TRANS-VAGINAL ULTRASOUND DIAGNOSIS
OF ADENOMYOSIS
WITH HISTOLOGIC CORRELATION

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CHNREG 001

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REQUIREMENTS FOR THE DEGREE

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               Dr C. Stewart
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Declaration

I, Reginald George Chunda, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole document or any portion of the contents in any manner whatsoever.

Signature

Date 9/1/2013
Declaration by supervisors

The research which Dr Reginald George Chunda has undertaken and the presentation of this dissertation was supervised by Professor Silke Dyer and Dr Chantal Stewart. This study was carried out while Dr Chunda was a registrar in the Department of Obstetrics and Gynaecology at the University of Cape Town.

We are satisfied that this was Dr Chunda's original work and that this dissertation should be submitted in partial fulfilment of the requirements for the degree Master of Medicine in Obstetrics and Gynaecology.

Supervisor: Professor S. Dyer

Signature: [Signature] Date: 9.11.2013

Supervisor: Dr C. Stewart

Signature: [Signature] Date: 9.11.2013
Abstract

Background: Adenomyosis, defined as the presence of ectopic endometrial tissue in the myometrium, is a cause of morbidity in afflicted women. Classically it presents with menorrhagia, dysmenorrhea and dyspareunia. Traditionally the diagnosis has been by histology of post-hysterectomy specimens with reported prevalence of 5%-70%. With advances in imaging techniques, pre-surgical diagnosis can be made with a reasonable accuracy using trans-vaginal ultrasound (TVS) and magnetic resonance imaging (MRI) with the former being preferred due to cost effectiveness. Accurate pre-surgical diagnosis would facilitate alternative treatment options to hysterectomy. Different sonographic features of adenomyosis have been reported and well correlated with histology; there is however no general consensus as to the most specific features and whether the frequencies of these sonographic features hold true in other population settings like South Africa. We therefore conducted a cross-sectional diagnostic study of pre-surgical TVS diagnosis of adenomyosis with post-hysterectomy histological correlation.

Aims/Objectives: The primary objective was to determine the diagnostic performance of TVS for the diagnosis of adenomyosis using post-hysterectomy histology as the reference standard. Secondary objectives were to determine the signs and symptoms in women with histologically confirmed adenomyosis and the prevalence of histological adenomyosis.
Setting: The study was conducted at Groote Schuur Hospital and New Somerset Hospital over a period of 11 months (May 2011 to April 2012).

Methodology: There were two study groups. In study group A, women scheduled for hysterectomy completed a questionnaire capturing clinical symptoms and underwent TVS examination. A TVS diagnosis of adenomyosis was made if three or more features suggestive of adenomyosis were present. After hysterectomy, the uteri were examined by histopathologists. Both ultrasonographers and histopathologists were blinded to other findings. The TVS diagnosis of adenomyosis was compared with histopathology results.

In study group B, histopathological results were collected prospectively in all women undergoing hysterectomy during the study period (including those in study group A). From the results, a histopathological profile of posthysterectomy specimens was made.

Results: There were 78 participants in group A. Histologically confirmed adenomyosis was found in 16 of the 78 women (20.5%). Seventy one clinical questionnaires were completed (missing data n=7). The only clinical finding that reached statistical significance was presence of a tender uterus in 31.5% of women with adenomyosis compared to 5.4% without adenomyosis (p<0.05). Other clinical features seen in women with adenomyosis were heavy menstrual bleeding (62.5%), dysmenorrhea (50%) and a uterus that was less than twelve weeks gestation (62.5%) but these findings did not
reach statistical significance compared to women without adenomyosis (p>0.05). Despite presence of characteristic signs and symptoms, a preoperative clinical diagnosis of adenomyosis was made in only 12.5% [95% CI: 3.5 - 36] of patients with histologically confirmed adenomyosis.

TVS diagnosis of adenomyosis had a sensitivity of 50% [95% CI: 28-72], specificity of 80.6% [95% CI: 69.2 -88.6], accuracy of 74.4% [95% CI: 63.7-82.7] and diagnostic odds ratio of 4.2 [95% CI: 1.3-13.4]. Of all TVS diagnostic features evaluated, heterogenous myometrial echotexture had the highest sensitivity 68.8% [95% CI: 44.4-85.8] but a poor specificity 62.9% [95% CI: 50.5-73.8]. The presence of subendometrial echogenic linear striations had the highest specificity 96.8% [95% CI: 89-99] and accuracy 78.2% [95% CI: 67.8-85.9] for the diagnosis of adenomyosis. TVS diagnosis of adenomyosis was ultrasonographer dependent.

Study group B comprised 261 women. Leiomyomas were the most prevalent histopathological diagnosis (63.2% ; 95% CI: 57.2-68.4), followed by adenomyosis with a prevalence of 20.3% [95% CI: 15.9-25.6].

**Conclusion**

Data from this prospective study showed that a clinical presentation of menorrhagia, dysmenorrhea and a tender uterus less than twelve weeks suggested a diagnosis of adenomyosis. Despite characteristic signs and symptoms, clinicians only diagnosed adenomyosis in about one in ten women.
The most predictive individual ultrasonographic feature was the presence of subendometrial echogenic linear striations. TVS diagnosis of adenomyosis had a high specificity and accuracy but a low sensitivity. This implies that if adenomyosis is suspected on clinical grounds, TVS has more value in refuting the diagnosis than confirming it. The presence of inter-observer differences indicates the need for skills training.
The following are acknowledged:

- The women who graciously agreed to participate in this study

- The Ultrasographers (Dr Sonia Constantatos, Dr Alison Boutall, Ms Shameema Mukadam) who despite their heavy workload kindly agreed to do the extra scans.

- Ms Shesley van Zyl (through the help of Prof Silke Dyer) who greatly helped with recruitment when it was proving almost impossible for the investigator to find time to recruit participants

- Dr Greg Petro, with his greatly valued input through study design and analysis

- Lastly but not least my Supervisors: Prof Silke Dyer and Dr Stewart who greatly helped with the protocol, analysis, critical evaluation of the dissertation write up.
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Outline of Dissertation

Below, a brief outline of the dissertation is given. The Vancouver Referencing system is used throughout the document.

**Chapter 1** Literature review

**Chapter 2** Aims and Objectives.

**Chapter 3** Settings, Methods and Statistical analysis

**Chapter 4** Results.

**Chapter 5** Discussion and Conclusion.
Abbreviations

The following abbreviations are used throughout the thesis

LH = Luteinising Hormone
TVS = Trans-vaginal Ultrasound
MRI = Magnetic Resonance Imaging
TAUS = Transabdominal Ultrasound
COC = Combined Oral Contraceptives
GnRH = Gonadotropin Releasing Hormone
UAE = Uterine Artery Embolisation
MRgFUS = Magnetic Resonance Guided Focussed Ultrasound
IUD = Intrauterine Device
IUS = Intrauterine System
VSUP = Video Sonography of Uterine Peristalsis
HSSG = Hysterosalpingoscintigraphy
D&C = Dilatation and curettage
HSG = Hysterosalpingography
hCG = Human Chorionic Gonadotrophic Hormone
Ig = Immunoglobulin
PPV = Positive Predictive Value
NPV = Negative Predictive Value
JZ = Junctional Zone
LNG = Levonorgestrel
Chapter 1

Literature review

The term adenomyosis refers to the presence of endometrial glands and stroma in the myometrium with surrounding hypertrophy and hyperplasia.

1.1 Historical Background

In 1860, Carl Von Rokitansky, a German pathologist, was the first to describe a case of adenomyosis. He found endometrial glands in the myometrium and designated this finding ‘cystosarcoma adenoids uterinum.’\(^1\) For many years, adenomyosis and endometriosis were considered as one condition called adenomyoma(-ta). As such, the early history of adenomyosis is interwoven with that of endometriosis.

In 1896, Thomas Stephen Cullen, a gynaecologist, systematically researched adenomyosis (at that time called ‘mucosal invasion’). He identified the epithelial tissue as ‘uterine mucosa’ and described the mechanism through which the mucosa invades the underlying tissue ‘through the presence in the myometrium of chinks or fissures’\(^1\) Cullen further reported women with adenomyosis had ‘lengthened menstrual periods’ associated with a ‘great deal of pain.’ He went on further to discuss treatment, stating that ‘abdominal hysterectomy is indicated, myomectomy is inapplicable, as the growth is so interwoven with the normal muscle that it cannot be shelled out.’\(^1\)
In the same year (1896) that Cullen published his works, von Recklinghauser published a book: ‘*Die Adenomyome und Cystadenomyome der Uterus und Tubenwandung*’ in which he divided adenomyoma(-ta) into two groups. The first group comprised adenomyomata situated at the periphery of the uterus, and the second group adenomyomata arising centrally (within the uterus).

This represents the first separation of what is now endometriosis (the first group) and adenomyosis (the second group).

In 1925 Frankl coined the word ‘*Adenomyosis uteri*’ to denote the mucosal invasion of the myometrium. He stated that he chose the name adenomyosis ‘which does not suggest any inflammatory genesis as do terms like *endometritis, adenomyositis* and *adenomyometritis*’.¹

The current commonly used definition of adenomyosis was elaborated by Bird C.C et al in 1972. They stated that: ‘*Adenomyosis may be defined as the benign invasion of the endometrium into myometrium, producing a diffusely enlarged uterus which microscopically exhibits ectopic non-neoplastic, endometrial glands and stroma surrounded by hypertrophic and hyperplastic myometrium*’.¹²³
1.2 Aetiology and Pathophysiology of Adenomyosis

1.2.1 Syndrome of Dislocated Basal Endometrium

Leyendecker et al postulated that adenomyosis arises due to dislocation of the basal endometrium into myometrium\(^4\). The risk of developing adenomyosis has been demonstrated to be high in parous women as well as following abortion, endometrial curettage and other uterine surgical procedures. It is thought that this leads to traumatisation of the endo-myometrial interface leading to migration of the basal endometrium into myometrium.\(^4,5,6,7\)

However it was noted that a significant number of non-parous women without a history of iatrogenic uterine trauma developed uterine adenomyosis\(^8\). In 1996, Kunz et al demonstrated uterine peristalsis and utero-tubal transport of spermatozoal size albumin macrospheres (using video sonography of uterine peristalsis (VSUP), hysterosalpingoscintigraphy (HSSG) and technetium - labelled albumin macrospheres of spermatozoal size). Leyendecker et al, proposed that dysfunctional uterine peristalsis leads to auto-traumatisation of the uterus that results in dislocation of basal endometrium to intra- and extra-uterine sites resulting in adenomyosis and endometriosis respectively\(^9\).

1.2.2 Oestrogen Imbalance (Hyperoestrogenism)

It has long been observed that adenomyosis is frequently associated with oestrogen dependent diseases as shown in Table 1.
In women with endometriosis and adenomyosis, Takahashi found the levels of oestradiol in menstrual blood to be higher than in healthy women, while peripheral levels were the same \(^4,10\). In studies of oestradiol concentration in menstrual blood, women with adenomyosis had levels more than 30pg/ml higher compared to women with normal ovulatory cycles and without adenomyosis \(^6,10,11\).

Yamamoto et al demonstrated that aromatase (P450A) and oestrone sulphotase levels were higher in adenomyotic foci than in the normal adjacent myometrium, endometrium and leiomyomata \((p<0.01)\). The investigators postulated that the high local levels of oestrogen were made by the local cytochrome P450A in adenomyotic uteri\(^{12}\).

**Table 1:** *Pathologies Found with Adenomyosis*\(^{6,13,14}\)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Percentage of women with Adenomyosis</th>
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1.2.3 Arrest of Müllerian Totipotential Cells

Proponents of this theory state that during embryogenesis, as the uterus develops from the fusion of the two müllerian ducts, some totipotential cells remain within the myometrium and with appropriate stimulation they differentiate into endometrium leading to adenomyosis. This is supported by development of adenomyosis in extra-uterine regions such as the rectovaginal septum. Adding weight to this hypothesis is a case report by Enatsu et al of adenomyosis in a 27yr old Japanese woman with the Rokitansky-Kuster-Hauser syndrome and thus no functional endometrium.

1.2.4 Adenomyosis as a Genetic Dysregulation Disease

In their study on apoptosis in eutopic and ectopic endometria, Matsumoto et al demonstrated that bcl-2 gene (cell death repressor) expression and Ki-67 (a proliferative marker) are cyclically expressed in response to hormonal changes in the eutopic endometrium but not in the ectopic endometrium in adenomyosis and contended that adenomyotic lesions do not originate in the basal endometrium but rather due to dysregulation of bcl-2 gene.

1.2.5 Adenomyosis as a Neoplastic Process

In his review on the pathophysiology of adenomyosis, Ferenczy noted that endometrial cells may invade the myometrium by amoeboid migration. In vitro studies by Gaetje et al, showed that endometriotic cells had invasive potential and their invasive index was similar to that of metastatic bladder cell lines. It has also been observed that invaginating endometrial glands express more LH/hCG receptors than eutopic endometrium, an observation
also seen in invasive trophoblast in choriocarcinoma and endometrial carcinoma\textsuperscript{11}.

1.2.6 Adenomyosis as an Immune Disease

Immunological changes associated with adenomyosis have been explored by various investigators. Ota et al, using immunohistochemistry, found increased expression of the major histocompatibility complex class II antigen (HLA-DR) in adenomyotic endometrium\textsuperscript{19,20}. Kreiner et al observed increased autoantibodies against phospholipids in endometriosis and adenomyosis as well as marked deposition of IgS and complement components\textsuperscript{21}. Ferenczy noted that lymphoid follicle-like structures, mostly located in the endomyometrial junction are rich in activated T helper cells which inhibit endometrial growth\textsuperscript{6}. He further theorised that it is possible that adenomyotic uteri are poor in activated T cells allowing invagination of endometrium into myometrium. Other abnormal immune phenomena observed in adenomyosis were strong expression of cell surface antigen, heat shock protein and adhesion molecules, aberrant expression of superoxide dismutase, glutathione oxidase and xanthine oxidase.\textsuperscript{22} Ota et al postulated that these abnormal immune responses might be involved in poor reproductive performance in adenomyosis\textsuperscript{19}. 
1.2.7 Hyperprolactinaemia

Murine studies have demonstrated that hyperprolactinemia leads to adenomyosis\textsuperscript{13}. In their studies on wistar albino rats, Ficicioglu et al induced hyperprolactinemia by fluoxetine and demonstrated that they developed adenomyosis\textsuperscript{23}. The authors suggested that high prolactin concentrations caused myometrial degeneration which lead to myometrial weakness and subsequent myometrial invasion by the endometrial basalis.

1.3 Histopathology of Adenomyosis

As per Bird’s definition, adenomyosis entails presence of ectopic endometrial glands and stroma within the myometrium with surrounding hypertrophy and hyperplasia. When the whole myometrium or one of the myometrial walls is diffusely involved (diffuse adenomyosis), there is a gross appearance of a globularly enlarged uterus in about 60\% of cases, but clinically the uterus rarely exceeds the size of a twelve weeks gestation\textsuperscript{6,11}. Langlois et al systematically studied 461 uteri to determine normal uterine weight and found parity to be an important factor in women less than 49 years of age\textsuperscript{6,11}. He reported upper normal limits of uterine weights as shown in Table 2.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
Parity & Weight \\
\hline
Nulliparous & 130g \\
Parity 1-3 & 210g \\
Parity\geq 4 & 250g \\
\hline
\end{tabular}
\caption{Upper Limits of Normal Uterine Weights}
\end{table}
Ferenczy et al reported that adenomyotic uteri range between 80-200g\(^6\); thus it can be seen they fall within normal limits as per Langlois above. Most investigators report the posterior wall to be more involved than the anterior wall and adenomyosis is almost never found in the lateral walls\(^6,11\).

Sometimes the uterus is focally involved leading to the appearance of a leiomyoma and in such instances it is called adenomyoma or focal adenomyosis. Adenomyomas have no clear cut margins and cannot be enucleated. Myometrial blood vessels traverse through the adenomyoma. On cross-section, there are haphazardly distributed hypertrophied muscle trabeculae surrounding foci of adenomyosis which may contain brown staining old blood that corresponds to hemolysed blood and hemosiderin pigment deposits\(^5,6,11\).

In contrast, leiomyomata compress the surrounding myometrium and have clear-cut well circumscribed margins leading to their easy enucleation. Myometrial blood vessels form a rim around the leiomyoma on doppler studies\(^6,11\).

### 1.3.1 Histopathological Diagnosis of Adenomyosis

Over the years various criteria have been used to histologically diagnose adenomyosis. The criteria differ in the distance from the endo-myometrial junction at which endometrial glands and stroma are found to make a diagnosis of adenomyosis\(^24\). Vercellini et al have noted that lack of consensus criteria has led to difficulties in doing epidemiological studies on adenomyosis.
and recommend using a 2.5mm cut-off as it is used by most histopathologists\textsuperscript{24}.

Mills et al proposed that a histopathological diagnosis of adenomyosis should be made when there is definite smooth muscle hypertrophy around foci of endometrial glands and stroma or when endometrial glands and stroma lie within the outer two-thirds of the uterine wall\textsuperscript{25}. This is the criteria used in the histopathology laboratory for both Groote Schuur and Somerset Hospitals and thus the criteria used for this study. (Personal communication, Prof Wainwright- Head Histopathology Department, University of Cape Town Groote Schuur Hospital)

1.4 Symptomatology of Adenomyosis

There are no symptoms pathognomonic of adenomyosis\textsuperscript{26}. According to Peric and Fraser, 35\% of women with adenomyosis diagnosed after hysterectomy are asymptomatic\textsuperscript{26}. Most studies on symptomatology of adenomyosis have included cases where adenomyosis was associated with other pathologies like leiomyomata. Considering studies with only adenomyosis on histology, Bird et al found heavy menstrual bleeding in 51.2\% of patients with adenomyosis\textsuperscript{26}, while Levgur et al in a study of 111 post hysterectomy uteri found menorrhagia to be present in 38.6\% of deep adenomyosis compared with 12.5\% of intermediate depth (p<0.001). Superficial depth was not associated with any menstrual irregularity\textsuperscript{27}. McCausland et al demonstrated that depth of adenomyosis on endometrial resection biopsy correlated with severity of heavy menstrual bleeding and that after resection or endometrial ablative
procedure, those with superficial adenomyosis tended to have better treatment results with a greater long-term likelihood of normal periods, whilst those with deep adenomyosis tended to continue having heavy periods requiring further intervention like hysterectomy\textsuperscript{28}.

Bird et al found a prevalence of dysmenorrhoea of 28.3% among women with adenomyosis only on histology\textsuperscript{26}. Levgur et al reported dysmenorrhoea in 77.8% of women with deep adenomyosis compared with 13.3% with intermediate depth adenomyosis (p<0.001)\textsuperscript{27}.

1.5 Epidemiological Factors

1.5.1 Prevalence

The reported prevalence of adenomyosis varies widely based on the technique used to obtain the myometrial sample (myometrial biopsy or hysterectomy) and the histologic criteria used for diagnosis. Table 3 shows some of the studies done on prevalence of adenomyosis.
Table 3: *Reported Prevalences of Histologically Confirmed Adenomyosis* \(^a\)

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Year</th>
<th>No of Patients</th>
<th>Prevalence</th>
<th>95% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCausland et al (^28,b)</td>
<td>1992</td>
<td>50</td>
<td>66</td>
<td>51-79</td>
</tr>
<tr>
<td>Vercellini et al (^24)</td>
<td>1995</td>
<td>1334</td>
<td>25</td>
<td>23-27</td>
</tr>
<tr>
<td>Seidman et al (^29)</td>
<td>1996</td>
<td>1252</td>
<td>39</td>
<td>36-42</td>
</tr>
<tr>
<td>Vavilis et al (^30)</td>
<td>1996</td>
<td>394</td>
<td>20</td>
<td>16-23</td>
</tr>
<tr>
<td>Parazzini et al (^31)</td>
<td>1997</td>
<td>707</td>
<td>28</td>
<td>20-38</td>
</tr>
<tr>
<td>Legvur et al (^27)</td>
<td>2000</td>
<td>111</td>
<td>32</td>
<td>24-42</td>
</tr>
<tr>
<td>Bergholt et al (^14)</td>
<td>2001</td>
<td>549</td>
<td>14</td>
<td>11 to17</td>
</tr>
<tr>
<td>Curtis et al (^32)</td>
<td>2002</td>
<td>1850</td>
<td>20</td>
<td>18-22</td>
</tr>
<tr>
<td>Panganamamula et al (^33)</td>
<td>2004</td>
<td>873</td>
<td>47</td>
<td>44-51</td>
</tr>
<tr>
<td>Kepkep et al (^34)</td>
<td>2007</td>
<td>70</td>
<td>37.1</td>
<td>26.8-48.8</td>
</tr>
<tr>
<td>Meredith et al (^35,c)</td>
<td>2009</td>
<td>1895</td>
<td>27.9</td>
<td>25.5-30.3</td>
</tr>
</tbody>
</table>

\(^a\)Hysterectomy was the surgical procedure used to obtain specimen unless otherwise specified

\(^b\)Operative Hysteroscopic myometrial biopsy was performed

\(^c\)Review of literature from 1966-2007

Seidman et al reviewed 1252 pathology reports on hysterectomy specimens from women enrolled in the Maryland Women’s Health Study. The frequency of adenomyosis ranged from 12% to 58% among the different hospitals and from 10% to 88% amongst 25 different pathologists\(^29\). Bird et al demonstrated that when pathologists took three routine sections, the prevalence of adenomyosis was 31% and when the sections increased to six, the prevalence increased to 61%.\(^6\)
1.5.2 Risk Factors for Adenomyosis

Investigators over the years have evaluated several risk factors for adenomyosis. Some of these are outlined below:

1.5.2.1 Parity

Women of high parity have an increased risk of having adenomyosis compared to those of low parity\textsuperscript{30,31,36}. In a study by Vercellini et al, the Odds Ratio of adenomyosis in women with one birth was 1.3 compared to 1.5 in women with one or more births \( [p<0.05] \), and their findings suggested adenomyosis did not seem to be associated with any particular clinical condition other than parity\textsuperscript{36}.

1.5.2.2 Health Habits

Smoking seems to decrease the risk of adenomyosis\textsuperscript{6,31}. Parazzini et al found a reduced risk of adenomyosis in smokers and the risk decreased with the number of cigarettes smoked per day; they found an OR of 0.8 for those that smoked less than 10 cigarettes per day compared with an OR of 0.6 for those that smoked more than 10 cigarettes per day \( [X^{2}_{\text{trend}} = 3.57, p=0.06] \)\textsuperscript{31}. Taran et al positively correlated history of depression with adenomyosis [57.1% vs 24.7%]; this is thought to be due to antidepressants which induce hyperprolactinaemia which then leads to adenomyosis\textsuperscript{37}.
1.5.2.3 Surgical trauma

Procedures like caesarean section, sharp endometrial curettage (D&C or evacuation of products of conception) are thought to predispose to developing adenomyosis because of disruption of the endo-myometrial interface. In a retrospective medical records review in Philadelphia USA, Panganamamula et al reported that adenomyosis was present in 412 out of 873 women [prevalence of 47.1%] and that history of any prior uterine surgery was significantly associated with the risk of developing adenomyosis with an OR 1.37 [95% CI 1.05-1.79].

At odds with the above, are the findings of Bergholt et al; in a retrospective medical chart review they evaluated records of 549 women undergoing hysterectomy in Denmark. The prevalence of adenomyosis was 10–18.2% depending on the various diagnostic criteria used. They found no association between risk of developing adenomyosis and prior caesarean section, endometrial curettage or evacuation of uterus, age, parity, indication for hysterectomy or number of myometrial samples taken for analysis.

1.6 Diagnosis of Adenomyosis

Histopathological confirmation of presence of endometrial glands and stroma within the myometrium forms the reference (gold) standard diagnosis of adenomyosis. Pre-hysterectomy diagnosis of adenomyosis can be made clinically or through biopsy and imaging techniques as outlined below.
1.6.1 A Suspected Clinical Diagnosis

The clinical diagnosis of adenomyosis has been called elusive or enigmatic largely because there are no symptoms pathognomonic of this disease. Reinhold et al. in their review noted that the rate of preoperative diagnosis of adenomyosis based on clinical findings is poor, ranging from 2.6 to 26% \(^{38}\).

1.6.2 Surgical Diagnosis

The gold standard for diagnosis of adenomyosis remains histological examination of post-hysterectomy uteri. Other less invasive surgical diagnoses have been explored\(^ {39}\). Dueholm et al. observed that the use of myometrial needle biopsy for the diagnosis of adenomyosis has a high specificity and may be both simple and safe, but it has a low sensitivity even if used with image directed biopsies and thus could hardly be recommended as a sufficiently accurate tool for the diagnosis of adenomyosis\(^ {40}\).

Hysteroscopic myometrial wall biopsy for the diagnosis of adenomyosis has been explored by several researchers\(^ {41,42}\). Darwish et al. studied 99 women with unexplained abnormal uterine bleeding not responding to hormonal therapy at an Egyptian university hospital. In one group they performed hysteroscopic biopsy using rigid forceps and the resectoscope (n=62); in the second group they performed hysterectomy (n=37). They found that rigid biopsy specimens demonstrated pathology in 19% of cases with an estimated prevalence of adenomyosis of 16% and 48% of samples were rejected as inadequate for evaluation. In the resectoscope group, pathology was demonstrated in 43% of cases with a prevalence of adenomyosis of 29% and
only 6% cases had suboptimal specimens due to thermal effects. In the hysterectomy group pathology was demonstrated in 56.5% of cases with a prevalence of adenomyosis of 24%. The authors concluded that myometrial biopsy using rigid biopsy forceps is inadequate and not recommended.

1.6.3 Imaging Diagnosis

1.6.3.1 Hysterosalpingography (HSG)

Hysterosalpingography was the first imaging modality used for the diagnosis of adenomyosis. The invaginating endometrium creates tracts through which radiopaque material penetrates producing characteristic radiological patterns. Goldberger et al were the first to report the characteristic findings of adenomyosis on HSG. Some of the adenomyosis hysterosalpingographic features reported are multiple spicules extending from the endometrium into myometrium and honeycomb or lollipop-like accumulation of contrast material in the myometrium. Due to its low overall accuracy, hysterosalpingography is no longer used as an imaging modality for the diagnosis of adenomyosis.

1.6.3.2 Pelvic Ultrasonography

The transabdominal and transvaginal approaches to pelvic ultrasonography have both been used for the diagnosis of adenomyosis. However, transvaginal ultrasound has proved superior to the transabdominal route.

Over the years a number of investigators have used TVS for the diagnosis of adenomyosis with histology as the reference standard. Key points learnt from these studies are summarised in Table 4.
Table 4: TVS Diagnosis of Adenomyosis (Key Points from Studies)

- The characteristic gross appearance of adenomyosis arises from the presence of endometrial glands or stroma within the myometrium; the image findings reflect the muscular hypertrophy and heterotopic endometrial tissue.
- TVS sonographic features of adenomyosis are subtle and cannot be inferred from hard copy images but must be diagnosed during the course of real time examination.
- TVS is highly observer dependent.
- When adenomyosis coexists with leiomyoma, doppler sonography may facilitate differentiation between leiomyomas and focal adenomyosis, with vessels forming a well-defined rim around myomas and entering the body of the mass in focal adenomyosis.
- Other features may mimic adenomyosis on TVS such as:
  - i) myometrial contractions (usually transient and disappear after 15 min)
  - ii) vascular calcifications
  - iii) endometrial carcinoma

Different image characteristics diagnostic of adenomyosis on TVS have been determined. Some of these are outlined in Table 5.
Table 5: TVS Features of Adenomyosis \textsuperscript{28,29,38,46,47}

- Myometrial nodules
- Sub-endometrial echogenic linear striations
- Poor definition and nodularity of the endomyometrial junction
- Pseudo-widening of the endometrium
- Anechoic lacunae or myometrial cysts or haemorrhagic foci within myometrium
- Heterogenous and hypoechogenic poorly described areas in the myometrium
- Globular appearing uterus not explained by presence of leiomyomas
- Asymmetry of the anterior and posterior myometrial walls
- Increased echotexture of the myometrium

To improve the overall diagnostic accuracy of TVS, Dueholm et al recommend using three or more criteria for the diagnosis of adenomyosis\textsuperscript{40}.

In their recent systematic review and metaanalysis on diagnostic accuracy of TVS for the diagnosis of adenomyosis, Meredith et al, analysed 14 trials identified from 1966 to 2007, with 1895 aggregate participants. The overall sensitivity was 82.5\% [95\% CI: 77.5-87.9], specificity was 84.6\% [95\% CI: 79.8-89.8], likelihood ratio of positive results of 4.7 [95\% CI: 3.1-7.0], likelihood ratio of negative result of 0.26 [0.18-0.39], diagnostic OR 20.0 [11.1-35.4]. The accuracy of TVS was similar between women symptomatic for adenomyosis and all women undergoing hysterectomy\textsuperscript{35}. 
1.6.3.3 Magnetic Resonance Imaging (MRI)

In premenopausal women, three different zones can be identified within the uterus on T2-weighted sagittal images of magnetic resonance imaging: the normal endometrium and endometrial secretions as a high signal intensity stripe; the stratum subvasculare as a band of low signal intensity (called the junctional zone) and the outer layer of the myometrium which is of intermediate signal intensity.

Changes in the junctional zone on MRI are used for the diagnosis of adenomyosis. Normal JZ thickness is said to be 2-8mm. JZ thickness of ≥12mm is said to be highly predictive of adenomyosis, while JZ thickness ≤8mm usually excludes the diagnosis. If the junctional zone thickness is between 8-12mm, ancillary MRI findings need to be used to make an MRI diagnosis of adenomyosis. 13,22,38,48

MRI is said to be less observer dependent compared with TVS. Several investigators have compared the diagnostic performance of MRI with that of TVS. Dueholm et al did a pooled analysis of some of these studies presented in Table 6. 40
Table 6: Diagnostic Performance of TVS and MRI for the Diagnosis of Adenomyosis in Consecutive Unselected Patients.

<table>
<thead>
<tr>
<th>Sample Size</th>
<th>Reinho lead</th>
<th>Bazot al</th>
<th>Dueholm et al</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (95%CI)</td>
<td>% (95%CI)</td>
<td>% (95%CI)</td>
<td>% (95%CI)</td>
</tr>
<tr>
<td>TVS:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>89 (71-97)</td>
<td>65 (48-79)</td>
<td>68 (44-86)</td>
<td>74 (63-82)</td>
</tr>
<tr>
<td>Specificity</td>
<td>89 (80-94)</td>
<td>98 (90-100)</td>
<td>65 (50-77)</td>
<td>87 (81-91)</td>
</tr>
<tr>
<td>PPV</td>
<td>71 (54-85)</td>
<td>93 (75-99)</td>
<td>42 (25-61)</td>
<td>68 (58-77)</td>
</tr>
<tr>
<td>NPV</td>
<td>96 (89-99)</td>
<td>85 (75-91)</td>
<td>85 (69-94)</td>
<td>89 (84-92)</td>
</tr>
<tr>
<td>MRI:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>86 (66-95)</td>
<td>78 (61-89)</td>
<td>70 (46-87)</td>
<td>78 (68-86)</td>
</tr>
<tr>
<td>Specificity</td>
<td>86 (76-92)</td>
<td>93 (84-97)</td>
<td>86 (76-93)</td>
<td>88 (83-92)</td>
</tr>
<tr>
<td>PPV</td>
<td>65 (47-79)</td>
<td>84 (67-93)</td>
<td>58 (37-77)</td>
<td>70 (60-79)</td>
</tr>
<tr>
<td>NPV</td>
<td>95 (87-98)</td>
<td>89 (80-95)</td>
<td>91 (81-96)</td>
<td>92 (87-95)</td>
</tr>
</tbody>
</table>

As shown in the Table 6, in the study by Dueholm et al, MRI had a higher specificity (86%) than TVS (65%; p=0.03), but there was no difference in sensitivities (70% and 68%, p=0.66). The authors concluded MRI was superior to TVS for the diagnosis of adenomyosis. In contrast, Reinhold et al studied prospectively 119 women and found no statistically significant difference between sensitivities (p=0.65) and specificities (p=0.75) for TVS and MRI. They concluded that TVS was as accurate as MRI in the diagnosis of adenomyosis.
Compared with MRI, TVS is less costly and widely available in most gynaecological units, hence it is recommended as the first line imaging modality for pre-surgical diagnosis of adenomyosis.\textsuperscript{13,38}

1.7 Management of Adenomyosis

Until recently, the definitive treatment of adenomyosis has been hysterectomy. With accurate pre-surgical diagnosis of adenomyosis, women can however be offered treatment alternatives.

Conservative surgical procedures such as laparoscopic myometrial electrocoagulation, laparoscopic adenomyomectomy and hysteroscopic endometrial resection or ablation are advocated in women with adenomyosis who wish to preserve their fertility\textsuperscript{13,28,52}.

Uterine artery embolization for the treatment of adenomyosis has been shown to relieve symptoms in the short term but not effective for long-term relief of adenomyosis related symptoms\textsuperscript{53,54,55,56,57,58,59}. Magnetic Resonance guided focussed ultrasound (MRgFUS) might present an alternative non-invasive approach for focal adenomyosis in selected patients\textsuperscript{53}.

Several hormonal methods have been tried for the treatment of adenomyosis. GnRH agonists are effective at relieving menorrhagia and dysmenorrhoea associated with adenomyosis during the time that they are given. Cessation of therapy leads to relapse of symptoms and long term use results in menopausal side effects\textsuperscript{60}. Danazol used as an intrauterine device is effective
in treating adenomyosis related symptoms with few androgenic side effects \cite{61,62,63}. Levornorgestrel intrauterine system (mirena) releasing 20mcg/day levonorgestrel causes marked and safe relief from adenomyosis associated menorrhagia \cite{53,64,65}.

1.8 Trans-vaginal Ultrasound Diagnosis of Adenomyosis in South Africa

There are very little data on adenomyosis in Sub-Saharan Africa, and South Africa in particular. In her thesis (Source: University of Cape Town Libraries), Jennifer Butt did an audit of hysterectomies performed in 2007 at Groote Schuur Hospital in South Africa. The findings demonstrated that out of a total of 334 hysterectomies performed 20 had adenomyosis (prevalence 6\%) \cite{66}; it is not stated whether these women had adenomyosis only or adenomyosis plus other pathologies and the criteria used for the histological diagnosis of adenomyosis was not stated. We could not identify any published studies on pre-surgical diagnosis of adenomyosis in South Africa.
Chapter 2

Aims and Objectives

2.1 Aim

This study sought to evaluate TVS diagnosis of adenomyosis with histologic correlation in a local study population.

2.2 Primary outcome:

Diagnostic performance of TVS for the diagnosis of adenomyosis compared to post-surgical histology.

2.3 Secondary Outcomes:

- Signs and symptoms of patients with histologically confirmed adenomyosis.

- Histological prevalence of adenomyosis in all patients undergoing hysterectomy for any indication over the study period.
Chapter 3

Methods and Materials

3.1 Study Design

This was a cross-sectional diagnostic study.

3.2 Setting

The study was conducted at Groote Schuur Hospital and New Somerset Hospital, Departments of Obstetrics and Gynaecology, University of Cape Town, South Africa. Groote Schuur Hospital is a large government-funded teaching hospital situated on the slopes of Devil's Peak in the city of Cape Town, Western Province. It was founded in 1938 and it is the main academic hospital for the University of Cape Town. For gynaecological services, women in the Western Province have two options: those with health insurance access gynaecologists in private hospitals while those without health insurance or who want to access public academic health services, utilise the state run institutions of which Groote Schuur is one of the main tertiary referral hospitals in the Western Province. Groote Schuur Hospital also receives referrals from other provinces in South Africa especially the Eastern Cape. Groote Schuur has a busy obstetrics and gynaecology ultrasound department offering level one to three services. New Somerset Hospital is a level two hospital that mainly does benign gynaecological surgery and the ultrasound service is mainly level one to level two. At both hospitals, adenomyosis is not consistently diagnosed or reported. The population of the Western Cape is multi-ethnic.
### 3.3 Sample size estimation

Using Open Epi statistical package, sample size estimation was as follows:

**Assumptions based on literature:**

- Prevalence of histologically proven adenomyosis
  
  *Assume 8%*  
  
  5-70%  
  
  6,7,24

- Sensitivity of Trans-vaginal ultrasound diagnosis of adenomyosis
  
  *Assume 85%*  
  
  57 – 97.5%  
  
  14,35

- Specificity of Trans-vaginal ultrasound diagnosis of adenomyosis
  
  *Assume 75%*  
  
  65-98%  
  
  14,35

Based on these assumptions, sample size was estimated using OpenEpi statistical calculator as shown in Table 7.
Table 7: Sample Size Estimation

Results from OpenEpi, Version 2, open source calculator\textsuperscript{67}

<table>
<thead>
<tr>
<th></th>
<th>Kelsey</th>
<th>Fleiss</th>
<th>Fleiss with CC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Size – With Histological Adenomyosis</td>
<td>5</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Sample Size- With no Adenomyosis on histology</td>
<td>58</td>
<td>51</td>
<td>70</td>
</tr>
<tr>
<td>Total sample size:</td>
<td>63</td>
<td>56</td>
<td>77</td>
</tr>
</tbody>
</table>

\textit{CC = continuity correction}

\textit{Results are rounded up to the nearest integer.}

Thus from Table 7, using Fleiss estimate with continuity correction, 77 participants \textit{(7 with histologically proven adenomyosis and 70 without adenomyosis)} were needed to have 80% power to detect adenomyosis using trans-vaginal ultrasound with sensitivity of 85% and specificity of 75%. The
prevalence of 8% was assumed from unpublished data from an MMed thesis on audit of hysterectomies at Groote Schuur Hospital\textsuperscript{66}.

### 3.4 Eligibility

Eligible study participants were women who had agreed to undergo a hysterectomy, for any indication.

#### 3.4.1 Inclusion Criteria

Women willing to participate in the study were approached for recruitment. The participants had to speak one of the major languages in the Western Province (English, Afrikaans or Xhosa).

#### 3.4.2 Exclusion Criteria

Women with any of the following, were excluded from the study

- Virgo Intacta
- Planned total laparoscopic hysterectomy with morcellation of the uterus
- Extensive vulvo-vaginal disease/malignancies precluding trans-vaginal sonography

### 3.5 Ethics

The procedures used in this study were in accordance with the guidelines of the Helsinki Declaration on Human Experimentation 2008 \textsuperscript{68}. The study was approved by the Human Ethics Research Committee of the University of Cape
Town. A modified World Health Organisation (WHO) informed consent form for clinical studies (modified for this study) was used to obtain informed consent from prospective study participants (appendix A).

3.6 Data Collection

Data were collected over a period of eleven months, from May 2011 to April 2012. The study was divided into two study groups (A and B). **Study group A** comprised all women who, before their hysterectomy, underwent interviewer-administered questionnaire (n=71) and TVS examination (n=78).

To determine the histological prevalence of adenomyosis, **Study group B** comprised all women who underwent hysterectomy at Groote Schuur Hospital in the study period (n=261). Figure 1 is a flow diagram for the study.
Figure 1: Study Flow Diagram

Study Group A
Patient Questionnaire, TVS

102 women approached to participate

2 declined

100 patients consented

22 patients excluded from analysis
- No uss done due to logistical reasons (n=11)
- Type of surgery changed (n=5)
- No surgery done (n=6)

78 included for analysis on TVS diagnosis of adenomyosis

7 patients had TVS but clinical data missing

71 patients included for analysis on clinical data

Study Group B
Surgery and Histology
(Groote Schuur Hospital)

261 women had Hysterectomies done at Groote Schuur Hospital including 62 women from group A

Histopathology data obtained on all (261) cases
3.6.1 Patient Questionnaire (Study Group A)

After obtaining signed informed consent, the study participants were interviewed regarding their symptoms using an interviewer administered questionnaire (appendix B). The interview was conducted in the ward at the time of pre-surgery admission.

The principal investigator collected all the data at the beginning of the study. Due to logistical problems, it was difficult to do consecutive sampling, hence patients were recruited depending on the availability of the investigator or a dedicated research nurse who assisted with recruitment and data collection in the latter half of the study.

3.6.2 Trans-vaginal Ultrasonography (Study Group A)

All participants in study group A underwent a TVS examination. Experienced ultrasonographers conducted the examinations using appropriate ultrasound machines (ALOKA alpha 10, ALOKA 3500SX and Toshiba Nemio XG) with a variable focus 7.5MHZ endovaginal transducer. The ultrasonographers who participated in this study were experienced at routine gynaecological ultrasounds but not TVS diagnosis of adenomyosis. Prior to this study, adenomyosis was not consistently looked for, nor reported on these routine scans. There was no training provided to the ultrasonographers on TVS diagnosis of adenomyosis prior to commencement of the study, but theoretical knowledge of the features and criteria used was provided. The ultrasonographers were blinded to findings from the interviewer-administered
questionnaire. Adenomyosis was diagnosed if three or more TVS adenomyosis features were detected. The ultrasound features were ticked by the ultrasonographer as being present or absent on a pre-specified check list (appendix C). All images were electronically stored.

3.6.3 Histological examination

Uterine specimens were sent for histological examination. A color coded sticker was attached to the histology request form to indicate to the pathologists the inclusion of the participant in the study for detailed histological examination specifically looking for adenomyosis. The pathologists were blinded to the TVS findings. A diagnosis of adenomyosis was made when there was definite smooth muscle hypertrophy around foci of endometrial glands and stroma or when endometrial glands and stroma lied within the outer two-thirds of the uterine wall.

3.7 Statistical Analysis

Data were entered into excel database and analysis was done using STATA version 12. Comparison between groups was done using two-sided Fisher’s exact test with two sided p-value of less than 0.05 being considered significant. 2 × 2 contingency tables of TVS diagnosis of adenomyosis results were generated using the histological diagnosis as the reference (Gold) standard as depicted in Table 8. The sensitivities, specificities, positive predictive values (PPV), negative predictive values (NPV), likelihood ratios (LR) and accuracies, with their respective 95% confidence intervals were calculated.
### Table 8: Sample 2 x 2 Contingency Table for the TVS Diagnosis of Adenomyosis

<table>
<thead>
<tr>
<th></th>
<th>Adenomyosis</th>
<th>No Adenomyosis</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive</strong></td>
<td>a</td>
<td>b</td>
<td>a+b</td>
</tr>
<tr>
<td><strong>TVS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Negative</strong></td>
<td>c</td>
<td>d</td>
<td>c+d</td>
</tr>
<tr>
<td><strong>False-negative</strong></td>
<td>False-negative</td>
<td>True-negative</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>a + c</td>
<td>b + d</td>
<td></td>
</tr>
</tbody>
</table>

**Sensitivity** = \( \frac{a}{a+c} \)

**Specificity** = \( \frac{d}{b+d} \)

**Positive Predictive Value (PPV)** = \( \frac{a}{a+b} \)

**Negative Predictive Value (NPV)** = \( \frac{d}{c+d} \)

**Positive Likelihood Ratio** = \( \frac{\text{sensitivity}}{1-\text{specificity}} \)

**Negative Likelihood Ratio** = \( \frac{\text{false negative rate}}{\text{true negative rate}} \)

**Diagnostic Odds Ratio** = \( \frac{\text{positive likelihood ratio}}{\text{negative likelihood ratio}} \)
The above measures of test performance are commonly used in literature on diagnostic studies but are dependent on the prevalence of the condition being tested\textsuperscript{69,70,71}. In order to determine a single indicator of test performance that is not prevalence dependent\textsuperscript{69,70}, diagnostic odds ratios (LR+/LR-) with their 95% confidence intervals were calculated for each TVS feature and for TVS diagnosis overall. Explanation of the tests used (with reference to this study) is summarized in Table 9.
Table 9: *Explanation of Statistical Tests Used in this Study*

- **Sensitivity**: the probability that TVS would produce a true positive result in patients with histologically confirmed adenomyosis.
- **Specificity**: the probability that TVS would produce a true negative result in patients without adenomyosis (histologically confirmed).
- **Positive predictive value**: the probability that a woman would have adenomyosis if positive TVS features were observed.
- **Negative predictive value**: the probability that a woman would not have adenomyosis if she had negative TVS diagnosis of adenomyosis.
- **Positive likelihood ratio (LR+)**: the odds ratio that a positive test result (TVS) would be observed amongst women with adenomyosis compared to the odds that the same result would be observed among women without adenomyosis. *The larger the LR+, the more useful a test is.*
- **Negative likelihood ratio (LR-)**: the odds ratio that a negative test (TVS) result would be observed in women with adenomyosis compared to the odds that the same test result would be observed among women without adenomyosis. *Useful tests have LR- close to zero and less useful tests have higher LR-.*
- **The diagnostic odds ratio (DOR)**: the ratio of odds of disease (adenomyosis) in test (TVS) positive relative to the odds of disease (adenomyosis) in test (TVS) negative. *The value of a DOR ranges from 0 to infinity, with higher values indicating better discriminatory test performance.* A value of 1 means that a test does not discriminate between patients with the disorder and those without it. *Values lower than 1 point to improper test interpretation (more negative tests among the diseased)*\(^{69}\).
Chapter 4
Results

Study Group A

There were 78 participants in this study group. Of these, 16 women had histologically proven adenomyosis. Clinical data were available on 71 women (missing data n= 7). The mean age in women with adenomyosis was 49.4yrs (SD 12.4) and in those without adenomyosis 49.9yrs (SD10.3). Ethnicity and obstetric characteristics were comparable (Table 10).

Table 10: Socio-Demographic and Obstetric Characteristics of Study Participants (n=71)

<table>
<thead>
<tr>
<th></th>
<th>Adenomyosis n=16*</th>
<th>No Adenomyosis n=55*</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colored</td>
<td>9(56.2)</td>
<td>33(60)</td>
<td>1</td>
</tr>
<tr>
<td>White</td>
<td>1(6.2)</td>
<td>4 (7.3)</td>
<td>1</td>
</tr>
<tr>
<td>Black</td>
<td>2(12.5)</td>
<td>18(32.7)</td>
<td>0.34</td>
</tr>
<tr>
<td>Asian</td>
<td>1(6.2)</td>
<td>0</td>
<td>0.23</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Obstetric history</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>2(12.5)</td>
<td>1 (1.8)</td>
<td>0.14</td>
</tr>
<tr>
<td>Parous</td>
<td>11(68.8)</td>
<td>54(98.2)</td>
<td>0.52</td>
</tr>
<tr>
<td>Previous Caesarean Section</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miscarriages</td>
<td>6(37.5)</td>
<td>7(12.5)</td>
<td>0.09</td>
</tr>
<tr>
<td>Ectopic</td>
<td>0</td>
<td>2(3.6)</td>
<td>1</td>
</tr>
<tr>
<td>TOP</td>
<td>0</td>
<td>1(1.8)</td>
<td>1</td>
</tr>
</tbody>
</table>

* figures in brackets are percentages

*TOP: Termination of pregnancy
CLINICAL FINDINGS

The clinical presentation of patients with and without adenomyosis are summarised in Table 11. Uterine tenderness was reported more commonly in women with adenomyosis (31.2%) compared to women without adenomyosis (5.4%; p<0.05). No significant differences were observed in the other clinical parameters. Most of the clinical examinations were done within one week of surgery.

Adenomyosis was suspected based on history and physical examination findings in two of sixteen patients (12.5%, 95% CI: 3.5 – 36) with histologically confirmed adenomyosis.

Table 11: Clinical Findings in Study Participants (n=71; missing data n=7)

<table>
<thead>
<tr>
<th></th>
<th>Adenomyosis n=16</th>
<th>No Adenomyosis n=55</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heavy Menstrual Bleeding</td>
<td>10 (62.5%)</td>
<td>28 (50.9%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Dysmenorrhoea</td>
<td>8 (50%)</td>
<td>25 (45.4%)</td>
<td>0.78</td>
</tr>
<tr>
<td>VAS score of period pain</td>
<td>6.3 (0-10)</td>
<td>6.8 (0-10)</td>
<td></td>
</tr>
<tr>
<td>Uterine Size (less than 12 wks)</td>
<td>10 (62.5%)</td>
<td>26 (47.2%)</td>
<td>0.40</td>
</tr>
<tr>
<td>Uterine Tenderness</td>
<td>5 (31.2%)</td>
<td>3 (5.4%)</td>
<td>&lt;0.01*</td>
</tr>
</tbody>
</table>

VAS: Visual analogue Scale

* statistically significant
INDICATIONS FOR HYSTERECTOMY

Abnormal uterine bleeding (AUB) was an indication for hysterectomy in 56.2% of patients with adenomyosis compared to 21.8% of patients without adenomyosis (p<0.05). The rest of the indications for hysterectomy are shown in Table 12.

Table 12: Indications for Hysterectomy (n=71; missing data n=7)

<table>
<thead>
<tr>
<th></th>
<th>Adenomyosis (n=16)</th>
<th>No Adenomyosis (n=55)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUB</td>
<td>9 (56.2%)</td>
<td>12 (21.8%)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Fibroids</td>
<td>4 (25%)</td>
<td>18 (32.7%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Pelvic Organ Prolapse</td>
<td>1 (6.2%)</td>
<td>13 (23.6%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Suspected Malignancy</td>
<td>2 (12.5%)</td>
<td>12 (21.8%)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*statistically significant
SONOGRAPHIC FINDINGS

All women in group A underwent TVS before hysterectomy. As outlined in the methodology, TVS diagnosis of adenomyosis required three or more diagnostic features of adenomyosis to be present. Of 62 patients with no adenomyosis on histology, there were 8 false positive TVS diagnoses. Of the 16 patients with histological adenomyosis, there were 8 false negative TVS diagnoses (Table 13).

Table 13: Comparison of TVS Diagnosis of Adenomyosis with Histopathology Results (n=78)

<table>
<thead>
<tr>
<th>Histopathological Adenomyosis(n)</th>
<th>TVS Adenomyosis (≥3 Features)</th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>8</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>8</td>
<td>50</td>
<td>58</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>16</td>
<td>62</td>
<td>78</td>
</tr>
</tbody>
</table>
The sensitivity, specificity, predictive values, accuracy and likelihood ratios of TVS in the diagnosis of adenomyosis are outlined in Table 14. Overall TVS had a high specificity (80.6%, 95% CI: 69.2-88.6), low sensitivity (50%, 95% CI: 28-72) and a good DOR (4.2, 95% CI: 1.3-13.4) for the diagnosis of adenomyosis.

**Table 14:** Diagnostic Performance of TVS for the Diagnosis of Adenomyosis (n=78).

<table>
<thead>
<tr>
<th>Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>50</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>80.6</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>40</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>86.2</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>74.4</td>
</tr>
<tr>
<td>LR+</td>
<td>2.58</td>
</tr>
<tr>
<td>LR-</td>
<td>0.62</td>
</tr>
<tr>
<td>DOR</td>
<td>4.2</td>
</tr>
</tbody>
</table>

PPV: positive predictive value  
NPV: negative predictive value  
LR+: likelihood ratio of a positive result  
LR-: likelihood ratio of a negative result  
DOR: diagnostic odds ratio
When single TVS features of adenomyosis were compared with histopathological results, only heterogenous myometrial echotexture was found to have statistical significance (Fisher’s Exact test p<0.05; Table 15).

**Table 15: Comparison of Single TVS features with Histopathology (n=78)**

<table>
<thead>
<tr>
<th>Histopathological Adenomyosis (n(%))</th>
<th>Yes</th>
<th>No</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=16)</td>
<td>(n=62)</td>
<td></td>
</tr>
<tr>
<td><strong>Globular Configuration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5(31.2%)</td>
<td>15(24.2%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>11(68.8%)</td>
<td>47(75.8%)</td>
<td>0.54</td>
</tr>
<tr>
<td><strong>Identification of Endomyometrial junction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8(50%)</td>
<td>15(24.2%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>8(50%)</td>
<td>47(75.8%)</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Subendometrial Echogenic Linear striations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1(6.2%)</td>
<td>2(3.2%)</td>
<td>0.5</td>
</tr>
<tr>
<td>No</td>
<td>15(93.8%)</td>
<td>60(96.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>Myometrial anteroposterior asymmetry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7(43.8%)</td>
<td>15(24.2%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>9(56.2%)</td>
<td>47(75.8%)</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>Myometrial Cysts</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2(12.5%)</td>
<td>4(6.5%)</td>
<td>0.6</td>
</tr>
<tr>
<td>No</td>
<td>14(87.5%)</td>
<td>58(93.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Heterogenous Myometrium</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11(68.8%)</td>
<td>23(37.1%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5(31.2%)</td>
<td>39(62.9%)</td>
<td>0.04*</td>
</tr>
</tbody>
</table>

*Statistically significant
The diagnostic performance of individual TVS features is shown in Table 16. Heterogenous myometrial echotexture had the highest sensitivity 68.8% [95% CI: 44.4-85.8], diagnostic odds ratio 3.7 [95% CI: 1.2-12.1] and NPV 88.6 [95% CI: 76 – 95.1] but a low specificity 62.9% [95% CI: 50.5-73.8]. The presence of subendometrial echogenic linear striations and myometrial cysts had the highest specificities 96.8% [95% CI : 89-99], 93.5% [95% CI: 84.6 - 97.5] and accuracies 78.2% [95% CI: 67.8-85.9], 76.9 [95% CI: 66.4 – 84.8] for the diagnosis of adenomyosis respectively.
Table 16: Diagnostic Performance of Individual TVS Features for the Diagnosis of Adenomyosis

\[ N = \text{Value} \]
\[ n \text{ to } n = 95\% \text{ Confidence Interval} \]

<table>
<thead>
<tr>
<th>Feature</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Accuracy (%)</th>
<th>LR+</th>
<th>LR-</th>
<th>DOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterogenous Myometrial Echotexture</td>
<td>68.8</td>
<td>62.9</td>
<td>32.4</td>
<td>88.6</td>
<td>64.1</td>
<td>1.8</td>
<td>0.5</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td>44.4 to 85.8</td>
<td>50.5 to 73.8</td>
<td>19.1 to 49.2</td>
<td>76 to 95.1</td>
<td>53 to 73.8</td>
<td>1.2 to 2.9</td>
<td>0.2 to 1.1</td>
<td>1.2 to 12.1</td>
</tr>
<tr>
<td>Poor definition of endomyometrial jxn</td>
<td>50</td>
<td>75.8</td>
<td>34.8</td>
<td>85.4</td>
<td>70.5</td>
<td>2.1</td>
<td>0.7</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td>28 to 72</td>
<td>63.8 to 84.8</td>
<td>18.8 to 55.1</td>
<td>73.8 to 93.4</td>
<td>59.6 to 79.5</td>
<td>1.1 to 4</td>
<td>0.4 to 1.1</td>
<td>1.1 to 9.8</td>
</tr>
<tr>
<td>Myometrial A-P asymmetry</td>
<td>43.8</td>
<td>75.8</td>
<td>31.8</td>
<td>83.9</td>
<td>69.2</td>
<td>1.8</td>
<td>0.7</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>23.1 to 66.8</td>
<td>63.8 to 84.8</td>
<td>16.4 to 52.7</td>
<td>72.2 to 91.3</td>
<td>58.3 to 78.4</td>
<td>0.9 to 1.8</td>
<td>0.5 to 1.2</td>
<td>0.8 to 7.7</td>
</tr>
<tr>
<td>Myometrial cysts</td>
<td>12.5</td>
<td>93.5</td>
<td>33.3</td>
<td>80.6</td>
<td>76.9</td>
<td>1.9</td>
<td>0.9</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>3.5 to 36</td>
<td>84.6 to 97.5</td>
<td>9.7 to 70</td>
<td>70 to 88.1</td>
<td>66.4 to 84.8</td>
<td>0.4 to 9.7</td>
<td>0.8 to 1.1</td>
<td>0.3 to 12.5</td>
</tr>
<tr>
<td>Subendometrial echogenic linear striations</td>
<td>6.25</td>
<td>96.8</td>
<td>33.3</td>
<td>80</td>
<td>78.2</td>
<td>1.9</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>1.1 to 28.3</td>
<td>89 to 99</td>
<td>6.2 to 79.2</td>
<td>69.6 to 87.5</td>
<td>67.8 to 85.9</td>
<td>0.2 to 20</td>
<td>0.8 to 1.1</td>
<td>0.17 to 23.6</td>
</tr>
<tr>
<td>Globular Configuration</td>
<td>31.2</td>
<td>75.8</td>
<td>25</td>
<td>81</td>
<td>66.7</td>
<td>1.3</td>
<td>0.9</td>
<td>1.43</td>
</tr>
<tr>
<td></td>
<td>14.2 to 55.6</td>
<td>63.8 to 84.8</td>
<td>11.2 to 46.8</td>
<td>69.2 to 89.1</td>
<td>55.6 to 76.1</td>
<td>0.5 to 3</td>
<td>0.6 to 1.3</td>
<td>0.43 to 4.8</td>
</tr>
</tbody>
</table>
The effect of ultrasonographer on the diagnostic performance of TVS is presented in Table 17. Ultrasonographer A and D had almost the same number of scans, but ultrasonographer A had the highest sensitivity (75%, 95% CI: 28-95), and Specificity (90%, 95% CI: 59-98). Ultrasonographer D missed the diagnosis in all patients with histologically confirmed adenomyosis.

**Table 17: Diagnostic Performance of TVS Depending on Ultrasonographer**

<table>
<thead>
<tr>
<th>Ultrasonographer</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Accuracy (%)</th>
<th>LR+</th>
<th>LR-</th>
<th>DOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>75</td>
<td>90</td>
<td>75</td>
<td>90</td>
<td>85.7</td>
<td>7.5</td>
<td>0.3</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>28 to 95</td>
<td>59 to 98</td>
<td>28 to 95</td>
<td>59 to 98</td>
<td>59 to 96</td>
<td>1.1 to 52</td>
<td>0.05 to 1.5</td>
<td>1.26 to 578</td>
</tr>
<tr>
<td>B</td>
<td>57.1</td>
<td>72.5</td>
<td>26.7</td>
<td>90.6</td>
<td>70.2</td>
<td>2.1</td>
<td>0.6</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>24.5 to 84.3</td>
<td>57.1 to 83.8</td>
<td>11 to 52</td>
<td>75.7 to 96.6</td>
<td>56 to 81</td>
<td>0.9 to 4.7</td>
<td>0.2 to 1.4</td>
<td>0.7 to 18</td>
</tr>
<tr>
<td>C*</td>
<td>1 scan</td>
<td>scanned one patient with adenomyosis only and correctly diagnosed her</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>0</td>
<td>96</td>
<td>0</td>
<td>75</td>
<td>75</td>
<td>2.8</td>
<td>0.9</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>71 to 99</td>
<td>0</td>
<td>50 to 90</td>
<td>50 to 90</td>
<td>0.06 to 120</td>
<td>0.7 to 1</td>
<td>0.5 to 177</td>
</tr>
</tbody>
</table>

Note: N=Value, n to n=95% Confidence Interval
Study Group B

HISTOPATHOLOGICAL FINDINGS

Two hundred and sixty one women underwent hysterectomy during the study period. Histopathological data were obtained for all 261 participants. The histological prevalence of adenomyosis was 20.3% [95% CI: 15.9 -25.6]. The prevalence of adenomyosis only on histology was 5.0% [95% CI: 2.95 -8.3]. Overall, leiomyomas were the most frequent histological finding, (63.2%, 95% CI: 57.2-68.8, Table 18).
Table 18: Histopathological Findings in Women who Underwent Hysterectomy at Groote Schuur Hospital (n=261)

<table>
<thead>
<tr>
<th>PATHOLOGY</th>
<th>NUMBER</th>
<th>PERCENTAGE OF ALL HYSTERECTOMIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenomyosis only</td>
<td>13</td>
<td>5%</td>
</tr>
<tr>
<td>Adenomyosis + endometrial polyps</td>
<td>3</td>
<td>1.10%</td>
</tr>
<tr>
<td>Adenomyosis + Leiomyoma</td>
<td>24</td>
<td>9.20%</td>
</tr>
<tr>
<td>Adenomyosis + Leiomyoma + Polyps</td>
<td>2</td>
<td>0.80%</td>
</tr>
<tr>
<td>Adenomyosis + Endometrioid Endometrial Cancer + Leiomyoma</td>
<td>2</td>
<td>0.80%</td>
</tr>
<tr>
<td>Adenomyosis + Endometrioid Endometrial Cancer</td>
<td>5</td>
<td>1.90%</td>
</tr>
<tr>
<td>Adenomyosis + Chronic Endometritis</td>
<td>1</td>
<td>0.40%</td>
</tr>
<tr>
<td>Adenomyosis + Leiomyoma + Carcinosarcoma</td>
<td>1</td>
<td>0.40%</td>
</tr>
<tr>
<td>Adenomyosis + Endometriosis</td>
<td>1</td>
<td>0.40%</td>
</tr>
<tr>
<td>Adenomyosis + UPSC</td>
<td>1</td>
<td>0.40%</td>
</tr>
<tr>
<td>Leiomyomas only</td>
<td>124</td>
<td>47.50%</td>
</tr>
<tr>
<td>Leiomyoma + Endometrial Cancer</td>
<td>5</td>
<td>1.90%</td>
</tr>
<tr>
<td>Leiomyoma + Chronic Endometritis</td>
<td>2</td>
<td>0.80%</td>
</tr>
<tr>
<td>Leiomyoma + Carcinosarcoma</td>
<td>1</td>
<td>0.40%</td>
</tr>
<tr>
<td>Leiomyoma + Adenosarcoma</td>
<td>1</td>
<td>0.40%</td>
</tr>
<tr>
<td>Leiomyoma + endometrial Polyps</td>
<td>3</td>
<td>1.10%</td>
</tr>
<tr>
<td>No Pathology</td>
<td>55</td>
<td>21.10%</td>
</tr>
<tr>
<td>Endometrioid Endometrial Cancer</td>
<td>2</td>
<td>0.80%</td>
</tr>
<tr>
<td>Chronic Endometritis</td>
<td>1</td>
<td>0.40%</td>
</tr>
<tr>
<td>Carcinosarcoma</td>
<td>3</td>
<td>1.10%</td>
</tr>
<tr>
<td>Endometrial Stromal Sarcoma</td>
<td>2</td>
<td>0.80%</td>
</tr>
<tr>
<td>Monckerberg’s medial calcific sclerosis</td>
<td>2</td>
<td>0.80%</td>
</tr>
<tr>
<td>Endometrial Polyps</td>
<td>1</td>
<td>0.40%</td>
</tr>
<tr>
<td>Cancer of Cervix</td>
<td>4</td>
<td>1.50%</td>
</tr>
<tr>
<td>Uterine Papillary Serous Carcinoma</td>
<td>1</td>
<td>0.40%</td>
</tr>
<tr>
<td>Smooth muscle tumor of unknown malignancy potential</td>
<td>1</td>
<td>0.40%</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>261</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>
Chapter 5

Discussion and Conclusion

Adenomyosis is defined as the presence of endometrial glands and stroma within the myometrium with surrounding hypertrophy and hyperplasia\(^1\). To the best of our knowledge, this is the first study in South Africa to prospectively investigate the performance of TVS for the diagnosis of adenomyosis.

In this study the histological prevalence of adenomyosis was 20.3%. Clinically, two out of three women with adenomyosis presented with dysmenorrhoea and a uterus less than twelve weeks. Half of the women with adenomyosis complained of menorrhagia. Although it was the only statistically significant clinical finding, the presence of a tender uterus was found in only a third of women with adenomyosis.

Classically the triad of uterine enlargement, dysmenorrhoea and menorrhagia suggests adenomyosis \(^73\). Our data show that menorrhagia, dysmenorrhoea, uterine tenderness and a uterine size less than twelve weeks commonly indicates adenomyosis. Our results are in keeping with other studies. Bird et al found 51.2% of patients with adenomyosis complained of menorrhagia\(^26\). Levgur et al reported dysmenorrhea in 77.8% of patients with adenomyosis\(^27\). In his review on adenomyosis, Matalliotakis et al noted that the adenomyotic uterus has been described as globular or boggy but rarely exceeding 12 weeks gestation in size\(^11\). Uterine tenderness was present in 54.5% of women with histologically confirmed adenomyosis in a study by Hunter et al\(^73\).
While the presence of signs and symptoms was suggestive of adenomyosis in at least 50% of women with adenomyosis in this study, clinicians made a pre-operative diagnosis of adenomyosis in only 12.5% women with histologically confirmed adenomyosis. This may indicate a reluctance to make a clinical diagnosis due to knowledge that signs and symptoms may be unreliable. Alternatively it may mean that clinicians pay insufficient attention to history and examination. Similar to our findings, Reinhold et al reported a low rate of preoperative clinical diagnosis of adenomyosis between 2.6 to 26%\textsuperscript{38}. The poor performance of clinical diagnosis of adenomyosis, highlights the need for additional pre-operative diagnostic methods.

TVS examination has been recommended as the first line diagnostic test for adenomyosis because it is cost-effective and readily available in most gynaecology units\textsuperscript{40}. Our study used an unselected patient population and TVS had a low sensitivity (50%), high specificity (80.6%), accuracy (74.4%) and a DOR of 4.2 for the diagnosis of adenomyosis. In a related study, Bazot et al reported a sensitivity and specificity of 80.9% and 100% respectively in selected patients who had menometrorrhagia but no evidence of uterine disease. In contrast in unselected patients the sensitivity and specificity were 38.4% and 97.5% respectively\textsuperscript{44}. Table 19 compares the sensitivity, specificity, PPV and NPV of our study with other studies.
Table 19: Sensitivity, Specificity, PPV and NPV of TVS for the Diagnosis of Adenomyosis from Previous Studies Compared with Index Study

<table>
<thead>
<tr>
<th>STUDY</th>
<th>N</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vercellini et al.</td>
<td>102</td>
<td>82.7</td>
<td>67</td>
<td>50</td>
<td>90.7</td>
</tr>
<tr>
<td>Bazot et al.</td>
<td>120</td>
<td>65</td>
<td>97.5</td>
<td>92.8</td>
<td>88.8</td>
</tr>
<tr>
<td>Ascher et al.</td>
<td>17</td>
<td>52.9</td>
<td>66.6</td>
<td>90</td>
<td>20</td>
</tr>
<tr>
<td>Fedele et al.</td>
<td>43</td>
<td>80</td>
<td>74</td>
<td>73</td>
<td>81</td>
</tr>
<tr>
<td>Reinhold et al.</td>
<td>100</td>
<td>86</td>
<td>86</td>
<td>71</td>
<td>94</td>
</tr>
<tr>
<td>Brosens et al.</td>
<td>34</td>
<td>86.6</td>
<td>57.9</td>
<td>61.9</td>
<td>84.6</td>
</tr>
<tr>
<td>Kepkep et al.</td>
<td>70</td>
<td>80.8</td>
<td>61.4</td>
<td>55.3</td>
<td>84.4</td>
</tr>
<tr>
<td>THIS STUDY</td>
<td>78</td>
<td>50</td>
<td>80.6</td>
<td>40</td>
<td>86.2</td>
</tr>
</tbody>
</table>

The sensitivity (50%) in our series was better than that reported by Bazot et al (38.4%) in their unselected study population but lower than the studies outlined in Table 19. In contrast, the specificity and NPV compared favourably with that reported in other studies.

There are a number of reasons why the sensitivity and PPV in our study was low. Our ultrasonographers lacked experience in TVS diagnosis of adenomyosis as they were using TVS features for the diagnosis of adenomyosis for the first time. Inclusion of patients with other diagnoses like enlarged uteri with leiomyomas might have decreased diagnostic performance of TVS. Lack of diligence with which the pathologists examined the histopathology specimens could have resulted in a pathologist missing a correctly TVS diagnosed case of adenomyosis.
On the other hand this study had a high specificity and NPV, probably because we used appropriate TVS features and criteria for the diagnosis of adenomyosis.

The variable diagnostic performance of TVS for the diagnosis of adenomyosis reported in the literature could be explained by differences in the main TVS adenomyosis diagnostic criteria selected. In several studies, the main criteria used for diagnosing adenomyosis was heterogenous myometrial echotexture\textsuperscript{34}. It is thought that this represents myometrial smooth muscle hyperplasia and hypertrophy reaction due to presence of ectopic endometrial glands within the myometrium \textsuperscript{75,77}. In the index study, presence of heterogenous myometrial echotexture had the highest sensitivity but a low specificity, while subendometrial echogenic linear striations had the highest specificity for the diagnosis of adenomyosis. Our results are closely in keeping with a previous study by Kepkep et al\textsuperscript{34}. The authors prospectively studied TVS diagnosis of adenomyosis in 70 consecutive patients scheduled for hysterectomy. The authors concluded that heterogenous myometrium had the highest sensitivity (80.8%) but it had a poor specificity (61.4%) while the presence of subendometrial echogenic linear striations was the most specific sonographic feature (95.5%) for the diagnosis of adenomyosis \textsuperscript{34}.

The DOR value of a diagnostic test is used to determine whether the test has value in discriminating the diseased from un-diseased. A test is said to be of value if DOR>1.0\textsuperscript{69}. However for practical purposes, sensitivity and specificity have more meaningful clinical value although they are prevalence dependent.
In the index study, a DOR of 4.2 implies that TVS is of value in the diagnosis of adenomyosis. The high specificity and low sensitivity imply that if a clinician suspects adenomyosis, TVS has more value in refuting the diagnosis than confirming it. In this context if a clinician would like to offer women with suspected adenomyosis alternative treatment to hysterectomy, MRI could be considered as an ancillary imaging test. Findings from a study by Dueholm et al, support this recommendation\textsuperscript{50}. The investigators studied 106 consecutive premenopausal women who underwent hysterectomy for benign reasons. MRI and TVS were compared for the diagnosis of adenomyosis. The sensitivities were 70\% [95% CI: 46-87] for MRI and 68\% [95% CI: 44-86] for TVS. The specificities were 86\% [76-93] for MRI and 65\% [95% CI: 50-77] for TVS. The combination of TVS and MRI produced the highest sensitivity 89\% [95% CI: 64-98] but did not improve specificity 60\% [95% CI: 44-73]. The authors concluded the combination of TVS and MRI produced the highest level of accuracy for the diagnosis of adenomyosis.

Based on the findings of our study, the following clinical algorithm may be proposed (Fig 2):
Fig 2: Proposed Clinical Algorithm for Adenomyosis

Clinically Suspected Adenomyosis
- Menorrhagia
- Dysmenorhoea
- Tender uterus
- Less than 12 weeks

TVS

NO Adenomyosis
Adenomyosis Unlikely

Adenomyosis

Adenomyosis Possible
Offer MRI
Offer Surgery (Hysterectomy)
Offer Alternative Treatment Like Mirena

No Adenomyosis
Adenomyosis Unlikely

Adenomyosis
Adenomyosis Likely

Recommended Pathway (Where MRI Available)
The reported prevalence of adenomyosis varies widely, from 5 to 70%\textsuperscript{6,14}. This wide range reflects differences in patient population, histopathological criteria used to diagnose adenomyosis and the diligence with which pathology specimens are examined\textsuperscript{14,44,47}. The histological prevalence of adenomyosis in our study falls within the reported range. The actual prevalence may have been over- or under-estimated depending on how thoroughly the pathologists examined the hysterectomy specimens. In our unit the number of sections taken varies according to the pathologist doing the examination and the gross pathology seen in the uterus. For the diagnosis of adenomyosis, on average two sections are taken from the anterior and posterior myometrial walls (personal communication- Prof Wainwright Head Histopathology Department, University of Cape Town). We did not standardize the number of histological uterine sections for this study. Bird et al demonstrated that when pathologists took three routine sections, the prevalence of adenomyosis was 31% and when the sections increased to six, the prevalence increased to 61%\textsuperscript{6}.

It is recognised that adenomyosis is rarely a single histopathological diagnosis. In this study adenomyosis was diagnosed with leiomyomas in 54.7% of cases followed by endometrial cancer in 9.4% of cases. Only in 5% of women adenomyosis was the sole diagnosis. Similar to our findings, Bromley et al found that 63% of patients with adenomyosis had concomitant leiomyomas\textsuperscript{72} and Kepkep et al reported adenomyotic uteri were accompanied primarily by leiomyomas in 38.5% of cases and secondarily endometrial hyperplasia in 30.8% of cases.
Discussion and Conclusion

Our study had some limitations. Ultrasonographers did not undergo prior training in TVS diagnosis of adenomyosis using the pre-specified criteria. Although this may have affected the overall diagnostic performance of TVS for the diagnosis of adenomyosis, the data in this study suggests even without prior training some ultrasonographers can easily grasp the concepts and achieve high diagnostic performance without prior training.

For logistical reasons, not all women undergoing hysterectomy in the study period could have the questionnaire administered and undergo TVS for the diagnosis of adenomyosis. The bias this might have introduced was minimal as recruitment to study group A was random subject to availability of the researcher. Moreover, the prevalence of adenomyosis in the study group that underwent TVS examination (study group A; 20.5%) was almost identical to the prevalence of adenomyosis over the entire study period (study group B; 20.3%).

Lack of standardization in the number of uterine sections taken for the histopathological diagnosis of adenomyosis may have affected our findings.

The strength of our study was in its prospective design and the blinding of ultrasonographers and histopathologists.

Conclusion

Adenomyosis was the second most common histopathological diagnosis after leiomyomas. Our data suggest that clinicians should suspect adenomyosis if a woman presents with menorrhagia, dysmenorrhoea and a tender uterus less
than twelve weeks size. The presence of echogenic linear striations and myometrial cysts on TVS supports a diagnosis of adenomyosis. The high specificity and low sensitivity of TVS demonstrated in this study implies that if a clinician suspects adenomyosis TVS would currently be of more value in refuting the diagnosis than confirming it. A clinical algorithm incorporating clinical findings, TVS and MRI may assist in patient management.

To improve sensitivity of TVS, future studies should focus on recruiting selected patients with symptoms suggestive of adenomyosis, training of ultrasonographers in TVS diagnosis of adenomyosis and standardizing the histopathological examination of post-hysterectomy uteri.
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44. Bazot M, Daraï E, Rouger J, Detcher R, Cortez A, Uzan S. Limitations of Transvaginal Sonography for the Diagnosis of Adenomyosis with


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INFORMED CONSENT

This informed consent form is for women who together with their gynaecologist have planned to undergo a hysterectomy, and who we are inviting to participate in research on adenomyosis. The title of our research project is:

Adenomyosis: Trans-Vaginal Ultrasound Diagnosis with Histological Correlation

Name of Principal Investigator: Dr Reginald George Chunda, MBBS

Supervisors: Prof Silke Dyer
Dr Chantal Stewart

Organization: University of Cape Town
Groote Schuur Hospital

This Informed Consent Form has two parts:
• Information Sheet (to share information about the research with you)
• Certificate of Consent (for signatures if you agree to take part)

You will be given a copy of the full Informed Consent Form
PART I: Information Sheet

Introduction

My name is Dr Reginald George Chunda, training at the University of Cape Town to become a specialist in obstetrics and gynaecology. We are doing research on ADENOMYOSIS, which we think is common amongst women who come to hospital with gynaecological problems necessitating hysterectomy (operation to remove the womb). I am going to give you information and invite you to be part of this research. Before you decide you are free to talk to anyone you feel comfortable with about the research.

There may be some words that you do not understand. Please ask me or any of the study doctors/staff and we will take time to explain to you.

1. What is Adenomyosis?

Adenomyosis is a gynaecological disease whereby part of the lining of the womb is displaced into the muscles of the womb.

2. Why are we doing this research?

Most women afflicted with this condition will have heavy menstrual period, painful menstrual period, enlarged womb and inability to conceive. Women might also have other diseases of the womb, like fibroids, together with adenomyosis. World-wide, the diagnosis of adenomyosis has been made through laboratory testing (histology) of the womb after it has been removed (hysterectomy). With developments in ultrasound technology there is growing evidence that adenomyosis can be diagnosed before hysterectomy and there is also growing evidence that adenomyosis can be treated with other means (like a hormone containing intrauterine {loop}system) other than hysterectomy. Thus if we can make a reliable diagnosis of adenomyosis, we can offer women an alternative treatment to hysterectomy.

The reason we are doing this research is to find out how good trans-vaginal ultrasound is in diagnosing adenomyosis in our setting.

3. What do I have to do if I agree to participate?

This research will involve an interview as regards the problems we are experiencing and a trans-vaginal ultrasound examination. After the operation (hysterectomy), we are going to compare the ultrasound examination findings with the histological (laboratory) findings.

4. Who can participate in this study?

We are inviting all women who together with their gynaecologist have elected to undergo a hysterectomy for their gynaecological problem.

5. Do I have to participate?

No. Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you participate or not, all the services you receive at this hospital will continue and nothing will change. If you choose not to participate in this research project, you will be offered the services that are routinely offered in this hospital for women undergoing hysterectomy. You may change your mind later and stop participating even if you agreed earlier.
6. **How long will it take?**

Your participation in the research project is a two off event; thus during your interview and ultrasound examination. Whether you participate in this research project or not, you will be given an appointment 6 weeks after your operation to check how you have recovered and also to give you results of histological examination of the womb.

7. **Are there any adverse outcomes for participating in the research?**

There are no adverse outcomes due to participation in this research project. The adverse outcomes that might arise are those related to hysterectomy that would arise whether you participate in this research or not. If you develop an adverse outcome, you will be treated accordingly regardless of whether you will participate in this research project or not.

8. **Are there any benefits for participating in the research?**

There are no benefits for you, but your participation is likely to help us find the answer to the research question which will benefit future generations in terms of offering alternatives to hysterectomy for those with adenomyosis.

9. **Will I be reimbursed?**

You will not be given any money or gifts for taking part in this research.

10. **Will my details be kept confidential?**

We will not be sharing the identity of those participating in the research. The information that we collect from this research project will be kept confidential. Information about you that will be collected during the research will be put away and no-one but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up with a lock and key. It will not be shared with or given to anyone except your gynaecologist.

11. **How will the results of the research be disseminated?**

The knowledge that we get from doing this research will be shared with fellow health workers and anyone interested through dissemination meetings. After these meetings, we will publish the results in order that other interested people may learn from our research.

12. **Do I have a right to refuse or withdraw from the research?**

You do not have to take part in this research if you do not wish to do so and refusing to participate will not affect your treatment at this hospital in any way. You will still have all the benefits that you would otherwise have at this clinic. You may stop participating in the research at any time that you wish without losing any of your rights as a patient here. Your treatment at this hospital will not be affected in any way.
13. Who can I contact if I need further information?

If you have any questions you may ask them now or later, even after you have had your ultrasound examination and interview. If you wish to ask questions later, you may contact me, my supervisors or the Human Ethics Research committee on the following:

Name: Dr Reginald George Chunda

Address: University of Cape Town
            Groote Schuur Hospital
            Department of Obstetrics and Gynaecology

Telephone: 078 472 7692
Hospital Speed Dial: 77147

E-mail: rchunda@gmail.com

Name: Dr Chantal Stewart

Address: Ultrasound Department
            University of Cape Town
            Groote Schuur Hospital
            Department of Obstetrics and Gynaecology

Name: Prof Silke Dyer

Address: Reproductive Medicine
            University of Cape Town
            Groote Schuur Hospital
            Department of Obstetrics and Gynaecology

This proposal has been reviewed and approved by the Human Ethics Research Committee (HERC), which is a committee whose task it is to make sure that research participants are protected from harm. If you wish to find out more about the HERC, you may contact:

Mrs Lamees Emjedi
Research Ethics Committee
E 52 Room 24, Old Main Building, Groote Schuur Hospital, Observatory
Telephone: 27 21 406 6338
Fax: 27 21 406 6411
Email: nosi.tsama@uct.ac.za and shuretta.thomas@uct.ac.za
PART II: Certificate of Consent

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Print Name of Participant__________________
Signature of Participant ___________________
Date __________________________
    Day/month/year

If illiterate
A literate witness must sign (if possible, this person should be selected by the participant and should have no connection to the research team). Participants who are illiterate should include their thumbprint as well.
I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness_____________________ AND Thumb print of participant
Signature of witness ______________________
Date ______________________
    Day/month/year

Statement by the researcher/person taking consent
I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:
1. Interview regarding her gynaecological problem
2. Trans-vaginal ultrasound examination
3. Hysterectomy

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this informed consent form has been provided to the participant.

Print Name of Researcher/person taking the consent________________________
Signature of Researcher/person taking the consent________________________
Date __________________________
    Day/month/year
Adenomyosis: Trans-vaginal Ultrasound Diagnosis with Histologic Correlation

Signs and Symptoms Questionnaire

Name of Patient______________________
Folder Number________________________
Date of Birth     _______/_______/________
Age______

Demographic Data

Parity Gravida_____ Para_____ Miscarriage______ TOP_____ Ectopic_____

Marital Status
Married       Single       Cohabiting
Other______________

Ethnicity
Colored       White       Black           Asian
Other________________________

Home Language
English       Afrikaans       Xhosa
Other________________________

PREVIOUS CAESAR
1       2       >2

Indication for Hysterectomy

1____________________________________________________________
2____________________________________________________________
3____________________________________________________________
1 Signs

1.1 Uterine Size on Clinical examination pre-surgery (Document size as per most recent clinical examination) *tick appropriately*

- a) Normal Size
- b) Bulky (6-8 weeks)
- c) 8-12 weeks
- d) Greater than 12 weeks
- e) Not documented

1.2 Uterine tenderness on clinical palpation

- a) Absent
- b) Mild
- c) Moderate
- d) Severe
- e) Not Documented

1.3 Date of Clinical Assessment

- a) Within 1 week of Surgery
- b) Within 1 month of Surgery (31 days)
- c) Within 3 months of Surgery (92 days)
- d) Within 6 months of surgery

1.4 Person who conducted the Examination

- a) Medical Student
- b) Intern (Medical Officer)
- c) Registrar
- d) Consultant

---

Appendix B

Study Number___________________
2 Symptoms

Note: If the patient is receiving treatment for symptoms, describe periods when not on treatment

2.1 My Periods are excessively heavy
   a) Completely agree □
   b) Mostly Agree □
   c) Mostly Disagree □
   d) Completely Disagree □

2.2 When I menstruate I Bleed Clots
   a) Completely agree □
   b) Mostly Agree □
   c) Mostly Disagree □
   d) Completely Disagree □

2.3 I feel pain during sexual intercourse
   a) Completely Agree □
   b) Mostly Agree □
   c) Mostly Disagree □
   d) Completely Disagree □

2.4 My Periods are painful
   a) Completely Agree □
   b) Mostly Agree □
   c) Mostly Disagree □
   d) Completely Disagree □

2.5 If 2.3 a or b: Describe Period Pain on a 10 point scale (0= no pain; 10= worst imaginable pain) put a mark on the line.

1 10

2.6 My Periods are Irregular
   a) Completely Agree □
   b) Mostly Agree □
   c) Mostly Disagree □
   d) Completely Disagree □

2.7 I have been trying to fall pregnant for the last year or longer without being able to fall pregnant
   Yes □
   No □

2.8 In the past there was a time when I wanted to have a baby but without success
   Yes □
   No □
2.9 I am Currently on treatment for problems with my periods (because they are too heavy or painful or irregular)

Yes [ ] No [ ]

2.10 If Yes, describe treatment (circle or tick more than one)

a) Cyclokapron [ ]

b) Anti-inflammatories [ ]

c) Combined oral contraceptives [ ]

d) Injectable Progestagens [ ]

e) Mirena [ ]

f) Other Specify__________________________________________________________

_____________________________________________________________________

3.0 Are you using contraceptive methods

Yes [ ] No [ ]

3.1a If yes (using contraceptive method), what method are you using

a) Injectable Progestagens

Last Injection on ___ / ____ / ______

b) Combined Oral Contraceptive pills

Last Used on ____ / ____ / ______

c) Copper T Intrauterine contraceptive Device

Inserted on _____ / ____ / ______

e) Mirena

Inserted on _____ / ____ / ______

f) Condoms

Last Used _____ / ____ / ______

f) Other___________________________________________________________
Adenomyosis: Trans-vaginal Ultrasound Diagnosis with Histological Correlation

Ultrasound /Histology Checklist

<table>
<thead>
<tr>
<th>Feature</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Globular uniformly enlarged uterus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assymmetry of the anteroposterior wall of the myometrium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor definition of the endometrial-myometrial interface</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogenous myometrial echo-texture (heterogenous poorly circumscribed areas within the myometrium)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sub-endometrial echogenic linear striations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subendometrial myometrial cysts</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Other Diagnoses

TVS DIAGNOSIS of ADENOMYOSIS

(Presence of at least 3 features)

Please tick all of the above as YES or NO depending on the presence or absence of the ultrasound feature. Tick YES for the trans-vaginal diagnosis of adenomyosis if at least 3 of the features are present.

Ultrasonographer

HISTOLOGICAL DIAGNOSIS

<table>
<thead>
<tr>
<th>Criteria Used</th>
<th>YES</th>
<th>NO</th>
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</thead>
</table>

Other Histological Diagnoses
24 March 2011

HREC REF: 081/2011

Dr RG CHUNDA,
OBSTETRICS & GYNAECOLOGY

Dear Dr CHUNDA,

PROJECT TITLE: ADENOMYSIS TRANS-VAGINAL ULTRASOUND DIAGNOSIS WITH HISTOLOGICAL CORRELATION

Thank you for submitting your new study to the Faculty of Health Sciences Human Research Ethics Committee

It is a pleasure to inform you that the Ethics Committee has formally approved the above-mentioned study.

Approval is granted until 28 March 2012

Please submit an annual progress report (FHS016) if the research continues beyond the expiry date. Please submit a brief summary of findings if you complete the study within the approval period so that we can close our file.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC. REF in all your correspondence.

Yours sincerely

APPROF MARC BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS

Federal Wide Assurance Number: FWAO0001637,
Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.
### Annual Progress Report

<table>
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<tr>
<td>HREC REF Number</td>
<td>081/2011</td>
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<tr>
<td>Protocol number (if applicable) &amp; Protocol title</td>
<td>ADENOMYOSIS: TRANS-VAGINAL ULTRASOUND DIAGNOSIS WITH HISTOLOGICAL CORRELATION</td>
</tr>
<tr>
<td>Principal Investigator</td>
<td>Dr Reginald George Chunda</td>
</tr>
<tr>
<td>Department / Office Internal Mail Address</td>
<td>Obstetrics and Gynaecology, Groote Schuur Hospital Old Main Building H-Floor</td>
</tr>
</tbody>
</table>

#### List of documentation

1. Protocol plus appendixes:
   a) Informed Consent Form
   b) Signs and Symptom Questionnaire
   c) Trans-vaginal Ultrasound/Histological Diagnosis Data Sheet

#### Approved

This serves as notification of annual approval, including all documentation described above.

#### Not approved

See attached comments.

#### Type of review

- □ Expedited
- □ Full committee

#### Expiry date

- 31 March 2013

#### Signature

Chairperson of the HREC

Date 31/1/2012

7 October 2010  Page 5 of 5  FHS016