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(i) Multicentre retrospective study for non-surgical diagnosis of superficial endometriosis.

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Multicentre retrospective study to assess diagnostic accuracy of ultrasound for superficial endometriosis – are we any closer?

Short Title: Ultrasound Diagnosis of Superficial Endometriosis

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Abstract

Background – To establish whether the ultrasound findings of minimal endometriosis are confirmed at laparoscopy and that a correlation can be established as to the anatomical sites in this mild form of the disease.

Aims - Patients with pain and suspicion of endometriosis had an ultrasound scan by a sinologist with expertise in endometriosis as part of their pre-operative workup.

Measurements and Main results - The clinical histories of 53 patients who had laparoscopy to investigate pelvic pain were reviewed. Ultrasounds were performed by a single Sonologist with expertise in endometriosis assessments between 2012 – 2015. The ultrasound findings were divided into sub groups as follows – presence of utero sacral ligament thickness, thickened peri colic fat, ovarian mobility and focal tenderness. These was compared with operative findings of those patients with superficial endometriosis.

Evidence Level 3 – observational studies with controls and health services research that includes adjustment for likely confounding factors.

Results – Seventy nine percent(42 / 53) of the patients had laparoscopic findings consistent with their ultrasound findings (95% CI 68-90%, $p<0.0001$). Of the subgroups that we reviewed utero sacral thickening ($p < 0.05$) and thickened peri colic fat ($p < 0.05$) were the most associated with superficial endometriosis at the time of laparoscopy.

Conclusion -

Markers on ultrasound that reliably demonstrated that inflammation (thickened utero sacral ligaments and thickened peri colic fat) were shown to be significantly associated with the disease.

Introduction

Endometriosis is a chronic benign condition, the diagnosis made when endometrial glands and stroma are found in locations outside the uterine cavity. Although typically not life-threatening, it is associated with significant morbidity and a negative impact on a woman's quality of life[1].

The hunt for a non-invasive test to diagnose mild-moderate endometriosis has been extensive[2]. Considering that the diagnosis of endometriosis is often delayed, the burden of

undiagnosed, untreated endometriosis remains poorly understood [3]. Superficial endometriosis presents a challenging surgical problem, particularly when we counsel patients of perceived surgical outcomes. Preoperative investigations are important in order to provide the patient and surgical team with information regarding the severity of the disease and the likely surgery required, thus improving patient knowledge and facilitating triage of resources and personnel.

One unit (MHW) has been managing severe endometriosis patients with a multidisciplinary team over the last six years. The aim of this study is to perform a retrospective univariate analysis to confirm which factors, if any, may be predictive of the presence of superficial endometriosis at the time of surgery. This information will then be used as the basis upon which to develop a scoring system which can be assessed prospectively in a future study.

Materials and Methods

All of the unit's surgical database was reviewed to detect patients who had undergone an ultrasound.

The variables scored in a univariate analysis for predictive capacity were:

- Utero-sacral thickness
- Thickened peri-colic fat
- Focal tenderness
- Ovarian immobility
- Filmy adhesions
- symptoms – dysmenorrhoea, dyschezia, dysuria and dyspareunia.

Ethics approval was obtained from Ethics approval was obtained through low risk ethics application Mercy Health Human Research Ethics Committee and Epworth Hospital.

prior to data collection. R16/41.

Ultrasounds were performed by a single gynaecologist/ sonologist with expertise in endometriosis assessments between 2012 – 2015. Surgeries at the three institutions were performed by surgeons trained in advanced laparoscopy and currently work in a tertiary endometriosis surgical unit. Patients who had deep infiltrative endometriosis, endometriomas

and adenomyosis were excluded. Adenomyosis was defined by the ultrasound findings of; heterogenous myometrium (venetian blinding), asymmetry of uterine walls and presence of myometrial cysts[4].

Statistical Analysis

Patient data were entered into an Excel database and imported to SAS version 9.4 (SAS Institute Inc. Cary NC) for analysis. Each potential US predictive parameter was analysed separately as follows: - utero sacral ligament thickness, thickened peri colic fat, ovarian mobility and focal tenderness. Other parameters collected were age, BMI and symptoms including dysmenorrhoea, dysuria, dyspareunia, dyschezia and dysmenorrhoea.

Descriptive statistics were used to summarise all variables. Continuous variables were described as mean and standard deviation. Categorical variables were described as frequency and percentage. The proportion of patients with confirmation of superficial endometriosis on laparoscopy was classified as laparoscopic findings consistent with their ultrasound findings was estimated with 95% confidence intervals. Difference in BMI and age between patients with positive and negative findings were tested using the analysis of variance. Standard diagnostic and agreement statistics were calculated to assess the predictive effects of individual soft marker and symptom on operation findings. Sensitivity, specificity and ROC curve were estimated. They are demonstrated as ROC curves (Figure 4) All statistical tests were two-sided at 5% significance level.(Table 1)

The data were assessed for accuracy of single marker predictiveness for superficial endometriosis.

Imaging Protocol

A transvaginal US was performed in the weeks prior to surgery, as part of routine pre-operative care and assessment of pelvic pain. Patients were assessed at any time of the menstrual cycle and the time between initial scanning and surgical date was not analysed in the present study. A Voluson E8, with a 5-9 MHz vaginal probe was used in all cases, and the scans were performed by a single experienced operator.

The operator has gained significant experience in the pre-operative ultrasound assessment of cases with known stage 4 and deep endometriosis working with this tertiary gynaecological unit. Evaluations were made of the uterus, ovaries and the pelvic peritoneum which included

the bladder, vesico-uterine pouch, pouch of Douglas, recto-cervical space, recto-vaginal septum, and posterior vaginal fornix.

Bowel preparation in the form of a fleet enema was used prior to ultrasound in a selected group of patient where there was a clinical suspicion of deep rectal endometriosis, or if it was required to allow adequate ultrasound assessment of the rectum, recto-sigmoid and rectovaginal septum. Patients with a finding of deep rectal endometriosis or rectovaginal disease were excluded from the present study due to their diagnosis of deep infiltrative endometriosis.

Bowel preparation in the form of fleet enema was used prior to ultrasound in a selected group of patients where there was a clinical suspicion of deep rectal endometriosis. The decision was made prior to the ultrasound by the referring clinician. Exclusion of deep endometriosis is important in any imaging assessment. If the rectal wall is involved then bowel preparation facilitates a detailed assessment of the rectal disease. Patients with deep endometriosis were excluded from the study. Bowel preparation is not required in the assessment of markers for superficial endometriosis.

Uterosacral ligaments were assessed by obtaining an axial view of the cervix, with angulation of the vaginal probe into the right and left para-cervical areas (Figure 1) These visceral ligaments were reported to be thickened if they were assessed to be greater than 3mm. Mobility and tenderness of the uterosacral ligaments were reported in conjunction with this at the time of the scan. Pericolic fat is the fat surrounding the colon. It is commonly involved in inflammatory processes involving the pouch and rectum. This was also reported in a dichotomous scoring system. Thickened pericolic fat appeared to have increased echogenicity / density secondary to inflammatory and fibrotic changes,and was firm to probe pressure. Thickened pericolic fat can be difficult to identify. On CT this is called fat stranding – altered appearance to the lipomatous tissue in rectal wall mesentry rather than rectal wall itself (Figure 1)

Normal pericolic fat is pedunculated adipose tissue, with ‘thickened pericolic fat ‘ equating to ‘fat stranding’ reported in inflammatory bowel conditions [5].

Results

Seventy nine percent (42 / 53) of the patients had laparoscopic findings consistent with their ultrasound findings (95% CI 68-90%, p<0.0001)(Table1). Detection of thickened pericolic fat was most associated with mild-moderate endometriosis at the time of laparoscopy. Utero

sacral ligament thickening (sensitivity 0.62, specificity 0.73, area under the ROC curve 0.67, $p<0.05$). ROC curves for the other variables ovarian mobility, focal tenderness and filmy adhesions are demonstrated (Table 2)

No association was found between age and operation findings or symptoms. Of the symptoms, dysmenorrhoea had the highest sensitivity (0.98, 95% CI 0.87-0.99) but a very low specificity (0.18, 95% CI 0.02-0.52). The predictive value of a positive test was 0.89(95%CI: 0.71-0.97) with presence of uterosacral thickening which matched laparoscopic findings.

Discussion

Endometriosis is thought to effect 1 in 10 women with patient healthcare costs estimated at 10 billion in the last decade in Australia comparable to type 2 diabetes[6]. The development of a non-invasive tool for the diagnosis of superficial endometriosis is of great importance in this cohort of patients who currently have a diagnostic laparoscopy and biopsy as gold standard for diagnosing endometriosis[7]. The importance of early diagnosis has been shown to benefit women in terms of offering management strategies to control symptoms and providing a language in which to express their situation to healthcare providers and the community[8].

Accurate diagnosis of deep infiltrative endometriosis with ultrasound scan is well recognised[9,10]. However, there is only a small body of work looking at the ultrasound diagnosis of superficial endometriosis[11].

Although this is a retrospective study with a small sample size, it indicates that superficial endometriosis can be detected with ultrasound scan by an experienced sonologist who has specialised in endometriosis and we would argue that the skill-set required to diagnose these findings could be introduced into the COGU training curriculum. Similar to obtaining sound surgical skills in the excision of endometriosis, ultrasound training in the assessment of endometriosis has a learning curve and appropriate exposure and training is required.

An important issue with the current study is the ultrasonologist's assessment of uterosacral ligament thickening. We have been unable to identify in the current medical literature a descriptive measurement in the ultrasound diagnosis of this thickening although there has been some literature on the evidence of fat stranding in patients with acute abdominal pain[12].

The figure of 3mm and immobility of the ligament was arbitrarily applied by the ultrasonologist based on many years of training and experience in the scanning of endometriosis and crucially the attainment of feedback from surgical colleagues in terms of correlation with surgical findings. Future work should look into reproducibility of this finding, not only is the measurement and mobility critical but in addition the location of the ultrasound probe and its close proximity to the cervix (figure 3). Traditional teaching in the ultrasound assessment of the uterosacral ligaments has not focussed on the medial insertion[13,14]. We have demonstrated a statistically significant association between uterosacral ligament thickening (>3mm) and the operative finding of superficial endometriosis. Some might argue that ligament thickening is in fact diagnosing deep infiltrative disease rather than superficial endometriosis. We would maintain that definition of deep disease is endometriosis invading at a depth of >/=5mm and that ligament thickening of >3mm is not representative of deep disease[15].

Endometriosis is known for a triad of pain symptoms however in our study, as in all other studies, we failed to demonstrate a symptom-based predictive tool[16,17,18].

Conclusion

This small study demonstrates that a skilled Sonologist with specific training may demonstrate superficial endometriosis that correlates to surgical findings with considerable accuracy. There has been extensive search for non-surgical diagnosis of endometriosis[19]. As the ultrasound assessment of superficial endometriosis advances with appropriate education and training, we believe that this less invasive tool may be able to make a diagnosis of mild endometriosis and potentially decrease the health care costs and complications associated with surgery. Appropriate pre-surgical assessment of the severity of endometriosis will allow improved education of patients, utilisation of theatre time and appropriate allocation of seniority of surgeon.

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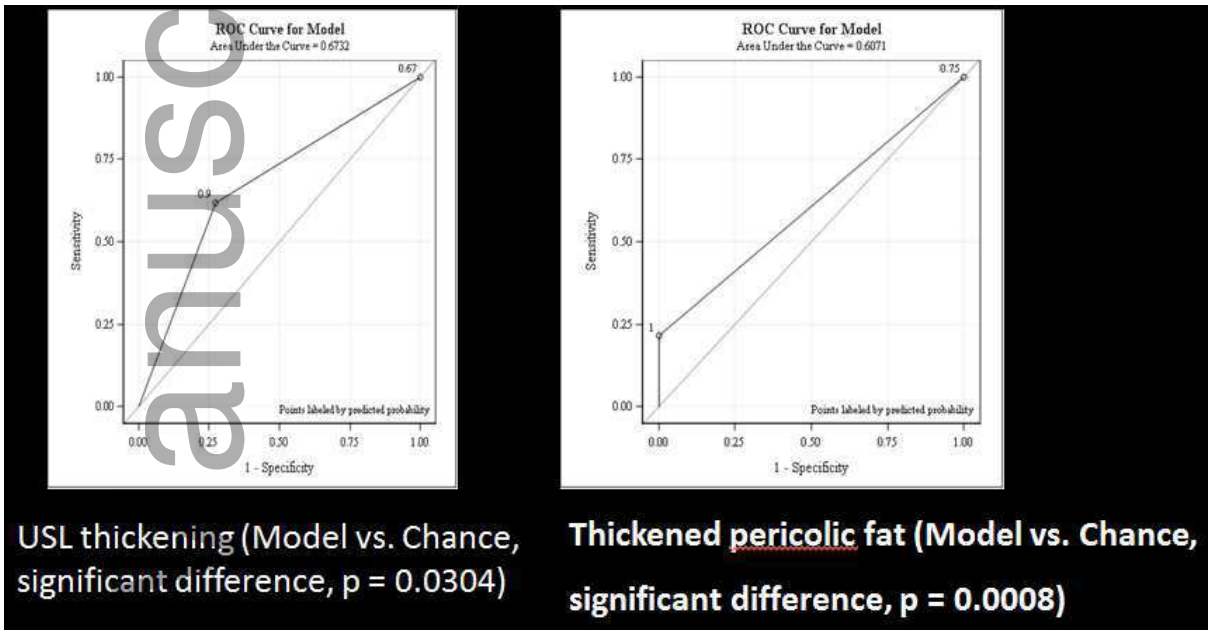
Lap match USS (n = 53, 30 patients missing)

	Number	Proportion	Standard Error	Lower 95% CI	Upper 95% CI	P-value
Yes	42	79.25%	5.57%	68.33%	90.16%	<0.0001

79% of the patients with the lap results were matched to their USS findings (95% CI 68-90%, p<0.0001).

Table 1: Laparoscopic findings matching USS findings



ROC curves for Uterosacral ligament thickening and thickened pericolic fat

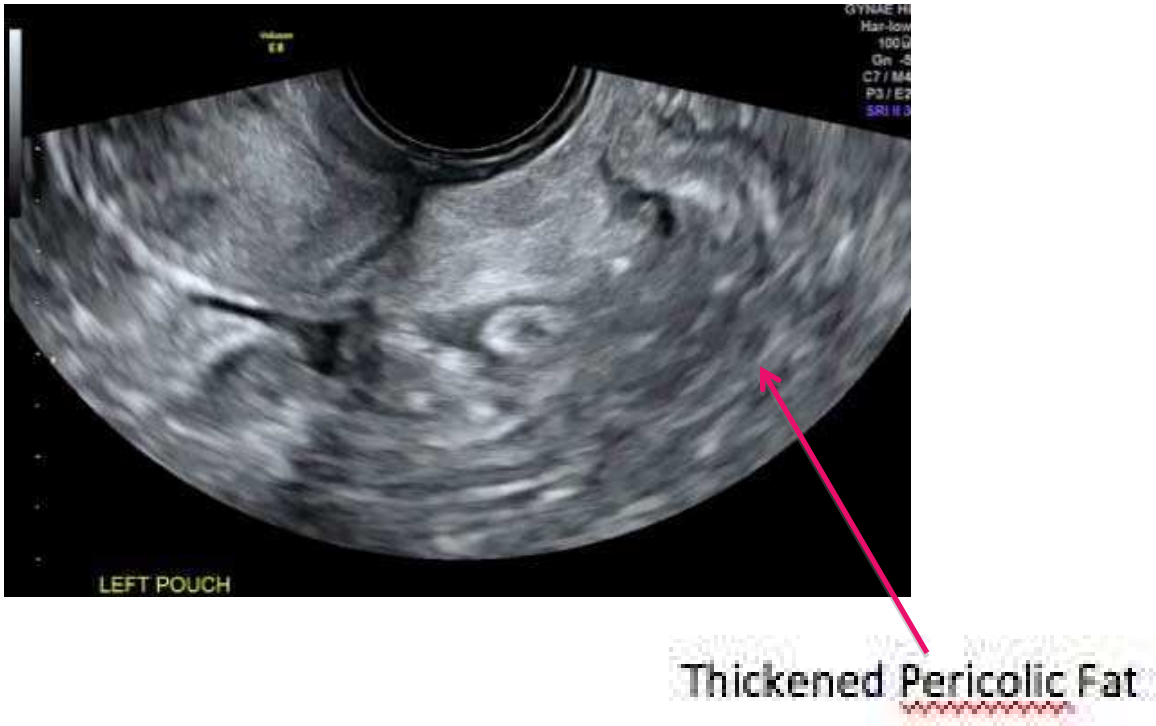


Figure 1. Demonstrating Thickened Pericolic fat.

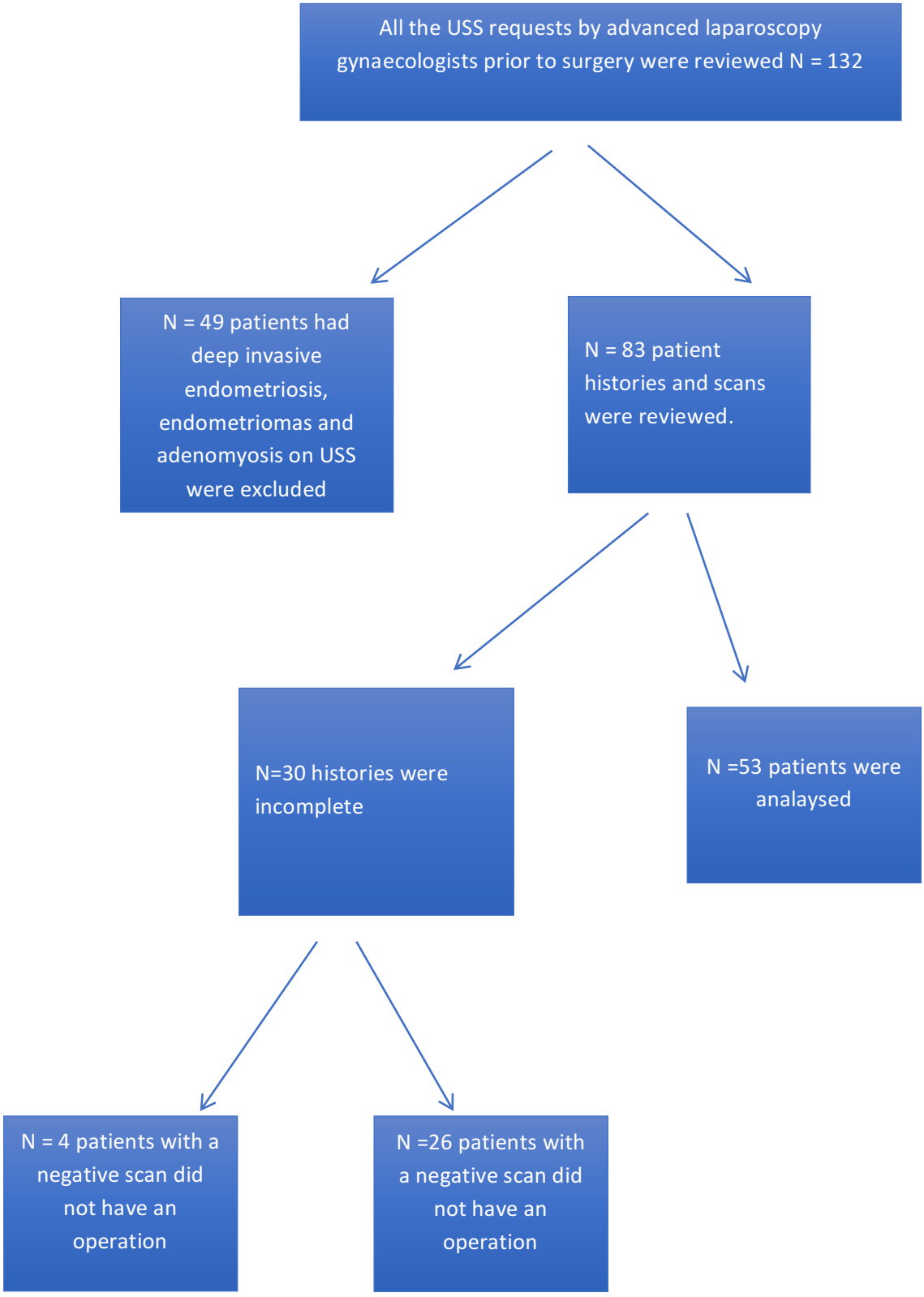


Figure 2: Participant Flow Diagram

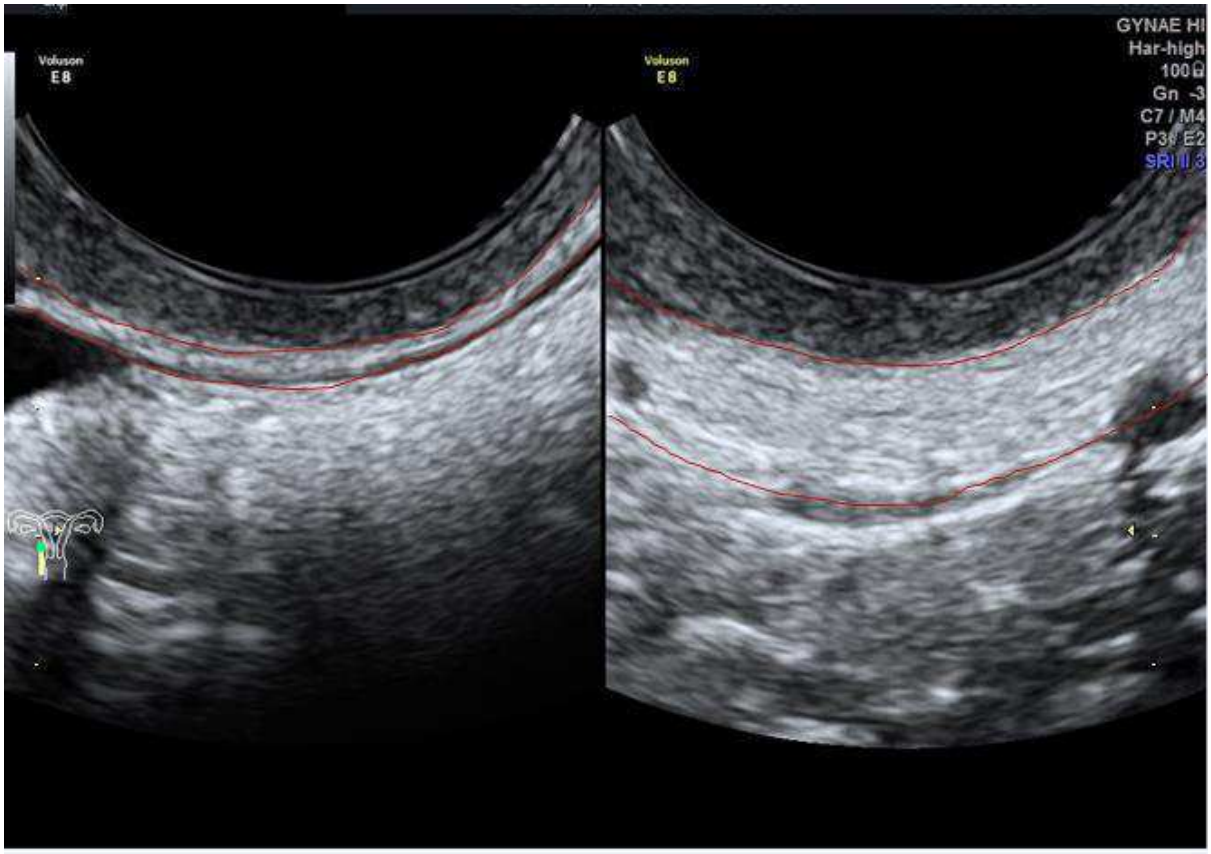


Figure 3 : Normal vs Thickened Uterosacral ligament on TV USS