An assessment of the accuracy and validity of sonographer-led transvaginal ultrasound scanning for deep endometriosis

by

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Glossary

Adenomyosis a condition in which tissue similar to the lining of the uterus (endometrial tissue) grows into the muscular wall of the uterus.

Certificate of Obstetric and Gynaecological Ultrasound (COGU) A subspecialisation qualification in ultrasound available to Australasian Obstetricians and Gynaecologists.

Deep Endometriosis a subtype of endometriosis characterised by lesions in the abdomen, extending on or under the peritoneal surface, which are frequently nodular and invasive in nature.

Dyschezia pain with opening bowel.

Dysmenorrhoea pain with menstrual periods.

Dyspareunia pain with sexual intercourse.

Endometriosis a disease characterised by the presence of endometrium-like epithelium and/or stroma outside the endometrium and myometrium, usually with an associated inflammatory process.

Endometriosis Centre of Excellence A specialist health facility providing multidisciplinary care for the diagnosis, treatment and ongoing management of endometriosis.

Gynaecologist a medical doctor specialising in the health of the female reproductive tract.

Radiologist a medical doctor specialising in medical imaging and the interpretation of medical images including ultrasound scans.

Soft Markers ovarian mobility and site-specific tenderness assessed during a transvaginal ultrasound examination which can be suggestive of superficial endometriosis.

Sonographer an accredited allied health professional specialising in the use of ultrasound imaging to acquire images and videos for the purpose of diagnosing disease.

Sonologist a medical doctor specialising in the performance and interpretation of ultrasound imaging.

Ultrasound a diagnostic imaging modality utilising high frequency sound waves to construct images of organs of the human body.

Abbreviations/ Acronyms

3D- Three-dimensional
AIUM- American Institute for Ultrasound in Medicine
ASRM/ AFS- American Society of Reproductive Medicine/ American Fertility Society
BMI- body mass index
BP- bowel preparation
COCP- combined oral contraceptive pill
COGU- Certificate of Obstetric and Gynaecological Ultrasound
cTVUS- community transvaginal ultrasound
DE/DIE- deep endometriosis/ deep infiltrating endometriosis
DICOM- Digital Imaging and Communication in Medicine
DL- diagnostic laparoscopy
ESHRE- European Society for Human Reproduction and Embryology
eTVUS- endometriosis transvaginal ultrasound
GnRH-a- gonadotropin releasing hormone agonists
IBS- irritable bowel syndrome
ICC- intraclass correlation coefficient
IDEA- International Deep Endometriosis Analysis
IUS- intrauterine system
IVF- in-vitro fertilisation
LR+- likelihood ratio positive
LR- - likelihood ratio negative
MRI- magnetic resonance imaging
NPV- negative predictive value
NSAID- non-steroidal anti-inflammatory drugs
OC- oral contraceptives
OE- ovarian endometriosis/ ovarian endometriomas
PBS- Pharmaceutical Benefits Scheme
PID- pelvic inflammatory disease
PPV- positive predictive value
POCUS- point of care ultrasound
POD- pouch of Douglas
QoL- quality of life
rTVUS- routine transvaginal ultrasound
RVS- rectovaginal septum
RWC-TVUS- rectal water contrast transvaginal ultrasound
SE- superficial endometriosis
SERMs- selective estrogen receptor modulators
SST- site specific tenderness
sTVUS- specialist transvaginal ultrasound
SVG- sonovaginography
TVUS/ TVS- transvaginal ultrasound
UBESS- ultrasound-based endometriosis scoring system
USL- uterosacral ligament
WES- World Endometriosis Society

Publications and Presentations

Publications relating to this thesis

Journal Articles

Deslandes, A., Parange, N., Childs, J.T., Osborne, B. and Bezak, E. (2020), Current Status of Transvaginal Ultrasound Accuracy in the Diagnosis of Deep Infiltrating Endometriosis Before Surgery. J Ultrasound Med, 39: 1477-1490. https://doi.org/10.1002/jum.15246

Deslandes, A., Parange, N., Childs, J.T., Osborne, B., Panuccio, C., Croft, A. and Bezak, E. (2022), How long does a transvaginal ultrasound examination for endometriosis take in comparison to a routine transvaginal ultrasound examination?. Australas J Ultrasound Med, 25: 20-27. https://doi.org/10.1002/ajum.12288

(Submitted for publication) **Deslandes, A.,** Parange, N., Childs, J.T., Osborne, B., Hull, ML., Panuccio, C., Croft, A. and Bezak, E., What is the accuracy of transvaginal ultrasound in the diagnosis of endometriosis when performed by a sonographer?

Conference Presentations (Oral)

Deslandes, A., Parange, N., Childs, J., Osborne, B., Panuccio, C. and Bezak, E. (2021), OP08.03: Intra- and interobserver variability of sonographic measurements of endometriotic nodules within the rectosigmoid colon. Presented at the International Society of Ultrasound in Obstetrics and Gynaecology, Virtual conference.

Conference Presentations (Poster)

Deslandes, A. (2020), Ten things which should prompt a sonographer to search for deep endometriosis. Presented at the 2020 Australasian Sonographers Association annual conference, Virtual Conference.

Deslandes, A. (2020), Ten things which should prompt a sonographer to search for deep endometriosis. Accepted for presentation at the 2020 Australasian Sonographers Association annual conference, Melbourne, Australia. (Cancelled due to COVID-19)

Deslandes, A., Parange, N., Childs, J.T., Osborne, B. and Bezak, E. (2019). What is the accuracy of transvaginal ultrasound in the assessment of deep infiltrating endometriosis when performed by a sonographer? A review of the current literature, Presented at WFUMB2019, Melbourne, Australia.

Other Publications

Journal articles

Deslandes, A, Croft, A, Panuccio, C. Three-dimensional gynaecological ultrasound, part one: How, when and why? *Sonography*. 2021; 1– 9. https://doi.org/10.1002/sono.12294

Deslandes, A, Croft, A, Panuccio, C. Three-dimensional gynaecological ultrasound part two: A pictorial essay. *Sonography*. 2021; 1– 10. https://doi.org/10.1002/sono.12293

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Koninckx, P. R., **Deslandes, A.,** Ussia, A., Di Giovanni, A., Hanan, G., Tahlak, M., Adamian, L., Keckstein, J., & Wattiez, A. (2021). Preoperative imaging of deep endometriosis: pitfalls of a diagnostic test before surgery. *Facts, views & vision in ObGyn*, *12*(4), 265–271.

Deslandes, A., Panuccio, C., Parasivam, S., Balogh, M. and Short, A. (2020), How to perform a gynaecological ultrasound in the paediatric or adolescent patient. *Australasian Journal of Ultrasound in Medicine,* 23: 10-21. doi:10.1002/ajum.12200

Conference presentations (oral)

Deslandes, A. (2021), How to perform a gynaecological ultrasound in the paediatric or adolescent patient. Presented at the 2021 Australasian Society of Ultrasound in Medicine, Virtual conference.

Deslandes, A. (2020), How to perform a gynaecological ultrasound in the paediatric or adolescent patient. Presented at the 2020 Australasian Sonographers Association annual conference, Virtual conference.

Deslandes, A. (2020), Soft Markers in the diagnosis of endometriosis: The subtle art of not stuffing it up! Presented at 2020 Australasian Sonographers Association annual conference, Virtual conference.

Condous, G, **Deslandes**, A and Thottungal, A (2020), New Ideas, Novel Techniques and Markers - Panel Discussion. Presented at Endometriosis Ultrasound Credential, Virtual Conference.

Deslandes, A., Pannucio, C., Parasivam, S., Balogh, M. and Short, A. (2020), How to perform a gynaecological ultrasound in the paediatric or adolescent patient. Accepted for presentation at the 2020 Australasian Sonographers Association annual conference, Melbourne, Australia. (Cancelled due to COVID-19)

Abstract

Endometriosis is a common, chronic gynaecological condition affecting as many as 1 in 9 female-born people. Characterised by the presence of endometrium-like epithelium and/or stroma outside of the uterus, it manifests in three ways; superficial endometriosis (SE), ovarian endometriosis (endometriomas) (OE), and/or deep endometriosis (DE), with the latter being the most severe and clinically challenging to manage. DE is defined as endometriosis lesions, typically nodules, which extend on or under the peritoneal surface and is able to invade adjacent structures, commonly causing disruption to normal anatomy.

Laparoscopy is considered the current 'gold standard' in diagnosis of all subtypes of endometriosis. Complex cases of DE may require an expert or multidisciplinary surgical team, sometimes resulting in abandoned surgeries. Preoperative transvaginal ultrasound (TVUS), in which the anterior and posterior pelvic compartments are assessed, can aid in diagnosis and surgical planning, however, this technique is often only available in specialised centres. As such, we aimed to assess the utility of TVUS in the diagnosis of endometriosis when performed by sonographers within an outpatient imaging centre.

Within this thesis, we present a systematic review of the literature, two unique research questions and two subsidiary research questions:

1 What is the accuracy of TVUS for DE when performed by a sonographer?
2 What is the intra and interobserver variability of sonographic measurements of endometriotic nodules within the rectosigmoid colon? And then the subsidiary questions
3 How long does a TVUS examination for endometriosis take in comparison to a routine TVUS (rTVUS) examination? and
4 What is the accuracy of TVUS soft markers in the diagnosis of SE when assessed by a sonographer?

In study 1, results of TVUS examinations performed by one of three sonographers were compared to surgical findings as the gold standard with diagnostic accuracy assessed for DE by anatomical locations. An overall sensitivity of 80%, specificity of 85.7%, positive predictive value (PPV) of 83.3%, negative predictive value (NPV) of 82.8%, likelihood ratio positive (LR+) of 7.85, likelihood ratio negative (LR-) of 0.18 and accuracy of 83% ($p<0.001$) was found, which suggested that the sonographers achieved a high level of

diagnostic accuracy for OE and DE affecting the posterior compartment. Soft markers (site specific tenderness and ovarian mobility) were also assessed against the presence of DE or SE with lower levels of accuracy achieved.

Study 2 explored the variability of scan findings. As it was not possible to repeat examinations, five sonographers (three participants of study 1 and two inexperienced sonographers) measured 13 rectosigmoid nodules off-line, with measurements repeated after an interval of one month. Interoperator agreement ranged from moderate to excellent (ICC= 0.7473 [CI 0.5353-0.9002] (length), 0.8125 [CI 0.6496- 0.9674] (height) and 0.8170 [CI 0.6489- 0.9302] (width). The experienced operators achieved better levels of agreement than the inexperienced operators with the inexperienced operators having a wider range of variation between the limits of agreement than experienced operators.

In Study 3, a retrospective case-control study was performed exploring how long it takes to perform a TVUS for endometriosis (eTVUS) in comparison to a rTVUS. The time taken to perform 199 eTVUS was compared with a control group of 105 rTVUS. eTVUS took significantly longer than rTVUS, with increases in the mean (8.4 minutes vs 13.8 minutes, 64%), median (7 minutes vs 12 minutes, 71%), minimum (4 minutes vs 7 minutes, 75%) and maximum (19 minutes vs 42 minutes, 121%) scan times.

In summary, these studies revealed that sonographers can accurately perform TVUS to diagnose endometriosis prior to surgery. To do so however, will add an average of 5.4 minutes to an rTVUS examination. Assessment of variability of measurements found good intraobserver agreement but wider levels of variation between operators. Future studies with larger populations would be helpful to further assess this technique.

Declaration

This thesis presents work carried out by myself and does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; to the best of my knowledge it does not contain any materials previously published or written by another person except where due reference is made in the text; and all substantive contributions by others to the work presented, including jointly authored publications, are clearly acknowledged.

Ms Alison Deslandes



28/3/2022

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1 Introduction

1.1 Background to the research

Endometriosis is defined by the 2021 international terminology for endometriosis, as

> "a disease characterized by the presence of endometrium-like epithelium and/or stroma outside the endometrium and myometrium, usually with an associated inflammatory process" (5).

It is common, affecting approximately 1 in 9 female-born people (approximately 800,000 Australians) (6), making it nearly as prevalent as breast cancer for which 1 in 7 Australian women will be diagnosed with by age 85 (7). It carries an estimated economic burden of $7.7 billion per annum in Australia (8). In women suffering from infertility, the prevalence is believed to be as high as 35-50% (9). Quality of life (QoL) for people with endometriosis can be poor and it is also associated with a significant diagnostic delay, with most sufferers waiting an average of 6.4 years for a diagnosis from the onset of symptoms (10).

Endometriosis is an incredibly complex condition in terms of its presentation, diagnosis and management and there is currently no known cure. Whilst the reproductive organs and the surrounding pelvic structures are most commonly affected, endometriosis can also develop in the thorax, upper abdomen and brain (9, 11).

Due to the complexity of endometriosis, a multidisciplinary approach to management is needed. The current consensus produced by the World Endometriosis Society (WES) suggests women with severe disease should be managed in centralised highly specialised endometriosis centres of excellence (2) through a combination of surgical, medical and associate therapies. In 2018, the Australian Government launched a National Action Plan for Endometriosis (8) which held similar objectives to that of the WES. The national action plan has also brought to the forefront of Australian healthcare what a complex and debilitating disease endometriosis is. In order to facilitate accurate triage of patients to

centres of excellence in a timely and efficient manner, a reliable and accurate method of diagnosis is needed.

1.1.1 Manifestation and aetiology of pelvic endometriosis

Endometriosis manifests in three ways: peritoneal/superficial endometriosis (SE), ovarian endometriotic cysts (endometriomas) (OE) and deep endometriosis (DE) (also referred to as deep infiltrating endometriosis (DIE)), with the latter being the most severe and clinically challenging to manage. The exact aetiology of endometriosis is not known but several hypotheses around this exist, with retrograde menstruation the most widely accepted (12). DE has a prevalence of 1-2% (12) and is defined as endometriosis:

> "extending on or under the peritoneal surface. They are usually nodular, able to invade adjacent structures, and associated with fibrosis and disruption of normal anatomy."(5)

DE often affects the uterosacral ligaments (USL), bowel, vaginal walls, rectovaginal septum (RVS), pouch of Douglas (POD), ureters and bladder. Severe endometriosis often leads to adhesions affecting the pelvic organs.

1.1.2 Symptoms of endometriosis

Dysmenorrhoea (pain with periods), chronic pelvic pain, dyspareunia (pain with sexual intercourse), dyschezia (pain with defecation), infertility and heavy menstrual bleeding (12) are all symptoms of endometriosis. In some cases, endometriosis is completely asymptomatic (12).

The presentation is varied and unfortunately, the nature and severity of symptoms may not always align with the severity of disease (13, 14) adding complexity to the capacity for diagnosis. The symptoms of endometriosis can also be mistaken for other conditions such as pelvic inflammatory disease (PID) and irritable bowel syndrome (IBS) (15).

1.1.3 Current gold standard in diagnosis of endometriosis

Laparoscopy has long been considered the current 'gold standard' in diagnosis (12, 15). Laparoscopy is a key-hole surgery in which a surgeon uses a camera to look inside the abdominal cavity through 3-4 small incisions (figure 1). A laparoscopic diagnosis of

endometriosis requires direct visualisation of the lesions and those lesions seen are typically biopsied during surgery. The diagnosis is considered confirmed when histopathology demonstrates the presence of two or more of these histologic features: endometrial epithelium, endometrial glands, endometrial stroma, and hemosiderin-laden macrophages with the lesion (16).

The reliance on laparoscopy for diagnosis is not without flaws. Not only is invasive, it is also costly and carries risks associated with anaesthesia and infection. If a diagnosis can be confirmed before embarking on a laparoscopy, this is reassuring to both patient and clinician as they can be confident that the disease will be able to be treated at the time of laparoscopy. Theoretically, any lesions found at diagnostic laparoscopy (DL) can be removed within the same session, but as the symptoms of endometriosis are broad and often, non-specific, there is always a chance that laparoscopy will be performed on people without endometriosis.

In cases of DE, extensive adhesion of the pelvic organs not discovered until the time of laparoscopy will make full treatment of the disease very challenging (figure 2). The procedure may be abandoned and rescheduled if adequate surgery time has not been allotted, the surgeon lacks the skill level required or the patient has not provided adequate consent to proceed with the required therapy (15). DE within the bowel (figure 3) presents one of the most complex surgical problems. Historically, when DE has been discovered at the time of surgery, a second surgery is often performed by a specialised team (consisting of an advanced gynaecological surgeon, urologist and/or colorectal surgeon). Adding an additional surgery is undesirable as this adds further cost to both the patient and the healthcare sector (17), causes social disruption to the patient (e.g. additional time away from work) and increases the risk of complications (e.g. due to unnecessary exposure to anaesthetics, or infection). For these reasons, a reliable method of non-invasive diagnosis is highly advantageous.

Given the increases in imaging capability, and the risks and limitations associated with laparoscopy, the updated 2022 European Society of Human Reproduction and Embryology (ESHRE) Endometriosis Guidelines (18) identified a need to redefine laparoscopic identification and histological confirmation as the gold-standard in endometriosis diagnosis. These guidelines instead propose that laparoscopic diagnosis only be performed after negative imaging results, or when empirical treatments have been unsuccessful (18),

whilst adding that "(the)development of novel and improvement of existing non-invasive methods of reliably detecting or excluding endometriosis is of paramount importance".

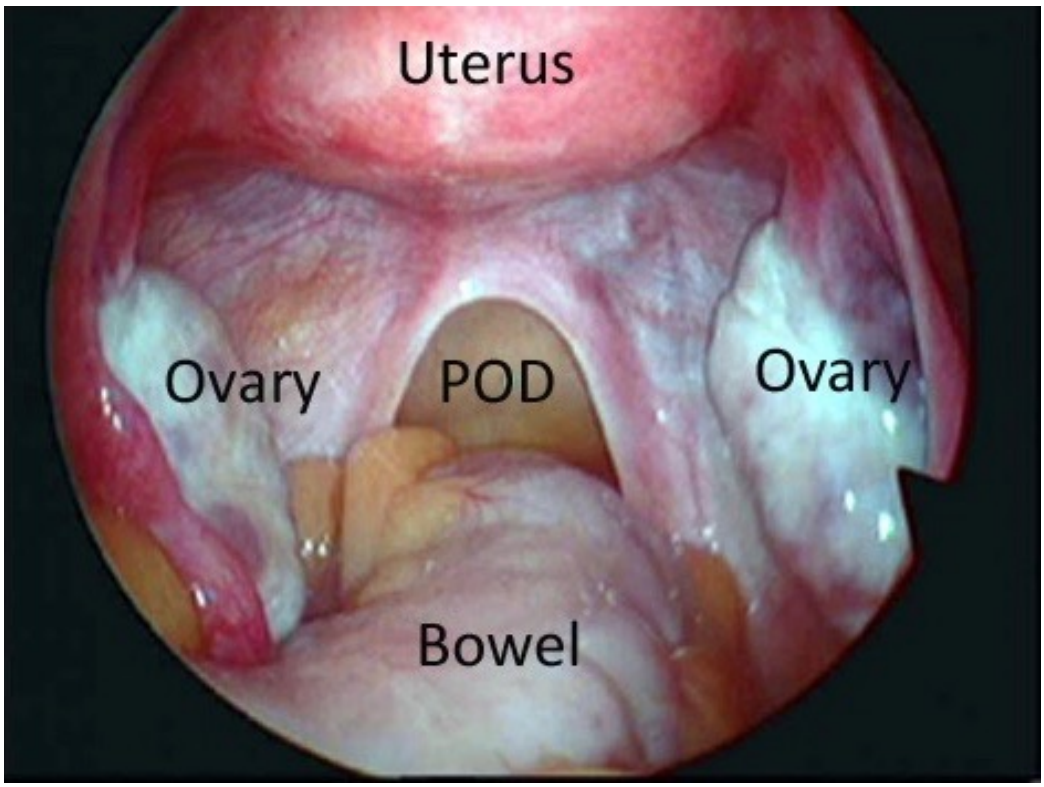


Figure 1 Laparoscopy image showing the normal structures of the female pelvis, free of endometriosis (Image courtesy of Dr Sofie Piessens)

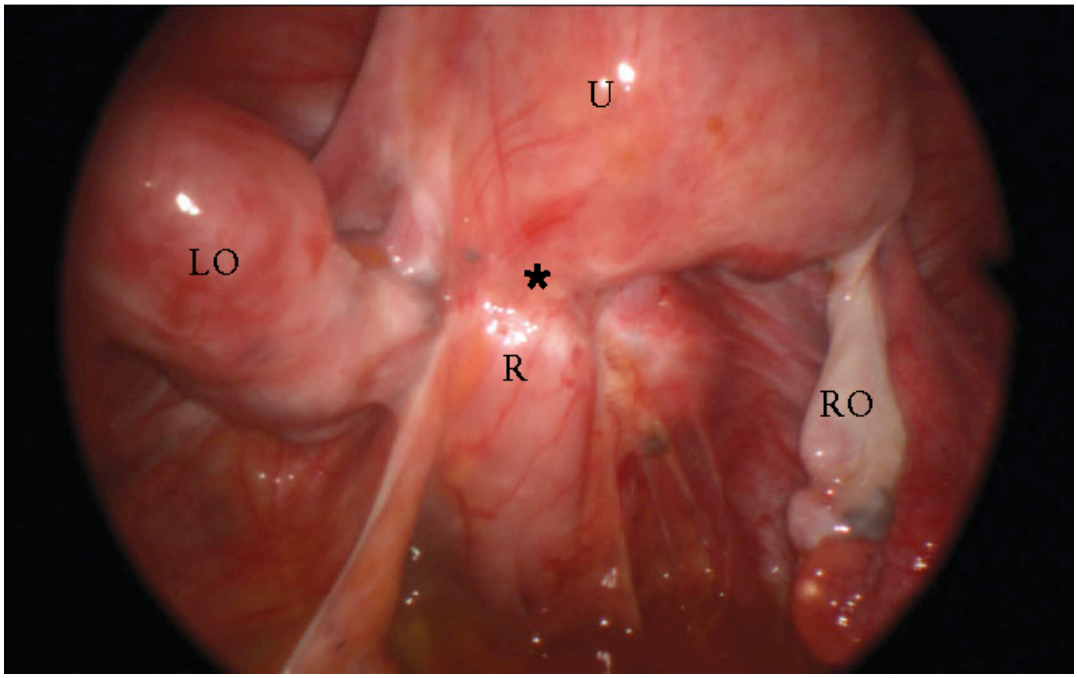


Figure 2 Laparoscopic image of a pelvis with extensive adhesions due to DE. U= uterus, R= rectum, LO= left ovary, RO= right ovary and * denotes the pouch of Douglas (POD) which is obliterated due to severe adhesions (From Reid *et al.* (19))

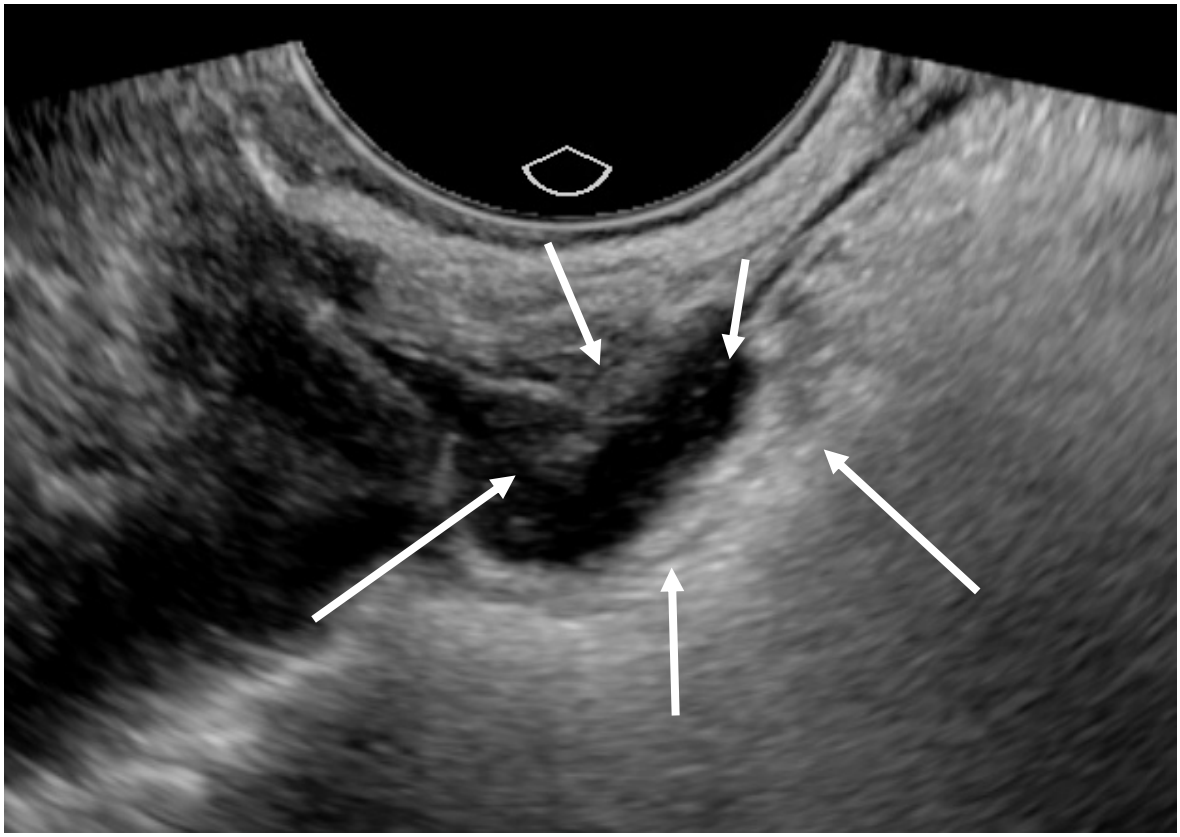


Figure 3 The white arrows are highlighting a nodule of endometriosis within the rectum visualised by transvaginal ultrasound (TVUS) (Image courtesy of Specialist Imaging Partners)

1.1.4 Staging of endometriosis

When surgical management of endometriosis is required, the disease is conventionally prescribed a stage based on a system proposed by the American Society of Reproductive medicine (ARSM) (14). The stages (I-IV) are assigned based on scores allocated to the lesions and adhesions found during DL with stage I representing the mildest form of the disease and stage IV, the most complex. Figure 4 is a copy of the worksheet used to calculate the stage (14). The staging system is used only to quantify the surgical complexity of endometriosis and does not align with the symptoms of endometriosis or predict fertility outcomes. As such, the WES supports the use of the ARSM staging system but concludes better systems need investigating and validating (13).

An ultrasound-based endometriosis scoring system (UBESS) has been proposed to assist in predicting surgical complexity (20). To date, the UBESS has failed to be sufficiently

validated for accuracy, reliability and reproducibility across centers and as such, is not yet routinely used (21).

(a) REVISED AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE CLASSIFICATION OF ENDOMETRIOSIS 1985

Patient's Name _____ Date: _____

Stage I (Minimal) 1-5 Laparoscopy_____Laparotomy_____Photography_____
Stage II (Mild) 6-15 Recommended Treatment _____
Stage III (Moderate) 16-40 _____
Stage IV (Severe) >40
Total _____ Prognosis _____

	ENDOMETRIOSIS	< 1 cm	1 – 3 cm	> 3 cm
Peritoneum	Superficial	1	2	4
	Deep	2	4	6
Ovary	R Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20
	POSTERIOR CULDESAC OBLITERATION	Partial		Complete
		4		40
Ovary	ADHESIONS	< 1/3 Enclosure	1/3-2/3 Enclosure	> 2/3 Enclosure
	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
Tube	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4*	8*	16

Figure 4 Worksheet for calculating stage of endometriosis (Revised American Fertility Society Classification of Endometriosis 1985 (14))

1.1.5 Management of endometriosis

1.1.5.1 Surgical management of endometriosis

Surgery for endometriosis can be performed as a laparotomy (open procedure) but is preferably (and most commonly) performed as a laparoscopy (22).

Two techniques for removal of SE are commonly employed: ablation and excision. Ablation involves the use of heat or lasers to burn (ablate) and vaporise the lesions (23). Ablation is quicker, simpler and cheaper than excision but is not suitable for all types of lesions (23). Excision involves cutting out and removing the deposits of endometriosis. It is more complicated than ablation, requiring longer surgical times and a more highly

skilled surgeon. Excision has been shown to be superior to ablation however in preventing recurrence of endometriosis (23) making it the preferred surgical technique.

DE presents the most challenging surgery. The WES state that excision is strongly preferred for DE and that this should only be undertaken by an advanced laparoscopic surgeon, ideally within a specialised endometriosis centre (13). The extensive adhesions often present with DE can make visualisation of individual deposits of endometriosis, and indeed the normal pelvic anatomy impossible. As such, surgery needs to be performed in a systematic and precise manner which typically involves a multidisciplinary surgical team, sometimes including a colorectal surgeon and urologist, led by an advanced gynaecological surgeon. Figure 5 shows a general outline of how surgery for DE is performed (22).

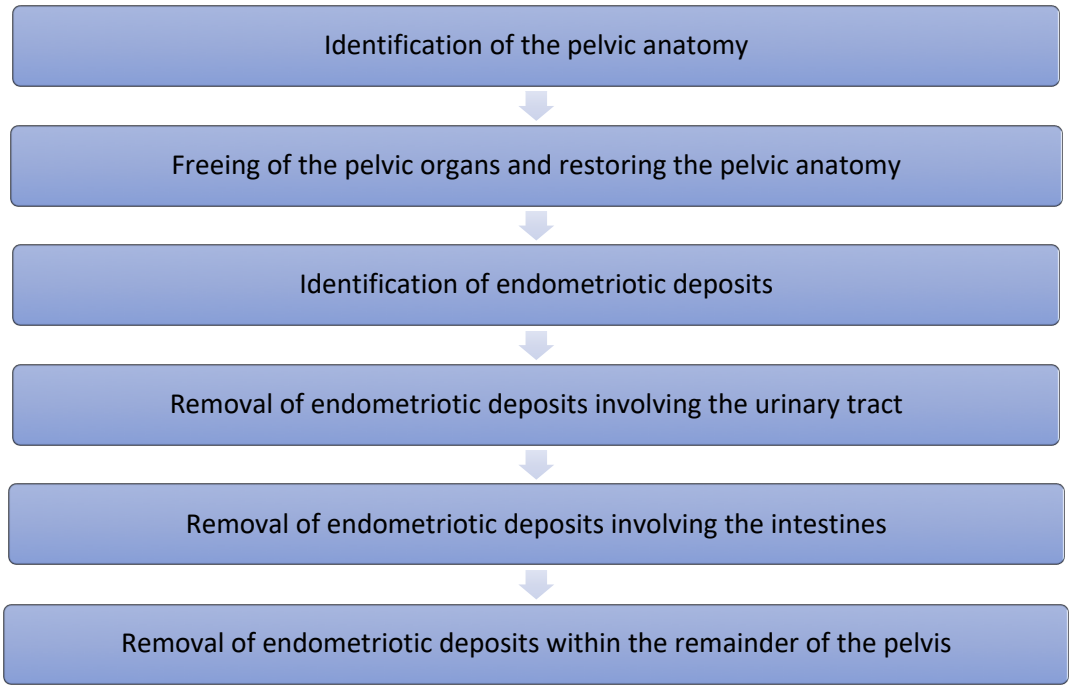


Figure 5 Step-by-step overview of the process of removing deep endometriosis (DE) with excision surgery

Deep endometriosis involving the bowel can be removed by "shaving", disc resection or, in severe cases, segmental resection (figure 6) (15). The technique most appropriate will vary on a case-by-case basis, guided by the preference of the colorectal surgeon and the wishes of the person with endometriosis. Generally, multiple nodules, nodules infiltrating >50% of the bowel circumference or nodules >3cm in size are indications for a segmental resection (15). Prior knowledge of this is invaluable to allow for comprehensive surgical planning and informed consent.

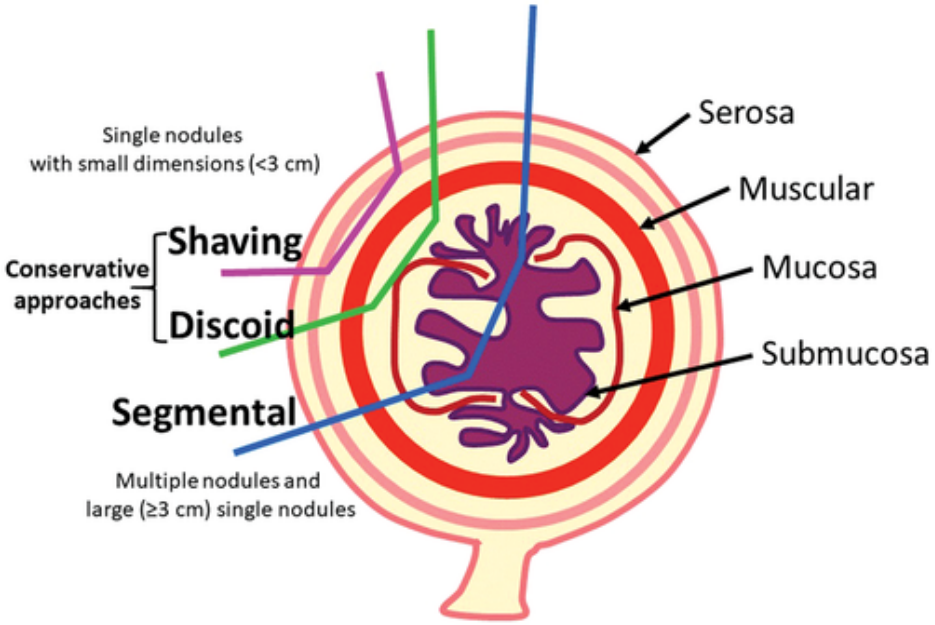


Figure 6 Cross sectional view of the bowel wall showing indications for each surgical technique (From Ota *et al.* (24))

Removal of ovarian endometriomas is challenging and whether or not an endometrioma should be removed is a complex decision taking into account the symptoms the person is experiencing, expertise of the surgeon and the desires of the person with the endometrioma (25). Endometriomas can be drained, ablated/ coagulated or excised, and each technique has risks and benefits (25). As such, there is no current consensus on the single best way to perform surgery for endometrioma. Excision or 'stripping' is often associated with lower rates of recurrence than ablation and has been shown to increase spontaneous conception rates (25, 26). However, excising a cyst from the ovary will always result in a small loss of ovarian parenchyma, and a secondary loss of ovarian reserve which can have a negative impact on future fertility prospects. Given the compromise on fertility due to endometriosis, this may not be acceptable to the person (25). A 'combined' or 'three-step method' (1) has more recently been proposed which involves ablation of the cyst, medical therapy and subsequent stripping at a later date to optimise future ovarian reserves and limit risk of recurrence. Whichever technique is utilised, it must be performed by an expert surgeon due to the intricate nature of the surgery and the risks involved (1).

1.1.5.2 Medical management of endometriosis

Historically, surgical management was believed to be the only way to manage endometriosis however, given the significant rates of recurrence of both endometriotic deposits and pelvic pain, non-invasive, medical therapies are highly desirable (1). Consequently, several medical therapies are available to be used as either a stand-alone

option or following surgery. Although excision surgery is generally considered the gold standard in treatment of endometriosis, no studies to date have compared directly medical versus surgical treatment of endometriosis, and thus there is no substantial evidence to establish the superiority of one approach over the other (27). D'Alterio *et al.* (28) found comparable pain control and QoL following surgical and medical therapies within their systematic review. The Practice committee of the ASRM states that:

> "Endometriosis should be viewed as a chronic disease that requires a lifelong management plan with the goal of maximising the use of medical treatment and avoiding repeated surgical procedures". (27)

A summary of the medical therapies utilised is presented in table 1 (1, 29). Medical therapies for endometriosis are often prescribed in a stepwise manner, outlined in figure 7 (29). An ideal medical therapy for endometriosis would be curative, reduce pain, be low in cost, have few significant side effects and be safe for long-term use. At the current time, no such therapy exists (1).

There are many medical therapies available, however the evidence supporting the benefits and efficacy of each is limited (1). Double-blinded placebo controlled clinical trials involving such treatments are challenging given these drugs commonly result in amenorrhoea, and some result in hypoestrogenic states which hinder blinding abilities (1). Many of these drugs are costly and, in Australia, not all are covered by the Pharmaceutical Benefits Scheme (PBS) (8). Several also have significant side effects (27, 30). Given the impacts of these drugs (physically and socially), reliable ways of non-invasively monitoring efficacy for the individuals taking them are essential to facilitate stopping of non-effective treatments. Imaging methods such as transvaginal ultrasound (TVUS) have the potential to provide this information.

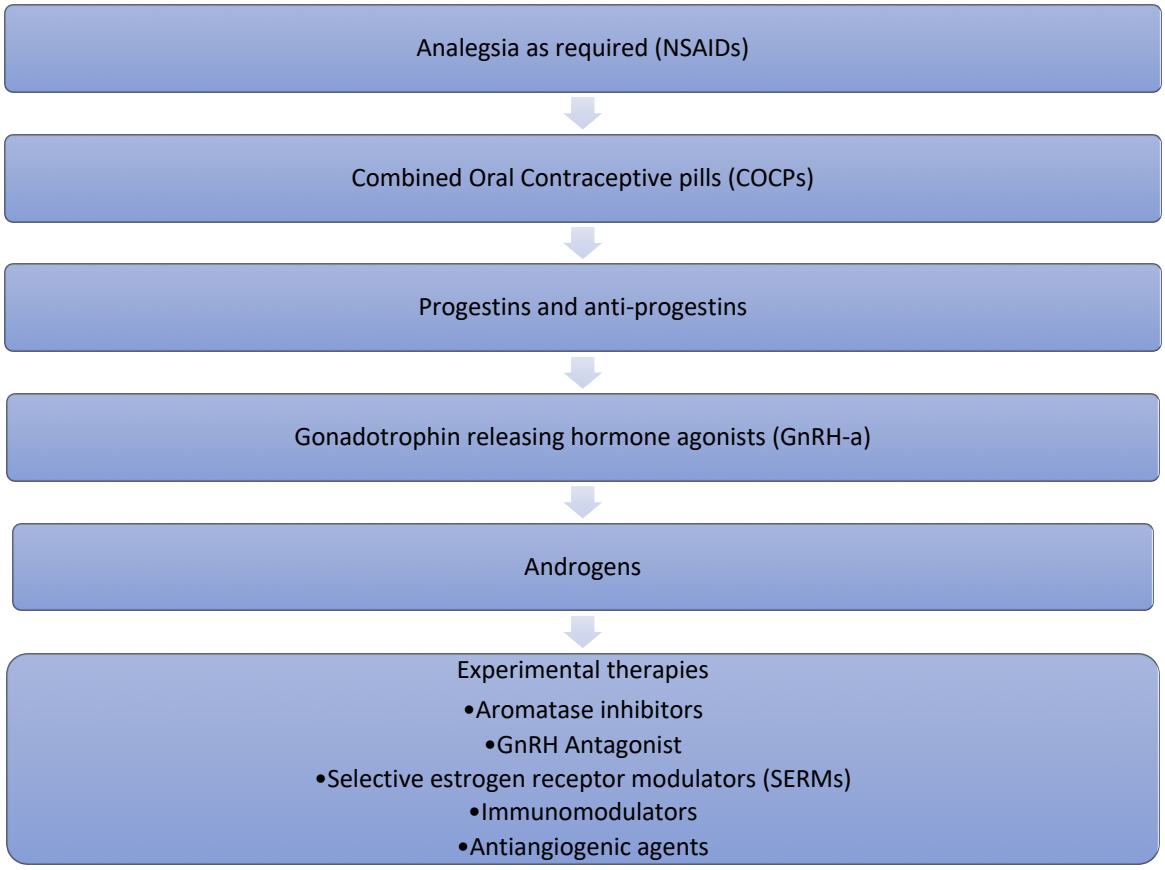


Figure 7 The stepwise flow of medical therapies employed for the treatment of endometriosis (1-4)

Table 1 A summary of the medical managements utilised for endometriosis (1-4)

Medical therapy	Common name	Mechanism of action	Side effects	Notes
Non-steroidal anti-inflammatory drugs (NSAIDs)	Ibuprofen Naproxen	Pain relief	• Gastrointestinal irritation	
Combined oral contraceptives (COCP)	The pill	Inhibit ovulation Decidualisation of lesion tissue	• Mood changes • Nausea • Headaches • Hypertension • Deep venous thrombosis (DVT)(rare)	
Progestins and anti-progestins	Visanne Primolut Provera/ Depo-provera Mirena® IUS Implanon™	Decidualisation and atrophy of lesion tissue	• Irregular bleeding • Mood changes • Weight gain • Acne • Breast tenderness	Progestins are a group of drugs (also known as gestogens, progestogens or progestogens) Delivery can be oral, injection or implant.
Gonadotrophin releasing hormone agonists (GnRH-a)	Lupron Zoladex	Down-regulation of the pituitary-ovary axis producing a hypo-oestrogenic state Atrophy of lesion tissue	• Hot flushes • Change in libido • Vaginal dryness • Headaches • Emotional lability • Acne • Myalgia • Decreased breast size	Not recommended for a treatment period beyond 6 months
Aromatase inhibitors		Inhibit oestrogen synthesis Atrophy of lesion tissue	• Hot flushes • Arthralgia • Myalgia • Osteoporosis	Sometimes used in conjunction with progestins
Androgens	Danazol	Alteration of the hypothalamic-pituitary-ovarian axis and uterus, including mild, impeded androgenic action Atrophy of lesion tissue	• Acne • Hirsutism • Voice changes • Emotional lability	Rarely used in current practice as side effects (such as virilization) are typically considered unacceptable.

1.1.5.3 Management of endometriosis- other therapies

Given the complex nature of endometriosis, a multidisciplinary approach to care is essential (8). This may encompass psychological therapies, diet and lifestyle support including vitamin and mineral supplements, physiotherapy of the pelvic floor and complementary therapies such as acupuncture and Chinese medicine, although the evidence for efficacy of some of these is lacking (2). Pain therapies such as nerve ablation and pain-specific medication (rather than hormonal treatments) may be of use (2, 27). The inclusion of a dedicated pain specialist may be appropriate for some people due to the high prevalence of endometriosis and co-existent conditions known to cause pain (such a pelvic floor dysfunction, IBS, interstitial cystitis and fibromyalgia). Many of the pain specific treatments available to date are still in the experimental phase for endometriosis (27).

The association between endometriosis and subfertility is high (9, 26) and as such, many people with endometriosis hoping to conceive a pregnancy may require the assistance of a fertility specialist. To date, there is little evidence as to the single best way to approach fertility management in people with endometriosis (2, 22, 26). Options for those wishing to achieve pregnancy whilst suffering from endometriosis include surgery, hormone therapies and in-vitro fertilisation (IVF).

1.1.6 Non-invasive methods of diagnosing endometriosis

1.1.6.1 Biomarkers

There are currently no blood-based diagnostic tests (biomarkers) in clinical use for endometriosis as there is currently insufficient evidence to support the use of any (18, 31). As use of blood tests is routine for many disease processes, substantial research on biomarkers has occurred (31, 32). Nisenblat *et al.* (32) in their 2016 Cochrane review on non-invasive methods of diagnosing endometriosis found that there was insufficient evidence to support the routine clinical use of any biomarker in the diagnosis of endometriosis, however biomarker research continues.

1.1.6.2 Magnetic Resonance Imaging (MRI)

Magnetic Resonance Imaging (MRI) is a non-invasive imaging modality utilising strong magnetic fields and radiofrequency currents to create three-dimensional (3D) images of the

body. MRI (figure 8) has some advantages over TVUS in the imaging of DE due to its larger field of view (allowing for detection of extra pelvic deposits) and simpler off-line review. The technique can be less invasive than TVUS as body coils (over the abdomen) are able to be utilised (33) negating the need for an intravaginal examination. MRI is however contraindicated in those with metal implants, cardiac pacemakers and severe claustrophobia (34). The use of an antispasmodic drug (such as Buscopan®) prior to imaging and the infusion of intravaginal or intrarectal contrast may be indicated in some people for optimal imaging of endometriosis (33) but not essential. The sensitivities and specificities of MRI are comparable to TVUS for DE (35-37). Like TVUS, this technique is also operator dependent with the skill and experience of the radiologist interpreting the images being highly influential in the accuracy. Bruyere *et al.* (38) found that an expert reader had sensitivity of 89% and specificity of 93% when reviewing MRI for DE. When read by a junior radiologist however, sensitivities and specificities fell to 49% and 90% respectively.

In Australia, access to MRI is more limited than that of TVUS and it is a costly examination. There is currently no Medicare rebate available for gynaecological MRI leaving most people $400-800 out of pocket for this type of imaging.

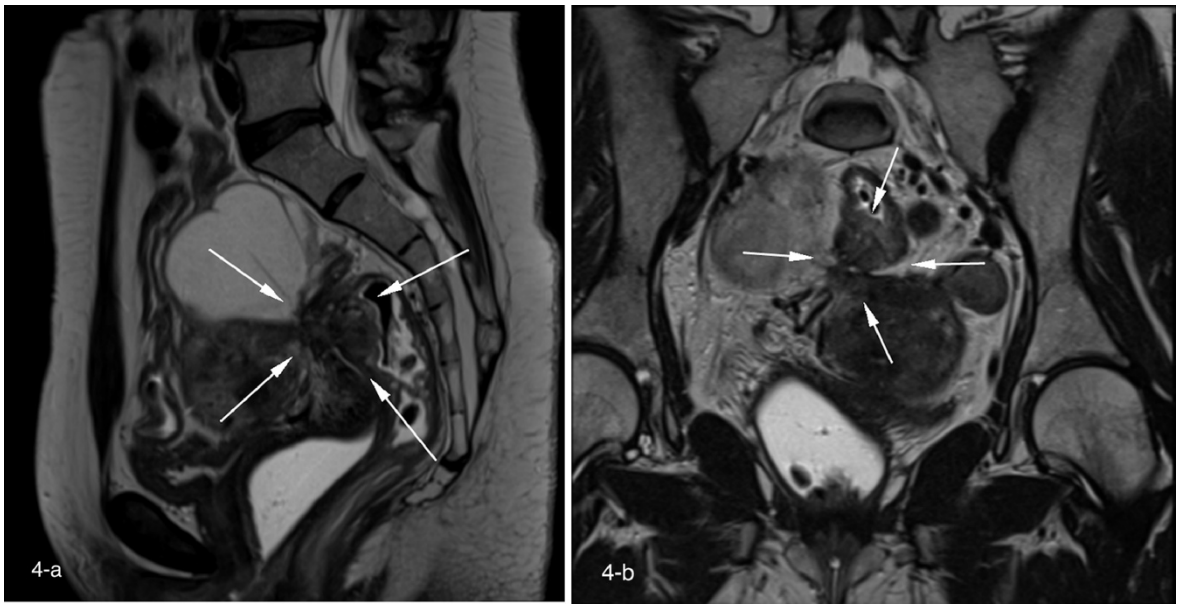


Figure 8 Magnetic Resonance Imaging (MRI) image of deep endometriosis (DE) (as indicated by the white arrows) (From Bruyere *et al.* (38))

1.1.6.3 Transvaginal Ultrasound (TVUS)

Transvaginal Ultrasound(TVUS) is performed by placing a slender probe (transducer) into a person's vagina (figure 9). The transducer emits and receives high-frequency sound waves to construct a grey scale image of the uterus, ovaries and surrounding tissue. TVUS is the gold standard in gynaecological imaging and is widely available, low in cost and well tolerated by most. As such, the initial imaging presentation for any person with symptoms of a gynaecological condition will typically be ultrasound. TVUS is well established in the diagnosis of OE (39). In the early 2000s, literature began reporting TVUS being used in the diagnosis of DE (40-42). In 2016, a consensus paper was published titled, *"Systematic approach to sonographic evaluation of the pelvis in women with suspected endometriosis, including terms, definitions and measurements: a consensus opinion from the International Deep Endometriosis Analysis (IDEA) group*" (43) outlining how the assessment for DE with TVUS should be performed.

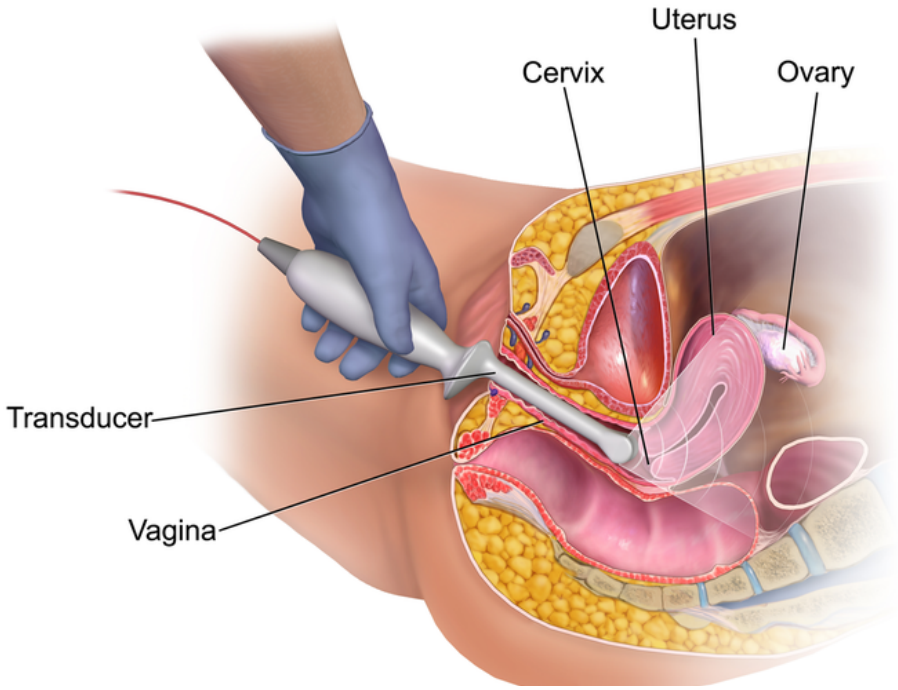


Figure 9 Graphic demonstration of transvaginal ultrasound being performed (From Wikimedia Commons (44))

The American Institute for Ultrasound in Medicine (AIUM) guidelines on performance of ultrasound to assess the female pelvis cover only a basic assessment of the uterus, ovaries/ adnexa and POD for fluid which would show only endometriomas (figure 10) (45). This has been, and remains to be, the common conventional method for assessing the pelvis with

ultrasound. When evaluating for DE, the examination needs to be extended to assess the pelvic organs for mobility and site specific tenderness (SST) as well as incorporate an assessment of the anterior pelvic compartment (bladder, ureters and vesicouterine space), and the posterior pelvic compartment (rectosigmoid colon, USL, POD, posterior vaginal wall/ fornix and RVS) (1).

Published literature to date has shown TVUS to be very accurate in the diagnosis of DE (figure 11) and over the past two decades, TVUS has become increasingly common in clinical use as a diagnostic tool prior to surgery (46-49). Currently, SE is not able to be reliably diagnosed with ultrasound although some reports have started appearing in the literature of the potential of TVUS to visualise SE (50).

Most of the published works to date validating the accuracy of TVUS for DE have come from specialist endometriosis centres of excellence or gynaecological pain clinics within large hospitals, with the scans predominantly performed by gynaecologists (47). There is a paucity of evidence within the literature on the accuracy of the technique away from these centres, within outpatient imaging clinics where prevalence of the disease is lower, and the scans are performed by a sonographer who has no surgical expertise (47).

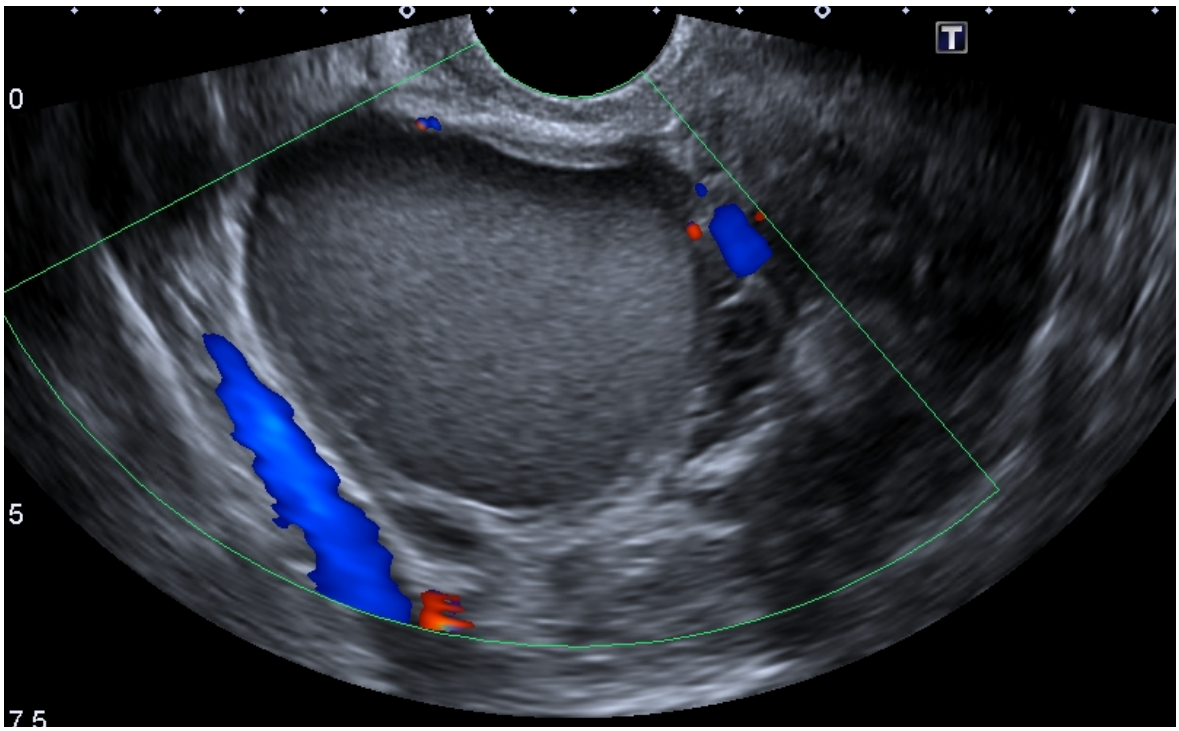


Figure 10 An ovarian endometrioma seen on transvaginal ultrasound (TVUS) (Image courtesy of Specialist Imaging Partners)

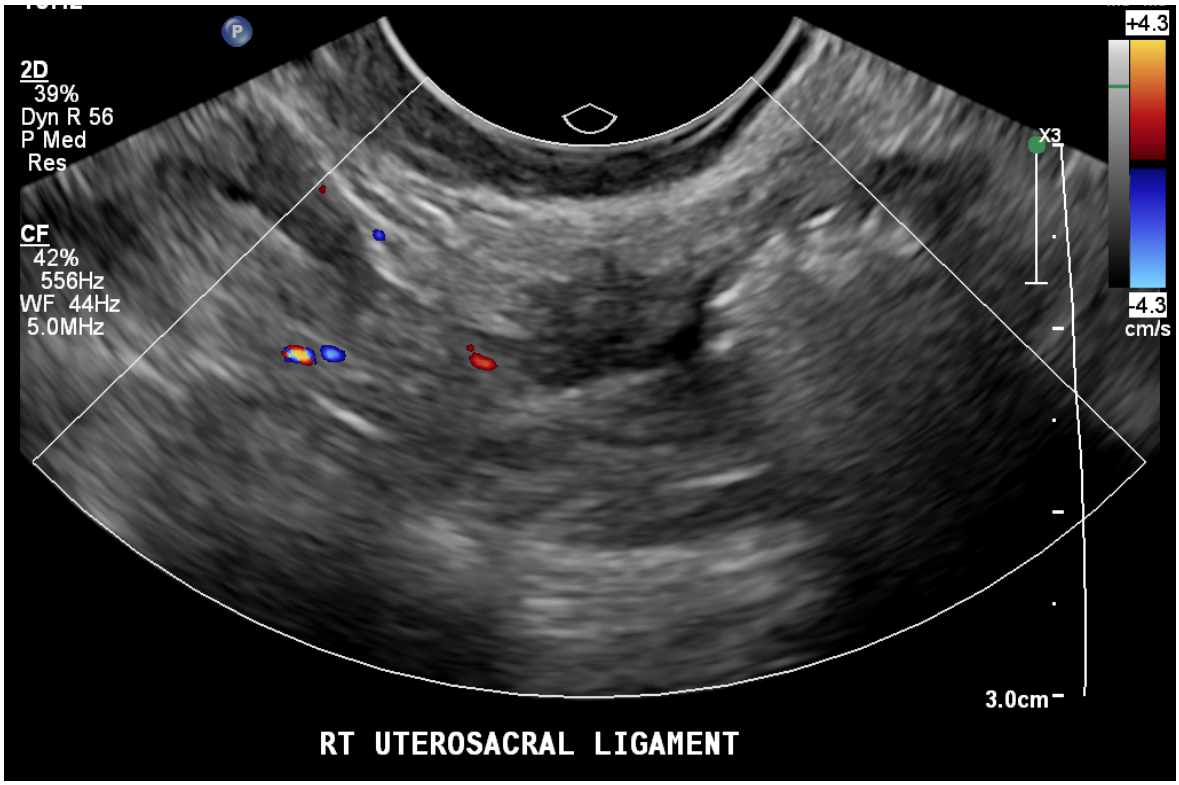


Figure 11 A deep endometriosis (DE) lesion infiltrating the right uterosacral ligament (USL) seen on transvaginal ultrasound (TVUS) (Image courtesy of Specialist Imaging Partners)

1.2 Research Problem

In 2013, The WES produced a consensus statement proclaiming that endometriosis should be managed within specialised endometriosis centres of excellence due to its complexity (2). As such, non-invasive methods of diagnosis within the community are critical, of which imaging must be an integral part, to be enabled to allow triage to such centres (13).

In Australia, ultrasound is commonly performed within an outpatient, private imaging clinic/ radiology practice, some of which are specialised in women's (obstetric and gynaecological) imaging, although most are general (i.e. performing all types of imaging). As such, data regarding the reliability and accuracy of TVUS when performed in community settings, such as outpatient women's ultrasound clinics will be critical as we move towards centres of excellence in order to facilitate accurate and timely referral for people with endometriosis.

1.3 Statement of aims

Primary Aims of this research are:

- To determine the diagnostic accuracy of TVUS when performed and reported by a specialised obstetric and gynaecological sonographer prior to surgery for DE.
- To determine the reliability of measurements of endometriotic bowel nodules on TVUS.

Subsidiary aims which arose during the conducting of research to address the main aims are:

- To determine the additional time burden TVUS for endometriosis (eTVUS) incurs in comparison to routine TVUS (rTVUS).
- To determine the accuracy of TVUS soft markers in the detection of SE when assessed by a sonographer.

1.4 Research process

The research presented herein was conducted in four steps:

1 A systematic review of the literature was performed to assess the current status of TVUS in the assessment of DE prior to surgery when performed by a sonographer. As inclusion of "sonographer" in our search terms yielded no results, our scope was expanded to encompass all operators and assess the technique generally.

2 A prospective cohort study was performed assessing the accuracy of TVUS performed for DE in a private women's ultrasound clinic by one of three specialist sonographers. The sonographers' reports were compared to laparoscopy as the gold standard.

3 An inter and intraobserver reliability study was performed in which five sonographers (three experienced and two inexperienced) reviewed endometriotic nodules affecting the rectosigmoid colon offline and variability between the measurements was assessed.

4 A retrospective case–control study was performed assessing the time taken to perform eTVUS in comparison to rTVUS.

1.5 Significance of the research

Transvaginal Ultraosund (TVUS) has an ever-increasing role in the non-invasive diagnosis of endometriosis, especially DE. To date, little evidence exists from outside of highly specialised centres of excellence as to the accuracy of this technique when performed by sonographers who are not expert in clinical diagnosis of gynaecological conditions nor whom have any surgical experience of endometriosis. The results of this study will inform as to the accuracy and reliability of TVUS for DE when performed within a community imaging setting rather than an endometriosis centre of excellence. This will expand access to the technique to more people with endometriosis in the future, especially those residing away from such centres. Furthermore, as treatment options for endometriosis progress more towards medical therapies with a reduction in the reliance on multiple surgeries, reliable imaging is essential to be able to monitor response to therapies.

1.6 Outline of the thesis

Chapter 2 of this thesis commences with a systematic review of the literature. A rigorous systematic review was performed in July of 2018 and reviewed in November of 2019. The resultant data was published in February 2020 and this publication, *Current Status of Transvaginal Ultrasound Accuracy in the Diagnosis of Deep Infiltrating Endometriosis Before Surgery (47)*, is incorporated into this thesis. The search was repeated in December 2021 with the most up to date literature also included in chapter 2.

The current status of literature segues efficiently into chapter 3 where the accuracy of TVUS performed by a sonographer is investigated. The research methodologies, results and conclusions are summarised again within a manuscript currently submitted for publication, *What is the accuracy of TVS for DIE when performed by a sonographer*, and has been incorporated into this thesis.

Chapter 4 explores reliability. A third manuscript written in the style of publication, *Interobserver variability of measurements of endometriotic nodules within the rectosigmoid colon,* reports and discusses the findings of a study investigating interobserver variability of endometriosis ultrasound.

Chapter 5 addresses the subsidiary question regarding how much time performing an eTVUS requires. This study was published in December 2021 and this publication, *How long does a transvaginal ultrasound examination for endometriosis take in comparison to a routine transvaginal ultrasound examination?,* is incorporated into the thesis.

All publications included in this thesis have been peer reviewed. The thesis is concluded in chapter 6 with a discussion of results, clinical recommendations, clinical applications, future works and finally, conclusions.

2 Review: Current Status of Transvaginal Ultrasound in the Diagnosis of Deep Endometriosis Prior to Surgery when performed by a Sonographer

The published article (47) forms the basis of this chapter.

Deslandes, A., Parange, N., Childs, J.T., Osborne, B. and Bezak, E. (2020), *Current Status of Transvaginal Ultrasound Accuracy in the Diagnosis of Deep Infiltrating Endometriosis Before Surgery*. J Ultrasound Med, 39: 1477-1490. https://doi.org/10.1002/jum.15246

2.1 Introduction and motivation

The primary objectives of the research presented in this thesis are to determine the diagnostic accuracy of TVUS performed and reported by a specialised obstetric and gynecological sonographer prior to surgery for DE, including the intra and interobserver variability of the technique and associated logistical aspects of performing this examination. In Australia, most TVUS examinations are performed by sonographers, an allied health professional expertly trained to perform ultrasound examinations, producing a series of still images and video clips, which are then reviewed and reported, typically off-line, by a medical doctor (usually a radiologist or sonologist). This two-tiered structure of examination and reporting presents a challenge for TVUS for endometriosis as it requires dynamic maneuvers to be performed and interpreted in real-time. Given the high prevalence of endometriosis, ensuring sonographers can perform such examinations with a high degree of diagnostic accuracy is paramount to helping to reduce the diagnostic delay associated with this disease. Considering this, a systematic review of the literature was undertaken to determine the current status of TVUS in the diagnosis of DE prior to surgery, when performed by a sonographer. Insights gained from the contemporary standing of research in this area were used to formulate the research questions and inform the initial design of studies in this thesis.

University of South Australia

Statement of Authorship

Title of	Current Status of Transvaginal Ultrasound Accuracy in the Diagnosis of Deep Infiltrating Endometriosis Before Surgery
Publication Status	**X** Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details Relevant reference details	Deslandes, A., Parange, N., Childs, J.T., Osborne, B. and Bezak, E. (2020), Current Status of Transvaginal Ultrasound Accuracy in the Diagnosis of Deep Infiltrating Endometriosis Before Surgery. J Ultrasound Med, 39: 1477-1490. https://doi.org/10.1002/jum.15246

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Contribution to the Paper Brief description of your work in this publication	**Study design, data collection, data analysis, writing and review**	
Overall Percentage (%)	**60%**	
Certification	**This is an original publication outlining research conducted for my masters thesis.**	
Signature	[redacted]	Date 10/3/2022

CO-AUTHOR CONTRIBUTIONS

By signing the Statement of Authorship, each author certifies that:

I. the candidate's stated contribution to the publication is accurate (as detailed above);

II. permission is granted for the candidate in include the publication in the thesis; and

III. the sum of all co-author contribution is equal to 100% less the candidate's stated contribution.

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Name of Co-Author 4	Prof Eva Bezak	
% Contribution to the Paper	10%	
Signature	[redacted]	Date 13/03/2022

Current Status of Transvaginal Ultrasound Accuracy in the Diagnosis of Deep Infiltrating Endometriosis Before Surgery

A Systematic Review of the Literature

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Abbreviations

3D, 3-dimensional; BP, bowel preparation; DIE, deep infiltrating endometriosis; POD, pouch of Douglas; RWC, rectal water contrast; SVG, sonovaginography; TVUS, transvaginal ultrasound; US, ultrasound; USL, uterosacral ligament

doi:10.1002/jum.15246

Endometriosis is a common gynecologic condition affecting as many as 1 per 10 women. Transvaginal ultrasound (TVUS) has become a frontline tool in the diagnosis of deep infiltrating endometriosis (DIE) before surgery. The primary aim of this review was to determine the accuracy of TVUS for DIE. The secondary aim was to determine accuracy specifically when a sonographer performed the TVUS examination. A systematic review was performed, searching literature by following a population, intervention, comparator, and outcome outline. MEDLINE, Embase, Emcare, and Google Scholar were searched in July 2018 and in November 2019. Including "sonographer" in the search terms yielded no results, so our terms were expanded. Two hundred and four articles were returned from the searches, and 35 were ultimately included in the final review. Analysis of the returned articles revealed the TVUS is a valuable diagnostic tool for DIE before surgery. Sensitivities ranged from 78.5% to 85.3%, specificities from 46.1% to 92.5%, and accuracies from 75.7% to 97%. Most authors reported site-specific sensitivities and specificities, which varied greatly between locations. Site-specific sensitivities ranged from 10% to 88.9% (uterosacral ligaments), 20% to 100% (bladder), 33.3% to 98.1% (rectosigmoid colon), and 31% to 98.7% (pouch of Douglas). Site-specific specificities ranged from 75% to 99.6% (uterosacral ligaments), 96.4% to 100% (bladder), 86% to 100% (rectosigmoid colon), and 90% to 100% (pouch of Douglas). Transvaginal ultrasound is an accurate tool in the diagnosis of DIE; however, limited data exist as to whether this technique is accurate when performed by sonographers. More evidence surrounding the reliability between operators is also needed.

Key Words—deep infiltrating endometriosis; endometriosis; sonographer; transvaginal ultrasound

Endometriosis is a common chronic gynecologic condition defined as the presence of endometrial glands and stromalike lesions outside the uterus. It affects as many as 1 per 10 women[1] and up to 35% to 50% of women with pelvic pain or infertility.[2] The quality of life for those with the condition can be poor, and many women have a diagnostic delay of 7 to 12 years because of the diversity of symptoms and lack of simple diagnostic tests.[1] Endometriosis manifests in 3 ways; peritoneal (superficial)

endometriosis, ovarian endometriosis (endometriomas), and deep infiltrating endometriosis (DIE), with the latter being the most severe and clinically challenging to manage.

Laparoscopy is currently considered the reference standard in diagnosis. In cases of DIE, extensive adhesion of the pelvic organs may not be discovered until the time of surgery. However, because of the complexity of these cases and the possible need to include additional specialist surgeons (colorectal, urologic, or both), this is undesirable. Research has been undertaken to investigate the usefulness of diagnostic imaging before surgery to improve patient treatment. Magnetic resonance imaging,[3,4] transrectal ultrasound (US),[5] and transvaginal ultrasound (TVUS) have all been shown to be useful. Given the low cost, ready availability, and current frontline use in routine gynecologic imaging, TVUS is now suggested as the frontline imaging technique when DIE is suspected. In cases of DIE infiltrating the bowel, multiple nodules, nodules infiltrating greater than 50% of the bowel circumference, and nodules greater than 3 cm in size may be indications for a bowel resection.[6] As such, accurate presurgical diagnosis is paramount to allow for optimal management and patient counseling.

The current consensus produced by the World Endometriosis Society suggests that women with severe disease should be treated in centralized specialist endometriosis centers.[7] To facilitate triage to such centers, an effective and accurate method of diagnosis is needed.[8] The primary aim of this systematic review was to determine the accuracy of TVUS in the diagnosis of DIE. The secondary aim was to ascertain whether variation exists between operators and, if so, how accurate a TVUS examination is when performed on the true front line by a sonographer within an outpatient imaging environment.

Methods

This systematic review was designed and performed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[9] All methods for inclusion/exclusion criteria, data extraction, and quality assessment were specified in advance. The review was not registered with any organization.

Data Sources

The search terms used were defined by using a population, intervention, comparator, and outcome plan and

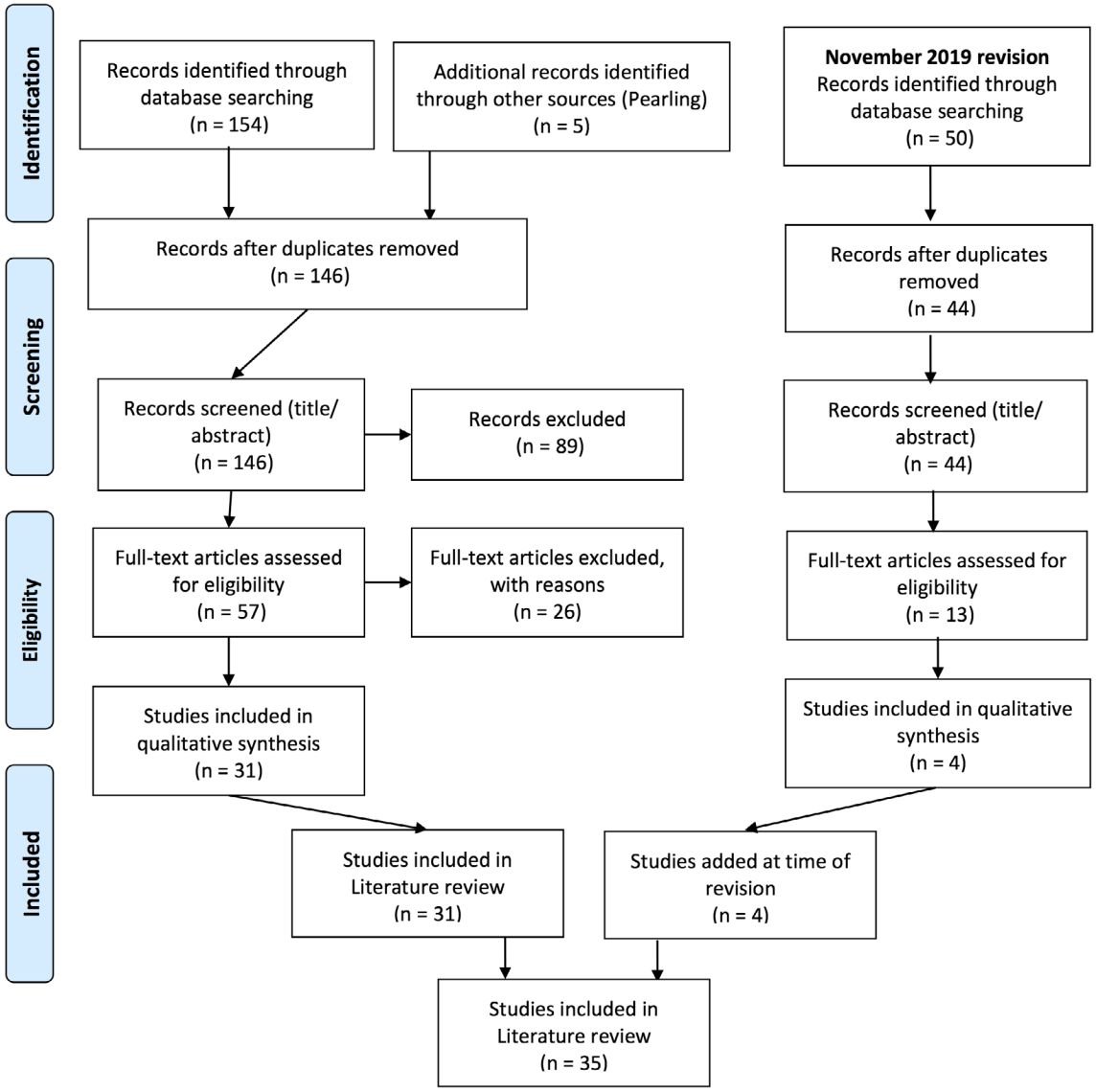
Table 1. The Population, Intervention, Comparator, and Outcome Plan Used for the Systematic Review

Item	Concept	Synonyms	Medical Subject Headings, MEDLINE	Medical Subject Headings, Emcare/Embase
Patient	Women with endometriosis	Endometrio* Deep infiltrating endometriosis DIE	Endometriosis	Endometriosis
Intervention (or Exposure)	Transvaginal ultrasound	Transvaginal ultrasound Endovaginal ultrasound Transvaginal ultrasonography Endovaginal ultrasonography Transvaginal sonogra* Endovaginal sonogra* Vaginal ultrasound Vaginal sonogra* Vaginal ultrasonography Sonovaginography	Ultrasonography	Ultrasound
Comparison	Surgery	Surgery Laparoscopy Laparoscopic surgery	General surgery or gynecology	Gynecologic surgery or laparoscopic surgery
Outcome	Accuracy	Accura* Precision Correct* Efficien* Reliab*		

can be seen in Table 1. Our original search terms included "sonographer/ultrasonographer"; however, this yielded no results, so our scope was expanded to cover "endometriosis," "ultrasonography/ultrasound," and "general surgery, gynecology/gynecologic surgery, or laparoscopic surgery." Our review focused on DIE because of its surgical complexity. Studies published between January 2000 and July 2018 were screened from 4 online databases (MEDLINE, Embase, Emcare, and Google Scholar). The search was conducted in July 2018. The results of the Google Scholar search were limited to the first 10 returned pages. The literature search was repeated in November 2019 following the same protocol to include articles published between July 2018 and November 2019. Four additional articles were included at this revision.

Inclusion criteria were as follows: (1) TVUS (or a variation such as 3-dimensional [3D] TVUS, sonovaginography [SVG], rectal water contrast [RWC] TVUS, or saline contrast TVUS); (2) participants underwent surgery (with or without a histologic examination); (3) the focus was on endometriosis in the ovaries,

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses flowchart outlining the return of records.



peritoneum, bowel, bladder, uterosacral ligaments (USLs), vaginal walls, rectovaginal septum, or pouch of Douglas (POD); and (4) original research articles only (not case studies, systematic reviews, or meta-analyses). Exclusion criteria were as follows: (1) conference articles; (2) non–English-language articles; (3) articles published before 2000; (4) articles covering non-TVUS procedures only (eg, magnetic resonance imaging and transrectal US); (5) articles reporting endometriosis manifestations other than DIE (ie, endometrioma and superficial disease); and (6) studies in which TVUS was not used as a standalone imaging modality (eg, combined transrectal and TVUS scanning).

Data Synthesis

Our screening method can be seen in Figure 1. The search revealed 154 articles, 16 of which were duplicates. Two authors (A.D. and B.O.) reviewed 141 articles by title and abstract against our inclusion/exclusion criteria. If a consensus was not reached as to whether an article met the criteria, it was included for the full-text review. Fifty-four articles were included for the full-text review by 2 people (A.D. and either E.B., N.P., or J.T.C.). If a consensus was not reached on whether an article met our inclusion/exclusion criteria, a third opinion was sought from an additional reviewer (B.O.), which revealed 28 articles. The critical appraisal was conducted with the Joanna Briggs Institute Critical Appraisal Checklist for Diagnostic Test Accuracy Studies.[10] Pearling of all articles revealed an additional 5 articles, 3 of which were included in our final review, taking our total included articles to 31. An additional 4 articles were added at the time of revision (performed according to the original protocol) taking our total to 35 included articles on diagnostic accuracy.

All articles were read in detail, and relevant data were extracted. The reported data were very heterogeneous, both in terms of the methods and language used, which led us to conclude that completing a meta-analysis while ensuring accurate data reporting was not possible. As such, the findings are presented as an integrative review.

Results and Discussion

Accuracy of TVUS

Overall accuracy was reported in only 7 articles,[11–17] with only 4 articles[11–14] reporting overall sensitivities and specificities. Sensitivities ranged from 78.5% to 85.3%, specificities from 46.1% to 92.5%, and accuracies from 75.7% to 97%. Most studies reported accuracy by specific locations, which are more relevant to surgical planning. Although variation in accuracy existed between locations, our findings suggest that TVUS as a diagnostic tool for DIE generally has excellent accuracy and should be used as both a diagnostic and surgical planning tool for DIE.

A limitation across most articles was that the surgeons were rarely blinded to the results of the US examinations, which could have potentially skewed the surgical findings. However, we acknowledge that this limitation was largely unavoidable.

Bladder

Table 2 summarizes the findings of bladder DIE across all articles. The true detection of endometriosis within the bladder was difficult to isolate, as some authors grouped the bladder with the anterior compartment, making it unclear in the literature exactly which areas were affected. Several authors reported sensitivities of 100%[14,19–21]; however, all had very small populations of bladder lesions within their sample groups. Conversely, Grasso et al[11] and León et al[22] had sensitivities of only 25% and 20%, respectively, but again had very small sample populations (3 and 5 cases). Of the 13 studies reporting bladder disease, only 2 had large enough sample populations to drawn any sort of meaningful conclusions. Fratelli et al,[23] with their sample population of 25 cases, had sensitivity of 61% and specificity of 99%. Savelli et al[24] had a sample population of 41 cases and found sensitivity of 44% and specificity of 100%. These more valid sample populations suggest that TVUS is a poor diagnostic tool for bladder DIE. Bladder endometriosis is uncommon, affecting 1% to 18% of women with endometriosis.[11,14] As such, very large sample populations are needed to produce statistically significant results.

A TVUS examination is normally performed with an empty bladder to optimize patient comfort and the image quality of the uterus. This, however, is not ideal for the detection of bladder lesions. As such, it is difficult to know whether the low sensitives reported by some authors were purely technical, given that it is widely accepted that a full bladder is required to

Table 2. Findings of Articles Covering Bladder DIE

Authors	Date	Participants	Bladder Disease	Technique	Data	Sensitivity	Specificity	PPV	NPV	LR+	LR–	Accuracy
Alborzi et al	2018	317	4	TVUS		100	99.68	80	100	313	0	99.68
Bazot et al	2004	142	7	TVUS		71.4	100	100	98.5	NS	NS	98.6
Fratelli et al	2013	420	25	TVUS		61	99	78	98	60.4	0.4	NS
Grasso et al	2010	33	6	3D TVUS		25	100	100	86.9	NS	NS	87.5
Guerrio et al	2008	88	4	TG TVUS		100	100	NS	NS	NS	0	NS
Hernández Gutiérrez et al	2019	48	6	TVUS		50	98	75	93	20.8	0.51	92
Holland et al	2013	198	5	TVUS		100	100	100	100	NS	0	NS
Holland et al	2010	201	9	TVUS		55.56	100	NS	NS	NS	0.44	NS
Hudelist et al	2011	129	4	TVUS		50	98	50	98	31.25	0.51	97
Hudelist et al	2009	200	4	TVUS		75	98	50	99	49	0.25	98
Lazzeri et al	2014	121	7	TVUS		100	96.4	63.6	100	28.5	0	97
León et al	2014	51	5	SVG (gel)		20	100	NS	NS	NS	0.8	NS
Savelli et al	2009	490	41	TVUS		44	100	100	95	NS	NS	95
Tammaa et al[a]	2015	65	4	TVUS	Operator A	67	97	51	98	20.7	0.34	95
Tammaa et al[a]	2015	65	4	TVUS	Operator B	67	97	50	98	20.7	0.34	95

LR indicates likelihood ratio; NPV, negative predictive value; NS, not specified; PPV, positive predictive value; and TG, tenderness-guided.
[a]Data from the same article.

adequately assess the bladder for any type of nodular disease.

Uterosacral Ligaments

Table 3 summarizes the findings of USL DIE across all articles. Endometriosis affecting the USL is common, and throughout the reviewed articles, the USLs were the most common sites of DIE. Fratelli et al[23] reported disease affecting the USLs in 61% of their participants at the time of laparoscopy. On US imaging, endometriosis of a USL is often suspected when the ligament is thickened,[8] meaning it is possible that some of the disease detected is superficial disease rather than DIE.[18] As such, it is again unclear within the reviewed articles whether authors were reporting on simply a thickened USL (possibly superficial disease) or whether nodules of DIE were found at surgery. From the reviewed literature, the USL appears to be one of the most difficult regions to detect disease. Of the 16 authors who included a USL assessment, 8 reported sensitivities of less than 70%.[3,11,12,19,20,23,25–27] Holland et al[20] reported sensitivity of only 10% for USL disease, although they concluded that this was potentially due to operator bias because in cases of extensive disease, smaller deposits (such as USL disease) become less important, so effort may not have been expended searching for those. We would argue, however, that given the proximity of the USL to the ureters, a careful evaluation of the USL is always essential for surgical mapping and the possible need for uterolysis.[28]

It was unclear as to why some sensitivities were lower than others. In the normal pelvis, the USLs are not seen with US, which may account for some of the poor accuracies encountered in this region.

Ovaries

No articles specifically reported on DIE affecting the ovaries. Although several authors reported "ovarian disease," it was unclear in most cases as to whether this was specifically endometriomas (the detection of which TVUS has a well-established usefulness in), adhesions, DIE, or a combination of these. As such, the true usefulness of TVUS in the detection of DIE involving the ovaries was impossible to define definitively. Although it likely encompassed both endometriomas and DIE, the overall accuracy of

Table 3. Findings of Articles Covering USL Endometriosis

Author	Date	USL Disease	Participants	Data	Technique	Sensitivity	Specificity	PPV	NPV	LR+	LR−	Accuracy
Alborzi et al	2018	151	317		TVUS	70.86	92.77	89.9	77.78	9.8	0.31	82.33
Bazot et al	2004	68	142		TVUS	70.6	95.9	94.1	78	NS	NS	83.8
Bazot et al	2007	73	81		TVUS	80.8	75	96.7	30	3.2	0.25	80.3
Fratelli et al	2013	173	420		TVUS	21	93	81	43	2.75	0.86	NS
Grasso et al	2010	9	33		3D TVUS	50	94.7	71.4	87.8	NS	NS	85.4
Guerrio et al	2008	64	88		TG TVUS	50	94	NS	NS	8	0.53	NS
Hernández Gutiérrez et al	2019	27	48		TVUS	59	43	57	45	1.03	0.94	52
Holland et al	2013	20	198		TVUS	10	99.6	57.1	90.7	11.87	0.908	NS
Hudelist et al	2011	30	129		TVUS	63	98	91	90	31.35	0.37	90
Hudelist, Oberwinkler et al[a]	2009	24	200	Right USL	TVUS	67	97	73	96	19.56	0.35	93
Hudelist, Tutties et al[a]	2009	43	200	Left USL	TVUS	84	86	62	95	5.76	0.19	86
Lazzeri et al[a]	2014	56	121	Right USL	TVUS	81.2	80.7	82.5	79.3	4.2	0.23	81
Lazzeri et al[a]	2014	67	121	Left USL	TVUS	87.9	83.6	86.6	85.2	5.37	0.14	86
Reid et al	2013	4	100		TVUS	40	95.6	50	93.5	NS	NS	NS
Reid et al	2014	4	189		SVG (gel)	40	97.8	50	96.7	17.9	0.61	94.7
Robinson et al	2018	22	81	Thickened USL	TVUS	51	55	56	50	NS	NS	53
Saccardi et al[a]	2012	9	54		TVUS	55.6	95.6	71.4	91.5	12.5	0.465	NS
Saccardi et al[a]	2012	9	54		SVG (saline)	88.9	95.6	80	97.7	19.99	0.11	NS
Tammaa et al[a]	2015	17	65	Operator A	TVUS	73	83	47	94	4.4	0.3	82
Tammaa et al[a]	2015	17	65	Operator B	TVUS	53	90	64	84	5.1	0.5	80
Vimercati et al	2012	66	90		TVUS	66.1	84.8	75.5	77.9	4.3	0.4	11

Abbreviations are as in Table 2.
[a]Data from the same article.

TVUS in the detection of ovarian disease ranged from 89.6%[14] to 100%.[29]

Alborzi et al[14] reported the lowest sensitivity of 62.2% (although they had specificity of 95.7%) in the "ovarian fossa." Although they did not define what US features they considered suggestive of DIE in the ovarian fossa, the use of the term ovarian fossa suggests that this represented more than endometriomas. The best sensitivity was reported by Vimercati et al,[12] who were able to show 100% sensitivity for the diagnosis of ovarian endometriosis. Although they provided a detailed description of what they classified as endometriomas, they too were nonspecific regarding what exactly constituted ovarian disease.

Holland et al[20] assessed and reported the presence of both ovarian endometriomas and ovarian adhesions. They reported good sensitivities and specificities for both, of 84% and 95.6% for endometriomas and 79.6% and 91.9% for adhesions, which grew slightly to 83.5% and 93.5% when adhesions were severe. There was some chance of bias within their results, as they found ovarian adhesions present in 94% of women with endometriomas. Given that the 2 operators performing the scans in their study had a "high level of experience," it is possible that the operators had come to assume that an adhesion may have been concurrently present with an endometrioma. It could also be argued that if 94% of women with an endometrioma have adhesions, it can safely be inferred that these will be present at surgery without prior confirmative imaging.

Pouch of Douglas

Table 4 summarizes the findings of POD obliteration across all articles. The presence of adhesions in the POD is critical information to obtain before surgery,[23] as obliteration of the POD will render visibility of the posterior compartment impossible laparoscopically.[6] The uterine "sliding sign" is a simple and well-established technique for assessing the POD with TVUS[8]; however, not all authors used this method. It should be noted that a negative sliding sign (suggesting obliteration of the POD) is not diagnostic of posterior compartment DIE and may be due to an endometrioma, hydrosalpinx, extensive peritoneal disease,[25] or another pelvic condition entirely.

The sensitivity of the uterine sliding sign varied from 31%[23] to 89%.[22] The low sensitivity reported by Fratelli et al[23] was possibly due to the retrospective

Table 4. Findings of Articles Covering POD Obliteration

Author	Date	Technique	POD Obliterated	Participants	Sensitivity	Specificity	PPV	NPV	LR+	LR–	Accuracy
Fratelli et al	2013	Sliding sign	199	420	31	90	73	59	2.97	0.77	NS
Holland et al	2010	Sliding sign	25	201	72	97.16	NS	NS	25.06	0.29	NS
Hudelist et al	2011	Bazot 2004[a]	21	129	76	100	100	96	163.5	0.23	96
Hudelist et al	2009	Bazot 2004[a]	30	200	87	98	90	98	49.11	0.14	97
Lazzeri et al	2014	NS	78	121	98.7	93	96.2	97.5	14.1	0.01	97
León et al	2014	Sliding sign	27	51	89	92	NS	NS	10.7	0.12	NS
Reid et al	2013	Sliding sign	30	100	83.3	97.1	92.6	93.2	29.2	0.17	93

Abbreviations are as in Table 2.
[a]Method outlined by Bazot et al.[13]

nature of their study. Lazzeri et al[21] reported the best sensitivity for POD obliteration of 98.7%; however, they provided no details as to how POD obliteration was determined.

Hudelist et al[27,29] did not use the sliding sign but rather a description coined by Bazot et al,[13] which rendered sensitivities of 76% and 87%, respectively: "Pouch of Douglas obliteration was considered complete when uterus, adnexa, and rectosigmoid colon were stuck together with loss of peritoneal structure and incomplete when peritoneal limits were partially identified with presence or absence of suspended or lateralized fluid collection." This description, although commonly cited in articles, is subjective and poorly reproducible with TVUS.

The prevalence of POD obliteration within some of the sample groups was quite high, with Reid et al[25] having 30% of participants with POD obliteration and Fratelli et al[23] having 47%. These large populations made the negative predictive values found by all authors strong and reassuring that a negative result on TVUS should be useful from a surgical planning perspective.

Rectosigmoid Colon

Deep infiltrating endometriosis affecting the bowel presents the biggest challenge from a surgical perspective. A specialized colorectal surgeon may be required to assist the gynecologist in removal of these lesions. Depending on the severity, segmental resection may be indicated, making the procedure highly invasive and placing a substantial burden on the person's quality of life, highlighting the importance of accurate surgical planning and patient counseling. Only 2 of the articles reviewed that reported the accuracy of rectosigmoid DIE found accuracy of less than 90%.[4,21] Given the high prevalence of disease within most study populations, this was an excellent result, showing TVUS to be an exceptionally useful tool for disease affecting the rectosigmoid colon.

Within the reviewed literature, the definition of what was "bowel" endometriosis was unclear. Some authors focused on DIE only (ie, lesions penetrating >5 mm into the bowel to within the muscularis propria or mucosal/submucosal layers), whereas others included superficial lesions on the bowel serosa under the umbrella of bowel endometriosis. The heterogeneity of descriptions made data analysis difficult.

The reported sensitivities, specificities, positive predictive values, negative predictive values, positive likelihood ratios, negative likelihood ratios, and accuracies of TVUS for DIE of the bowel are summarized in Table 5. Some authors reported separate accuracies for the rectum and sigmoid[23] or rectosigmoid and rectum,[21] with marginally better sensitivities shown by authors who reported the rectum alone (Table 5). We would propose that this differentiation is essential, as an assessment of the rectosigmoid colon above the level of the uterine fundus with TVUS is technically difficult. The sensitivity of TVUS for bowel endometriosis varied greatly. Rather poor sensitivity of 33.3% was reported by both Holland et al[20] and Grasso et al.[11] Grasso et al[11] reported "sigmoid colon" and "rectovaginal septum" disease but not the rectum specifically. Holland et al[20] had a large study group (n = 198) but a low incidence of bowel disease (n = 11), making statistically significant conclusions difficult to draw. Both authors had very high specificities (100% and 98.9%, respectively), likely due to the small populations within both studies. Only 2 authors reported the sigmoid separately and showed lower sensitivities within the sigmoid colon, 69% by Fratelli et al[23] and 33% by Grasso et al,[11] with both of these studies having limitations. Fratelli et al[23] performed a retrospective study, and Grasso et al[11] only had 4 participants with endometriosis within the sigmoid colon, making their results not statistically significant. The sigmoid colon will often appear too high in the field of view of a TVUS examination for simple interrogation, making detection of disease in this location challenging. Gonçalves et al[30] found this to be true, especially when other pelvic diseases such as endometriomas or fibroids were present.

Twelve of the 31 authors who reported bowel DIE found sensitivities of greater than 90% for detecting bowel disease.[15,17,22,27,29,31–37] Several of the authors who reported sensitivity of less than 50% had study populations with a very low incidence of bowel endometriosis.[3,11,20] Baggio et al[38] hypothesized that the low sensitivities in their study were possibly due to the gynecologists who were scanning being "less expert" in identifying the appearances of the bowel, as that was beyond their normal scope of practice.

High specificities were reported for bowel endometriosis, with 100% achieved in 7 studies

Table 5. Findings of Articles Covering Bowel Endometriosis

Author	Date	BP	Bowel Disease	Participants	Site	Technique	Sensitivity	Specificity	PPV	NPV	LR+	LR–	Accuracy
Abrao et al	2007	Yes	54	104	Rectosigmoid	TVUS	98.1	100	98	100	NS	NS	99
Alborzi et al	2018	Yes	52	317	Rectum	TVUS	88.46	98.87	93.88	97.76	78.14	0.12	97.16
Baggio et al	2016	No	49	92	Rectosigmoid	TVUS	41	93	91	58	NS	NS	NS
Bazot et al	2004	No	47	142	Rectosigmoid	TVUS	87.2	96.8	93.2	93.9	NS	NS	93.7
Bazot et al	2007	No	56	81	Rectosigmoid	TVUS	92.6	100	100	90	NS	0.17	95.1
Bergamini et al	2010	Yes	51	61	Rectosigmoid	RWC TVUS	96	90	98	81.8	NS	NS	NS
Ferrero et al	2011	Yes	48	96	Rectosigmoid	RWC TVUS	93.8	97.9	97.8	94	45	0.06	95.8
Ferrero et al[a]	2019	No	118	262	Rectosigmoid	TVUS	88.1	95.8	94.5	90.8	21.15	0.12	92.4
Ferrero et al[a]	2019	Yes	118	262	Rectosigmoid	TVUS	90.7	95.8	94.7	92.6	21.76	0.10	93.5
Fratelli et al[a]	2013	NS	126	420	Rectum	TVUS	66	99	98	87	94.5	0.34	NS
Fratelli et al[a]	2013	NS	63	420	Sigmoid	TVUS	69	98	85	95	30.7	0.32	NS
Gonçalves et al	2009	Yes	67	194	Rectosigmoid	TVUS	97	100	100	98	NS	0.02	99
Grasso et al	2010	No	4	33	Sigmoid	3D TVUS	33.3	100	100	91.3	NS	NS	91.6
Guerriero et al	2008	NS	49	88	Rectosigmoid	TG TVUS	67	92	NS	NS	8.17	0.36	NS
Guerriero et al[a]	2018	NS	66	159	Rectosigmoid	TG TVUS	84.8	87.1	82.4	89.0	6.576	0.174	NS
Guerriero et al[a]	2018	NS	66	159	Rectosigmoid	3D TVUS	89.4	93.5	90.8	92.6	13.856	0.113	NS
Hernández Gutiérrez et al	2019	Yes	32	48	Rectosigmoid	TVUS	81	62	81	62	2.16	0.30	75
Holland et al	2013	NS	11	198	Rectosigmoid	TVUS	33.3	98.9	60	96.9	31.5	0.674	NS
Holland et al	2010	NS	14	201	Rectosigmoid	TVUS	45.16	100	NS	NS	NS	0.29	NS
Hudelist et al	2011	NS	31	129	Rectosigmoid	TVUS	90	99	97	97	88.51	0.1	97
Hudelist, Oberwinkler et al	2009	No	48	200	Rectum	TVUS and PV	96	98	94	99	48.56	0.04	98
Hudelist, Tutties et al[a]	2009	No	43	195	Muscularis	TVUS	98	99	98	99	150.24	0.02	99
Hudelist, Tutties, et al[a]	2009	No	43	195	Mucosa	TVUS	62	96	53	97	16	0.4	94
Jiang et al	2017	NS	110	198	Rectosigmoid	RWC TVUS	88.2	97.3	98	88	41.67	0.13	92.4
Lazzeri et al[a]	2014	No	40	121	Rectosigmoid	TVUS	79.2	84.9	77.6	86.1	5.25	0.24	83
Lazzeri et al[a]	2014	No	83	121	Rectum	TVUS	94.1	86.1	94.1	86.1	6.77	0.06	92
León et al	2014	Yes	13	51	Rectosigmoid	SVG (gel)	100	93	NS	NS	14	NS	NS
Piketty et al	2009	No	66	134	Rectosigmoid	TVUS	90.7	96.5	97.1	88.9	NS	NS	NS
Reid et al	2013	No	20	100	Rectosigmoid	TVUS	85	91.3	70.8	96.1	NS	NS	NS
Reid et al	2014	No	43	189	Rectosigmoid	SVG (gel)	88.4	95.5	79.2	96.5	12.9	0.12	92.1
Saba et al	2012	NS	30	59	Rectosigmoid	TG TVUS	73	86	NS	NS	5.317	0.309	NS
Saccardi et al[a]	2012	No	6	54	Rectosigmoid	TVUS	33.3	91.7	31.3	91.7	4	0.727	NS
Saccardi et al[a]	2012	No	6	54	Rectosigmoid	SVG (saline)	66.7	93.8	57.1	95.7	10.66	0.355	NS
Savelli et al	2011	No	56	69	Rectosigmoid	TVUS	91.1	100	100	28.6	NS	NS	91.4
Tammaa et al[a]	2015	NS	16	65	Rectosigmoid	TVUS	93	96	88	98	23.3	0.1	95
Tammaa et al[a]	2015	NS	16	65	Rectosigmoid	TVUS	94	98	94	98	45.9	0.1	97
Valenzano Menada et al[a]	2008	Yes	29	90	Rectum	RWC TVUS	97.1	100	100	91.3	NS	0.03	97.8
Valenzano Menada et al[a]	2008	Yes	29	90	Rectum	TVUS	92.8	90.5	97	79.2	9.74	0.47	92.2
Vimercati et al	2012	No	82	90	Rectosigmoid	TVUS	77.8	94.4	77.8	94.4	14	0.2	91.1

PV indicates pelvic examination; other abbreviations are as in Table 2.
[a]Data from the same article.

(Table 5).[11,15,16,30,33,36,37] The lowest reported specificity was 84.1% by Lazzeri et al,[21] with no clear cause, as their study reported scant details of the scanning method. Due to the complex surgical complexity of bowel DIE, these high specificities should generate much reassurance in the presurgical counseling sphere.

The use of bowel preparation (BP) was not standard. Gonçalves et al[30] specifically studied the use of TVUS with BP and strongly advocated for this technique when assessing the bowel. Ferrero et al[39] directly compared TVUS with BP to TVUS without BP and found no benefit to the addition of BP. This was our finding across all studies, excluding those who used the RWC TVUS technique. Generally, there was no significant improvement in sensitivities, specificities, or accuracies for the detection of bowel DIE with TVUS when BP was included (Table 5).

Variant Techniques of TVUS

Several variant techniques of TVUS for DIE have been proposed and assessed, especially to improve detection and characterization of bowel disease (Table 5). Twenty-three of the 35 studies we reviewed used conventional TVUS. Of the remaining, 2 focused on 3D TVUS[11,40]; 4 studied RWC TVUS[32,34,37,41]; 3 used the SVG technique with either US gel[22,26] or saline[3] as the contrast medium; and a tenderness-guided TVUS approach was used by 3 authors.[19,40,42] It is difficult to draw meaningful conclusion with such a small number of studies, but the accuracy of these techniques was not significantly different from that of conventional TVUS (Tables 2–5). Three authors tested direct comparisons of variant techniques to conventional TVUS. Valenzano Menada et al[37] directly compared conventional TVUS to RWC TVUS in the assessment of rectosigmoid lesions. Although they found that RWC TVUS added little value to the detection of lesions, RWC TVUS vastly improved the diagnosis of the level of infiltration (sensitivity of 95.7% versus 56.5%).

Similarly, Saccardi et al[3] directly compared TVUS, SVG (saline contrast), and magnetic resonance imaging and found that SVG did improved detection of posterior-compartment DIE. This study was, however, small (only 54 participants and 6 cases of rectosigmoid DIE), so further studies directly comparing techniques are needed.

Guerriero et al[40] found that 3D TVUS improved detection of rectosigmoid lesions compared to 2-dimensional TVUS. However, Grasso et al[11] failed to show that 3D TVUS provided superior value to conventional TVUS compared to other authors in this review.

The limitation of these techniques is the added technical complexity and learning curve[40] they require. The addition of saline contrast requires a second operator. The infusion of a contrast medium (whether saline or gel) requires a rectal or vaginal examination, which is out of the scope of practice of a sonographer, meaning that these techniques must be performed by or under the supervision of a physician, which limits their availability and their suitability as frontline techniques.

Operator Qualifications and Experience

The qualifications and experience of the TVUS operator and the center from which the study was performed are detailed in Table 6. Reporting of the qualifications and experience of each operator and setting of each study was inconsistent, and the information not stated in 14 of the 35 articles reviewed. Twelve of the 21 studies that did report qualifications used gynecologists.[4,11,14,16,17,20,23,25,29,31,32,36] Within the reviewed literature, only 1 study reported using a sonographer.[12] If TVUS is to become an effective and routine frontline tool, it is essential for sonographers to perform these scans within an outpatient setting. On the basis of the currently available data, it is unclear whether sonographers can accurately do this.

It was commonly discussed in the literature that the accuracy of TVUS for the detection of DIE was linked to the experience of the operator.[17,23,26,27] Reporting of the experience level of the operators was varied and often unhelpful, with vague and subjective terms such as "the operator had extensive experience in gynecologic imaging" used.[4,15,16,20,31,32,43] In many cases, the experience of the operator was not stated at all.

Fratelli et al,[23] Holland et al,[16] Tammaa et al,[17] and Guerriero et al[19] all concluded that their operators were highly experienced, and this was likely a contributing factor to the high levels of agreement detected in their studies. All agreed in their discussions that further studies are needed to investigate the differences in accuracy between less-experienced

operators, particularly those outside the tertiary referral setting.[17] Fratelli et al[23] concluded that operator experience was linked to the detection rate; however, their reported sensitivities and specificities did not reflect this. They stated that their 3 operators had 4 to 20 years of experience and showed similar accuracies. As with any skill, it can be inferred that more experience will yield better results; however, it may be that experience is only a factor to a point, and once proficiency has been obtained (perhaps in less than 4 years of scanning), additional experience does not substantially affect detection rates; however, there is no available evidence to confirm this.

Most studies were performed within specialized endometriosis centers or gynecologic pain clinics.[4,17,21,23,26,27] As such, the sample populations were highly selective with a high incidence of disease. It is likely that those working within these settings quickly become expert at the technique, whereas those working in a more generalized setting will be exposed to less disease and therefore will be slower to develop the pattern recognition skills needed; however, again, there is no evidence to verify this. Additionally, the reported sensitivities and specificities of TVUS were likely influenced by the high prevalence of disease within these centers.

A study by Rosefort et al[44] was the only article we reviewed to give any insight into this. When comparing findings of a "trained" operator within a specialist referral center against scans performed by "untrained" operators outside the referral center, they found that TVUS had a very poor detection rate for DIE. That study lacked robust standardized protocols, and it goes without saying that at least minimum training is required for a diagnostic test to be accurate. It does, however, suggest that those outside specialized units may not yet be receiving the training needed to assess for DIE with TVUS. As such, more studies beyond such specialized centers are required to further validate the findings in this review.

Limited Interobserver Data

Evaluation of the reproducibility of any diagnostic test is a crucial aspect of assessing its accuracy. Within our returned search results, interobserver agreement was only reported in 2 studies.[19,23] In both studies, all operators were gynecologists, and all were highly experienced in performing TVUS examinations, with a minimum of

Table 6. Qualifications of the TVUS Operator, Experience, and Whether the Study Came From a Specialized Endometriosis Center or a Gynecologic Pain Center

Author	Date	Operators	Operator Qualification	Experience, y	Specialist Center
Alborzi et al	2018	1	Gynecologic sonologist	30	No
Baggio et al	2016	2	Physicians	0	No
Bazot et al	2007	1	Radiologist	"Extensive"	NS
Bergamini et al	2010	1	Gynecologist	"Extensive experience"	Yes
Ferrero et al	2011	2	Physicians	NS	Yes
Ferrero et al	2019	2	Gynecologist	"Extensive experience"	NS
Fratelli et al	2013	3	Gynecologic sonologist	4–20	Yes
Gonçalves et al	2009	1	Radiologist	NS	NS
Grasso et al	2010	1	Gynecologic sonologist	20	NS
Hernández Gutiérrez et al	2019	1	Gynecologist	"Expert in gynecologic US"	Yes
Holland et al	2013	2	Gynecologic sonologist	"high level of expertise"	Yes[a]
Holland et al	2010	4	Gynecologic sonologist	"high level of expertise"	Yes[a]
Jiang et al	2017	2	Physicians	NS	NS
Piketty et al	2009	1	Radiologist	"Experienced"	No
Reid et al	2013	1	Gynecologic sonologist	NS	Yes[a]
Reid et al	2014	2	Gynecologic sonologist and fellow	NS	Yes
Savelli et al	2011	NS	Gynecologist	NS	Yes
Tammaa et al	2015	2	Gynecologic sonologist	>3000 scans	Yes[a]
Vimercati et al	2012	1	Sonographer	>10 years	NS

Abbreviations are as in Table 2.
[a]Multicenter study.

4 years scanning experience[23] or having performed at least 3000 previous scans.[17] An additional 2 authors, Fratelli et al[23] and Holland et al,[16] reported the accuracy of multiple operators by comparing the accuracy of each operator independently rather than reliability. Where sensitivities and specificities were reported between operators,[16,17,23] results were closely matched in most cases, suggesting that TVUS can be an accurate method of assessment for DIE regardless of the operator. If TVUS is truly to become a widespread frontline tool in the diagnosis of DIE, further studies on interoperator reliability and variability are needed. A limitation of this review was that our search terms did not specifically encompass this, and as such, additional evidence may exist that has not been included in this review.

Conclusions

To date, there is a good body of published data regarding the accuracy of TVUS for the detection of DIE affecting the posterior pelvic compartment. Evidence suggests that TVUS is poor at detecting bladder DIE. The diagnostic accuracy for DIE overall was good. Many of the studies reviewed used inconsistent descriptors and varying terminology, making comparisons of results difficult. It was evident that more recent publications (2017 onward) had adopted the International Deep Endometriosis Analysis group consensus on the classification of endometriosis with US.[8] As such, future studies should be more uniform, making data synthesis, meta-analysis, and future research progress easier.

Given the surgical complexity of DIE, TVUS is undoubtedly a great asset when this disease is present. Within the current literature, there is scant evidence on interoperator reliability to suggest that these results are reproducible.

There are little data to date derived from sonographer-led scanning rather than scanning performed by gynecologists. Most of the published articles were conducted in specialized settings (eg, endometriosis centers and gynecologic pain clinics), making it unclear whether these techniques are accurate when performed by sonographers within the more common setting of outpatient imaging practices. As endometriosis is a common condition, evidence to support the accuracy of TVUS in a generalized setting has the potential to expand services, reduce diagnostic delays, and give patients with DIE a noninvasive yet highly accurate diagnostic test.

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2.2 Discussion and Conclusion

From the reviewed data, it is apparent TVUS has a well-established high level of diagnostic accuracy for the detection of DE affecting the posterior pelvic compartment, with accuracies of 75.7%-97% reported (35, 51-53). The current evidence suggests that TVUS is poor at detecting bladder DE, which may be in part due to technical aspects of TVUS. Given the complexity of managing DE, whether surgically or otherwise, TVUS undoubtedly is of high value.

There were some gaps identified within the current literature. Firstly, there is scant evidence on interoperator reliability to suggest that these results are reproducible. As this was not, however, expressly sought within the search strategy, there may be publications on this which this review may have not encompassed. Additionally, there appears to be a deficit of data derived from sonographer-led scanning rather than scanning performed by gynaecologists. Most of the published articles originated from specialised settings (e.g., endometriosis centres of excellence and gynaecologic pain clinics). It is therefore unknown whether the same level of diagnostic accuracy is retained when these studies are translated into the wider clinical setting and these techniques are performed by sonographers within outpatient imaging practices.

2.4 Updated search of the literature

The search was repeated to identify up to date literature on 20 December 2021. This search revealed 132 articles (25 of which were duplicates). After title and abstract review, twenty-seven articles underwent full text review and 12 were ultimately included for analysis (54-65). Similar to the previously published review, the data were very heterogeneous, however there was more consistency seen in the ultrasound techniques and anatomical descriptions reported in the papers which outlined detailed TVUS methodology. This was largely due to the use of the 2016 IDEA consensus guidelines (43) as the basis for scanning protocols in several studies (57, 59, 61, 63, 65). The results will be discussed below in an integrative review.

2.4.1 Accuracy of Transvaginal Ultrasound (TVUS)

The reported accuracy of TVUS, broken down by anatomical sites, is reported in table 2 and will be discussed below in sections 2.4.3-7. Overall accuracy was reported in only a single study with a detailed ultrasound methodology revealing TVUS to have a sensitivity of 78%,

specificity of 97%, positive predictive value (PPV) of 89%, negative predictive value (NPV) of 93% and accuracy of 92% (59), in agreement with previously reviewed data. No papers within this review reported on intra or interobserver variability.

Table 2 Table outlining reported accuracies at specific anatomical site within the various studies reviewed. Key: n= number, sTVUS= specialist transvaginal ultrasound, cTVUS= community transvaginal ultrasound, SVG= sonovaginography, RWC-TVUS= rectal water contrast transvaginal ultrasound, NS= not specified, PPV= positive predictive value, NPV= negative predictive value, LR+= likelihood ratio positive, LR-= likelihood ratio negative, POD= pouch of Douglas, BP= bowel preparation, Y= yes, N= no

Author	*Date*	*participants (n)*	*cases (n)*	*Technique*	*Data*	*Sensitivity*	*Specificity*	*PPV*	*NPV*	*LR+*	*LR-*	*Accuracy*
Uterosacral ligaments												
Bartlett et al.	2019	83	32			0	NS	NS	NS	NS	NS	NS
Zhang et al.	2019	118	85			95.3	90.9	96.4	88.2	NS	NS	94.1
Indrielle-Kelly et al.	2020	49	34			74	67	83	53	2.21	0.4	71
Pattanasri et al. **	2020	75	32		sTVUS	56	93	86	74	NS	NS	NS
Pattanasri et al. **	2020	44	21		cTVUS	0	96	0	51	NS	NS	NS
Yin et al.	2020	198	170			96.47	85.7	97.6	80	6.75	0.04	94.95
Barra et al. **	2021	281	156		SVG	77.6	88.8	89.6	76	6.9	0.3	82.6
Barra et al. **	2021	281	156		RWC-TVUS	80.1	92.8	93.3	78.9	11.1	0.2	85.8
Ros et al.	2021	172	88			96.6	82.1	85	95.8	5.41	0.04	89.5
POD obliteration												
Arion et al.	2019	269	41	sliding sign		72.3	93.9	68.2	95.1	12	0.29	NS
Bartlett et al.	2019	83	7	NS		0	NS	NS	NS	NS	NS	NS
Indrielle-Kelly et al.	2020	49	40	sliding sign		88	89	97	62	7.87	14	88
Pattanasri et al. **	2020	75	42	NS	sTVUS	69	79	81	81	NS	NS	NS
Pattanasri et al. **	2020	44	13	NS	cTVUS	15	100	100	74	NS	NS	NS
Goncalves et al.	2021	120	56	NS		83.9	89.1	87	86.4	NS	NS	NS
Bladder												
Bartlett et al.	2019	83	3			0	NS	NS	NS	NS	NS	NS
Indrielle-Kelly et al.	2020	49	9			89	100	100	98	∞	0.11	98
Pattanasri et al. **	2020	75	16		sTVUS	0	98	0	75	NS	NS	NS
Pattanasri et al. **	2020	44	21		cTVUS	0	100	0	68	NS	NS	NS
Yin et al.	2020	198	3			66.7	100	100	99.5	**	0.33	99.5
Goncalves et al.	2021	120	4			75	99.1	75	99.1	NS	NS	NS
Rectosigmoid colon												
Bartlett et al.	2019	83	15	Rectosigmoid	TVUS	0	NS	NS	NS	NS	NS	NS
Chen et al.	2019	29	15	Rectum	TVUS	26.7	85.7	66.7	52.2	1.87	0.86	55.2
Sandre et al.	2019	37	31	Rectosigmoid	RWC-TVUS	94	100	100	75	∞	0.06	NS
Indrielle-Kelly et al.**	2020	49	17	Rectosigmoid	TVUS	94	84	76	96	6.2	0.07	88
Indrielle-Kelly et al.**	2020	49	10	Rectum	TVUS	100	100	100	100	∞	0	100
Pattanasri et al. **	2020	44	19	Rectosigmoid	cTVUS	0	100	0	91	NS	NS	NS
Pattanasri et al. **	2020	75	4	Rectosigmoid	sTVUS	71	98	94	90	NS	NS	NS
Yin et al.	2020	198	79	Rectosigmoid	TVUS	94.94	94.96	92.6	96.6	18.84	0.05	95.9
Barra et al. **	2021	281	156	Rectosigmoid	SVG	82	98.5	95.8	92.9	54.1	0.2	93.6
Barra et al. **	2021	281	156	Rectosigmoid	RWC-TVUS	95.2	99.5	98.8	98	188.5	0.05	98.2
Goncalves et al.	2021	120	53	Rectosigmoid	TVUS-BP	96.23	98.5	98.1	97.1	NS	NS	NS

2.4.2 Operator Qualification and Experience

The qualifications and experience of the operators preforming the scans are outlined in table 3. It was again clear that most studies were performed within specialist endometriosis centres resulting in diagnostic efficacy assessment within a high-risk population only, a limitation which was acknowledged by Chen *et al.* (56). In most studies, the TVUS examinations were performed by gynaecologists with training in ultrasound. Only two studies (Bartlett *et al.* (55) and Pattanasri *et al.* (60)) evaluated TVUS performed by sonographers and reviewed for reporting by radiologists as is typical Australian practice. In both studies, usefulness of routine transvaginal ultrasound (rTVUS) was assessed and although neither elaborated on ultrasound methodology in much detail, it is likely these were performed in line with current imaging guidelines (45, 66), which do not include an assessment of the anterior or posterior compartments. This would explain the 0% sensitivities across all areas (see table 2) reported by these two studies as it goes without saying that in order to see disease, one must actually look for it.

Table 3 Table outlining qualifications of the ultrasound operators and origin of the reviewed study (e.g. specialist endometriosis centre). Key: NS= not specified, COGU= Certificate of Obstetric and Gynaecological Ultrasound Y= yes, N= no.

Author	*Date*	*Operators (n)*	*Operator qualification*	*experience*	*Specialist centre*
Bartlett et al.	2019	NS	Sonographer/ subspecialised radiologist	NS	N
Chen et al.	2019	NS	Physician or sonographer	>10 years	Y
Sandre et al.	2019	3	Gynaecologist	NS	NS
Arion et al.	2019	NS	Gynaecologist	NS	Y
Zhang et al.	2019	1	NS	NS	NS
Indrielle-Kelly et al.	2020	2	Gynaecologist	>10 years	Y
Pattanasri et al.	2020	NS	Sonographer/ radiologist or COGU	NS	N
Yin et al.	2020	1	NS	NS	NS
Ros et al. (a)	2021	2	Gynaecologist	NS	Y
Barra et al.	2021	2	Gynaecologist	>500 scans	NS
Goncalves et al.	2021	2	Radiologists	>10 years	Y
Ros et al. (b)	2021	2	Gynaecologist	NS	Y

2.4.3 Bladder

The reported diagnostic accuracy of bladder DE across all published works can be seen in table 2. Wide ranging sensitivities were reported for DE affecting the bladder from 0% (55, 60) to 89% (59) however, specificities were typically high. Whilst reassuring, these high specificities are expected given the low prevalence of bladder endometriosis, which was reported to be 2% by Ros *et al.* (62) in their extensive audit of bladder DE. The prevalence of bladder DE was significantly higher in the study by Pattanasri *et al.* (60) than all others with 37 cases across their 119 participants. This brings into question how DE was determined surgically, which may have been different to the methods employed in other studies. Of particular note, within their study, Ros *et al.* (62) found bladder DE was never present sonographically without other deposits of DE or adenomyosis coexisting on TVUS.

Ros *et al.* (62) discovered TVUS had the ability to perfectly predict findings of bladder DE at cystoscopy but this required examinations to be performed with a moderate amount of urine in the bladder, a state which is not always attainable when performing TVUS which requires bladder emptying to optimise visualisation of the uterus.

2.4.4 Uterosacral ligament (USL)

The USL's are the most commonly affected anatomical site of DE visible on ultrasound, with nodules found in up to 70% of cases, which occur in isolation in up to 80% of cases (67). Within the original review outlined in the published manuscript, the sensitivities varied considerably suggesting USL disease can be challenging to diagnose sonographically. The previously highest reported sensitivity of 88.9% by Saccardi *et al.* (68) when performing sonovaginography (SVG) was vastly surpassed by Zhang *et al.* (57), Yin *et al.* (63) and Ros *et al.* (61) with sensitivities for 95.3%, 96.5% and 96.6% respectively (table 2). Yin *et al.* (63) outlined in detail the thorough and systematic approach they took to assessing the USLs. This was similar to the approach proposed by Leonardi *et al.* (69) (70). It is likely that this progress in refinement of sonographic technique, and subsequent education of ultrasound professionals will result in continuing increases in the diagnostic accuracy of TVUS for USL DE. The three articles which reported sensitivities >95% all came from specialist endometriosis centres.

Whether this increase in accuracy will translate beyond such specialist centres is however, unclear. Pattanasri *et al.* (60) compared accuracy of "specialist transvaginal ultrasound (sTVUS)" (defined as those performed by gynaecological sonologists) with "community transvaginal ultrasound (cTVUS)" (defined as those performed by sonographers within general (community) radiology settings). As the specialist group only reported a sensitivity of 56%, it suggests the high sensitivities reported in endometriosis centres of excellence may not be translating into routine practice yet. It must be noted, however, that no details were included within this paper as to the scanning protocols employed and as such, some sTVUS may not have included a comprehensive assessed for DE.

2.4.5 Rectosigmoid colon

The rectosigmoid colon was the most investigated location with eight of the 12 studies reporting on accuracy of this location (table 2) (55, 56, 58-60, 63-65). This is likely due to the complexity associated with surgical management rectosigmoid DE making non-invasive diagnosis prior to surgery imperative (15). When excluding Pattanasri *et al.* (60) and Bartlett *et al.* (55), who reported on rTVUS, the performance of TVUS for the detection of rectosigmoid DE was excellent with high sensitivities and specificities reported across the board (table 2). The exception to this was Chen *et al.* (56), who reported a sensitivity of only 26.7%, and an accuracy of only 55.2% which was well below the reported accuracy of all other studies and indeed, any within our published review. Their study however focused specifically on rectovaginal septum endometriosis infiltrating the bowel which is a rare subtype suggesting that accuracy in this specific location may be lower than accuracy affecting the upper rectal region.

The study by Goncalves *et al.* (64) reported a novel perspective comparing TVUS to DL. By having two independent surgical experts review video of DL procedures, they discovered TVUS was far more sensitive in the detection of rectosigmoid DE (96.2% TVUS vs 5.7% and 3.8% DL). This is an immensely significant finding, not only confirming the high value of TVUS as a presurgical tool in cases of rectosigmoid DE, but also raising questions around DL as the current "gold standard" for diagnosis of all subtypes of endometriosis.

2.4.6 Ovaries

Within the reviewed articles, there was only a small amount of discussion regarding endometriosis affecting the ovaries. This is likely because ultrasound has a long-established usefulness in the detection of OE, however, when assessing TVUS performed by a variety of providers, Pattanasri *et al.* (60) reported a sensitivity of 84% and a specificity of 60%, suggesting improvements can be made to diagnostic accuracy. Interestingly, cTVUS had a sensitivity of 69% and specificity of 100%, compared to a sensitivity and specificity of 88% and 69% for sTVUS (60). Whilst the exact cause of this disparity is unknown, it may be due to the somewhat atypical appearance endometriomas can exhibit in some cases (71). It may be that specialist sonologists are more cognisant of this than community operators and as such, may accurately characterise some endometriomas generalists may overlook but in turn, this may lead to a higher false positive rate. Opposing results were seen by Bartlett *et al.* (55) however, who reported 18 cases of ovarian endometrioma detected on rTVUS within their study, which were all found to be true positives. Detection of endometriomas only resulted in a sensitivity of 22% in the diagnosis of endometriosis sonographically (55), highlighting the need for comprehensive assessments of the anterior and posterior compartment in order to enhance diagnosis (43).

When comparing TVUS to DL, Goncalves *et al.* (64) reported identical sensitivities for both modalities (94.7%), however TVUS had a far superior specificity (95.1% vs 78.9%), further highlighting the value in quality pre-operative imaging.

2.4.7 Pouch of Douglas (POD) obliteration

Sensitivities and specificities for POD obliteration detected by TVUS were typically good (table 2). Arion *et al.* (54) assessed the utility of the sliding sign performed during gynaecological appointments as a point of care ultrasound (POCUS) technique. Given the high NPV in their study, they proposed the sliding sign could be a useful triage tool for determining whether a general or subspecialised gynaecologist should perform surgery for endometriosis, a sentiment which was echoed by Reid *et al.* (72). The NPV

achieved by Arion *et al.* (54) was not achieved by any other authors, however, suggesting more education and development of professionals may be needed. Within the cTVUS group, Pattanasri *et al.* (60) reported a sensitivity and specificity of 15% and 100% respectively. It is perhaps possible these findings reflect the diagnostic accuracy of *not* routinely including an assessment of the sliding sign. Given the simplicity of performing the technique, and its great clinical usefulness as a predictor of surgical complexity and bowel disease (19), incorporation of the sliding sign into all rTVUS examinations would be reasonable.

2.4.8 Conclusion

The updated literature again showed TVUS to be a valuable tool in the diagnosis of DE with high levels of diagnostic accuracy shown across most studies, except for those utilising only rTVUS techniques rather than a dedicated assessment for endometriosis.

The reporting of the data was more uniform within the updated search than the original search, likely due to the good uptake of the IDEA consensus for the formulation of TVUS protocols (43).

A very interesting discovery was presented by Goncalves *et al.* (64) who found TVUS to have superior diagnostic accuracy to DL in some instances, bringing into question the suitability of our current "gold standard". Furthermore, the recent 2022 updated ESHRE guidelines state:

> "Laparoscopy is no longer the diagnostic gold standard (for the diagnosis of endometriosis) and it is now only recommended in patients with negative imaging results and/or where empirical treatment was unsuccessful or inappropriate." (18)

There was again no data derived from sonographer-led scanning of comprehensive TVUS protocols for DE and most data originated in specialised endometriosis centres. With the move towards imaging for diagnosis of endometriosis away from DL, it is of critical importance that these techniques fall within the capabilities of sonographers working in outpatient imaging facilities. In the next chapter, we will be investigating the diagnostic accuracy of TVUS when performed by Australian sonographers, within an outpatient women's imaging centre.

3 What is the accuracy of transvaginal ultrasound in the diagnosis of endometriosis prior to surgery when performed by a sonographer?

A manuscript currently under review for publication forms the basis of this chapter.

What is the accuracy of transvaginal ultrasound in the diagnosis of endometriosis prior to surgery when performed by a sonographer?

3.1 Introduction and Motivation

A sonographer is an accredited allied health professional who performs ultrasound examinations. Although highly skilled experts in ultrasound imaging, sonographers undergo different training than medical doctors. As such, it is unlikely any would possess the same clinical understanding of gynaecological pathophysiology as a gynaecologist. As has been established in the previous chapters, it is clear that TVUS has an important role to play in improving diagnosis of endometriosis. As most of the studies reviewed in chapter 2 were performed in specialised endometriosis or gynaecological pain clinics, and most scans were performed by gynaecologists skilled in ultrasound rather than sonographers, it is unclear whether sonographers, especially those within outpatient imaging settings, would produce the same level of diagnostic accuracy published to date.

This chapter presents a prospective longitudinal cohort study involving 201 women who underwent TVUS for endometriosis (with 53 included in the final analysis), with the objective to assess the diagnostic accuracy of TVUS for the diagnosis of endometriosis when performed by sonographers within an outpatient women's imaging setting.

University of South Australia

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By signing the Statement of Authorship, each author certifies that:

IV. the candidate's stated contribution to the publication is accurate (as detailed above);

V. permission is granted for the candidate in include the publication in the thesis; and

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Title: What is the accuracy of transvaginal ultrasound for endometriosis when performed by a sonographer within an outpatient women's imaging centre?

Short title: Sonographer accuracy of TVUS for DE

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Abstract

Objectives: To assess the diagnostic accuracy of transvaginal ultrasound (TVUS) for the diagnosis of endometriosis when performed by sonographers within an outpatient women's imaging setting.

Methods: A prospective longitudinal cohort study was performed. The study group comprised of 201 women who presented to a women's imaging centre between September 2019 and September 2020. All participants underwent a comprehensive transvaginal ultrasound assessment, based on the International Deep Endometriosis Analysis (IDEA) group consensus, performed by one of three experienced sonographers. Laparoscopy was performed within 12 months as the reference standard. Complete TVUS and surgical data was available for 53 women who were included in the final analysis.

Results: Pelvic endometriosis of any subtype was confirmed at surgery in 50/53 (94.3%) participants, with 25/53 (47.2%) having deep endometriosis (DE) nodules and/or ovarian endometriomas present. TVUS for the detection of DE had overall sensitivity of 84.0%, specificity of 89.3%, PPV of 87.5%, NPV of 86.2% LR+ of 7.85, LR- of 0.18 and accuracy of 86.8% ($p<0.001$). Reduced ovarian mobility had a poor sensitivity for detecting ovarian fossa superficial endometriosis (SE), local adhesions and/ or localised DE or endometrioma (Left= 61.9% and right=13.3%) but high specificities (left= 87.5% and right=94.7%). Site-specific tenderness (SST) of the ovaries or posterior compartment was correlated against the presence of localised SE, DE or adhesions with low sensitivities (left ovary= 29.7%, right ovary= 11.8% and posterior compartment= 35.9%) and moderate specificities (left ovary= 81.3%, right ovary= 84.2% and posterior compartment= 71.4%). When cases with DE present were excluded, performance of SST had comparable accuracy for the detection of isolated SE. The correlation of sonographic soft markers to surgically detected endometriosis

failed to reach statistical significance in all locations except for reduced left ovarian mobility (p=<0.001).

Conclusion: Sonographers working in an outpatient women's imaging setting are able to detect DE with a high level of diagnostic accuracy however, the performance of soft markers in the detection of SE was poor.

Introduction

Endometriosis is a common, chronic gynaecological condition affecting as many as 1 in 9 female-born people (1) with three presenting subtypes; superficial endometriosis (SE), ovarian endometriosis (endometrioma) and deep endometriosis (DE). Often causing severe pain, subfertility and pelvic adhesions (2), endometriosis is a complex condition, frequently accompanied by a diagnostic delay of approximately 6.4years (3). As such, current international management guidelines suggests people with severe disease should be managed in centralised, specialised endometriosis centres (4). Consequently, wide accessibility to non-invasive diagnostic methods, such as imaging, are imperative in order to reduce the diagnostic delay and facilitate timely triage to specialist centres for management (5).

As DE is the most severe subtype of the disease, and presents the most complex therapeutic problem, over the last two decades, transvaginal ultrasound (TVUS) has been extensively studied to aid in the diagnosis and management of DE with its accuracy well established (6-11). In 2016, the International Deep Endometriosis Analysis (IDEA) group published a consensus statement outlining how TVUS can be used to diagnose DE by direct visualisation of lesions and how sonographic "soft markers" (site-specific tenderness (SST) and ovarian immobility) can be used to raise suspicion of all endometriosis subtypes including SE (5). This consensus statement has provided a framework upon which all imaging professionals can structure a comprehensive TVUS examination for endometriosis allowing the technique to be offered in stand-alone imaging settings, distant to the managing gynaecological and surgical teams. The diagnostic accuracy of TVUS within such settings however remains unclear. The objective of this study was to assess the diagnostic accuracy of TVUS for endometriosis, when performed in accordance with the IDEA consensus, by medical sonographers within an outpatient women's imaging setting.

Methods

Study design

A prospective longitudinal cohort study was performed. The study design was drafted prior to the start of the study, based on the Standards for Reporting of Diagnostic Accuracy (STARD) guidelines (12). The study was approved by the University of South Australia (UniSA) institutional ethics review board (UniSA Human research ethics project number 202217). Written informed consent was obtained from all participants. No funding was obtained for this study.

Study population

All patients presenting to an outpatient ultrasound clinic, specialising in obstetric and gynaecological imaging, in Adelaide, South Australia, for an endometriosis ultrasound, or a pelvic ultrasound with a clinical suspicion of endometriosis between September 2019 and September 2020 who met the inclusion criteria were invited to take part. Inclusion criteria included: people over the age of 18 years and those undergoing TVUS with a clinical suspicion of endometriosis. No upper age limit was imposed. Participants were excluded if TVUS was not performed, was not performed by one of three study sonographers (AD, CP, AC), they did not have surgery within 12 months of their TVUS or surgical data could not be obtained.

Transvaginal Ultrasound (TVUS) technique

The TVUS was completed by one of three experienced specialist obstetric and gynaecological sonographers (Australian Sonographers Accreditation Registry (ASAR) Accredited Medical Sonographers (AMS)). All three sonographers (AD, CP and AC) had between 10-20 years ultrasound experience and more than five years of experience scanning

for DE specifically. All TVUS were performed in line with the standard imaging protocol of endometriosis ultrasound, incorporating a systematic, methodical approach to scanning based on the methods of the IDEA consensus statement (5). Scans were performed at any stage of the participants' menstrual cycles.

The uterus and ovaries were assessed in two planes looking for signs of adenomyosis, endometriomas and any other pathology. The uterine cavity was assessed with three-dimensional ultrasound to assess shape and the junctional zone for signs of adenomyosis. Mobility of the ovaries was tested with probe pressure (+/-abdominal pressure with the sonographer's free hand) to assess for possible adhesions and SST (video 1). The mobility of the uterus was assessed with abdominal pressure and probe pressure for assessment of the 'sliding sign (5) (video 2).

The anterior compartment was evaluated to assess the bladder, ureters, anterior vaginal wall and vesicouterine space. Scans were routinely performed with an empty bladder to optimise both patient comfort and visualisation of the uterus and ovaries. As such, bladder visualisation was often suboptimal.

The posterior compartment was evaluated to assess the rectovaginal septum (RVS), rectosigmoid colon, retrocervical region (uterosacral ligaments (USL), torus uterinus and posterior vaginal fornix) and pouch of Douglas (POD). No bowel preparation was used for the assessment of the rectosigmoid colon.

DE was documented as definitive when hypoechoic solid nodules were seen within any of the regions outlined above (5) (figure 1). An endometrioma was confirmed by the presence of an avascular, unilocular cystic lesion containing low-level "ground glass" like echoes (figure 2) (13). The POD was considered obliterated when the sliding sign was negative (video 3). The presence of 'soft markers' (SST or poor ovarian mobility) was considered suggestive of DE, local adhesions or superficial endometriosis (SE).

The scan was extended to include a transabdominal approach when the fundus of the uterus or either ovary was not fully visualised by TVUS alone. An assessment of the kidneys was performed if posterior compartment disease was discovered, to exclude hydronephrosis secondary to ureteric compromise.

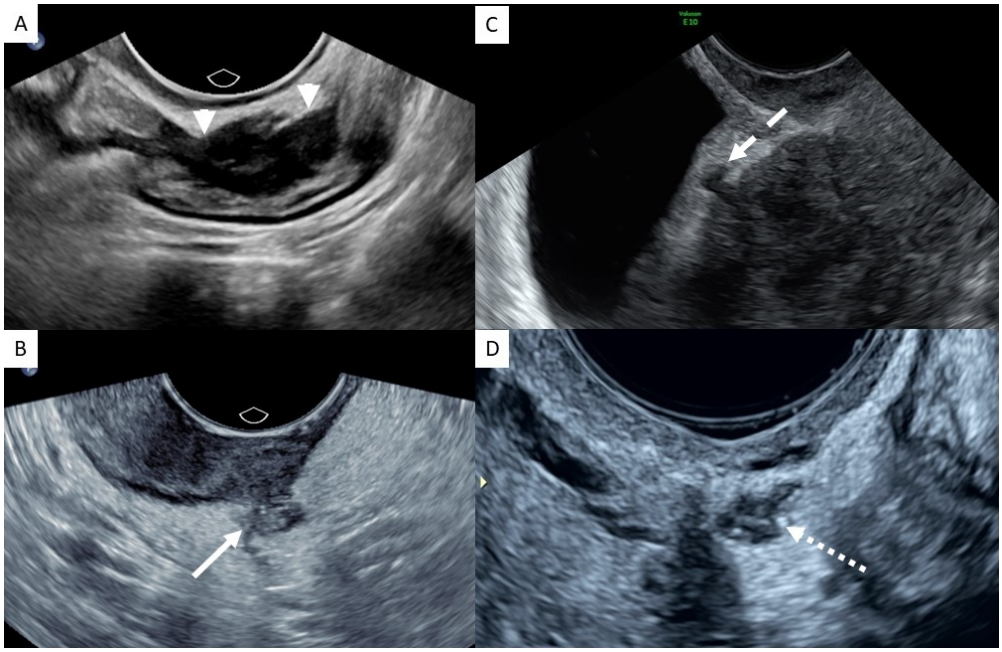


Figure 1: Transvaginal ultrasound images depicting nodules of endometriosis within the (A) anterior rectal wall (arrowheads), (B) torus uterinus (solid arrow), (C) bladder (large dashed arrow) and (D) uterosacral ligament (small dashed arrow).

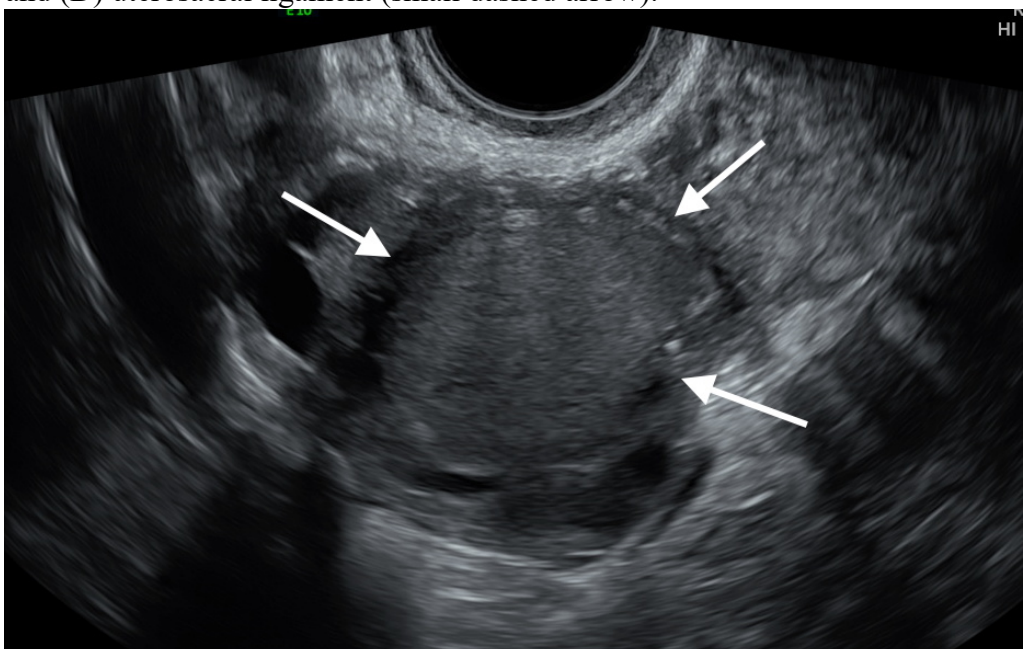


Figure 2: Transvaginal ultrasound image demonstrating an avascular, unilocular, cystic lesion containing low-level "ground glass" like echoes (white arrows). This is typical of an ovarian endometrioma.

Scans were performed on either a Philips Epiq ultrasound system with a C10-3MHz or C8-5MHz transvaginal transducer, a Phillips IU22 ultrasound system with a C10-3 transducer, or a GE Voluson E10 with a 5-8MHz transducer. Initial reports were written by the sonographers at the time of the scan. Still images and cine clips as well as the sonographer's report were reviewed by a radiologist and a formal report was generated. Surgeons only received the formal radiologist's report and were blinded to the sonographer's report.

Surgical technique

Surgery (laparoscopy or laparotomy) was used as the reference standard to reflect current practice (14). Participants were free to select a surgeon of their choice to perform the surgery meaning surgical intervention was performed by one of 17 gynaecological surgeons. The gold standard diagnosis of endometriosis was made if there was: (1) direct visualisation of at least one lesion attributable to endometriosis, (2) complete obliteration of the pouch of Douglas, with a secondary observation of other locations of DE or (3) histologically confirmed endometriosis (15).

Data extraction and synthesis

All demographic and TVUS data was entered into a Microsoft Excel spreadsheet (Microsoft excel version 16.30, Microsoft Corporation 2019) by primary author (AD) after review of the sonographers' reports and surgical reports. Surgical reports were reviewed by two authors (AD and NP). If agreement was not reached as to the nature of surgical findings, surgical reports were reviewed by a third author for clarification (MLH). Where ambiguity still existed, the performing surgeon was contacted via email for clarification. Data entry was performed twice, and the two spreadsheets cross checked for quality assurance.

Statistical analysis

Demographic data and prevalence of disease was reported with descriptive statistics. Sensitivity, Specificity, positive predictive value (PPV), negative predictive value (NPV), likelihood ratio positive (LR+), likelihood ratio negative (LR-) and accuracy were calculated for each anatomical site as well as overall as per standard definitions (16). A confidence interval (CI) of 95% was sought to determine the diagnosis of endometriosis. A Fisher's exact test was used to determine significance with $p<0.05$ considered statistically significant. SPSS software was used for the calculations (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp) and an online Microsoft Excel calculator was used for the calculation of CIs (17).

Prior to beginning data collection, a biostatistician was consulted to determine the minimum sample group needed. A population of 100 (including at least 45 participants with the disease) was estimated to achieve 83% power to detect a change in sensitivity from 0.6 to 0.8 using a two-sided binomial test and 88% power to detect a change in specificity from 0.6 to 0.8 using a two-sided binominal test. The target significance level was 0.05 (18).

Results

Two-hundred and three (203) women agreed to take part, of which two were ineligible (one was under 18 years of age and one did not have an endometriosis ultrasound), with surgical correlation available for 53 who were included in the final analysis (figure 3). The mean age of all participants was 31.4 years (±8.7 years) (range 18-56 years). Two of the women in our final analysis were aged over 50 years. The mean time interval between TVUS and surgery was 106 days (±87.3 days) (range 1-318). The most common reasons for presentation were pelvic pain (35%), dysmenorrhoea (32%) and heavy menstrual bleeding (16%). 15/53 (28%) had a known history of endometriosis confirmed through prior laparoscopy. Data on the use

of contraceptives was not collected. The participants' demographic and clinical characteristics are shown in Table 1.

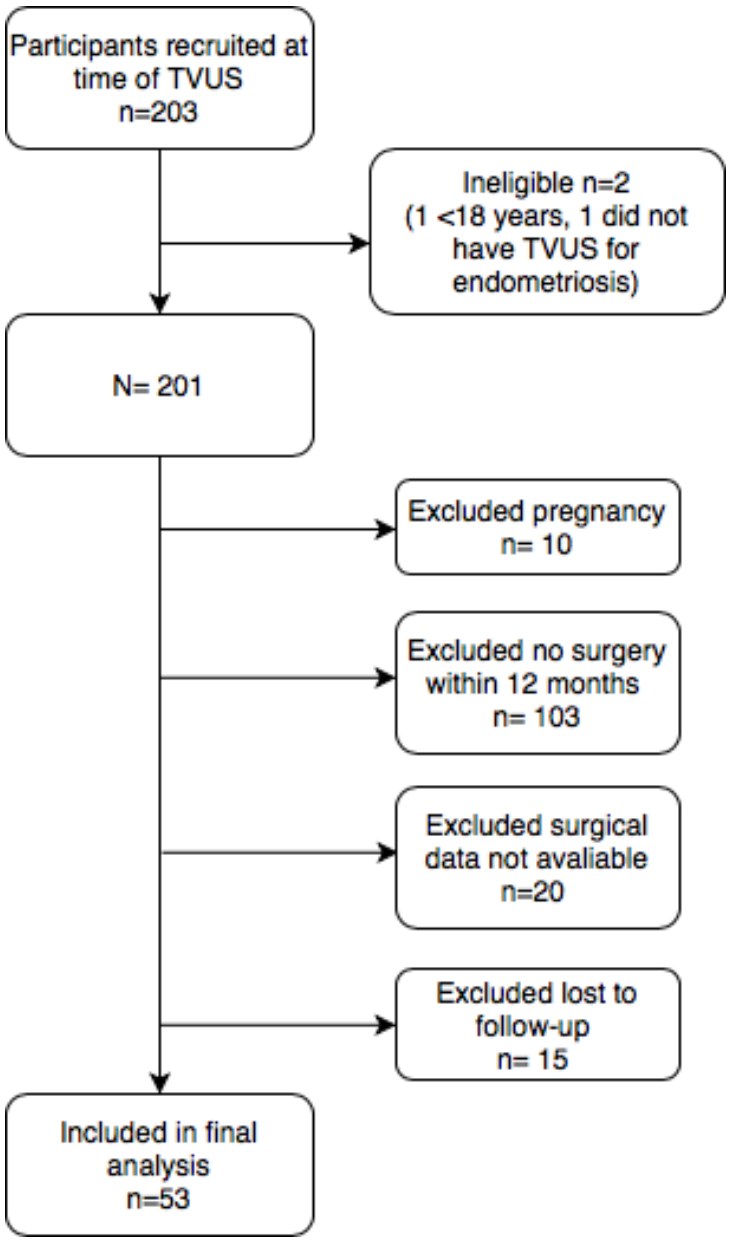


Figure 3: Flow chart of the participant recruitment with reasons for exclusion from final analysis.

Table 1: Patient characteristics and indication for performing TVUS. Key: TVUS= transvaginal ultrasound, HMB= heavy menstrual bleeding, AUB= abnormal uterine bleeding, PR= per rectum, FH= family history, PH= past history.

Participant characteristics		
Age (years)	31.4 (Range 18-56)	
Day between TVUS and surgery	106 (Range 1- 318)	
Indication for TVUS		
	All participants	**Final Analysis**
Pelvic Pain	64/201 (32%)	17/53 (32%)
Dysmenorrhoea	60/201 (30%)	10/53 (19%)
Dyspareunia	28/201 (14%)	4/53 (8%)
Dyschezia	8/201 (4%)	2/53 (4%)
HMB	32/201 (16%)	4/53 (8%)
AUB	18/201 (9%)	2/53 (4%)
PR bleeding	2/201 (1%)	2/53 (4%)
Subfertility	24/201 (12%)	4/53 (8%)
FH endometriosis	7/201 (3%)	0/53 (0%)
PH endometriosis	51/201 (25%)	15/53 (28%)
Urinary Symptoms	2/201 (1%)	1/53 (2%)
Known ovarian cysts/ endometrioma	12/201 (6%)	4/53 (8%)
Non-specified clinical suspicion of endometriosis	15/201 (7%)	9/53 (17%)
Follow-up of previous scans	15/201 (7%)	5/53 (9%)
Follow-up medical therapy for endometriosis	3/201 (1%)	0/53 (0%)
Surgical planning	11/201 (5%)	8/53 (15%)

Pelvic endometriosis of any subtype was confirmed at surgery in 50/53 (94.3%) participants. SE only was present in 25/53 (47.2%) and DE nodules and/or ovarian endometriomas were present in 25/53 (47.2%). The distribution of the different sites of pelvic DE is reported in Table 2. Two of the 25 participants with SE only had superficial lesions directly visualised sonographically.

Table 2: The findings of endometriosis at surgery including subtypes of disease and different anatomical sites of pelvic DE. Key: n= number, %=percentage, SE= superficial endometriosis, DE= deep endometriosis, USL= uterosacral ligament, RVS= rectovaginal septum.

Findings of endometriosis at surgery		
	n	**%**
Participants	53	100%
Endometriosis present (all subtypes)	50	94%
SE only present	28	53%
DE present	22	42%
Endometrioma	6	11%
Rectosigmoid DE	4	8%
USL DE	17	32%
Vaginal DE	2	4%
Bladder DE	0	0%
RVS DE	0	0%
Ureteric DE	1	2%
Obliterated POD	5	9%

Transvaginal Ultrasound (TVUS) direct visualisation of deep endometriosis nodules

Of the participants with DE, TVUS demonstrated evidence of this in 21/25 giving an overall sensitivity of 84.0%, specificity of 89.3%, PPV of 87.5%, NPV of 86.2% LR+ of 7.85, LR- of 0.18 and accuracy of 86.8% ($p<0.001$). The sensitivity, specificity, PPV, NPV, LR+, LR- and accuracy of TVUS at specific anatomical locations are given in Table 3. There was no DE present within the anterior compartment or RVS in any participant. Three ureteric nodules occurred in one participant, none of which were detected by TVUS. There was one false negative case of POD obliteration which was due to inadequate pressure being applied to elicit the sliding sign due to significant pain, which the sonographer documented in their report. There were two false positive cases of DE within the rectosigmoid colon, one of which was likely due to the presence of adhesions distorting the bowel wall mimicking a nodule sonographically. One false positive case of vaginal wall DE was likely due to the presence of previous hysteropexy sutures, causing the vaginal wall to appear bulky on ultrasound

Table 3: Diagnostic accuracy of TVUS for DE by location. Key: PPV= positive predictive value, NPV= negative predicative value, LR+= likelihood ratio positive, LR-=likelihood ratio negative, CI= confidence interval

Site	Sensitivity (95% CI)		Specificity (95% CI)		PPV	NPV	LR+	LR-	Accuracy	p value
Ovarian Endometrioma	8/10	80 (49.0-94.3)	44/47	93.6 (82.8-97.8)	72.7	95.7	12.5 (4.0-39.1)	0.21 (0.06-0.74)	91.2	<0.001
Anterior compartment										
Ureter	0/0	**	52/55	94.5 (85.2-98.1)	**	100	**	**	**	**
Bladder	0/0	**	53/53	100 (93.2-100)	**	100	**	1	100	**
UV space	0/0	**	53/53	100 (93.2-100)	**	100	**	1	100	**
Posterior compartment										
POD obliteration	4/5	80 (37.6-96.4)	46/48	95.8 (86.0-98.9)	66.7	97.9	19.2 (4.6-79.9)	0.21 (0.04-1.21)	94.3	<0.001
Rectosigmoid colon	6/6	100 (60.9-100)	47/49	95.9 (86.3-98.9)	75	100	24.39 (6.3-95.2)	**	96.3	<0.001
RVS	0/0	**	53/53	100 (93.2-100)	**	100	**	1	100	**
USL	16/21	76.2 (54.9-89.4)	33/35	94.3 (81.4-98.4)	88.9	86.8	13.33 (3.4-52.3)	0.25 (0.12-0.55)	87.5	<0.001
Posterior Vaginal Wall	2/2	100 (34.2-100)	48/51	94.1 (84.1-98.0)	40	100	16.9 (5.7-51.0)	**	96.1	0.007

Table 4: Diagnostic accuracy of TVUS soft markers for the detection of SE, adhesions and DE by location. Key: PPV= positive predictive value, NPV= negative predicative value, LR+= likelihood ratio positive, LR-= likelihood ratio negative, CI= confidence interval

Site	Prevalence	Sensitivity (95%CI)		Specificity (95%CI)		PPV	NPV	LR+ (95%CI)	LR- (95%CI)	Accuracy	p value
Ovarian Mobility											
Reduced left ovarian mobility	39.6%	13/21	61.9 (40.9-79.3)	28/32	87.5 (71.9-9.0)	76.5	77.8	4.95 (1.87-13.145)	0.435 (0.25- 44.71)	77.4	<0.001
Reduced right ovarian mobility	28.3%	2/15	13.3 (3.7-37.9)	36/38	94.7 (82.7-98.5)	50	73.5	2.53 (0.39-16.38)	0.915 (0.74-1.13)	71.6	0.568
Site Specific Tenderness											
Left Ovary	69.8%	11/37	29.7 (17.5-45.8)	13/16	81.3 (57.0-93.4)	78.6	33.3	1.58 (0.51-4.93)	0.86 (0.63-1.18)	45.3	0.51
Right Ovary	64.2%	4/34	11.8 (4.7-91.8)	16/19	84.2 (62.4-94.5)	57.1	34.8	0.75 (0.18-2.98)	1.05(0.83-1.32)	37.8	0.691
Posterior Compartment	73.6%	14/39	35.9 (22.7-51.6)	10/14	71.4 (45.4-88.3)	77.8	28.6	1.26 (0.49-3.18)	0.89 (0.59-1.35)	45.3	0.748
Site Specific Tenderness (DE cases excluded)											
Left Ovary	64.3%	7/18	38.9 (20.3-61.4)	8/10	80 (49.0-94.3)	77.8	42.1	1.94 (0.49-7.64)	0.76(0.47-1.24)	53.6	0.417
Right Ovary	57.1%	1/16	6.3 (1.1-28.3)	10/12	83.3 (55.2-95.3)	33.3	40	0.375 (0.04-3.67)	1.13 (0.85-1.49)	39.2	0.56
Posterior Compartment	64.3%	5/18	27.8 (12.5-50.1)	6/10	60 (31.3-83.2)	55.6	31.6	0.69 (0.24-2.01)	1.20(0.67-2.15)	39.2	0.677

Transvaginal Ultrasound (TVUS) suggestion of endometriosis from soft markers

The association between ovarian mobility, SST and endometriosis can be seen in table 4. Reduced ovarian mobility had a poor sensitivity for detecting ovarian fossa SE and adhesions, USL adhesions, localised DE and/or endometrioma (left 61.9% and right 13.3%) but high specificities (left= 87.5% and right=94.7%).

SST of the ovaries or posterior compartment was correlated against the presence of localised SE, DE and/or adhesions with low sensitivities and moderate specificities (table 4). When DE cases were excluded, the performance of SST for the detection of isolated SE revealed comparable accuracy, as outlined in table 4. The correlation of soft markers to surgically detected endometriosis failed to reach statistical significance ($p \geq 0.05$) in all locations except for reduced left ovarian mobility ($p < 0.001$).

Discussion

The aim of this study was to assess the accuracy of TVUS in the diagnosis of endometriosis when performed by sonographers within an outpatient women's imaging centre. High specificities (93.6-100%), and good sensitivities (76.2-100%), were seen across all anatomical locations for DE nodules. There were no cases of DE within the bladder, uterovesical fold or RVS in our final analysis group, in line with the known low prevalence of disease in these locations (19). The sensitivities achieved by the sonographers in this study are comparable to other published diagnostic accuracy studies, many of which came out of specialised endometriosis or gynaecological pain clinics (6). A sensitivity of 100% for the detection of rectosigmoid DE has been previously reported by one other author only (20). Like our study, their study had a small population (51 participants), however twice the prevalence of bowel disease.

Many studies to date have reported sensitivities >90% for detection of rectosigmoid DE, giving great diagnostic confidence to the utility of TVUS for rectosigmoid DE (15, 21-28).

The uterosacral ligaments were the most affected location within our study (37.5%) in line with other published works (15, 29-35). Our sensitivity of 76.3% for detection of USL DE is slightly higher than the pooled sensitivity of 61% reported by Gerges *et al.* (36) in a recent meta-analysis, with our specificity of 94.3% on par with the pooled finding of 95%.

This study also assessed the utility of soft markers for the detection of SE, with no statistically significant association between SST and either SE or DE found. Reid *et al.* (37) found ovarian mobility to have a low sensitivity in the detection of SE but high specificity which is in keeping with the results of this study. As there is a small amount of published data within the literature on the accuracy of soft markers (37-39), larger studies are needed to confirm that the reported high specificities are reproducible to ensure false-positive imaging does not inadvertently lead to people undergoing unnecessary surgery. With reports of direct visualisation of SE via TVUS beginning to appear within the literature (40), the future usefulness of soft markers as a surrogate sign of SE may be uncertain. Given the scant evidence supporting a statistically significant association between SST and endometriosis, we would suggest that tenderness be used as proposed by Guerriero *et al.* (41) to guide sonographers or sonologists towards areas which should be assessed carefully for sonographic signs of endometriosis of any subtype, rather than as a reportable marker. As ovarian immobility has been shown to have a high association with DE (42), routine testing of ovarian mobility at the time of all TVUS examinations is a useful tool. If poor mobility is

detected, this should prompt performance of a comprehensive TVUS assessment for DE, or an on-referral for such imaging if extension of scanning is not possible.

Although we were able to recruit 201 participants to the study, many did not go on to have surgery, making our final study population lower than we had desired. This was in part due to the COVID-19 pandemic, which arrived in Australia when many of our participants were due to undergo surgery. COVID-19 resulted in a temporary suspension of non-urgent surgeries within Australia, which in turn caused many of our participants to have surgery delayed or cancelled, excluding them from our final analysis. To slightly compensate for this, opted to include participants with surgery within 12 months of TVUS, however, our original intention had been to limit this to a 6-month interval. This created a limitation to this study as it is possible disease may have progressed in this interval. Another hinderance to our final study population was a high rate of participants electing not to undergo surgery. While this occurred for a range of reasons (such as pregnancy or opting for medical management), in some cases, several participants with normal imaging reported being disinclined to undergo surgery for fear it would be futile. This suggests that pre-test counselling is an important aspect in the use of imaging for endometriosis diagnosis to ensure patients understand that current standard methods of TVUS can accurately "rule in" endometriosis in cases of deep or ovarian disease, but cannot yet reliably "rule out" the disease in those with isolated SE. The method of ultrasound imaging, utilising a sonographer to acquire images for off-line review by a sonologist or radiologist, which is common practice in several parts of the world, has created many barriers to the uptake of assessment for DE with TVUS amongst sonographers (43-45). Primarily, an established imaging community have needed to learn novel techniques. As some of these techniques require the performance

of dynamic maneuvers, having a scan reported by a clinician who is not the person performing the techniques presents a challenge (43). This study has shown that experienced sonographers can perform these techniques with a high degree of diagnostic accuracy. Several learning curve studies have been published showing less expert operators and those exposed to less disease to be slower to acquire the pattern recognition required to confidently and accurately diagnose endometriosis by TVUS (46, 47). As such, the results of this study may not be reproducible by less experienced sonographers or those working within a general radiology setting. Further studies exploring accuracy in these settings would be helpful. As endometriosis is a common, but complex disease, the current consensus produced by the World Endometriosis Society (WES) suggests women with severe disease should be managed in centralised, specialist endometriosis centres (4). Wider access to TVUS to diagnose endometriosis is imperative to allow efficient and timely triage to such centres. As such, the ability of sonographers to perform TVUS confidently and accurately for endometriosis within outpatient imaging centres is essential.

A strength of this study was the rigorous ultrasound methodology employed, in line with the IDEA consensus statement (5) and its prospective design.

There were several limitations to this study. Firstly, there was wide variation encountered in the wording used to report surgical findings. As we were aiming to assess “real-world” performance, surgery was performed by a surgeon of each participant’s choice. This resulted in 17 different surgeons performing the reference standard surgeries creating some variation between surgical technique and language used in reporting.

The lack of data around use of contraceptives is also a limitation of this study as contraceptive use may have altered to state a disease between TVUS and surgery.

Additionally, the high prevalence of participants positive for endometriosis (93.4%) in our final analysis resulted in a significant selection bias. Whilst undesirable, this is largely unavoidable given the need to use surgery as the reference standard, as surgery will only be performed in cases where a clinical suspicion of the disease is high enough to warrant an invasive procedure.

Our small study population of 53 is likely the cause of the wide CIs reported for sensitivity and specificity. This population also failed to capture any cases of DE within the bladder or RVS. As there is a known low prevalence of disease in these locations, future large multi-centre studies would be helpful to capture the high participant numbers needed to gain statistically significant data from these locations. Finally, although we met our desired number of positive cases for strong power overall (50 participants with endometriosis), caution is needed when interpreting the site-specific sensitivities and specificities due to lower prevalence of disease per location.

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Disclosures

Nil

Video 1: https://youtu.be/GSrGjfT21cE

Gentle pressure is being applied with the transvaginal transducer to the left ovary. With this pressure, the ovary can be seen to be moving freely away from the uterus and pelvic sidewall.

Video 2: https://youtu.be/YPZwhb9Qz6A

Gentle pressure is being applied with the transvaginal transducer to this anteverted uterus from the anterior fornix of the vagina. The uterus and cervix are seen to slide freely away from the bowel posteriorly suggesting the pouch of Douglas is not obliterated.

Video 3: https://youtu.be/wyM65QLdsRc

Gentle pressure is being applied with the transvaginal transducer to this anteverted uterus from the anterior fornix of the vagina. The uterus and cervix do not slide freely away from the bowel posteriorly suggesting the pouch of Douglas is obliterated. The rectal wall also appears to contain a large nodule of endometriosis.

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3.2 Discussion and conclusion

Upon review of the surgical findings of 53 women who underwent TVUS for endometriosis, it was discovered that TVUS had an overall sensitivity of 84.0%, specificity of 89.3%, PPV of 87.5%, NPV of 86.2% likelihood ratio positive (LR+) of 7.85, likelihood ratio negative (LR-) of 0.18 and accuracy of 86.8% ($p<0.001$) for the detection of DE. Soft markers typically performed poorly for the detection of SE and only 2 of 25 women with isolated SE had this directly visualised by TVUS suggesting future research into the use of TVUS to diagnose this subtype of endometriosis is needed.

This study had several limitations. Firstly, despite recruiting double the number of participants required, for reasons beyond control as outlined in the paper, it was not possible to get complete data for as many as initially anticipated, reducing the power of this study. The interval of up to 12 months between TVUS and surgery was selected due to the COVID-19 pandemic causing disruption of non-urgent surgeries. This long interval created a limitation as some disease may have changed between TVUS and surgery. Additionally, some bias exists within this study due to the large number of participants with endometriosis and the lack of data around contraceptive use. Fifteen participants also had a previous diagnosis of endometriosis which may have introduced bias. These participants were included however as these scans were performed primarily for the assessment of new disease deposits. Furthermore, this study did not give any insight into the intra or interobserver reliability of this technique. As such, this will be investigated in the next chapter.

This study found that sonographers can indeed perform ultrasound for endometriosis with a comparable level of diagnostic accuracy to previously published works which were reviewed in chapter 2, confirming the main aim of this research.

4 Intra and Interobserver variability of sonographic measurements of endometriotic nodules within the rectosigmoid colon

A manuscript prepared for publication forms the basis of this chapter. *Intra and inter variability of sonographic measurements of endometriotic nodules within the rectosigmoid colon.*

4.1 Introduction and Motivation

In the previous chapter, it was discovered that sonographers can perform TVUS for the diagnosis of endometriosis with a good level of diagnostic accuracy. The methodology employed within the previous study however did not shed any light on the important question of reliability and reproducibility of results, or in other words, if the TVUS examination was repeated, would the same results be seen either by the original sonographers or others? Testing of reproducibility is difficult with TVUS examinations as this requires study participants to undergo a second intrusive test which is not clinically indicated. As such, alternate methods often need to be employed to test reliability of TVUS. In this case, we opted to focus on measurement reproducibility of rectosigmoid colon as significant discrepancy in these measurements could alter management (15).

This chapter presents an intra and interobserver study which aimed to assess the intra and interoperator variability of sonographic measurements of endometriotic nodules within the rectosigmoid colon. Differences were evaluated between sonographers highly experienced in TVUS for DE and sonographers with limited experience in TVUS for DE.

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Statement of Authorship

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VII. the candidate's stated contribution to the publication is accurate (as detailed above);

VIII. permission is granted for the candidate in include the publication in the thesis; and

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Title: Intra and Interobserver variability of sonographic measurements of endometriotic nodules within the rectosigmoid colon

Short title: Sonographic measurements of bowel endometriosis

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Abstract

Background: Transvaginal ultrasound is a valuable tool in the diagnosis of deep endometriosis with details of lesion location and size essential for therapy planning and surveillance. A vital aspect of diagnostic accuracy is reliability and reproducibility.

Aims: To assess the intra and interoperator variability of sonographic measurements of endometriotic nodules within the rectosigmoid colon.

Materials and Methods: Five sonographers (three experienced and two inexperienced) reviewed 13 ultrasound images of endometriotic bowel nodules. The sonographers measured each nodule in three orthogonal planes using an offline DICOM viewer. The measurements were repeated at an interval of approximately one month. Interobserver and intraobserver agreement was calculated using an intraclass correlation coefficient (ICC). Bland-Altman plots were constructed to assess intraoperator limits of agreement, any variation related to size of the nodules and interoperator limits of agreement with the mean of experienced operator measurements plotted against inexperienced operator measurements.

Results and Conclusions: Interoperator agreement ranged from moderate to excellent (ICC= 0.7473 [CI 0.5353-0.9002] (length), 0.8125 [CI 0.6496- 0.9674] (height) and 0.8170 [CI 0.6489- 0.9302] (width)). There was poor to excellent levels of agreement between experienced and inexperienced operators (ICC= 0.8975 [CI 0.5146- 0.9733] (length), 0.8903 [0.6138- 0.9674] (height) and 0.8506 [CI 0.3316- 0.9770] (width)). The experienced operators achieved better levels of agreement than the inexperienced operators. Inexperienced operators had a wider range of variation between the limits of agreement than experienced operators (14.2mm versus 9.1mm). The Bland-Altmann plots revealed no significant association between size and levels of variation.

Introduction

Endometriosis is a common, chronic gynaecological condition affecting approximately 1 in 9 female-born people in Australia (1). Whilst laparoscopy has long been considered the gold standard in diagnosis of endometriosis, transvaginal ultrasound (TVUS) has developed and been widely studied as a non-invasive diagnostic method for ovarian endometriomas (OE) and deep endometriosis (DE) with its accuracy well established (2). To date, few intra and interobserver studies have investigated the performance of TVUS for endometriosis (3-10). Given the difficulty and potential ethical limitations of subjecting people to non-clinically indicated TVUS, the reliability of TVUS as a diagnostic technique is still ambiguous.

Endometriosis affecting the rectosigmoid colon presents one of the most challenging therapeutic situations, with surgical management being complex and requiring a highly specialised multidisciplinary team (11). Nodules >3cm in length may be indicated for segmental bowel resection, a procedure which requires astute planning and careful pre-surgical counselling (11). Without an accurate and reliable diagnosis prior to surgery, such cases may require two-step surgeries. It is therefore of vital importance that when rectosigmoid nodules are detected by TVUS, their reported size is accurate. Moreover, with medical management of endometriosis becoming increasingly favoured over repeated surgical interventions (12), non-invasive monitoring of lesion size is helpful. In these situations, it is essential nodules are measured accurately and likely levels of variation known.

The specific variability of sonographic measurement of endometriotic nodules affecting the rectosigmoid colon has been scantly studied and published in scientific literature (3-5). This study aims to assess the intra and interoperator variability of sonographic measurements of endometriotic nodules within the rectosigmoid colon between

sonographers highly experienced in TVUS for DE and sonographers with limited experience in TVUS for DE working in an outpatient women's imaging centre.

Methods

Consent was obtained from the sonographers participating. Images used were sourced from people who had consented to having images used for research. This project was approved by the University of South Australia Human Research Ethics Committee (project number 202217).

An intra and interobserver study was performed. Five Accredited Medical Sonographers (AMS) (as per the Australia Sonographers Accreditation Registry [ASAR]) participated in this study. Three were specialist obstetric and gynaecological sonographers with extensive experience in TVUS for DE (i.e. having performed > 1000 TVUS specifically for DE). The remaining two sonographers had minimal experience performing TVUS of DE (one paediatric sonographer and one general sonographer, both of whom do not routinely perform TVUS for DE). Each operator reviewed 13 cases of rectosigmoid endometriosis nodules. To test the variability between individual and different operators, the same 13 cases were reviewed and measured in two sessions by each operator, approximately one month apart to avoid recall bias. For each case, the reviewed images included a still image of the nodule in the longitudinal plane and a still image in the transverse plane. Identifying information was removed for the reviewed images where possible, the reduce recall bias. Images were reviewed offline on a single remote workstation using RadiAnt DICOM viewer 5.5.1 software (Medixant, 2020, Poland)(13). Lighting within the room was kept consistent for each operator across each session (room lights on, door closed, blinds closed blocking out window light). The

measurement protocol was tested by an external sonographer for quality control in July 2020 and all participating sonographers were blinded to the measurements of other participants and their own previous measurement results.

Measurement protocol

The participants reviewed each of the 13 images and obtained measurements, regardless of the shape of the lesion, using the straight-line measurement tool within the software package in three orthogonal planes (Figure 1) as proposed by the International Deep Endometriosis Analysis (IDEA) group consensus (14). From the longitudinal image, maximum length and height were measured with maximum width measured from the transverse image. One measurement was performed by each sonographer in each plane during each sitting. Measurements were observed by a scribe who transcribed to an Excel spreadsheet (Excel for Office 365 MSO, Microsoft, 2018, USA) for data storage. The mean measurement for each nodule in each plane was calculated for all measurements from operators A, B and C to represent the mean of the experienced operators. The mean of measurements for each nodule in each plane for operators D and E represent the mean of the inexperienced operators.

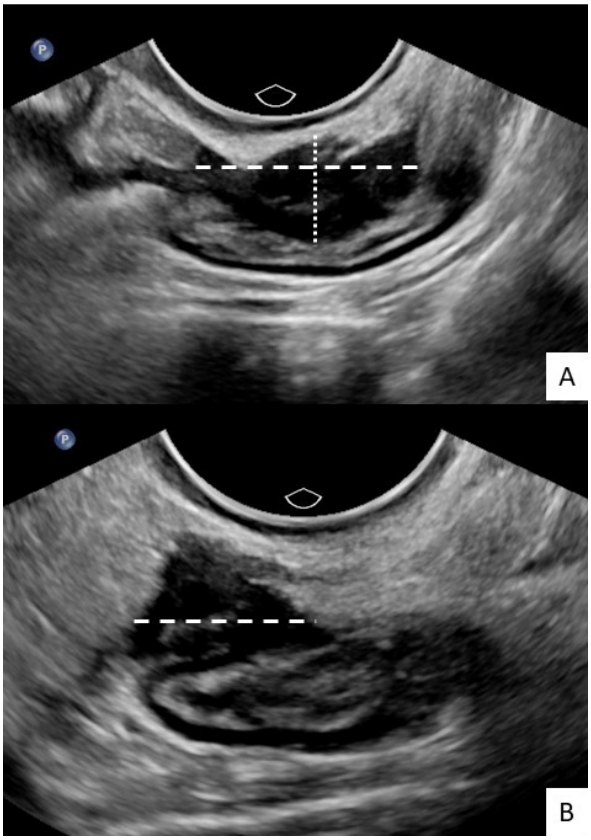


Figure 1: The measurement technique used to acquire measurements the rectosigmoid endometriotic nodules. A is a longitudinal image from which length (dashed line) and height (dotted line) were measured. B is a transverse image of the same nodule used for obtaining the width measurement (dashed line).

Statistical analysis

Inter and intraobserver agreement between the sonographer's measurement accuracy was calculated using an intraclass correlation coefficient (ICC) with a confidence interval (CI) of 95% where 0= no agreement and 1= perfect agreement, <0.5= poor agreement, 0.5-0.75= moderate agreement, 0.75-0.9= good agreement, 0.9= excellent agreement (15). ICC estimates were based on a single rater value (k=5), absolute agreement, 2-way mixed-effects model (15). ICC was also calculated for the mean of the experienced operators' measurements and the mean of the inexperienced operators' measurements. Bland-Altman plots were constructed to evaluate any changes in levels of agreement related to the size of nodules between experienced and inexperienced

operators and also to compare limits of agreement between the two groups (16). Bland-Altman plots were also constructed to assess levels of intraoperator agreement within each of the operators own measurements and whether any intraoperator variation existed relating to nodule size.

The sample size of 13 resulted from convenience sampling. Prior to performing statistical analysis, a retrospective sample size calculation was performed using an online sample size calculator which confirmed a sample of 13 was adequate for a minimum acceptable ICC 0.4, expected ICC 0.75 with a significance level of 0.05 to achieve a power of 80% (17). A biostatistician was consulted to verify that this analysis method was satisfactory. The statistical analysis was performed using MedCalc for Windows Version 19.6.1 (MedCalc Software, Osteend, Belgium).

Results

Five sonographers (three experienced and two inexperienced) measured 13 nodules in three planes over two sessions (totalling 390 measurements). Operators A, B and C represent the experienced sonographers and operators D and E, the inexperienced sonographers. The interrater ICC calculation for all operators were performed with the results of the first data collection only. The results of data collection two were used in the calculations of the means of experienced and inexperienced operators and for the intraoperator calculation. The inter and intraoperator ICC results and Bland-Altman levels of agreement can be seen in table 1.

Table 1: Interoperator and intraoperator agreement for sonographic measurement of endometriosis nodules within the rectosigmoid colon. The intraclass correlation co-efficient (ICC) was calculated using a two-way mixed effect, absolute agreement and is based on single measurement. Levels of agreement are centred on ICC 0= no agreement and 1= perfect agreement, <0.5= poor agreement, 0.5-0.75= moderate agreement, 0.75-0.9= good agreement, 0.9= excellent agreement(15). The levels of agreement are defined from the 95% confidence intervals (CI).

INTEROPERATOR RESULTS

	Bland-Altman Analysis		ICC Single measure		
	mean difference	95% limits of agreement	ICC	CI (95%)	Level of Agreement
			All Operators (k=5)		
Length	***	***	0.7473	(0.5353- 0.9002)	Moderate- excellent
Height	***	***	0.8125	(0.6496- 0.9275)	Moderate- excellent
Width	***	***	0.8170	(0.6489- 0.9302)	Moderate- excellent
			Experienced vs Inexperienced Operators		
Length	2.39	-2.5- 6.8	0.8975	(0.5146- 0.9733)	Moderate- excellent
Height	1.42	-4.1 - 2.1	0.8903	(0.6138- 0.9674)	Moderate- excellent
Width	2.39	-2.5 - 6.9	0.8506	(0.3316- 0.9596)	Poor- excellent

INTRAOPERATOR RESULTS

	Bland-Altman Analysis		ICC Single measure		
	mean difference	95% limits of agreement	ICC	CI (95%)	Level of Agreement
			Operator A		
Length	1.31	-2.4 - 3.7	0.9678	(0.8988- 0.9900)	Good- excellent
Height	0.63	-1.8 - 1.9	0.9789	(0.9324- 0.9935)	Excellent
Width	1.52	-4.0 - 4.7	0.9270	(0.7827- 0.9770)	Good- excellent
			Operator B		
Length	1.38	-5.3 -3.8	0.9031	(0.7235- 0.9690)	Good- excellent
Height	0.75	-2.6- 3.4	0.9015	(0.7188- 0.9685)	Good- excellent
Width	1.18	-3.7- 3.0	0.9620	(0.8837-0.9882)	Good- excellent
			Operator C		
Length	0.92	-2.5 - 1.7	0.9922	(0.9750-0.9976)	Excellent
Height	1.06	-4.4 - 3.0	0.9478	(0.8419- 0.9836)	Good- excellent
Width	0.82	-2.4 - 1.5	0.9824	(0.9425- 0.9946)	Excellent
			Operator D		
Length	1.98	-2.7 - 6.7	0.8186	(0.3218-0.9480)	Poor- excellent
Height	1.27	-5.1 - 3.9	0.8153	(0.5125-0.9392)	Moderate- excellent
Width	1.48	-4.4 - 3.4	0.9403	(0.8230-0.9812)	Good- excellent
			Operator E		
Length	1.89	-6.5 - 5.6	0.9429	(0.8267-0.9821)	Good- excellent
Height	0.88	-2.7 - 2.6	0.9732	(0.9145-0.9917)	Excellent
Width	2.28	-6.9 - 7.3	0.8363	(0.5432- 0.9473)	Moderate- excellent

Intraoperator variability

The three experienced operators (operators A, B and C) all obtained good to excellent level of intraoperator agreement for all measurements in all three planes however, the inexperienced operators (operators D and E) showed less uniform agreement as outlined in table 1.

The Bland–Altman limits of agreement ranged from ∼−6.9mm to +7.3 mm between the inexperienced operators, however showed a smaller range of variation amongst experienced operators at ∼−5.3mm to +3.8 mm (table 1). These were set against the range of mean nodule length 10.5–49.1 mm, height 2.5-29.7 mm and width 4.6-32.3mm (figure 2).

Interoperator variability

The interoperator results are outlined in table 1. There was moderate to excellent levels of agreement (ICC= 0.7473 [CI 0.5353-0.9002] between all operators when measuring nodule length however good to excellent levels of agreement were achieved for both height and width measurements of the nodules (ICC= 0.8125 [CI 0.6496- 0.9674] (height) and 0.8170 [CI 0.6489- 0.9302] (width)). When assessing the mean of experienced operator measurements against the mean of the inexperienced operators' measurements, poor to excellent levels of agreement were exposed (ICC= 0.8975 [CI 0.5146- 0.9733] (length), 0.8903 [0.6138- 0.9674] (height) and 0.8506 [CI 0.3316-0.9770] (width)).

Bland-Altmann plots showed similar 95% limits of agreement to the intraoperator findings ranging from ∼-2.5 to +6.8 mm which were set against the range of mean nodule length 10.5- 49.1 mm, height 2.5- 29.7 mm and width 4.6- 32.3mm (figure 3). This suggests that experience does not factor strongly when assessing the interoperator

variability of measurements. The Bland-Altman plots did not reveal any relationship between lesion size and measurement variability.

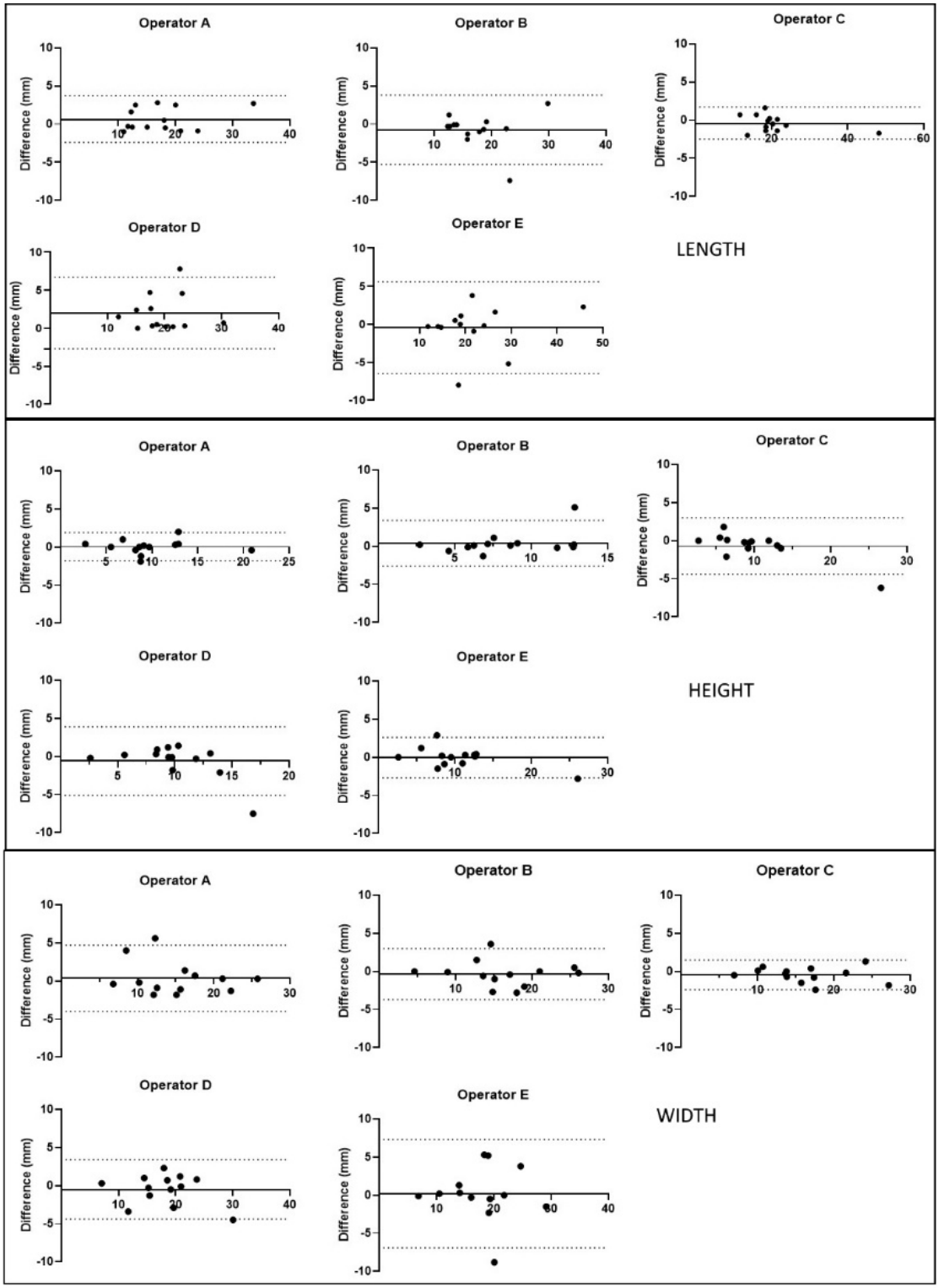


Figure 2: Bland-Altman (mean versus difference) plots showing the levels of intraoperator variation for each of the five operators' length, height and width measurements. Error bars are dissecting at the 95% limits of agreement.

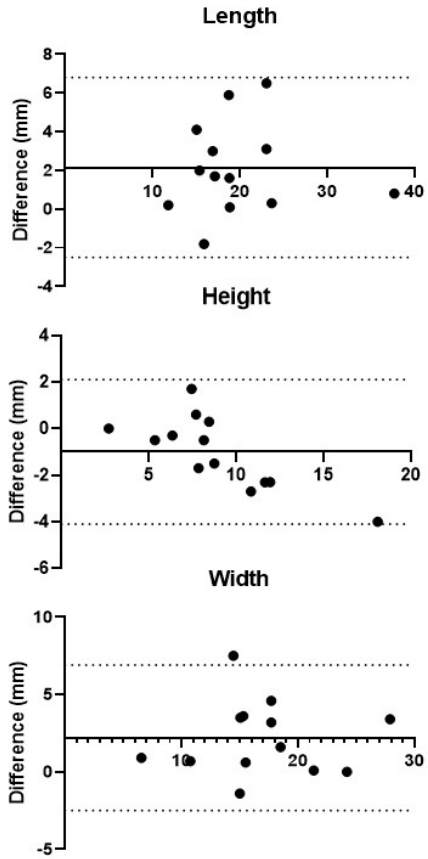


Figure 3: Bland-Altman (mean versus difference) plot showing levels of agreement between the mean of experienced operators (operators A, B and C) measurements against the mean of inexperienced operators (operators D and E) measurements in each of the three planes. Error bars are dissecting at the 95% limits of agreement.

Discussion

This study has shown moderate to good levels of interoperator reliability in the sonographic measurement of endometriosis nodules within the rectosigmoid colon. The experienced operators all obtained good to excellent level of intraoperator reproducibility however wider variation was seen among inexperienced operators. These findings are similar to other studies in this area with Bean *et al.* (3) reporting good levels of interobserver reliability of endometriotic nodules affecting the bowel (ICC = 0.88 [CI 0.72-0.95]) and a variation of ~-6 – 5mm for nodule measurements. Egekvist *et al.* (4) found similar variation of 11-14mm (46-51%) in length

measurements of rectosigmoid endometriotic nodules. Given the wider interoperator variation seen in our study, we would suggest serial scans should be performed by the same experienced sonographer when TVUS is used to monitor nodules for response to therapy or progression. If this is not possible, a margin of error of up to 9-14mm should be borne in mind by clinicians, which is in keeping with the reports of other studies (3, 4).

Our use of a two-way mixed-effect model ICC means our results are only directly applicable to the raters included in the study (15). Whilst not ideal, this was unfortunately unavoidable due to the methodology employed. It is therefore reassuring to see that our findings were like those found in similar studies giving further encouragement if applying these findings in clinical practice(3, 4).

Pathological confirmation of endometriosis was not available for the reviewed nodules as not all patients opted for surgical management. As the accuracy of TVUS in the diagnosis of rectosigmoid endometriosis nodules is well established, with a recent meta-analysis showing sensitivities of 89% and specificities of 97% for this technique(18), we felt confident in inferring that the sonographically imaged lesions would likely be confirmed endometriosis if pathological correlation were performed.

Significant interobserver variation was observed in one particular nodule (nodule 11) (figure 4). Due to its large size and irregular shape, it is possible that the operators had difficulty confirming the true boundaries of this nodule. This was also the only nodule within the sampled measurements >3cm in length and which showed the "*Indian headdress sign/ moose antler sign*" and the "*pulling sleeve sign*" due to excessive extrinsic retraction of the bowel(14). Despite the Bland-Altman analysis not showing higher error with larger nodules, the small sample size in this study and the additional features of this nodule make it unknown whether this was due to chance or larger

variation applies to all large nodules with these features. Future studies on intra and interoperator variability focusing specifically on large/ complicated rectosigmoid lesions would be helpful. Measurements of such nodules in three orthogonal planes will never be able to fully estimate the actual length of bowel involved due to the extensive retraction present. It is therefore imperative that when such nodules are encountered in clinical practice, not only is great care given in accurate measurements but also clear descriptors of the morphology as outline in the IDEA consensus(14) utilised within written reports to guide therapy. Care must also be taken when utilising ultrasound to monitor response to medical therapies to ensure information provides to managing clinicians and patients is as accurate as possible given the inherent difficulties in imaging such lesions.



Figure 4: Longitudinal image of nodule 11 which caused significant interobserver variation. Due to its large size and excessive extrinsic retraction ("*Indian headdress sign/ moose antler sign*" and "*pulling sleeve sign*"), the sonographers all had difficulty confirming the true boundaries of this nodule.

A strength of this study was the comparison of measurements performed by five operators. Both Bean *et al.* (3) and Egekvist *et al.* (5) compared variability between just two operators whilst Egekvist *et al.* (4) used pairwise measurements with three

operators. The use of five operators gives a larger, more robust dataset and reduces the chance of bias due to the individual operator's ability. The long-time interval (one month) between acquisition of measurements also reduces the risk of recall bias within the intraoperator measurement. Additionally, the assessment of sonographer practice is very relevant to the performance of gynaecological ultrasound in Australia and New Zealand which typically involves sonographers performing scans and measurements for which reports are written off-line, usually by a clinician who has no interaction with the patient, purely from preselected still images. Future studies assessing the real-time performance of sonographers in this setting however would be very valuable.

Our use of consecutive sampling was a strength of this study design as it reflects the uncertainty which sonographers and sonologists encounter in normal sonographic clinical practice. Our 13 nodules were sourced from seven patients with no selection bias included. The consecutive collection of images from genuine patients made our sample images representative of the realities of clinical practice with the size and location of the nodules varying randomly. Similarly, the sonographic clarity of each image was diverse as the clarity with which a nodule is seen sonographically varies clinically.

While our study found discrepancy between measurements performed by experienced compared to less experienced operators, describing experience is difficult as it is rather subjective what qualifies an operator as being "experienced". We classed those sonographers participating in this study as highly experienced if they had performed >1000 TVUS specifically for DE. Our "inexperienced" sonographers were classed as those who did not routinely perform TVUS for DE. All sonographers participating in this study however were very experienced in ultrasound, each having over 10 years' experience as an AMS. Different levels of variation may apply to those with little

experience in ultrasound generally. Our findings contrast those in a previous study by Egekvist *et al.* (5) who found little variation between an experienced operator (nine years gynaecological ultrasound experience) and a very inexperienced operator (medical student). As such, further investigation of the required training and continuing experience needed to obtain reliable measurements would be clinically helpful for those people who may not be able to return to a specialised centre for monitoring of nodule size (e.g. those residing in rural areas).

A limitation of this study was the use of still images off-line to test variability. As ultrasound is typically performed by a sonographer or sonologist interrogating a lesion in real-time, reviewing still images does not fully replicate the way in which sonographic measurements would be obtained in clinical practice. This methodology made assessment of the boundaries of the nodules more challenging for the participating sonographers as they did not have the opportunity to assess the whole lesion and generate a mental image of its exact size, shape and features as they do during real-time scanning. As such, this is a potential limitation to the accuracy of our findings. This study was also not able to compare interobserver variation in the detection of lesions as this would require real-time scans to be repeated by multiple operators. Given the need for people to undergo an additional, non-clinically necessary TVUS in order to do this, we felt this was inappropriate however we do acknowledge other reliability studies have been performed in this method (3-6, 9).

However, as gynaecological ultrasound in Australia and New Zealand typically involves sonographers performing scans and measurements for which reports are written off-line, often by a clinician who has no interaction with the patient purely from preselected still images, knowledge that this can be done accurately should provide reassurance to reporting and referring clinicians alike.

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4.2 Discussion and conclusion

Five sonographers (three experienced and two inexperienced) measured 13 nodules in three planes over two sessions to test the intra and interoperator variability of sonographic measurements of endometriosis nodules within the rectosigmoid colon. Moderate to good levels of interoperator reliability were noted for nodule length (ICC= 0.7473 [CI 0.5353-0.9002] and good to excellent levels of agreement were achieved for both height (ICC= 0.8125 [CI 0.6496- 0.9674]) and width (0.8170 [CI 0.6489-0.9302]). Bland-Altman plots did not reveal any relationship between lesion size and measurement interoperator variability. The three experienced operators all obtained good to excellent level of intraoperator agreement for all measurements in all three planes however, the inexperienced operators showed less uniform agreement.

This study had several limitations. An ultrasound examination would usually be performed by a sonographer or sonologist interrogating a lesion in real-time. As such, reviewing still images does not fully replicate the way in which sonographic measurements would be obtained in clinical practice. This methodology made assessment of the boundaries of the nodules more challenging for the participating sonographers as they did not have the opportunity to assess the whole lesion and generate a mental image of its exact size, shape and features as they do during real-time scanning. The use of video clips for offline review would make a more accurate replica of clinical practice whilst still negating the need to perform a second TVUS and is a methodology which should be employed in future studies.

Additionally, this study had a very small sample population which resulted wide confidence intervals for the reported results.

Within these limitations, this study found moderate to excellent levels of interoperator agreement. Experienced operators had better levels of intraoperator agreement than inexperienced operators. This suggests that measurements of endometriotic bowel nodules on TVUS have a good level of reliability, especially when TVUS is performed by an experienced sonographer, thus addressing the second aim of this thesis.

5 How long does a transvaginal ultrasound examination for endometriosis take in comparison to a routine transvaginal ultrasound examination?

The published article (73) forms the basis of this chapter.

Deslandes, A., Parange, N., Childs, J.T., Osborne, B., Panuccio, C., Croft, A. and Bezak, E. (2022), *How long does a transvaginal ultrasound examination for endometriosis take in comparison to a routine transvaginal ultrasound examination?* Australas J Ultrasound Med, 25: 20-27. https://doi.org/10.1002/ajum.12288

5.1 Introduction and Motivation

Previously in this thesis, the accuracy and reliability of sonographer performed TVUS for endometriosis have been explored. Whilst conducting the research for these important questions, a subsidiary question arose relating to the additional time required to complete a comprehensive TVUS examination for endometriosis. The logistical aspect of this technique is important to consider in relation to expanding access to this useful and much needed investigation. The systematic procedure, suggested by the IDEA group within their consensus statement, clearly outlines what constitutes an ultrasound for endometriosis (74) and this has been translated into protocol publications outlining how sonographers can perform these scans by both Fang *et al.* (75) and Leonardi *et al.* (76). These protocols both involve interrogating several additional anatomical locations sonographically which requires additional scanning time. How much time exactly is required, however, remains unknown. As awareness of endometriosis increases (6), there is pressure mounting to have endometriosis ultrasound performed more frequently to contribute to earlier diagnosis and improve the experience of people with endometriosis. As such, insight into the time differential

between rTVUS and eTVUS would be helpful to the ultrasound community to assist imaging departments in the implementation of these examinations by ensuring sonographers have adequate time to perform the task without additional pressure being placed upon them.

This study aimed to determine the additional time needed for a sonographer to perform a TVUS including an assessment for DE in comparison to rTVUS within a specialised women's imaging practice.

University of South Australia

Statement of Authorship

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Contribution to the Paper Brief description of your work in this publication	**Study design, data collection, data analysis, writing and review**	
Overall Percentage (%)	**60%**	
Certification	**This is an original publication outlining research conducted for my masters thesis.**	
Signature	[redacted]	Date 10/3/2022

CO-AUTHOR CONTRIBUTIONS

By signing the Statement of Authorship, each author certifies that:

X. the candidate's stated contribution to the publication is accurate (as detailed above);

XI. permission is granted for the candidate in include the publication in the thesis; and

XII. the sum of all co-author contribution is equal to 100% less the candidate's stated contribution.

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How long does a transvaginal ultrasound examination for endometriosis take in comparison to a routine transvaginal ultrasound examination?

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Abstract

Introduction: This study aimed to determine the additional time needed to perform an endometriosis transvaginal ultrasound (eTVUS) compared to routine transvaginal ultrasound (rTVUS).

Methods: A retrospective case–control study was performed. The study group included 199 eTVUS performed between September 2019 and September 2020. The control group comprised 105 consecutive rTVUS studies performed in the same time period. The time stamps on the ultrasound images of all cases in both groups were reviewed to determine the time taken to perform each study. Mean, median, minimum and maximum scan times for both groups were calculated as was percentage difference between scan times. A two-tailed, unpaired t-test of the normalised data and a Mann–Whitney U test assessing time difference of scans between two groups were performed with P value <0.05 considered statistically significant.

Results: Performing eTVUS took significantly longer than rTVUS with increases in the mean (8.4 vs 13.8 min, 64%), median (7 vs 12 min, 71%), minimum (4 vs 7 min, 75%) and maximum (19 vs 42 min, 121%) scan times. The Mann–Whitney U test indicated a statistically significant difference in the median scan times (5.0, CI 4.0–6.0), $P < 0.001$. An independent t-test of the normalised data revealed a significantly larger mean scan time for eTVUS than rTVUS, Mean = 9.05 95%CI [13.17–4.94], $t(302) = 4.327$, $P < 0.001$. $R^2 = 0.583$.

Conclusion: Endometriosis transvaginal ultrasound added an average 5.4 min to rTVUS, which is statistically significant. For ultrasound departments wanting to offer this technique, doubling the scan time allocated to perform a transvaginal ultrasound (TVUS) is suggested.

Keywords: transvaginal ultrasound, gynaecology, endometriosis, sonographer, allotted time.

Introduction

Ultrasound is the front-line imaging modality in the assessment of all gynaecological conditions, with transvaginal ultrasound (TVUS) being the imaging modality of choice.[1] Endometriosis is one such gynaecological condition, affecting 1 in 9 women and female-born people,[2] with the ovaries, posterior cul-de-sac and uterosacral ligaments the most commonly affected sites.[3] Typical symptoms of endometriosis include pelvic pain, abnormal uterine bleeding and subfertility.[3] As such, many people with endometriosis will present for ultrasound scans to assess for the cause of these symptoms. Despite the frequency of endometriosis, an assessment of the anterior and posterior compartments is not a routine inclusion in Australasian or American gynaecological ultrasound guidelines,[1,4] even with many studies to date showing good diagnostic accuracy for this technique.[5–10] Skill of the sonographer and sonologist/radiologist,[11–13] clinical knowledge,[13] scan time availability and lack of adequate Medicare reimbursement[14] are all factors which can pose a barrier for the performance of a comprehensive

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examination for endometriosis, including an assessment of the anterior and posterior compartments, as part of a routine pelvic ultrasound. As many ultrasound departments experience very high patient loads, finding the additional time needed to extend scans can be challenging. However, with clinical and consumer awareness of endometriosis growing,[2] there is momentum from both professionals and consumers alike to have an assessment for endometriosis during TVUS performed when indicated or even routinely.[15] This study aims to determine the additional time needed for a sonographer to perform a TVUS including an assessment for deep endometriosis in comparison with routine transvaginal ultrasound (rTVUS) within a specialised women's imaging practice.

Methods

Study design

A retrospective case–control study was performed. The study group included patients who underwent endometriosis transvaginal ultrasound (eTVUS), performed by one of three experienced sonographers (AD, CP or AC), at a private women's imaging clinic in Adelaide, South Australia. The control group was comprised of cases who underwent a rTVUS at the same practice by the same three sonographers in the same time period. The three sonographers had between 10 and 25 years of experience performing gynaecological ultrasound and had each performed >1000 eTVUS examinations previously.

Transvaginal ultrasound protocol

All cases were scanned according to the standardised protocols of the practice, based on current guidelines.[1,16] The scanning protocols employed for both the rTVUS and eTVUS are outlined in Table 1.

The rTVUS was performed in line with the guidelines of the Australasian Society of Ultrasound in Medicine (ASUM)[1] with TVUS only being performed unless the patient did not consent to TVUS or the entirety of the uterus and ovaries could not be assessed via TVUS (e.g. when large fibroids were present).[1] Scans were routinely performed with an empty bladder to optimise both patient comfort and improve visualisation of the uterus and ovaries. For rTVUS, the uterus, endometrium and ovaries were measured and assessed for signs of pathology. A three-dimensional volume of the uterine cavity was obtained. Mobility of the ovaries was tested with probe pressure and site-specific tenderness (SST) noted. Status of the 'sliding sign'[17] was investigated, and the pouch of Douglas (POD) was assessed for the presence of fluid only.

eTVUS was performed in line with the International Deep Endometriosis Assessment (IDEA) group consensus.[16] eTVUS studies were acquired as per the rTVUS, with the addition of a dedicated assessment of the anterior compartment (bladder, ureters and vesicouterine space) and the posterior compartment (rectovaginal septum, rectosigmoid colon, uterosacral ligaments/torus uterinus and posterior vaginal fornix) (Table 1). The POD was assessed for both the presence of fluid and endometriotic nodules during the eTVUS protocol. No bowel preparation was used for the assessment of the rectosigmoid colon.

Table 1: The scanning protocols used for both rTVUS and eTVUS.

Protocol inclusion	rTVUS	eTVUS
Uterus + volume measurement	✓	✓
Cervix	✓	✓
Colour Doppler assessment of cervix	✓	✓
Endometrium + thickness measurement	✓	✓
Colour Doppler assessment of endometrium	✓	✓
3D volume of uterine cavity	✓	✓
Ovaries +volume measurement	✓	✓
Ovarian mobility	✓	✓
Ovarian site-specific tenderness	✓	✓
Uterine sliding sign	✓	✓
Pouch of Douglas	Assessed for fluid only	Assessed for fluid and nodules of endometriosis
Vaginal wall/posterior vaginal fornix	✗	✓
Uterosacral ligaments/torus uterinus + measurement	✗	✓
Rectosigmoid colon	✗	✓
Rectovaginal septum	✗	✓
Bladder	✗	✓
Ureters	✗	✓
Vesicouterine space	✗	✓
Bladder mobility	✗	✓

rTVUS, routine transvaginal ultrasound; eTVUS, endometriosis transvaginal ultrasound.

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Scans were performed using a Philips Epiq Elite ultrasound system with a C10-3MHz 2D transvaginal transducer or a C8-5 MHz 3D transvaginal transducer (Philips Medical Systems, Andover, MA, USA), a Philips IU22 ultrasound system with a C10-3 transvaginal transducer (Philips Medical Systems) or a GE Voluson E10 with a 5-8 MHz transducer (GE Healthcare, Chicago, IL, USA).

Case identification and data collection

A sample size calculation was performed prior to data collection using G-power software,[18] which found for a power of 0.95 and an effect size of 0.5, and a minimum sample size of 105 was needed for each group.

Data were retrospectively collected from the practice picture archiving computer system (PACS) and Contrast ONE (Contrast Imaging solutions, Brisbane, Australia). The study group (eTVUS) was comprised of 201 consecutive cases who presented for TVUS with a clinical suspicion of endometriosis between September 2019 and September 2020 inclusive. The cases in the control group were identified by performing a filtered search of reports for pelvic ultrasounds within the same data range, where the reports did not contain the word 'endometriosis', which excluded any cases who underwent eTVUS. Consecutive records of 127 cases were reviewed until 105 cases had been identified to form the control group. Two cases were excluded from the eTVUS group, resulting in the scan times from 199 cases being included (Table 2).

The time stamps on the ultrasound images of all cases in both groups were reviewed. The start time was defined as the earliest time stamp on stored images. The end time is defined as the latest time stamp on stored images. Scan times were recorded in whole minutes only. If images in addition to TVUS were performed (e.g. pelvic floor, kidneys, transabdominal imaging), only the time taken for the TVUS segment was included. Data were double entered for quality assurance. Cases were excluded if: time stamps were not visible, studies were only performed transabdominally, TVUS was incomplete, or scans took place over two episodes. The reasons for exclusion from the final analysis can be seen in Table 2.

Table 2: Reasons for exclusion of cases.

Excluded cases		
Reason	**rTVUS group**	**eTVUS group**
TA only	5	
Incomplete TVUS	7	
No time stamps	1	1
Different sonographer	6	
Endometriosis scan	1	
Early pregnancy scan	2	
Scan performed over two episodes		1
Total	22	2

TA, transabdominal ultrasound; TVUS, transvaginal ultrasound; rTVUS, routine transvaginal ultrasound; eTVUS, endometriosis transvaginal ultrasound.

Statistical analysis

Mean, median, minimum and maximum scan times for both groups were calculated as was percentage difference between scan times for the two groups. Data were checked for normalcy. The non-normally distributed raw data were analysed using a two-tailed unpaired non-parametric test (Mann–Whitney U test) assessing time difference of scans between the two groups (rTVUS vs eTVUS), with a P value <0.05 considered statistically significant. The data were also transformed, and the normalised data analysed using a two-tailed, unpaired parametric t-test. Statistical analysis was performed using GraphPad Prism version 8.0.0 for Windows (GraphPad Software, San Diego, CA USA).

Ethical approval

This project was approved by the University of South Australia Human Research Ethics Committee (project number 204082).

Results

The distribution of scan times for both groups can be seen in Figures 1 and 2. Performing eTVUS took significantly longer than performing rTVUS with increases in the mean (8.4 vs 13.8 min, 64%), median (7 vs 12 min, 71%), minimum (4 vs 7 min, 75%) and maximum (19 vs 42 min, 121%) scan times as outlined in Table 3. The data did not follow a Gaussian distribution (Figure 2). The Mann–Whitney U test indicated that there was a statistically significant difference in the median scan times of 5.0 min (CI 4.0 = 6.0), U ($N_{RTVS} = 105$, $N_{ETVS} = 199$) = 3243, $P < 0.001$.

An independent t test of the normalised data revealed that eTVUS took significantly longer than rTVUS, Mean = 9.05 95% CI [13.17–4.94], t(302) = 4.327, $P < 0.001$. $R^2 = 0.583$. Overall, the mean eTVUS time was 5.4 min longer than the mean time of rTVUS.

When broken down by the performance of the individual sonographers, similar trends were noted as outlined in Table 3.

Discussion

This study has shown that performing eTVUS adds a statistically significant amount of time to rTVUS with a 71% increase in the median scan times and 64% increase in the mean scan times. To the best of our knowledge, this is the first paper published to date assessing the additional time burden of performing eTVUS in comparison with rTVUS. When broken down between individual sonographers as outlined in Table 3, there was a discrepancy between the percentage differences seen between sonographer B and sonographer C (mean 97% vs 43%, median 100% vs 41%, minimum 100% vs 75% and maximum

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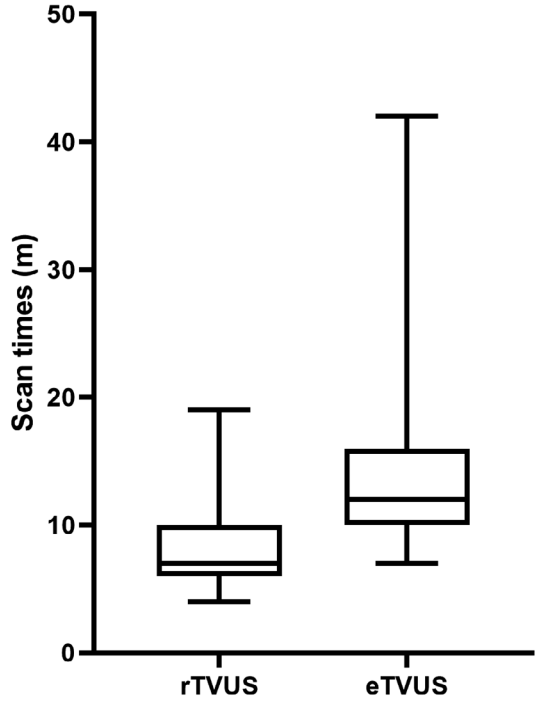


Figure 1: F A box and whisker plot of the distribution of scan times for both the rTVUS and eTVUS group.

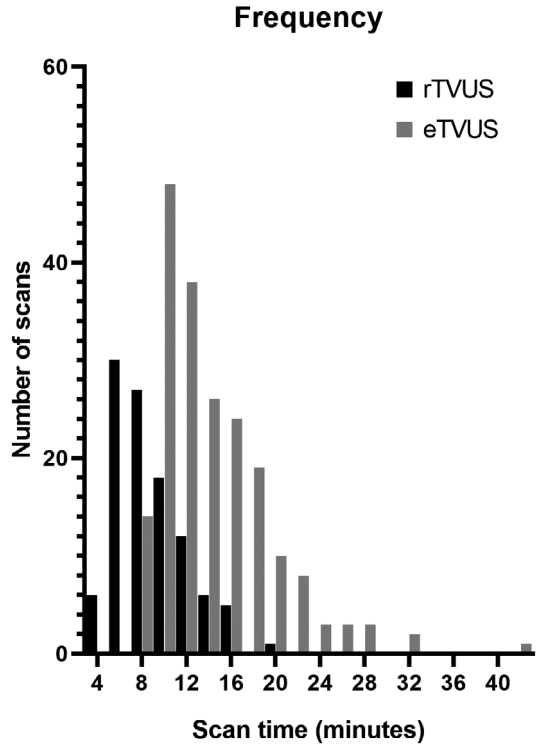


Figure 2: A histogram of the frequency distribution of scan times for both the rTVUS and eTVUS group. The data do not follow a Gaussian distribution.

Table 3: Scan times for both groups with simple statistics (mean, median, minimum and maximum) plus absolute and percentage differences between the groups.

Scanning times (min)			
	rTVUS	**eTVUS**	**Difference (%)**
All sonographers			
n	105	199	–
Mean (±SD)	8.4 (±3.2)	13.8 (±5.2)	5.4 (64%)
Median	7	12	5.0 (71%)
Minimum	4	7	3.0 (75%)
Maximum	19	42	23.0 (121%)
IQR (25%, 75%)	6.0–10.0	10.0–16.0	–
Sonographer A			
n	50	36	–
Mean (±SD)	8.9 (±3.5)	16.4 (±6.4)	7.5 (84%)
Median	8	16	8.0 (100%)
Minimum	4	7	3.0 (75%)
Maximum	19	32	13.0 (68%)
IQR (25%, 75%)	6.0–11.3	11.3–20.8	–
Sonographer B			
n	29	122	–
Mean (±SD)	6.9 (±2.4)	13.6(±5.2)	6.7 (97%)
Median	6	12	6.0 (100%)
Minimum	4	8	4.0 (100%)
Maximum	15	42	27.0 (180%)
IQR (25%, 75%)	5.0–7.5	10.0–16.0	–
Sonographer C			
n	26	41	–
Mean (±SD)	8.6 (±2.9)	12.3 (±3.5)	3.7 (43%)
Median	8.5	12	3.5 (41%)
Minimum	4	7	3.0 (75%)
Maximum	15	21	6.0 (40%)
IQR (25%, 75%)	6.0–10.3	10.0–14.3	–

180% vs 40%). As scan times typically were relatively quick (rTVUS mean 8.4 min vs eTVUS mean 13.8 min), these differences were not as stark when comparing the minute values.

A strength of this study was its large sample size in both the study and control groups. This large sample size suggests our

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reported means are likely quite accurate and allowed us to include the outliers, highlighting that in cases of severe endometriosis (e.g. multiple nodules and extensive adhesions), extremely long scan times can be required, much more so than seen in rTVUS. One eTVUS took 42 min to perform which was significantly longer than most other eTVUS cases. This case involved extensive deep endometriosis with multiple nodules in multiple anatomical locations (Figure 3) and extensive adhesions (Videos 1 and 2) causing distortion to the normal pelvic anatomy. It should also be noted that this was 180% longer than the longest rTVUS (19 min). It must therefore be considered that although infrequently occurring, cases of severe endometriosis encountered during eTVUS can result in excessively long scan times being required.

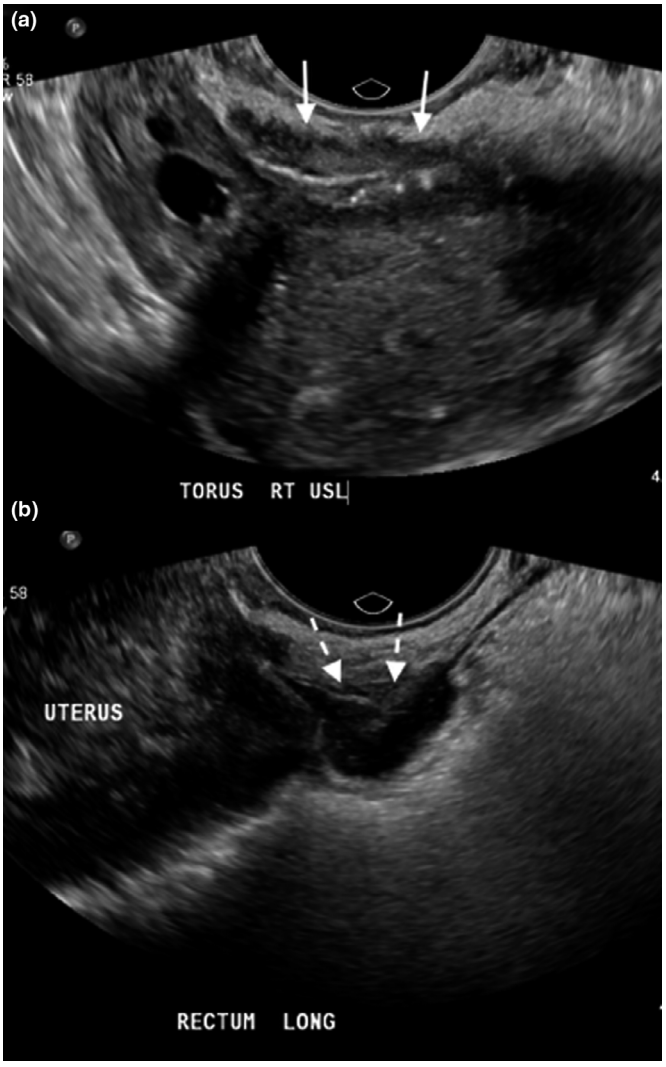


Figure 3: Two nodules of endometriosis seen within the pelvis of the case which took 42 minutes. A large nodule of endometriosis is seen within the right uterosacral ligament, extending into the torus uterinus as shown by the white solid arrows (a). A nodule of endometriosis was also seen within the rectal wall (b) as depicted by the dashed arrows. Also present in this case were extensive pelvic adhesions, including obliteration of the pouch of Douglas and a left ovarian cyst (not pictured).

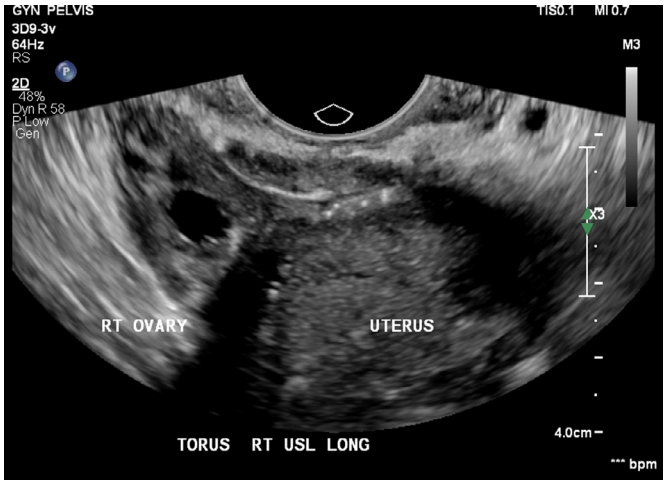


Figure 4: Gentle pressure is being applied to the right ovary and uterus with the transvaginal transducer. The right ovary and uterus can be seen to move together, along with the right uterosacral ligament and the large nodule within. This is due to dense adhesions in this region. Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/ajum.12288

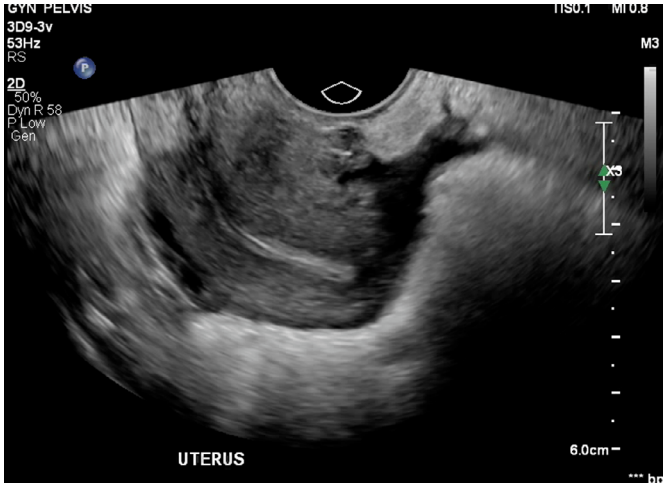


Figure 5: The uterine *sliding sign'* manoeuvre is being performed by applying gentle pressure with the transvaginal transducer to the posterior vaginal fornix. The posterior wall of this retroverted uterus and the adjacent anterior rectal wall are not seen to move apart freely suggesting obliteration of the pouch of Douglas. Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/ajum.12288

Despite evidence in favour of eTVUS first appearing within the literature nearly two decades ago,[19] eTVUS is still

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predominantly only available in specialised gynaecological imaging centres throughout Australia, with rTVUS typically performed as the norm in general imaging settings, even when patients present with a clinical suspicion of endometriosis.[15] Several proponents of eTVUS have advocated for the incorporation of eTVUS into all rTVUS, regardless of the scan indication,[15,20] whilst others have pushed for a minimum of quality ultrasound assessment, which includes assessment of the anterior and posterior compartments for people with suspected endometriosis prior to surgical intervention.[21] There is a paucity within the literature explaining why the uptake of eTVUS within routine sonographic practice has been slow. Skill of the sonographer and sonologist/radiologist[11–13] and clinical knowledge[13] have been alluded to within published works as such barriers. Additionally, the need to perform dynamic assessments (when the sonographer performing these is not the clinician reporting the findings), lack of adequate remuneration and scan time limitations have also been anecdotally reported in our professional encounters and conversations as barriers to the uptake of this technique. This study has shown that performing eTVUS adds an average of 5.4 min to rTVUS, which, whilst not excessive, is a significant additional time requirement, which needs to be considered when formulating scanning protocols. In Australia, as there is currently no additional remuneration from Medicare for extending an rTVUS to include eTVUS,[14] this additional time allocation may be cost prohibitive in some centres.

Endometriosis is a very common condition and currently carries a diagnostic delay of approximately 6.4 years.[22] As people presenting for gynaecological ultrasound do not represent the general population, but rather those with a high likelihood of various gynaecological conditions, the prevalence of endometriosis amongst patients presenting for gynaecological ultrasound is likely far higher. Leonardi *et al.*[23] reported that approximately 28% of patients presenting for TVUS in a gynaecology-focused ultrasound practice had a high clinical suspicion of endometriosis. The addition of an assessment of the anterior and posterior compartments would therefore be a high value inclusion to many rTVUS examinations and could aid in reducing the diagnostic delay, especially in cases of deep endometriosis.[24] Although the additional time required to perform eTVUS may be undesirable for patients, especially if experiencing pelvic pain, within their review, Deed *et al.*[25] found TVUS to typically be well accepted by patients, especially if adequately informed of the need for such imaging. As such, it is likely that with sufficient informed consent, the additional time burden required to complete an eTVUS would likely result in an improved patient experience; however, studies exploring this hypothesis are needed. Given the potential for improved outcomes for patients, inclusion of eTVUS into both local departmental scanning protocols and future national guideline updates should be considered. If the additional time requirement presented is prohibitive, reallocation of time from other aspects of gynaecological ultrasound protocols with lower clinical value, such as extensive TAS or routine kidney imaging,[26] could be contemplated.

We were unable to locate any published works to date which can aid clinicians in planning for adequate time allocation for eTVUS. Whilst several guidelines exist to aid departments in the design of scanning protocols for gynaecological ultrasound,[1,4,16] there is no guidance for what constitutes an appropriate scan time. We hope that this work can be well utilised by ultrasound departments in the formation of protocols for the inclusion of eTVUS when indicated.

There are several limitations within this study that must be considered if doing this. Firstly, the times reported in this study were obtained retrospectively from the review of time stamps to judge transvaginal scan times. As these only represent when images were taken, and sonographers may spend time before the acquisition of the first image or after the acquisition of the last image assessing structures in real time, this may have resulted in an under reporting of the true time taken to perform both rTVUS and eTVUS.

Additionally, any extension images required (such as transabdominal views or kidney images) were excluded from our analysis. The reported times also do not take into account the time sonographers spend communicating with patients, gaining consent, having patients prepare for examination (e.g. emptying bladder and undressing) and performing post exam duties (e.g. having patients redress, cleaning and disinfecting transvaginal probes and writing worksheets). As such, the reported times do not represent the appointment times required to complete the examination. The sonographers involved in this study also report that completing the required sonographers report or worksheet for complex eTVUS cases is significantly more time-consuming than for rTVUS. Measurement of this was beyond the scope of this study.

This study was completed within a specialised women's imaging centre. The sonographers involved in this study were all very experienced and specialised in obstetric and gynaecological ultrasound. As such, these findings may not translate to less experienced or more generalised sonographers. Although the mean additional time needed for eTVUS was 5.4 min, a less experienced or non-specialised sonographer would likely need longer to complete both rTVUS and eTVUS. Median scan times of eTVUS were double that of rTVUS for one of our participating sonographers, despite extensive experience. We would therefore suggest that, if looking to incorporate an assessment for endometriosis into rTVUS appointments, practices consider doubling the time allocated to performing a TVUS. In-house time audits could be performed to assess how this would translate to examination times within a specific department. Future prospective studies assessing time allocation for eTVUS would be beneficial, as would studies from general imaging settings to further support the development of robust, thorough and achievable scanning protocols.

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Conclusion

Endometriosis transvaginal ultrasound took an average of 5.4 min longer to perform than rTVUS, which resulted in significantly longer mean (64%) and median (71%) scan times. As there is currently no additional Medicare rebate offered for performing eTVUS rather than rTVUS, an assessment for endometriosis could be cost prohibitive in some Australian centres. As such, future reviews of the Medicare Benefit Scheme must take this into account to ensure patient access to eTVUS is not impeded and diagnosis is not avoidably delayed.

To the authors' knowledge, this is the first published study looking at time allotment for eTVUS. As this study was performed within a specialised women's imaging practice, these findings may not translate to less experienced or more generalised sonographers. Therefore, future prospective studies assessing time provision for eTVUS would be beneficial as would studies from general imaging settings.

Author Contributions

Alison Deslandes: Conceptualization (lead); Data curation (equal); Formal analysis (lead); Investigation (lead); Methodology (lead); Project administration (lead); Writing-original draft (lead); Writing-review & editing (equal). **Nayana Parange:** Conceptualization (supporting); Formal analysis (supporting); Investigation (supporting); Methodology (supporting); Supervision (supporting); Writing-review & editing (equal). **Jessie Childs:** Conceptualization (supporting); Formal analysis (supporting); Investigation (supporting); Methodology (supporting); Supervision (supporting); Writing-review & editing (equal). **Brooke Osborne:** Conceptualization (supporting); Formal analysis (supporting); Investigation (supporting); Methodology (supporting); Supervision (supporting); Writing-review & editing (equal). **Catrina Pannucio:** Data curation (equal); Writing-review & editing (equal). **Anthea Croft:** Data curation (equal); Writing-review & editing (equal). **Eva Bezak:** Conceptualization (supporting); Formal analysis (supporting); Investigation (supporting); Methodology (supporting); Project administration (supporting); Supervision (lead); Writing-review & editing (equal).

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Conflict of Interest

Alison Deslandes is a director of ASUM. Catrina Panuccio is the managing director of Specialist Imaging Partners.

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5.2 Discussion and conclusion

This study identified that eTVUS took an average of 5.4 minutes longer to perform than rTVUS, which resulted in significantly longer mean (64%) and median (71%) scan times. This suggests that in order to implement this scanning technique, the allotted times for rTVUS will likely be insufficient.

The main limitation of this study was the use of data from a specialised women's imaging centre. As mentioned within the published study, the sonographers involved in this study were all very experienced and had each performed in excess of 1000 eTVUS examinations. Most Australian sonographers performing gynaecological ultrasound are employed within a general imaging (radiology) setting. It is therefore unlikely they would perform the same volume of endometriosis imaging and as such, would not be as skilled in this specific technique as a result of the reduced exposure. Consequently, it is very likely that the minute values reported in this study would not translate to this population and these sonographers would require even more time to complete these scans. Furthermore, this study looked at the acquisition time of images only. After the completion of an examination, sonographers are required to document their findings in a preliminary report or worksheet. As scanning for endometriosis is more comprehensive than rTVUS, reporting findings is also more time consuming. Measuring this was beyond the scope of this study however is an important consideration for departments wishing to implement eTVUS.

These findings help to shed further light on the additional time requirement for performing TVUS for endometriosis and will be valuable in increasing access to this useful technique.

6 Summary and Conclusion

This thesis investigated the accuracy and reliability of sonographer led TVUS in the diagnosis of endometriosis. The ability of sonographers to accurately diagnose endometriosis with TVUS has the potential to reduce diagnostic delays associated with this disease, expediate triage to the appropriate teams for management and improve the patient experience for people with endometriosis.

6.1 Summary of main findings

Chapter 2 of this thesis, presented a review of the literature assessing the current status of TVUS prior to surgery within published works (47). This review showed that when comprehensive scanning protocols, including an assessment of the anterior and posterior compartments, were implemented (i.e. eTVUS), TVUS was a valuable tool in the diagnosis and surgical planning of cases of posterior compartment DE and ovarian endometrioma. However, more data regarding anterior compartment DE is needed.

The review of the literature revealed that most of the published studies to date have been conducted in specialised settings (e.g. endometriosis centres of excellence or gynaecological pain clinics), where specialist gynaecologists often performed the scans, and those performing the scans worked closely with the subsequent surgical teams. It was therefore unclear whether the same accuracy could be achieved when the eTVUS was performed by sonographers within the more common setting of outpatient imaging practices, working distant to the clinical and surgical teams.

Many of the reviewed studies used inconsistent descriptors and varying terminology which made it difficult to compare results directly. However, in 2016, the IDEA group consensus on the classification of endometriosis with ultrasound was published (43) and

publications reporting on research after the release of this consensus appeared to be adopting the IDEA proposed nomenclature (57, 59, 61, 63, 65). This became more evident within the updated literature search performed in December 2021, where the reporting of the data was overall more uniform than the original search, due to the good uptake of the IDEA consensus for the formulation of eTVUS protocols (43). Not only did the uptake of these protocols result in easier to interpret research, there was a notable increase in diagnostic accuracy of DE within the USLs, one of the most commonly affected regions (52), suggesting that systematic protocols are leading to better accuracy (57, 61, 63). Of interesting note was the large number of studies identified within the updated search. This search only encompassed the previous two years yet brought 12 new studies (compared to 35 spanning 19 years in our original search), highlighting this to be a rapidly evolving area of research and clinical interest. The gap within the current published works of sonographer-led scanning resulted in an unknown as to whether the same level of diagnostic accuracy is retained when these studies are translated into the wider clinical setting and these techniques are performed by sonographers within outpatient imaging practices. In response to this, and to address the first aim of this thesis, chapter 3 investigated the accuracy of TVUS in the diagnosis of endometriosis prior to surgery when performed by a sonographer. To address this research question, a prospective longitudinal cohort study was performed. The study group comprised of 201 women who presented to a specialist outpatient women's imaging centre in Adelaide, South Australia between September 2019 and September 2020 for a comprehensive eTVUS, performed in line with the IDEA group consensus protocol (43). Laparoscopy was performed within 12 months as the reference standard. Complete TVUS and surgical data was available for 53 women who were included in the final analysis. The results revealed that in 50/54 (94.3%) of participants, pelvic

endometriosis of any subtype was confirmed at surgery, with 25/53 (47.2%) having DE nodules and/or ovarian endometriomas present. Endometriosis transvaginal ultrasound (eTVUS) for the detection of DE had overall sensitivity of 84.0%, specificity of 89.3%, PPV of 87.5%, NPV of 86.2% LR+ of 7.85, LR- of 0.18 and accuracy of 86.8% ($p<0.001$). To address the subsidiary question, sonographic 'soft markers' were also assessed revealing that reduced ovarian mobility had a poor sensitivity for detecting ovarian fossa SE local adhesions and/or localised DE or endometrioma (Left= 61.9% and right=13.3%), but high specificities (left= 87.5% and right=94.7%). Site-specific tenderness (SST) of the ovaries or posterior compartment was correlated against the presence of localised SE, DE or adhesions with low sensitivities (left ovary= 29.7%, right ovary= 11.8% and posterior compartment= 35.9%) and moderate specificities (left ovary= 81.3%, right ovary= 84.2% and posterior compartment= 71.4%). Comparable results for the detection of isolated SE were seen when cases of DE were excluded. The correlation of sonographic soft markers to surgically detected endometriosis failed to reach statistical significance in all locations except for reduced left ovarian mobility ($p=<0.001$).

When viewed in comparison, sonographer-led scanning performed with a similar or superior accuracy to other published works reviewed in chapter 2, drawing the conclusion that sonographers working in an outpatient women's imaging setting can detect DE with a high level of diagnostic accuracy however, the performance of soft markers in the detection of SE was poor.

This study had several limitations. Firstly, despite recruiting double the number of participants required, for reasons beyond control, complete data was not available for as many participants as desired (100 participants in the final analysis had been wanted), reducing the power of this study.

This study did not give any insight into the intra or interobserver reliability of any aspect of this technique, a question which had remained after reviewing the literature in chapter 2. As this stayed an unanswered, yet important aim of this thesis, in chapter 4, this question was sought to be resolved by a retrospective reliability study. Due to the difficulty in repeating non-clinically indicated TVUS, the study was designed to assess reliability of measurements only. In this study, five sonographers (three experienced and two inexperienced) reviewed and measured 13 ultrasound images of endometriotic nodules within the rectosigmoid colon over two session, one month apart. Interoperator agreement ranged from moderate to excellent (ICC= 0.7473 [CI 0.5353-0.9002] (length), 0.8125 [CI 0.6496- 0.9674] (height) and 0.8170 [CI 0.6489- 0.9302] (width)). There was poor to excellent levels of agreement between experienced and inexperienced operators (ICC= 0.8975 [CI 0.5146- 0.9733] (length), 0.8903 [0.6138- 0.9674] (height) and 0.8506 [CI 0.3316- 0.9770] (width)).

The experienced operators achieved better levels of agreement than the inexperienced operators. Inexperienced operators had a wider range of variation between the limits of agreement than experienced operators (14.2 mm versus 9.1 mm).

Some published works relating to inter and intraoperator variability of rectosigmoid nodules exist within the published works (77-79). While all showed similar results, most were able to incorporate a rigorous methodology involving repeat TVUS scanning in real-time, which replicates sonographic practice more accurately than the study in this thesis achieved.

Whilst the research presented in chapters 2, 3 and 4 was performed, a subsidiary question arose regarding how expansion of TVUS for endometriosis into outpatient imaging settings will be achieved, and specifically, how much time will be required to

perform these scans. Chapter 5 presented a retrospective case-control study which was performed to determine the additional time needed to perform an eTVUS compared to rTVUS (73). The study group was comprised of the participants recruited into the study presented in chapter 3 and included 199 eTVUS scans. The control group comprised 105 consecutive rTVUS studies performed in the same time period. The time stamps on the ultrasound images of all cases in both groups were reviewed to determine the time taken to perform each study. It was found that performing eTVUS took significantly longer than rTVUS with increases in the mean (8.4 minutes vs 13.8 minutes, 64%), median (7 minutes vs 12 minutes, 71%), minimum (4 minutes vs 7 minutes, 75%) and maximum (19 minutes vs 42 minutes, 121%) scan times. The Mann-Whitney U test indicated a statistically significant difference in the median scan times (5.0, CI 4.0-6.0), $p<0.001$. Whilst other works have been published to educate sonographers on how to perform eTVUS (75, 76), and assist in the reporting of eTVUS (80), this was the first study published investigating this research question and can hopefully help guide clinical practice and assist imaging departments wishing to offer this technique in the formulation of their practice protocols. A limitation of this study was the assessment of times within a specialist women's imaging centre, from scans performed by very experienced, specialised obstetric and gynaecological sonographers. As such, these results may not directly translate into general imaging settings.

6.2 Future Works

This is the first work investigating the diagnostic accuracy of TVUS for endometriosis, in line with the established international consensus guidelines (43), where imaging has been performed and interpreted by medical sonographers. While this work was performed in an outpatient imaging facility, it was a practice with a specialisation in

obstetric and gynaecological imaging, with the sonographers involved all being expert in this aspect of sonography. Therefore, future works should focus on the translation of this technique into general radiology practices to provide greater access to this valuable technique as this thesis has not addressed this specific gap.

While it was found direct visualisation of DE sonographically correlated strongly with DE at surgery, the correlation of soft markers to isolated SE was poor. This creates challenges for reporting clinicians in outpatient settings, to ensure they are not over diagnosing. Future work into the value of soft markers maybe helpful, however, as reports of direct visualisation of SE are beginning to appear within the literature, likely due to a greater refinement of eTVUS techniques and higher resolutions transducers becoming available, future research focusing on direct visualisation of SE, rather than soft markers will likely be of most benefit to patients and clinicians alike (50).

The testing of intra and interobserver variation in TVUS imaging is challenging due to the intrusive nature of this technique, however further knowledge on variability would be helpful to reassure patients that their results are reliable. Future works further assessing reliability would be valuable to this body of knowledge. The use of cine (video) clips for off-line review could be employed in future studies to overcome the difficulty of repeating non-clinically indicated TVUS whilst mimicking a more "real world" situation of real-time scanning than reviewing still images only.

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APPENDIX A Links to videos within manuscripts

Chapter 3 videos

Video 1: https://youtu.be/GSrGjfT21cE

Gentle pressure is being applied with the transvaginal transducer to the left ovary. With this pressure, the ovary can be seen to be moving freely away from the uterus and pelvic sidewall.

Video 2: https://youtu.be/YPZwhb9Qz6A

Gentle pressure is being applied with the transvaginal transducer to this anteverted uterus from the anterior fornix of the vagina. The uterus and cervix are seen to slide freely away from the bowel posteriorly suggesting the pouch of Douglas is not obliterated.

Video 3: https://youtu.be/wyM65QLdsRc

Gentle pressure is being applied with the transvaginal transducer to this anteverted uterus from the anterior fornix of the vagina. The uterus and cervix do not slide freely away from the bowel posteriorly suggesting the pouch of Douglas is obliterated. The rectal wall also appears to contain a large nodule of endometriosis.

Chapter 5 videos

Video 1: https://youtu.be/8DXafc65Ot4

Gentle pressure is being applied to the right ovary and uterus with the transvaginal transducer. The right ovary and uterus can be seen to move together, along with the right uterosacral ligament and the large nodule within. This is due to dense adhesions in this region.

Video 2: https://youtu.be/cYN5Z9uMZ84

The uterine ‘sliding sign’ manoeuvre is being performed by applying gentle pressure with the transvaginal transducer to the posterior vaginal fornix. The posterior wall of this retroverted uterus and the adjacent anterior rectal wall are not seen to move apart freely suggesting obliteration of the pouch of Douglas.

APPENDIX B Ethics Completion (project 202217)

University of South Australia | Research and Innovation Services

Human Research Ethics Committee

Annual Report, Extension, Project Completion

SECTION 1: PROJECT DETAILS			
Chief Investigator	Ms Alison Deslandes		
Project Title	What is the accuracy and validity of transvaginal ultrasound performed by sonographers in the diagnosis of deep infiltrating endometriosis prior to surgery?		
Project Number	202217	Original Approval Date	17/9/2019

APPROVAL FROM NON-UNISA HREC	
Does this project have non-UniSA HREC ethics approval?	
☐ Yes – *please attach a copy of the approval from the Primary HREC for the annual report or approved extension request*	☒ No

SECTION 2: PROJECT STATUS – Please select your reason for completing this form			
Status	**Select**	**Indicate Date**	**Instruction**
In Progress	☐	Anticipated Date of completion:	Go to Section 5
Extension Required	☐	Anticipated Date of completion (*maximum 1 additional year)*:	Go to Section 5
Discontinued / Not commenced	☐	Date work was stopped:	Go to Section 3
Completed	☒	Date of completion: 21/03/2022	Go to Section 4

SECTION 3: DISCONTINUED/ NOT COMPLETED PROJECTS		
Section 3.1 Did the project commence?	☐ Yes	☐ No
Section 3.2 Detail why the project was discontinued or did not commence, including whether this created any ethical issues and if so, how they were resolved. If data were collected, detail what has been done with them to destroy or secure them (please provide details below)		
Go to Section 7		

SECTION 4: COMPLETED PROJECTS –			
Section 4.1 List original aims of the project (from the original approved application):			
1. Determine if sonographers can accurately diagnose endometriosis on ultrasound prior to surgery, using the surgical and histological diagnosis as the gold standard. 2. Determine if sonographers reports are comparable in accuracy to those generated by a radiologist. 3. Determine if there is agreement between operators in the measurement of rectosigmoid deep infiltrating endometriosis (DIE) nodules and to what extent experience of the operator affects accuracy. 4. Determine whether sonographers, within an outpatient women's ultrasound setting, can accurately perform TVS for the diagnosis of DIE and whether variation exists between operators as to the accuracy of the measurements they obtain.			
Section 4.2 Were the aims of the project achieved? Provide a brief summary of the findings to date below:		☒ Yes	☐ No
Aims 1, 3 and 4 have been achieved with findings to be reported in thesis. Data was collected for aim 2 however the decision was made not to analyse this data as the workload involved was not achievable within scope and time frame of a Masters Project.			
Section 4.3 Have study participants been informed of the results? Provide details. Yes. Those that indicated they would like to be informed have been emailed with a summary of the findings.	☒ Yes	☐ No	☐ N/A
Go to Section 7			

SECTION 5: PROJECTS IN PROGRESS

Section 5.1 Please provide a brief outline of how data collection is progressing, including if any participants have already been involved in the project:

Section 5.2 Indicate current stage and progress of the project *(tick one)*:

☐ Project Establishment/Planning ☐ Recruitment ☐ Data Collection
☐ Data Analysis ☐ Write Up ☐ Other

Section 5.3 List the version numbers and approval dates of the Participant Information Sheet and Consent Form used (where applicable):

Documents	Version number and date	Date Approved
Participant Information Sheet		
Consent Form		

Go to Section 6 if an Extension is Required; otherwise go to Section 7

SECTION 6: EXTENSION REQUIRED

Section 6.1 Explain why an extension of ethics approval is requested:

Go to Section 7

SECTION 7: CLINICAL TRIALS

Complete this section if this study is a clinical trial only, otherwise go to Section 8.

Please note that section 5.5.9 of the National Statement states that it may be unethical for a researcher to continue a clinical trial if:

a) there are or have been substantial deviations from the trial protocol;
b) adverse effects of unexpected type, severity, or frequency are encountered; or
c) as the trial progresses, the continuation of the trial would disadvantage some of the participants as determined by the researchers or others monitoring the trial.

Section 7.1 Tick one of the following for this study:

☐ Clinical trial with full industry sponsorship
☐ Clinical trial with sponsorship from a collaborative or non-profit group
☐ Clinical trial initiated by the Chief Investigator

Section 7.2 Is this study being conducted under either:

Clinical Trial Exemption (CTX) Scheme	☐ Yes	☐ No
Clinical Trial Notification (CTN) Scheme	☐ Yes	☐ No

Section 7.3 Does the study have a Data Safety Monitoring Committee (or similar) which has reviewed the study in the past 12 months? If yes, attach a copy of the Committee's report and describe the potential impact on ethical acceptability and the need for action.

Section 7.4 If a safety report is not available, is action planned on the basis of any safety information received in the last 12 months?	☐ Yes	☐ No

If yes, describe the potential impact on ethical acceptability and the need for action.		
Section 7.5 Has the trial been registered on a publicly accessible register complying with international standards? If yes please provide the names of register(s) and **registration number(s).**	☐ Yes	☐ No

SECTION 8: ETHICAL ISSUES			
Tick YES or NO to the following questions.			
Section 8.1 Have you departed at all from the approved project? If 'YES' provide details below and confirm if a Project Variation form has been submitted for approval of these changes. If you have departed from the approved project and a Project Variation form has NOT been submitted, complete and submit the Project Variation form for approval.		☒ Yes	☐ No
An amendment was made to the project to seek consent for participants to be contacted by phone to allow for follow-up of results. This was approved by the HREC on 15/10/2019. No other variations to the original application occurred.			
Section 8.2 Did any participants withdraw from the project during this year? If 'YES', provide details below:	☐ Yes	☒ No	☐ N/A
Section 8.3 Did any ethical implications arise during the research? If 'YES' provide details below, including whether or not they were foreseen, and how they were resolved		☐ Yes	☒ No
Section 8.4 Have any participants suffered harm or adverse effects? If YES, provide the date reported to UniSA HREC? If not provide details as to why not and submit the reports.	☐ Yes	☒ No	☐ N/A
Section 8.5 Have any complaints been received regarding the project? If 'YES' provide the date, source and nature of the complaint, actions taken, and the current status (resolved/in process/other). Include the date UniSA HREC or detail why no notification occurred.		☐ Yes	☒ No
Section 8.6 Has the project been audited by the sponsor, the Human Research Ethics Office or any other body since the last progress report was submitted? If YES, provide details.		☐ Yes	☒ No
COMPLETE THE FOLLOWING 2 QUESTIONS ONLY IF YOU HAVE CONDUCTED RESEARCH IN A COUNTRY OTHER THAN AUSTRALIA-			

Section 8.7 Did you identify any legal, ethical, governmental or other local requirements that you needed to meet? If YES, provide details.		☐ Yes	☐ No
Section 8.8 Did you meet all such requirements and has written evidence been provided to the ethics office? If YES, provide details. If not, provide details as to why written evidence has not yet been submitted and provide a copy of the relevant document(s).	☐ Yes	☐ No	☐ N/A

SECTION 9: DATA STORAGE ***Please note: Data must be stored as specified in the approved project. All data must eventually be destroyed, unless explicit consent is obtained from the participants to archive their data.***

Section 9.1 State how and where your data is being stored. Have all records (including data) been maintained in a manner consistent with the arrangements and security measures that were proposed in the approved application? If NO, provide details and submit the Project Variation form for approval

All data has been stored/ managed in line with our original DMP.
Hardcopies have been destroyed except for the original consent forms which are being stored at Specialist Imaging Partners in line with their protocols for storage of patient files.
All Soft copy data (deidentified) (ultrasound reports, surgical reports, consent forms, data tables) are currently stored on the UniSA OneDrive assigned to Alison Deslandes with a back-up copy on USB drive (password protected) which is currently in the filing cabinet assigned to Alison Deslandes in BJ154.
Post completion of thesis, all data remaining will be left with the principal supervisor (Prof Eva Bezak).

Section 9.2 How long will the data be kept after the end of the project?

5 years

Section 9.3 Has there been any breach of confidentiality or data security issues, which includes identifying information? If 'YES' provide details of actions to remedy the breach, including date reported to UniSA HREC or reasons why it was not reported	☐ Yes	☒ No

SECTION 10: DECLARATION

☒ I confirm that the research has been undertaken as per the approved project.

[redacted] *Chief Investigator Signature*	Alison Deslandes *Printed Name*	21/03/2022 *Date*
[redacted] *Supervisor's Signature (students only)*	Eva Bezak *Printed Name*	21/3/2022 *Date*

APPENDIX C Ethics completion (project 204082)

University of South Australia | Research and Innovation Services

Human Research Ethics Committee

Annual Report, Extension, Project Completion

SECTION 1: PROJECT DETAILS			
Chief Investigator	Ms Alison Deslandes		
Project Title	How much time is needed for a sonographer to add an endometriosis protocol to a basic pelvic ultrasound		
Project Number	204082	Original Approval Date	14/7/2021
APPROVAL FROM NON-UNISA HREC			
Does this project have non-UniSA HREC ethics approval?			
☐ Yes – *please attach a copy of the approval from the Primary HREC for the annual report or approved extension request*	☒ No		

SECTION 2: PROJECT STATUS – Please select your reason for completing this form			
Status	**Select**	**Indicate Date**	**Instruction**
In Progress	☐	Anticipated Date of completion:	Go to Section 5
Extension Required	☐	Anticipated Date of completion (*maximum 1 additional year)*:	Go to Section 5
Discontinued / Not commenced	☐	Date work was stopped:	Go to Section 3
Completed	☒	Date of completion: 01/12/2021	Go to Section 4

SECTION 3: DISCONTINUED/ NOT COMPLETED PROJECTS		
Section 3.1 Did the project commence?	☐ Yes	☐ No
Section 3.2 Detail why the project was discontinued or did not commence, including whether this created any ethical issues and if so, how they were resolved. If data were collected, detail what has been done with them to destroy or secure them (please provide details below)		
Go to Section 7		

SECTION 4: COMPLETED PROJECTS –		
Section 4.1 List original aims of the project (from the original approved application):		
Determine the additional time needed for a sonographer to perform a comprehensive examination of deep endometriosis with transvaginal ultrasound in comparison to a routine transvaginal ultrasound.		
Section 4.2 Were the aims of the project achieved? Provide a brief summary of the findings to date below:	☒ Yes	☐ No
Yes aim were achieved and results have been published in a peer reviewed journal https://onlinelibrary.wiley.com/doi/full/10.1002/ajum.12288		
Section 4.3 Have study participants been informed of the results? Provide details.	☐ Yes	☐ No ☒ N/A
Go to Section 7		

SECTION 5: PROJECTS IN PROGRESS
Section 5.1 Please provide a brief outline of how data collection is progressing, including if any participants have already been involved in the project:

Section 5.2 Indicate current stage and progress of the project *(tick one)*:

☐ Project Establishment/Planning ☐ Recruitment ☐ Data Collection
☐ Data Analysis ☐ Write Up ☐ Other

Section 5.3 List the version numbers and approval dates of the Participant Information Sheet and Consent Form used (where applicable):

Documents	**Version number and date**	**Date Approved**
Participant Information Sheet		
Consent Form		

Go to Section 6 if an Extension is Required; otherwise go to Section 7

SECTION 6: EXTENSION REQUIRED

Section 6.1 Explain why an extension of ethics approval is requested:

Go to Section 7

SECTION 7: CLINICAL TRIALS

Complete this section if this study is a clinical trial only, otherwise go to Section 8.

Please note that section 5.5.9 of the National Statement states that it may be unethical for a researcher to continue a clinical trial if:

a) there are or have been substantial deviations from the trial protocol;
b) adverse effects of unexpected type, severity, or frequency are encountered; or
c) as the trial progresses, the continuation of the trial would disadvantage some of the participants as determined by the researchers or others monitoring the trial.

Section 7.1 Tick one of the following for this study:

☐ Clinical trial with full industry sponsorship
☐ Clinical trial with sponsorship from a collaborative or non-profit group
☐ Clinical trial initiated by the Chief Investigator

Section 7.2 Is this study being conducted under either:

Clinical Trial Exemption (CTX) Scheme	☐ Yes	☐ No
Clinical Trial Notification (CTN) Scheme	☐ Yes	☐ No

Section 7.3 Does the study have a Data Safety Monitoring Committee (or similar) which has reviewed the study in the past 12 months? If yes, attach a copy of the Committee's report and describe the potential impact on ethical acceptability and the need for action.

Section 7.4 If a safety report is not available, is action planned on the basis of any safety information received in the last 12 months? If yes, describe the potential impact on ethical acceptability and the need for action.	☐ Yes	☐ No

Section 7.5 Has the trial been registered on a publicly accessible register complying with international standards? If yes please provide the names of register(s) and **registration number(s).**	☐ Yes	☐ No

SECTION 8: ETHICAL ISSUES			
Tick YES or NO to the following questions.			
Section 8.1 Have you departed at all from the approved project? If 'YES' provide details below and confirm if a Project Variation form has been submitted for approval of these changes. If you have departed from the approved project and a Project Variation form has NOT been submitted, complete and submit the Project Variation form for approval.		☐ Yes	☒ No
Section 8.2 Did any participants withdraw from the project during this year? If 'YES', provide details below:	☐ Yes	☐ No	☒ N/A
Section 8.3 Did any ethical implications arise during the research? If 'YES' provide details below, including whether or not they were foreseen, and how they were resolved		☐ Yes	☒ No
Section 8.4 Have any participants suffered harm or adverse effects? If YES, provide the date reported to UniSA HREC? If not provide details as to why not and submit the reports.	☐ Yes	☐ No	☒ N/A
Section 8.5 Have any complaints been received regarding the project? If 'YES' provide the date, source and nature of the complaint, actions taken, and the current status (resolved/in process/other). Include the date UniSA HREC or detail why no notification occurred.		☐ Yes	☒ No
Section 8.6 Has the project been audited by the sponsor, the Human Research Ethics Office or any other body since the last progress report was submitted? If YES, provide details.		☐ Yes	☒ No
COMPLETE THE FOLLOWING 2 QUESTIONS ONLY IF YOU HAVE CONDUCTED RESEARCH IN A COUNTRY OTHER THAN AUSTRALIA-			
Section 8.7 Did you identify any legal, ethical, governmental or other local requirements that you needed to meet? If YES, provide details.		☐ Yes	☐ No
Section 8.8 Did you meet all such requirements and has written evidence been provided to the ethics office? If YES, provide details.	☐ Yes	☐ No	☐ N/A

If not, provide details as to why written evidence has not yet been submitted and provide a copy of the relevant document(s).			

SECTION 9: DATA STORAGE ***Please note: Data must be stored as specified in the approved project. All data must eventually be destroyed, unless explicit consent is obtained from the participants to archive their data.***

Section 9.1 State how and where your data is being stored. Have all records (including data) been maintained in a manner consistent with the arrangements and security measures that were proposed in the approved application? If NO, provide details and submit the Project Variation form for approval

All data has been stored/ managed in line with our original DMP.
All Soft copy data tables (deidentified) are currently stored on the UniSA OneDrive assigned to Alison Deslandes with a back-up copy on USB drive (password protected) which is currently in the filing cabinet assigned to Alison Deslandes in BJ154.
Post completion of thesis, all data remaining will be left with the principal supervisor (Prof Eva Bezak).

Section 9.2 How long will the data be kept after the end of the project?

5 years

Section 9.3 Has there been any breach of confidentiality or data security issues, which includes identifying information? If 'YES' provide details of actions to remedy the breach, including date reported to UniSA HREC or reasons why it was not reported	☐ Yes	☒ No

SECTION 10: DECLARATION

☒ I confirm that the research has been undertaken as per the approved project.

[redacted] *Chief Investigator Signature*	Alison Deslandes *Printed Name*	21/03/2022 *Date*
[redacted] *Supervisor's Signature (students only)*	Eva Bezak *Printed Name*	21/3/2022 *Date*