility on TVS and the presence of abnormal surgical findings. When the abnormal, immobile state of an ovary is evaluated individually (that is, the contralateral ovary is noted to be normal and mobile), the only significant surgical feature associated with right *only* or left *only* ovarian fixation on TVS was the corresponding right only or left only ovarian fixation at surgery ($p = 0.01$ and $p = 0.02$, respectively). Although ovarian fixation was not significantly associated with USL DE, 75.1% of women with left USL DE had left ovarian fixation versus 28.0% without left USL DE ($p = 0.08$).

Table 5 displays the results for the association between ovarian immobility and surgical features, in the absence of endometrioma ($n = 143$). When participants with endometriomas, posterior compartment DE, and/or POD obliteration were excluded from the analysis, left ovarian immobility and left USL SE was the only significant correlation ($p = 0.014$). The accuracy, sensitivity, specificity, PPV and NPV for ovarian immobility at TVS and the presence

Table 1A
Symptoms significantly associated with endometrioma presence and location at surgery among participants with endometrioma ($n = 46$).

Symptom	Prevalence of symptom %	Endometrioma location, prevalence Site, *n*, %	*p*-value
Rectal bleeding	10.1	Right, 7, 22.6	0.006
		Left, 7, 22.6	0.012
Dyschezia	43.9	Left, 20, 64.5	0.006
Left lower quadrant pain	34.9	Left, 15, 48.4	0.023
Dysmenorrhea	66.1	Right, 22, 71.0	0.042
		Left, 25, 80.6	0.016
		Bilateral, 12, 75.0	0.038
Tenesmus	20.1	Right only, 6, 40.0	0.030

Fisher's exact test was used to calculate p-values. *Legend: n*: number, Right: participants with either solitary right endometrioma or right endometrioma in the presence of left endometrioma ($n = 31$), Left: participants with either solitary left endometrioma or left endometrioma in the presence of right endometrioma ($n = 31$), Bilateral: participants with endometriomas on both right and left ovaries ($n = 16$), Right only: participants with only solitary right endometrioma ($n = 15$).

Table 1B
Significant associations between symptoms and DE location diagnosed surgically among all participants ($n = 189$).

Symptom	Prevalence of symptom%	DE location	DE present among participant with symptom *n*, %	*p*-value
Dysmenorrhea	66.1	Rectosigmoid colon	12, 92.3	0.038
Dyschezia	43.9	Rectosigmoid colon	5, 38.5	0.005
		Posterior compartment	33, 57.9	0.007
Rectal bleeding	10.1	Rectosigmoid colon	5, 38.5	0.005
		Posterior compartment	12, 21.1	0.002
		Anterior rectum/Rectosigmoid colon	10, 22.2	0.004
Tenesmus	20.1	Posterior compartment	18, 31.6	0.009
Right lower quadrant pain	32.8	Posterior compartment	23, 40.4	0.046
		Rectovaginal septum	8, 72.7	0.007
Left lower quadrant pain	34.9	Posterior compartment	24, 42.1	0.049
		Rectovaginal septum	8, 72.7	0.015
		Anterior rectum	17, 47.2	0.036

Fisher's exact test was used to calculate p-values. *Legend:* n = number, DE: deep endometriosis; Posterior compartment: anterior rectum, rectosigmoid colon, vagina, rectovaginal septum and/or uterosacral deep endometriosis ($n = 57$), Anterior rectum ($n = 36$), Rectosigmoid colon ($n = 13$), Anterior rectum/Rectosigmoid colon ($n = 43$), Rectovaginal septum ($n = 11$).

Table 2
Locations of identified superficial endometriosis among participants with superficial endometriosis ($n = 122$).

Disease Location	Participants, *n*, %
Left USL	73, 59.8
Right USL	62, 50.8
Left pelvic sidewall	57, 46.7
Right pelvic sidewall	44, 36.1
POD	42, 34.4
Uterovesical pouch	26, 13.8
Left pararectal space	17, 21.3
Right pararectal space	12, 9.8
Diaphragm	1, 0.8

USL: uterosacral ligament, POD: pouch of Douglas.

of ipsilateral pelvic sidewall SE, in women without endometrioma/POD obliteration/DE, for the left ovary was: 71%, 16%, 87%, 27% and 78%, respectively; and for the right ovary was: 82%, 7.0%, 94%, 14% and 87%, respectively.

Site-specific tenderness

Data for vNRS scores were available for 108/189 (57.1%) participants and for 63/112 (56.3%) participants without endometrioma/DE/POD obliteration for the SST analysis. There was a statistically significant association between left adnexal SST and left pelvic sidewall SE ($p = 0.027$) in the absence of endometrioma/DE/POD obliteration ($n = 112$). Mean vNRS scores for left adnexal SST were 6.5 versus 4.6 for participants with versus without left pelvic sidewall SE. The VNRS scores for SST were not significantly associated with ovarian immobility or location of endometrioma and/or DE.

Discussion

We have demonstrated that ultrasound-based 'soft markers' may provide valuable insight into the extent of endometriosis. Ovarian immobility was significantly associated with SE, DE, and POD obliteration, in the presence and absence of ovarian endometrioma. In the left adnexa, SST was significantly associated with SE of the left pelvic sidewall. This study helps to further characterize the relation between ovarian fixation and SST on TVS and specific endometriosis types and locations [2,11].

Consistent with previous research, the current study was unable to demonstrate a significant relationship between symptoms and the location of SE. Diarrhea was the only symptom significantly associated with isolated SE. The association between gastrointestinal symptoms (i.e. abdominal pain, bloating, nausea, constipation, vomiting, painful bowel movements, diarrhea) and the presence of endometriosis has been well documented in the literature [18–20], however this relationship is not well understood. A study by Maroun et al. found that most women with gastrointestinal symptoms (92.5%) and concurrent endometriosis did not have endometriosis that involved the bowel [18]. The aforementioned study also found diarrhea was more prevalent in women with a history of IBS, and the relationship between IBS and endometriosis has been previously reported [21]. The findings from the current study reinforce the importance of obtaining a detailed patient history, including the assessment of bowel symptoms, in women with suspected endometriosis.

Another important finding in this study was that self-reported right and left lower quadrant pain was significantly associated with ovarian immobility on the corresponding side, even in the absence of endometrioma. This finding suggests that the location of ovarian

Table 3
Symptoms significantly associated with ovarian immobility on TVS among participants without endometrioma ($n = 143$).

Ovary fixed	Symptom	Symptom present *n*, %	Symptom absent *n*, %	*p*-value
Right $n = 16$	Dyschezia	11, 19.6	4, 5.6	0.024
	Dyspareunia	13, 16.3	2, 4.2	0.048
	RLQ pain	9, 20.5	5, 6.1	0.019
	Tenesmus	7, 28	8, 7.8	0.011
Left $n = 24$	LLQ pain	12, 26.7	8, 9.9	0.021
	Rectal bleeding	4, 44.4	18, 15.1	0.047
	Tenesmus	8, 32.0	14, 13.6	0.039
Bilateral $n = 7$	LLQ pain	5, 11.1	0, 0.0	0.005
	RLQ pain	5, 11.4	0, 0.0	0.004
	Tenesmus	4, 16.0	2, 1.9	0.013

Fisher's exact test was used to calculate *p*-values. *Legend*: TVS: transvaginal ultrasound, *n*: number, RLQ: right lower quadrant, LLQ: left lower quadrant.

Table 4
Surgical findings significantly associated with ovarian fixation on transvaginal ultrasound in all participants ($n = 189$).

	Surgical feature	Surgical feature present *n*, %	Surgical feature absent *n*, %	*p*-value	*p*-adjusted (FDR)
Presence versus absence of surgical findings associated with right ovarian fixation on TVS, $n = 44$	Right endometrioma, $n = 31$	20, 64.5	23, 14.7	<0.001	<0.001
	Right only endometrioma, $n = 15$	9, 60.0	34, 19.8	0.001	0.003
	Left endometrioma, $n = 31$	18, 58.1	25, 16.0	<0.001	0.094
	Bilateral endometriomas, $n = 16$	11, 68.8	32, 18.7	<0.001	<0.001
	Posterior compartment DE, $n = 57$	26, 45.6	18, 13.6	<0.001	<0.001
	Rectal and rectosigmoid DE, $n = 43$	24, 55.8	20, 13.7	<0.001	<0.001
	Rectal DE, $n = 36$	19, 52.8	25, 16.3	<0.001	<0.001
	Rectosigmoid colon DE, $n = 13$	10, 76.9	34, 19.3	<0.001	<0.001
	RVS and/or vaginal DE, $n = 16$	8, 50.0	36, 20.8	0.014	0.034
	RVS DE, $n = 11$	7, 63.6	37, 20.8	0.004	0.012
	Right USL SE, $n = 62$	21, 33.9	23, 18.3	0.027	0.059
	POD obliteration, $n = 47$	31, 66.0	13, 9.2	<0.001	<0.001
	Bowel surgery, $n = 40$	23, 57.5	21, 14.1	<0.001	<0.001
Presence versus absence of surgical findings associated with left ovarian fixation on TVS, $n = 55$	Right endometrioma, $n = 31$	21, 67.7	32, 20.5	<0.001	<0.001
	Right only endometrioma, $n = 15$	10, 66.7	43, 25.0	0.001	0.003
	Left endometrioma, $n = 31$	19, 61.3	34, 21.8	<0.001	<0.001
	Left only endometrioma, $n = 15$	8, 53.3	45, 26.2	0.036	0.075
	Bilateral endometrioma, $n = 16$	11, 68.8	42, 24.6	0.001	0.003
	Posterior compartment DE, $n = 57$	30, 52.6	25, 18.9	<0.001	<0.001
	Rectal and rectosigmoid DE, $n = 43$	26, 60.5	29, 19.9	<0.001	<0.001
	Rectal DE, $n = 36$	21, 58.3	34, 22.2	<0.001	<0.001
	Rectosigmoid colon DE, $n = 13$	9, 69.2	46, 26.1	0.002	0.006
	RVS and/or vaginal DE, $n = 16$	10, 62.5	45, 26.0	0.007	0.020
	Vaginal DE, $n = 11$	7, 63.6	48, 27.0	0.015	0.037
	POD obliteration, $n = 47$	33, 70.2	22, 15.5	<0.001	<0.001
	Bowel surgery, $n = 40$	26, 65.0	29, 19.5	<0.001	<0.001
Presence versus absence of surgical findings associated with bilateral ovarian fixation on TVS, $n = 31$	Right endometrioma, $n = 31$	17, 54.8	13, 8.3	<0.001	<0.001
	Right only endometrioma, $n = 15$	6, 40.0	24, 14.0	0.018	0.043
	Left endometrioma, $n = 31$	17, 54.8	13, 8.3	<0.001	<0.001
	Left only endometrioma, $n = 15$	6, 40.0	24, 14.0	0.018	0.043
	Bilateral endometrioma, $n = 16$	11, 68.8	19, 11.1	<0.001	<0.001
	Posterior compartment DE, $n = 57$	21, 36.8	10, 7.6	<0.001	<0.001
	Rectal and Rectosigmoid DE, $n = 43$	19, 44.2	12, 8.2	<0.001	<0.001
	Rectal DE, $n = 36$	15, 41.7	16, 10.5	<0.001	<0.001
	Rectosigmoid DE, $n = 13$	8, 61.5	23, 13.1	<0.001	<0.001
	RVS and/or vaginal DE, $n = 16$	6, 37.5	25, 14.5	0.029	0.062
	RVS DE, $n = 11$	5, 45.5	26, 14.6	0.019	0.043
	POD obliteration, $n = 47$	26, 55.3	5, 3.5	<0.001	<0.001
	Bowel surgery, $n = 40$	19, 47.5	12, 8.1	<0.001	<0.001

Fisher's exact test was used to calculate *p*-values. Benjamini-Hochberg adjusted *p*-values have been reported to indicate the false discovery rate due to multiple comparison.
Legend: *n*: number; FDR: false discovery rate; TVS: transvaginal ultrasound; DE: deep endometriosis; RVS: rectovaginal septum; USL: uterosacral ligament; POD: pouch of Douglas; posterior compartment DE: DE involving the USL, RVS, vagina, and/or rectosigmoid/anterior rectum; SE: superficial endometriosis.

adherence to surrounding structure may play a role in the site of pelvic pain symptoms. In the context of endometriomas, a significant association between left lower quadrant pain and left sided endometrioma was demonstrated.

Diagnostic accuracy results for ovarian immobility at TVS and location of ipsilateral pelvic sidewall SE showed a low sensitivity and PPV, for both the right (7% and 14%, respectively) and left (16% and 27%, respectively) ovary in women with isolated SE. However, the specificity and NPV was high for both ovaries (right ovary: 94% and 87%, respectively and left ovary: 87% and 78%, respectively). This high specificity and NPV is encouraging, as this result suggests that women with a mobile ovary at ultrasound (in the absence of endometrioma/POD obliteration/DE) may be less likely to have ipsilateral pelvic sidewall SE. However, the results from the current study are based on a very small population and larger studies are required to provide a more accurate assessment of ovarian immobility for the prediction of presence/absence of SE.

Although the sensitivity and PPV for ovarian immobility and pelvic sidewall SE was low, our study suggests there is an association between ovarian immobility and USL and pelvic sidewall SE, even in the absence of other forms of endometriosis. The ability to predict an increased risk of USL and pelvic sidewall SE when ipsilateral ovarian immobility is seen on TVS may allow for improved surgical triaging and planning. It is within the skill set of many general gynecologists to perform excision and/or ablation of endometriosis within the pelvis. However, depending on the location and extent of the disease, advanced laparoscopic skill may be required.

Furthermore, the findings from this study support the significant positive correlation between ovarian immobility and the severity of pelvic endometriosis. Even in the absence of endometrioma, ovarian immobility seen on TVS appears to be significantly associated with the presence of posterior compartment DE and POD obliteration. As such, our study can support

Table 5
Significant surgical findings associated with ovarian fixation on TVS in participants without endometrioma ($n = 143$).

	Surgical feature	Prevalence of surgical feature *n*	Prevalence of absent surgical feature *n*	Surgical feature present *n*, %	Surgical feature absent *n*, %	*p*-value	*p*-adjusted (FDR)
Presence versus absence of surgical findings associated with fixation of the right, left or both ovaries on TVS ($n = 33$)	Posterior compartment DE	27	114	11, 40.7	22, 19.3	0.024	0.053
	Rectum, Rectosigmoid DE	16	123	9, 50.0	24, 19.5	0.013	0.034
	Rectum DE	17	124	8, 47.1	25, 20.2	0.028	0.059
	Rectosigmoid DE	4	137	3, 75.0	30, 21.9	0.040	0.075
	RVS and/or vaginal DE	8	133	5, 62.5	28, 21.1	0.018	0.043
	RVS DE	6	135	4, 66.7	29, 21.5	0.027	0.058
	Left USL SE	54	86	21, 38.9	12, 14.0	0.001	0.003
	Right USL SE	42	98	15, 35.7	18, 18.4	0.040	0.075
	POD obliteration	17	124	12, 70.6	21, 16.9	<0.001	<0.001
	Bowel surgery	18	123	10, 55.6	23, 18.7	0.001	0.005
Presence versus absence of surgical findings associated with right ovarian fixation on TVS ($n = 16$)	Posterior compartment DE	27	114	7, 25.9	9, 7.9	0.016	0.275
	Rectum, Rectosigmoid DE	16	123	7, 38.9	9, 7.3	0.001	0.016
	Rectum DE	17	124	6, 35.3	10, 8.1	0.005	0.034
	Rectosigmoid DE	4	137	3, 75.0	13, 9.5	0.005	0.034
	RVS and/or vaginal DE	8	133	4, 50.0	12, 9.0	0.006	0.036
	RVS DE	6	135	4, 66.7	12, 8.9	0.002	0.021
	Left USL SE	54	86	12, 22.2	4, 4.7	0.002	0.023
	Right USL SE	42	98	10, 23.8	6, 6.1	0.007	0.037
	POD obliteration	17	124	9, 52.9	7, 5.6	<0.001	<0.001
	Bowel surgery	18	123	8, 44.4	8, 6.5	<0.001	<0.001
Presence versus absence of surgical findings associated with left ovarian fixation on TVS ($n = 24$)	Left USL SE	54	86	16, 29.6	8, 9.3	0.003	0.026
	POD obliteration	17	124	8, 47.1	16, 12.9	0.002	0.023
	Surgical excision of SE	89	52	20, 22.5	4, 7.7	0.035	0.112
Presence versus absence of surgical findings associated with bilateral ovarian fixation on TVS ($n = 7$)	Rectum, Rectosigmoid DE	16	123	3, 16.7	4, 3.3	0.045	0.128
	Rectum DE	17	124	3, 17.6	4, 3.2	0.038	0.117
	Left USL SE	54	86	7, 13.0	0, 0.0	0.001	0.016
	Right USL SE	42	98	5, 11.9	2, 2.0	0.026	0.091
	Left pelvic sidewall SE	41	100	5, 12.2	2, 2.0	0.023	0.088
	Right pelvic sidewall SE	29	111	4, 13.8	3, 2.7	0.034	0.112
	Surgical excision of SE	89	52	7, 7.9	0, 0	0.049	0.128
	RVS DE	6	135	2, 33.3	5, 3.7	0.029	0.099
	POD obliteration	17	124	5, 29.4	2, 1.6	<0.001	<0.001
	Bowel surgery	18	123	4, 22.2	3, 2.4	0.005	0.034

Fisher's exact test was used to calculate p-values. Benjamini-Hochberg adjusted p-values have been reported to indicate the false discovery rate due to multiple comparison. Legend: n: number; FDR: false discovery rate; TVS: transvaginal ultrasound; DE: deep endometriosis; RVS: rectovaginal septum; USL: uterosacral ligament; POD: pouch of Douglas; posterior compartment DE: DE involving the USL, RVS, vagina, and/or rectosigmoid/anterior rectum; SE: superficial endometriosis.

previously published recommendations to include ovarian mobility in the ultrasound assessment for DE mapping and prediction of surgical complexity [4,7].

In cases of isolated SE, left adnexal SST was significantly associated with left pelvic sidewall SE at laparoscopy. In our study, this was the only location of SST that corresponded to superficial disease location seen surgically. Due to the small subset of women with isolated SE and high number of missing SST values, it was not possible to perform diagnostic accuracy analysis for SST and SE location in this group.

In a study by Yong et al., a combination of TVS- and vaginal examination-elicited pain achieved a sensitivity of 81% for participants with abnormal superficial findings (without endometrioma or DE) on laparoscopy [11]. However, when researchers analyzed adnexal tenderness compared to the laterality of disease, the test declined in its sensitivity and increased in specificity. Considering our findings were significant on the left, and not the right, we are optimistic but cautious regarding the utility of ultrasound to detect superficial disease. One possible explanation for the fair overall association between SST and SE is the patient

population; only women with chronic pelvic pain and/or a history of endometriosis were included. The vNRS scores may be falsely higher secondary to non-endometriosis pelvic pain conditions. Larger studies with various patient populations are needed to confirm whether an association exists between SE and SST.

A criticism of the study is there may have been inter/intraobserver variation in the pressure applied with the ultrasound probe between the two observers. Secondly, there may be a degree of subjectivity in ovarian mobility assessment. However, there is some evidence to suggest that interobserver detection of ovarian adhesions on TVS is reliable [22]. The concept of ovarian mobility assessment is also not very different from POD obliteration assessment, for which there is evidence of inter/intraobserver reliability [23,24].

Additionally, gold standard histopathological confirmation of endometriosis was not available for all participants reported as having SE. However, previous studies have used the visual diagnosis alone as an equivalent [16,17]. The majority of surgeries performed in this study were performed by advanced laparoscopic surgeons with experience in the identification and surgical management of endometriosis, thus likely reducing the false positive and negatives diagnoses. Lastly, the sub-analysis for 'soft markers' contained a small number of women and there were missing data values for SST. The authors can hypothesize that both the lengthy time required to perform a comprehensive ultrasound for endometriosis and the discomfort it often elicits may have prevented some examiners from completing the SST component. In addition, not all women underwent their ultrasound examination at the same unit or by the same examiner, which limited the ability of the authors to continually ensure complete data collection.

Moreover, despite the prospective nature of the study, there were areas where missing data may impact the results of the study. As the historical data was collected by individual surgeons rather than a standard intake form completed by participants, this created a source of bias, resulting in some missing data. Again, the multicenter design of the study limited the ability of the authors to continually ensure complete data collection. As stated above, one of the primary outcomes of the study was to determine whether ovarian mobility corresponded to surgical findings of endometriosis and for this, we had complete data collection.

Finally, we acknowledge there are potential flaws in the study population selected. In particular, if a main goal is to better understand SE, it may be that exclusion of women with endometriomas and/or DE will strengthen the validity of test results. As well, it may be prudent to consider excluding women who have a known history of endometriosis, as test characteristics may be impacted (higher prevalence of disease and a higher pre-test probability of disease).

In conclusion, in addition to a significant association with endometrioma, posterior compartment DE and POD obliteration, ovarian immobility on TVS appears to be associated with isolated SE localized to the pelvic sidewall and USL. Site-specific tenderness may also be a sign of isolated sidewall SE. Future research in the form of a randomised controlled based study may lead to a more robust conclusion regarding the value of ultrasound soft markers for the prediction of isolated SE. Furthermore, these potential TVS 'soft markers' may be useful in the development of a model to predict isolated SE preoperatively, thereby improving surgical planning for these women.

Details of ethics approval

Ethics approval from the Human Research Ethics Committee, Sydney West Area Health Service, Nepean campus, Penrith, Australia (Study # 06/049).

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Conflict of interest

None.

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Appendix A. Supplementary data

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