Ultrasound-based assessment and management of postmenopausal bleeding and endometrial polyps

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Signed declaration statement of originality and personal contribution to work

I, Michael Wong, declare that the work presented in this thesis is my own. Where information has been derived from other sources, I can confirm that this has been indicated in the thesis. I was personally involved in the design of all the studies and the recruitment of all patients. I performed all the ultrasound scans except where indicated, collected all the data, and carried out all the statistical analyses.

Signature:

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Date: 30.09.2021

Abstract

This thesis has evaluated aspects of ultrasound-based assessment and management of women with postmenopausal bleeding and endometrial polyps.

The efficacy of transrectal ultrasound scan (TRS) was assessed in 103 consecutive postmenopausal women with an axial uterus. TRS was accepted by two-thirds of the women and the proportion of satisfactory endometrial assessments was significantly higher on TRS compared to transvaginal scan (TVS), 91% (95% CI 84-98) vs 62% (95% CI 50-74), respectively. In the subgroup of 50 women with postmenopausal bleeding and an axial uterus, the endometrial thickness measured significantly thinner on TRS by a median of 1.2mm (IQR 0.4-3) compared to TVS. Furthermore, subjective pattern recognition for endometrial cancer was less accurate on TVS compared to TRS when the uterus is in an axial position.

The interrater reliability of ultrasound subjective pattern recognition for endometrial cancer was prospectively assessed in 40 women with postmenopausal bleeding and a thickened endometrium (≥4.5mm); a good level of agreement (κ = 0.78, 95% CI 0.61-0.95) was found between an expert and an average operator.

The diagnostic accuracy of ultrasound subjective pattern recognition for endometrial cancer was assessed in 240 consecutive women with postmenopausal bleeding and a thickened endometrium (≥4.5mm) and available histology. It performed well with a sensitivity and specificity of 88% (95% CI 77-95) and 97% (95% CI 94-99), respectively. The presence of focal malignancy within endometrial polyps was the most common cause of a false-negative diagnosis of endometrial cancer.

Endometrial cancer was diagnosed on ultrasound by subjective pattern recognition and simultaneously assessed for the presence of deep myometrial invasion and cervical stromal invasion in 51 women. We found that the accuracy of ultrasound in the preoperative staging of endometrial

cancer was comparable to MRI (sensitivity and specificity, 86% vs 77% and 66% vs 76%, respectively).

A clinical model was presented to estimate the risk (low, intermediate, or high) of pre-malignancy or malignancy in postmenopausal endometrial polyps. The model included polyp size, the presence or absence of intralesional cystic spaces and the patient's BMI as clinical variables. Accordingly, approximately one-third of postmenopausal polyps would be categorised as high- or intermediate-risk and they would account for over 90% of all premalignant/malignant polyps, while the remaining polyps would be categorised as low-risk with a 1/18 risk of pre-malignancy or malignancy. The overall accuracy of the model in predicting premalignant or malignant postmenopausal polyps was 92% (95% CI 86.0-97.4).

The natural history of expectantly managed endometrial polyps was assessed retrospectively in 112 polyps over a median follow-up of 22.5 months (range 6-136). We found that polyps' growth rates varied, and it was not possible to predict an individual polyp's growth based on the patient's clinical characteristics or polyp's morphological features. Polyp's growth rate was not associated with the risk of developing abnormal uterine bleeding (AUB). Some polyps underwent spontaneous regression (7/112, 6%) and this occurred more frequently among premenopausal women and those who were symptomatic of AUB.

Impact statement

In this thesis, we showed that a transrectal ultrasound scan (TRS) is more effective than a transvaginal scan (TVS) in achieving a satisfactory endometrial assessment in postmenopausal women with an axial uterus. Importantly, the subjective diagnosis of endometrial cancer was less accurate on TVS compared to TRS, when the uterus is axial. Therefore, in women with postmenopausal bleeding (PMB) and an axial uterus, clinicians could consider TRS or saline infusion sonography to reduce the risk of missing a diagnosis of endometrial cancer.

Ultrasound subjective pattern recognition has good interrater reliability and diagnostic accuracy for endometrial cancer in women with PMB. Compared to the measurement of endometrial thickness alone, ultrasound subjective pattern recognition has the potential to diagnose endometrial cancer earlier and thereby improve the prioritisation of women for histological confirmation and surgery. Future studies should evaluate the cost-effectiveness and patient satisfaction with ultrasound subjective pattern recognition.

We have shown that it is feasible to simultaneously diagnose endometrial cancer and assess for myometrial and cervical stromal invasion at women's initial ultrasound scan for postmenopausal bleeding. The accuracy of ultrasound and MRI were comparable in the preoperative staging of endometrial cancer. This streamlined ultrasound-based approach may benefit women by reducing the number of hospital visits, delays in surgery and the cost of MRI scans.

We proposed a model to divide women with postmenopausal endometrial polyps into low-, intermediate- or high-risk groups of pre-malignancy or malignancy, based on the polyp size, intralesional cystic spaces and patient's BMI. Our model performed well with an accuracy of 92% and it has been internally validated. Future research should include an external validation of our model. Clinically, our model may facilitate the discussion between women and their clinicians regarding the management options of

polyps. Furthermore, it may also assist clinicians in prioritising women for surgery according to the risk of malignancy.

We found that polyps' growth rate could not be predicted by patients' clinical characteristics or polyps' morphological features. Moreover, routine monitoring of polyp size on ultrasound did not predict the development of abnormal uterine bleeding in asymptomatic women. Some polyps appeared to regress spontaneously, and they occurred more frequently among premenopausal women and those with a history of abnormal uterine bleeding. More research is needed on the role of managing women with endometrial polyps expectantly, and the priority should be to identify women who may avoid unnecessary surgery.

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List of abbreviations

3D – three-dimensional

AH – atypical endometrial hyperplasia

A-mode – amplitude mode

AP – anterior posterior

AUB – abnormal uterine bleeding

AUC – area under the curve

BGCS – British Gynaecological Cancer Society

B-mode – brightness mode

BRCA – Breast cancer gene

CA125 – cancer antigen 125

CHAID – Chi-squared Automatic Interaction Detection algorithm

CI – confidence interval

CSI – cervical stromal invasion

CT – computer tomography

CXR – chest X-ray

DCE – dynamic contrast-enhanced

Dist-OCO – distance from the lower margin of the tumour to the outer cervical os

DMI – deep myometrial invasion

DNA – deoxyribonucleic acid

DWI – diffusion-weighted imaging

EB – endometrial biopsy

EBRT – external beam radiotherapy

EC – endometrial cancer

EH – endometrial hyperplasia

EMJ – endometrial-myometrial junction

ER – oestrogen receptor

ESGO – European Society of Gynecological Oncology

ESP – European Society of Pathology

ESTRO – European Society for Radiotherapy and Oncology

ET – endometrial thickness

FIGO – International Federation of Gynaecology and Obstetrics

GDOTU - Gynaecological Diagnostic and Outpatient Treatment Unit

GFR – glomerular filtration rate

GIS – gel-infusion sonography

HPF – high-power field

HRT – hormone replacement therapy

Hz – hertz

IMRT – intensity-modulated radiotherapy

IETA – International Endometrial Tumour Analysis

IOTA – International Ovarian Tumour Analysis

IQR – interquartile range

IUCD – intrauterine contraceptive device

L1CAM – L1 Cell Adhesion Molecule

LR – likelihood ratio

LVSI – lymphovascular space invasion

MI – myometrial invasion

MMMT – malignant mixed Mullerian tumours

M-mode – motion mode

MMR – mismatch repair

MPR – multi-planar reformatting

MRI – magnetic resonance imaging

MSI – microsatellite instability

MSI-H – microsatellite-high

MSI-L – microsatellite-low

MSS – microsatellite-stable

NHS – National Health Service

NICE – National Institute for Health and Care Excellence

NLCN – North London Cancer Network

PCOS – polycystic ovarian syndrome

PET – positron emission tomography

PFR – pulse repetition frequency

PMB – postmenopausal bleeding

POLE – DNA Polymerase Epsilon gene

PR – progesterone receptor

PTE – peritumoral enhancement

PTEN – Phosphatase and tensin homolog

REC – risk of endometrial cancer

SEE – sub-endometrial enhancement

SIS – saline-infusion sonography

SLN – sentinel lymph node

SPR – subjective pattern recognition

STARD – Standards for Reporting of Diagnostic Accuracy Studies

STROBE – Strengthening the Reporting of Observational Studies in Epidemiology

STUMP – smooth muscle tumour of uncertain malignant potential

T2WI – T2-weighted imaging

TCGA – The Cancer Genome Atlas

TGC – time gain compensation

TP53 – tumour protein p53

TRS – transrectal ultrasound scan

TVCD – transvaginal ultrasound with colour Doppler

TVS – transvaginal ultrasound scan

UCH – University College Hospital

UCL – University College London

UCLH - University College London Hospitals NHS Foundation Trust

UK – United Kingdom

VMAT – volumetric modulated arc radiotherapy

VR – volume rendering

WHO – World Health Organisation

WINPEPI – PEPI-for-Windows

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Hypotheses

This thesis will investigate the following hypotheses:

- Among postmenopausal women with an axial uterus, the proportion of satisfactory endometrial assessment is higher on transrectal ultrasound scans compared to transvaginal scans.

- Ultrasound subjective pattern recognition has good interrater reliability in the diagnosis of endometrial cancer.

- Ultrasound subjective pattern recognition has good diagnostic accuracy for endometrial cancer in women with postmenopausal bleeding.

- Ultrasound can be used in the preoperative staging of endometrial cancer for myometrial and cervical stromal invasion and the accuracy is not inferior to MRI.

- A decision tree model can be used to predict the risk of pre-malignancy or malignancy in postmenopausal endometrial polyps based on the patient's clinical characteristics and the polyp's morphological features on ultrasound.

- The growth rate of expectantly managed endometrial polyps can be predicted by the patient's clinical characteristics and the polyp's morphological features on ultrasound.

Aims

The aims of this thesis are:

- To compare the proportions of satisfactory endometrial assessment on transrectal and transvaginal ultrasound scans among postmenopausal women with an axial uterus. Also, to compare their respective measurements of endometrial thickness and diagnostic accuracy for endometrial cancer.

- To assess the interrater reliability of ultrasound subjective pattern recognition for endometrial cancer in women with postmenopausal bleeding.

- To assess the diagnostic accuracy of ultrasound subjective pattern recognition for endometrial cancer in women with postmenopausal bleeding.

- To compare the accuracy of ultrasound and MRI in the preoperative staging of endometrial cancer for myometrial and cervical stromal invasion.

- To create a decision tree model to predict the risk of pre-malignancy or malignancy in postmenopausal endometrial polyps using patients' clinical characteristics and polyps' morphological features on ultrasound.

- To assess the growth rates of expectantly managed endometrial polyps and to identify the associated predictive factors.

Thesis layout

This thesis is divided into four main sections:

Part 1: Background, which includes chapters 1-8. Chapter 1 summarises the embryology, anatomy, and physiology of the uterus. Chapters 2 and 3 outline the common uterine pathologies, including endometrial cancer. Chapters 4 and 5 present the principles of ultrasound and its current use in assessing women with postmenopausal bleeding. Chapters 6 and 7 describe the preoperative staging of endometrial cancer and its current management. Chapter 8 concludes part 1 with a summary of the background.

Part 2: Methods, which includes chapters 9-18. They describe the general methods including study design and procedures that apply to all the studies included in this thesis.

Part 3: Results, which includes chapters 19-24. Each chapter is based on an individual study and includes the introduction, specific additional methods, and the results.

Part 4: Discussion, conclusions, and future studies, which include chapters 25-30. It contains the discussion segments of each study from part 3. The final chapter is an overall conclusion which summarises the findings and their clinical significance with suggestions for future research.

Part 1 – Background

Chapter 1 Normal uterus

1.1 Uterine embryology

In humans, Müllerian organogenesis is responsible for the development of the uterus, fallopian tubes and upper third of the vagina (Witschi, 1959).

In both genetically female and male embryos, the Müllerian (paramesonephric) ducts are formed at the beginning of week 5 by the invagination of coelomic epithelium on the lateral aspect of the paired urogenital ridges (Guioli et al., 2007). These Müllerian ducts then extend caudally along the length of the Wolffian (mesonephric) ducts. As the Müllerian ducts reach the pelvis, they cross over the Wolffian ducts to lie on their medial aspect. By the end of week 8, the two Müllerian ducts fuse to form a single common uterovaginal canal. The tip of the Müllerian ducts at the posterior wall of the urogenital sinus corresponds to the future location of the cervix.

In the absence of anti-Müllerian and testosterone hormones, the Müllerian ducts continue to develop after week 8. In the cranial end of the Müllerian ducts, they remain separate to form the fallopian tubes; whereas, caudally they fuse to become the uterus (Robbins et al., 2015).

Between weeks 18-20, smooth muscles begin to appear in the female genital tract and by week 24 the vaginal, uterine, and tubal muscular cells are relatively well developed.

Cervical glands appear at around week 15. Endometrial glands are usually found later at approximately week 19; however, the endometrium will remain poorly developed in most term infants.

In an unselected population, congenital uterine malformations are found in approximately 3.5-8.5% of women (Chan et al., 2011). There is currently no evidence to suggest that uterine malformation is a risk factor for endometrial malignancy as the co-existence of the two is only rarely reported in case reports in the literature (Gao et al., 2017).

1.2 Uterine anatomy and histology

The uterus is a fibromuscular structure that is made up of the uterine corpus and the cervix, with the uterine corpus, further divided into the fundus, body and isthmus (Ellis, 2011). The muscular fibres of the uterus reflect its embryological origin from the Müllerian ducts with the fibres crisscrossing diagonally to each other.

Within the uterine muscular wall lies the endometrial cavity, which is lined by the endometrium. Histologically, the endometrium consists of glands, stroma, and blood vessels. The endometrium merges with the mucosa of the fallopian tubes superiorly and with the endocervical epithelium inferiorly. The endometrium is made up of two layers, the basal layer (stratum basalis) that is adjacent to the myometrium and the functional layer (stratum functionalis), which is further subdivided into the superficial compact layer (stratum compactum) and the deeper spongy layer (stratum spongiosum) (Ferenczy and Bergeron, 1991). The basal layer consists of non-secretory tubular glands and compact stroma with minimal mitotic activities in both the glands and the stroma.

Glandular changes in the endometrium are found in most pathological conditions of the endometrium. There are three types of endometrial glandular cells, which are secretory (most abundant), ciliated and clear cells. The recognition of ciliated cells in pathology specimens is useful in postmenopausal women as these cells are sensitive to the influence of oestrogens and their presence raises suspicions about an endogenous or exogenous oestrogenic stimulus.

The blood supply to the uterus is primarily from the uterine arteries, which originate from the internal iliac arteries; they run parallel to the uterus and anastomose with the ovarian vessels in the pampiniform plexus. Within the myometrium, the arcuate and radial branches of the uterine vessels anastomose with each other and they penetrate the myometrium assuming a circumferential course (Farrer-Brown et al., 1970).

The lymphatics of the uterus and the upper two-thirds of the vagina drain into the internal and external iliac lymph nodes; however, some may also drain into the superficial inguinal, para-aortic and sacral lymph nodes (Ellis, 2011).

1.3 Menopausal changes to the uterus

Once the endogenous ovarian production of cyclical oestrogen and progesterone diminishes after menopause, the uterus undergoes atrophic changes. Both the uterine length and uterine corpus:cervix ratio in postmenopausal women are reduced compared to premenopausal women, 3.5-7.5cm vs 8-9cm and 2:1 vs 1-1.5:1, respectively (Langer et al., 2012). Typically, the atrophic endometrium appears hyperechoic and thin, usually 1-2mm, on ultrasound. Calcified uterine arcuate vessels are commonly seen in older women, especially in those with risk factors of systemic vascular disease, such as diabetes mellitus or hypertension (Occhipinti et al., 1991). A small amount of hypoechoic intracavitary fluid in an otherwise atrophic endometrial cavity (mucometra) may also be noted, which is usually due to postmenopausal cervical stenosis (Langer et al., 2012).

Histologically, the endometrial glands decrease in size and become sparse in postmenopausal women, while the stroma becomes more fibrous. However, some postmenopausal endometrium may appear differently with a cystic-atrophy pattern. In cystic atrophy, the glands are typically distended by a non-specific transudate and the epithelium lining these distended glands is flattened and inactive. There are two hypotheses of how these

glands become distended: i. there was endometrial hyperplasia without atypia at the time of menopause, which subsequently regresses as the hormonal support is gradually withdrawn after menopause; however, the pre-existing architecture of the cystic changes remains without any accompanying cellular activity; and ii. there is an obstruction to the endometrial gland ostia caused by postmenopausal stromal fibrosis. As the postmenopausal endometrium continues to produce a seromucinous secretion, obstructed glands will, therefore, continue to accumulate this secretion in their lumen and causing the observed distention (Mutter and Prat, 2014).

1.4 Exogenous hormones and their effects on the endometrium

The use of exogenous hormones is very common in women for contraception, postmenopausal hormone replacement, treatment of dysfunctional uterine bleeding, dysmenorrhoea, subfertility and premalignant or malignant conditions of the endometrium or breast.

The most common exogenous hormones are oestrogen and progestin. Oestrogen essentially induces endometrial proliferation in the glands, stroma, and vasculatures. On the other hand, progestin down-regulates oestrogen and progesterone receptors in the endometrium, and the effects of progestin will depend on the prior priming of the endometrium by oestrogen.

Persistent exposure to oestrogen, whether it is endogenous due to anovulatory menstrual cycles, or exogenous due to unopposed oestrogen therapy, can lead to a disorganised proliferation of the endometrium, endometrial hyperplasia or even adenocarcinoma.

Prolonged exposure to progestin, usually in the treatment of dysfunctional uterine bleeding, can lead to endometrial atrophy; however, later this could also be complicated by secondary necrosis of the superficial endometrium.

Postmenopausal hormone replacement therapy can be given as oestrogen alone in women who have had a previous hysterectomy or as combined oestrogen and progestins regimens in all other women. Unopposed oestrogen-only hormone replacement therapy should not be given to women who did not have a hysterectomy because of the approximately 6-fold increased risk of endometrial cancer, which is related to the dosage and duration of the oestrogen-only treatment (Cushing et al., 1998, Labrie et al., 2009, Weiderpass et al., 1999).

To reduce the risk of endometrial hyperplasia or adenocarcinoma, either cyclical or continuous combined oestrogen and progestin replacement therapy is given to women without a history of hysterectomy. The cyclical combined treatment uses daily oestrogen in the first 21-25 days of the month while progestin is added in the last 10-13 days, which results in a scheduled monthly withdrawal bleed in postmenopausal women. In contrast, continuous combined therapy down-regulates both oestrogen and progesterone receptors and leads to an atrophic endometrium (Piegsa et al., 1997).

Tamoxifen is an anti-oestrogen medication that is commonly used in the treatment of oestrogen-receptor-positive breast cancers. It competes with circulating endogenous oestrogen in the endometrium; however, in a low endogenous oestrogen state, tamoxifen is a weak oestrogenic agonist in the endometrium (Cohen et al., 1997). Therefore, in premenopausal women, the overall oestrogenic stimulation of the endometrium is reduced, but in postmenopausal women, the weak agonistic property of tamoxifen can lead to an increased risk of endometrial hyperplasia, adenocarcinoma, and polyps (Schlesinger et al., 1998). The risk is related to the duration of therapy and there is an approximately 4-fold increase after five years of treatment (Bernstein et al., 1999).

Raloxifene is an alternative selective oestrogen receptor modulator to tamoxifen. The theoretical benefit of raloxifene is that it suppresses oestrogen receptors in the breast while it does not lead to a proliferation of the endometrium (Boss et al., 1997, Pinkerton and Goldstein, 2010).

Letrozole and anastrozole are examples of aromatase inhibitors that are also used to treat oestrogen receptor-positive breast cancers and they work by inhibiting the peripheral conversion of steroids into the circulating oestrogen (Smith and Dowsett, 2003). An overall reduction in systematic levels of oestrogen leads to endometrial atrophy without increasing the risk of endometrial hyperplasia or malignancy.

Women may also consume naturally occurring plant-based oestrogens, termed phytoestrogens, whether intentionally or unintentionally through their diet, such as soybeans, grains, seeds, etc. Short-term and low-dose consumption of dietary is unlikely to have a noticeable effect on the endometrium; however, persistent consumption of high doses of phytoestrogens may increase the risk of endometrial cancer in postmenopausal women (Tempfer et al., 2009, Bandera et al., 2009).

Systemic corticosteroids are commonly used to treat inflammatory or autoimmune disorders, such as asthma, inflammatory bowel disease, arthritis, etc. Because of the progestogenic effect of corticosteroids, long-term treatment with corticosteroids may lead to the development of endometrial atrophy.

Chapter 2 Uterine pathologies: demographics and histology

2.1 Endometritis

Endometritis is usually a histological diagnosis when there is an abnormal presence of inflammatory cells in the endometrium; however, the diagnosis can be difficult as inflammatory cells are also found in the normal endometrium. Furthermore, the clinical symptoms of fever, lower abdominal pain, and cervical or adnexal tenderness on bimanual examination could be absent in women diagnosed with endometritis histologically.

Endometritis can be associated with specific micro-organisms such as Neisseria, chlamydia, mycoplasma, cytomegalovirus, herpes simplex virus, and tuberculosis; or it can be non-specific to a micro-organism, such as in women with intrauterine contraceptive devices, postpartum, post-abortion or a pyometra.

Infection with Actinomyces Israelii is reported to be associated with the use of intrauterine contraceptive devices. It is an anaerobic organism that can be found incidentally on routine cervical smear tests. If women are asymptomatic, treatment may not be required; however, some women may be complicated by pelvic actinomycosis. The duration of the IUCD being in-situ is the most important risk factor for actinomycosis with 85% of all infections related to the use of 3 years or more (Valicenti et al., 1982).

Pyometra is a clinical observation when pus accumulates within the uterine cavity. This is thought to be due to a blockage in the cervical canal, which could be caused by postmenopausal cervical stenosis, cervical tumour, or foreign bodies. Squamous metaplasia has been reported to occur in the surface epithelium and glands of women with pyometra; however, squamous cell carcinoma rarely occurs (Bewtra et al., 2005).

2.2 Endometrial metaplasia

Endometrial metaplasia is a histological diagnosis that refers to the change in cellular differentiation to a different type of cell, which is not normally found in the endometrium. The finding of endometrial metaplasia alone is usually not sufficient to help with the decision on clinical management. A further assessment to look for a possible underlying cause is essential.

Endometrial metaplasia can be caused by a degenerative, hormonal, or neoplastic process. The most common endometrial metaplasia is when endometrial glands are replaced by serous, mucinous, or squamous cells.

Embryologically, the correct cellular differentiation of the Müllerian tract has been shown to involve the homeobox genes (Samuel and Naora, 2005). Dysregulation of the homeobox HOXA10 gene is not only associated with endometrial metaplasia but also plays a role in the progression of endometrial cancer by promoting endometrial-mesenchymal transition (Yoshida et al., 2006).

2.3 Endometrial polyps

Endometrial polyps are localised overgrowths of the endometrial glands, stroma and blood vessels, which commonly protrude into the uterine cavity (Nijkang et al., 2019). The pathogenesis of polyps is unclear, it is thought to be caused by a monoclonal overgrowth of the endometrial stromal cells with a secondary polyclonal growth of the endometrial glands (Fletcher et al., 1992). Other genetic studies found that there are at least 4 different subgroups of polyps with rearrangements in the 6p21-p22, 12q13-15 and 7q22 regions, respectively; the fourth subgroup has a normal karyotype (Dal Cin et al., 1995).

Most endometrial polyps are not sensitive to the circulating hormones of oestrogen and progesterone, and therefore they lack the cyclical changes

in comparison to their adjacent normal endometrium. In polyps that contain functional glands, they are usually less developed, and their activities may not coincide with the normal menstrual cycle.

Endometrial polyps can be of various sizes with larger-sized polyps being associated with tamoxifen. Tamoxifen-associated polyps are also more likely to have mucinous metaplasia, premalignant or malignant changes (Deligdisch et al., 2000, Cohen, 2004).

The prevalence of endometrial polyps in an unselected population of Danish women aged 20-74 was 7.8%. Polyps were rare (0.9%) in women below the age of 30, while up to 25% of women on hormone replacement therapy were found to have polyps (Dreisler et al., 2009).

The most common symptoms of endometrial polyps are intermenstrual bleeding, menorrhagia or abnormal vaginal discharge; however, in a prevalence study of polyps, 82% of histologically confirmed polyps were not associated with any symptoms of abnormal uterine bleeding (Dreisler et al., 2009).

Macroscopically, polyps usually have a smooth outline, and some may show evidence of haemorrhage or necrosis, although necrosis is not a common feature of benign polyps. Microscopically, polyps are diagnosed when at least two of the following three features are confirmed: 1. Irregularly shaped and positioned glands, 2. Stroma altered by fibrosis or excessive collagen, and 3. Thick-walled blood vessels (Mutter and Prat, 2014). In postmenopausal endometrial polyps, a common histological finding is dilated cystic glands that are lined by atrophic endometrium; this appearance may reflect the state of the endometrium when it was still active, which was followed by regression in the postmenopausal years.

Some endometrial polyps may harbour evidence of premalignant or malignant cells. However, it is important to distinguish between endometrial cancers that grow in a polypoid fashion from a focal endometrial malignancy that develops from a benign endometrial polyp. In the latter case, according to Scott (1953), it must fulfil the following criteria: 1. The carcinoma must be confined to one surface of the polyp, 2. The base of the polyp must be

benign, and 3. The surface of the endometrium around the base of the polyp must show no malignant changes.

The prevalence of pre-malignancy or malignancy in endometrial polyps is estimated to be approximately 5% in postmenopausal women and 1% in premenopausal women by a recent meta-analysis (Uglietti et al., 2019). Reported risk factors that are associated with premalignant or malignant endometrial polyps are women aged over 60, obesity, use of tamoxifen, history of abnormal uterine bleeding, diabetes mellitus or hypertension (Sasaki et al., 2018).

There is currently no consensus on the management of endometrial polyps, especially in asymptomatic women who are diagnosed with polyps on routine imaging. However, as there is no reliable way to rule out the presence of malignancy in polyps, surgical removal of all polyps is commonly offered in clinical practice by most clinicians.

2.4 Endometrial hyperplasia

Endometrial hyperplasia is a non-specific term that is used to describe an increase in the endometrial glands and the thickening of the endometrium. According to the 2014 WHO classification, endometrial hyperplasia is divided into two distinctly different types: 1. Non-atypical endometrial hyperplasia and 2. Atypical endometrial hyperplasia or endometrial intraepithelial neoplasia (Zaino et al., 2014). The previous classifications of endometrial hyperplasia using the terms simple non-atypical, simple atypical, complex non-atypical and complex atypical endometrial hyperplasia should no longer be used.

2.4.1 Non-atypical endometrial hyperplasia

Non-atypical endometrial hyperplasia originates from normal endometrium that underwent a global increase in gland density, size, and shape, in response to an unopposed oestrogenic stimulation. An increased oestrogenic stimulation may occur due to anovulatory cycles at the time of perimenopause, women with polycystic ovarian syndrome, use of exogenous oestrogen hormones, and uncommonly ovarian granulosa cell tumour or thecoma.

Women with non-atypical endometrial hyperplasia may be asymptomatic; however, most women will eventually develop symptoms of abnormal vaginal bleeding. If the unopposed oestrogenic stimulation persists and the endometrial hyperplasia is untreated, there is a 2-4-fold increase in the risk of developing endometrioid endometrial cancer (Zeleniuch-Jacquotte et al., 2001).

Macroscopically, non-atypical endometrial hyperplasia appears as an irregularly thickened endometrium and is sometimes described as polypoid endometrium.

2.4.2 Atypical endometrial hyperplasia or Endometrial intraepithelial neoplasia

Atypical endometrial hyperplasia and endometrial intraepithelial neoplasia are two interchangeable terms. Atypical endometrial hyperplasia is distinctly different from non-atypical endometrial hyperplasia because it is caused by a monoclonal proliferation of genetically mutated premalignant glands that are prone to malignant transformation (Mutter et al., 2000a).

Genetic mutations that are known to occur in endometrioid endometrial cancer are also found in atypical endometrial hyperplasia, such as mutation of the K-Ras gene (Mutter et al., 1999), presence of microsatellite instability

(Mutter et al., 1996), inactivation of the PTEN tumour suppressor gene (Mutter et al., 2000b) and PAX2 gene (Monte et al., 2010).

It is difficult to estimate the prevalence of atypical endometrial hyperplasia as some women may remain asymptomatic; however, among endometrial samples obtained from women who were symptomatic of abnormal uterine bleeding, approximately 1% of women were found to have atypical endometrial hyperplasia (Semere et al., 2011). Compared to women with endometrioid endometrial cancer, women with atypical endometrial hyperplasia are generally nine years younger (Semere et al., 2011). Risk factors for atypical endometrial hyperplasia include obesity, polycystic ovarian syndrome, women of postmenopausal age, use of tamoxifen and history of subfertility. In women who are diagnosed with atypical endometrial hyperplasia, concurrent endometrioid endometrial cancer can be found in approximately one in three women who undergo a hysterectomy (Semere et al., 2011).

Macroscopically, atypical endometrial hyperplasia may appear as a localised thickening of the endometrium. Microscopically, atypical endometrial hyperplasia is diagnosed by identifying changes in the endometrial architecture (glands exceed that of stroma in a ratio >1), cytology (nuclear and cytoplasmic features of the architecturally crowded glands differ from the normal background glands), size (maximum linear dimension exceeds 1mm) and the exclusion of benign mimics, such as non-atypical endometrial hyperplasia or polyps (Mutter and Prat, 2014). It is also important to consider the diagnosis of endometrial cancer if cribriform, maze-like or villoglandular architecture is present, or if there is evidence of myometrial invasion (Mutter and Prat, 2014).

2.5 Endometrial cancer

Endometrial cancer (EC) is a heterogeneous group of malignancies derived from the endometrial glandular epithelial cells. The majority of EC are

endometrioid adenocarcinoma which resembles the appearance of endometrial glands histologically; however, mucinous, and squamous differentiation is common. The less common, non-endometrioid, group of ECs include clear cell adenocarcinoma, serous adenocarcinoma and carcinosarcoma.

According to Cancer Research UK, EC is the 4th most common cancer in women in the UK and each year approximately 9400 women are diagnosed with EC (Cancer Research UK, 2020). The incidence rate of EC is highest among women aged between 75-79. In the past three decades, the EC incidence rate has increased by approximately 50%. In general, 3 in 4 women with EC survive beyond 5 years. The stage of disease at the time of diagnosis and women's age are two of the most important prognostic factors. One-third of all EC are caused by obesity, and it is estimated that 34% of EC are preventable.

Traditionally, EC can be divided into type 1 (endometrioid adenocarcinoma and its variants) and type 2 (non-endometrioid carcinomas) tumours (Bokhman, 1983). Type 1 tumours are thought to be oestrogen-dependent; whereas, type 2 tumours are non-oestrogen dependent and are more aggressive (Lax and Kurman, 1997). There are also differences in their pathogenesis. For example, type 1 tumours commonly begin with PTEN or PAX2 inactivation, followed by positive oestrogen hormone selection, clonal proliferation as endometrial intraepithelial neoplasia/atypical hyperplasia and then turning into invasive malignancy (Monte et al., 2010). A similar stepwise progression into malignancy is less frequently observed in type 2 tumours.

Although this dualistic model helps describe the majority of EC, some tumours have overlapping clinical, morphological, and genomic features. This could be due to tumour heterogenicity where more than one histological subtype may be present, for example, some tumours having a mixture of endometrioid and non-endometrioid adenocarcinomas. Furthermore, endometrioid EC is graded according to its degree of differentiation; in poorly differentiated (grade 3) endometrioid

adenocarcinoma, their clinical features are more like type 2 rather than type 1 tumours.

Histological subtypes of EC include endometrioid adenocarcinoma and its variants (endometrioid adenocarcinoma with squamous differentiation, mucinous adenocarcinoma, secretory adenocarcinoma, ciliated cell adenocarcinoma, villoglandular adenocarcinoma, endometrioid carcinoma with sertoliform differentiation), serous adenocarcinoma, clear cell adenocarcinoma, carcinosarcoma, undifferentiated carcinoma, neuroendocrine carcinoma, small cell carcinoma, squamous cell carcinoma and miscellaneous types (Mutter and Prat, 2014).

2.5.1 Endometrioid adenocarcinoma and its variants

Endometrioid EC and its variants are the most commonly encountered EC and they account for up to 80% of all EC (Amant et al., 2005). The majority of endometrioid EC arise from a background of endometrial hyperplasia under the influence of an oestrogenic stimulation; however, some tumours could also arise from an atrophic endometrium (Mutter et al., 2000b).

The most common presenting symptom in women with endometrioid EC is postmenopausal bleeding or abnormal uterine bleeding in premenopausal women. However, smaller, or earlier staged tumours may be asymptomatic.

Most endometrioid EC are in the uterine corpus with a preference towards the anterior wall and they are less commonly found in the lower uterine segment. Macroscopically, endometrioid EC may appear as a single tumour, multiple tumours, or a diffusely thickened endometrium. It can be difficult to assess the degree of myometrial invasion on gross examination. The level of tumour exophytic growth within the uterine cavity does not correlate well with the presence of a deep myometrial invasion (Mariani et al., 2002).

Microscopically, the appearance of endometrioid EC resembles proliferative endometrium. Malignancy is diagnosed with the presence of at least one of

the following: meandering interconnected lumens formed by folded sheets of the neoplastic epithelium, irregular angulated and tapering glandular contours, a cribriform pattern of glands, or a solid area of the glandular epithelium (Mutter and Prat, 2014).

Endometrioid EC is graded into well-differentiated (grade 1), moderately differentiated (grade 2) or poorly differentiated (grade 3), according to the International Federation of Gynaecology and Obstetrics (FIGO), which is recommended by the World Health Organisation (WHO) (Creasman, 2009). Grading is performed based on the proportion of solid non-squamous areas within a tumour; grade 1, 2 and 3 tumours show ≤5%, 6-50% and >50% of non-squamous solid growth, respectively.

2.5.2 Serous adenocarcinoma

Serous EC accounts for up to 1-10% of all EC (Amant et al., 2005). Compared to endometrioid EC, they are usually diagnosed in women who are older, less obese and without a history of endometrial hyperplasia (Hendrickson et al., 1994).

Macroscopically, serous EC can appear as an exophytic intrauterine tumour, which is not dissimilar to endometrioid EC. Also, not infrequently, serous EC and serous endometrial intraepithelial carcinoma (EIC) can be found within the endometrial polyps (Zheng et al., 1998).

Microscopically, serous EC resembles the appearance of high-grade serous ovarian adenocarcinoma.

Serous EC is an aggressive disease, up to 70% of tumours that were thought to be confined within the uterus preoperative may have extrauterine metastasis at the time of surgery (Cirisano et al., 2000). Unlike endometrioid EC, the depth of MI or the grade of serous EC is not useful in predicting the stage of disease or the risk of recurrence (Carcangiu and Chambers, 1995). This could be due to the spread of serous EC via tubal reflux without necessarily invading deeply into the myometrium (Snyder et al., 2006), the

resulting peritoneal carcinomatosis may explain the high recurrence rate of serous EC (Hendrickson et al., 1982). Even when serous EC is found to be confined within an endometrial polyp only, up to 60% of tumours may recur following surgery (Silva and Jenkins, 1990). The current first-line treatment for serous EC is hysterectomy, bilateral salpingo-oophorectomy, omentectomy, peritoneal cytology, and para-aortic and pelvic lymph node dissection.

2.5.3 Clear cell adenocarcinoma

Clear cell EC accounts for 1-6% of all EC (Amant et al., 2005). Compared to endometrioid EC, they are more common in older women (Abeler and Kjørstad, 1990).

Macroscopically, clear cell EC does not have any unique appearance that distinguishes it from other histological subtypes of EC, but unlike endometrioid EC, it is more commonly found with a background of an atrophic endometrium.

Microscopically, clear cell EC may have a papillary, solid, tubolocystic or a mixture of these patterns.

Compared to endometrioid EC, clear cell EC is more aggressive. They tend to present at a more advanced stage with a higher risk of deep MI and lymph node metastasis. The 5-year disease-free survival is approximately 43-68%, with two-thirds of women suffering from a recurrence following treatment (Abeler et al., 1996).

2.5.4 Mixed type of carcinoma

Some EC may have more than one malignant histological subtype within a single tumour. An effort is made to estimate the volume percentages of each of the histological subtypes; however, this can sometimes be difficult from

a biopsy sample, given that there are tumour heterogenicity and the risk of sampling error. A more accurate histological diagnosis may not be possible until the final hysterectomy specimen is available.

2.5.5 Carcinosarcoma

Carcinosarcoma is a malignant tumour with both epithelial and mesenchymal components. They were previously called malignant mixed Mullerian tumours (MMMT) or malignant mixed mesodermal tumours. However, it is now clear that these tumours are primary epithelial tumours, which have developed a mesenchymal component mimicking the epithelial to mesenchymal transition, therefore in 2003, they have been renamed carcinosarcoma (Castilla et al., 2011).

2.5.6 Undifferentiated carcinoma

Undifferentiated EC accounts for less than 2% of all EC (Amant et al., 2005). Histologically, they contain malignant epithelial cells, but the cells are not otherwise differentiated. In a large series of undifferentiated EC, the median age at diagnosis was 65 years and 58% of women had the early-staged disease; the overall 5-year survival was 57% (AlHilli et al., 2019). The stage of the disease is the strongest prognostic factor in women with undifferentiated EC.

2.5.7 Squamous cell carcinoma

Squamous cell EC is rare. Many women have a history of endometritis or pyometra before the diagnosis of squamous cell EC (Kennedy et al., 1995). It may also be associated with benign squamous metaplasia of the endometrium (ichthyosis uteri), which often follows a chronic intrauterine

infection. The prognosis of squamous cell EC is very poor. Some studies reported that only 1 in 4 women survives with a median of 9 months following the diagnosis. There is no evidence that adjuvant radiotherapy improves survival; however, the combination of cisplatin-based chemotherapy and adjuvant radiotherapy may improve survival in some women (Sorosky et al., 1995).

2.5.8 Synchronous endometrial and ovarian carcinoma

Differentiating between synchronous endometrial and ovarian carcinoma against metastatic endometrial or ovarian cancer is important clinically because the prognosis is better in women with synchronous primary tumours (Liu et al., 2013). Signs that favour a metastatic disease of the endometrium rather than an ovarian primary include the finding of tumour deposits on the surfaces of both ovaries, whereas disparate histological subtypes of endometrial and ovarian tumours favour the diagnosis of independent primaries.

2.5.9 Tumours metastatic to the endometrium

Metastatic disease to the endometrium can often be recognised by the typical histological features of the primary tumour, for example, the “single-cell” pattern of invasive lobular breast cancer.

Most metastatic disease to the endometrium originates from the cervix or the ovary. It is uncommon for other primary tumours to metastasize to the endometrium; however, this may occur with breast, colon, stomach, and pancreatic cancers.

2.6 Uterine smooth muscle tumours

Most uterine smooth muscle tumours are benign leiomyomas. Uterine sarcomas account for approximately 3% of all uterine malignancies (Amant et al., 2009).

2.6.1 Leiomyoma

Uterine leiomyoma is a benign smooth muscle tumour, which can be found in up to 30% of women over the age of 30 (Payson et al., 2006). Afro-Caribbean women are at higher risk of leiomyoma compared to Caucasian women (Day Baird et al., 2003).

Some women with leiomyoma may be asymptomatic, while others may experience symptoms of abnormal uterine bleeding, pelvic pain or abdominal distention, which may depend on the size and location of their leiomyoma (Stewart, 2015).

The exact pathogenesis of leiomyoma is unknown; however, the increased oestrogen sensitivity found in leiomyoma suggests that steroid hormones may play a part in their tumorigenesis (Marsh and Bulun, 2006). Also, interestingly, each leiomyoma is found to be a distinct clone arising from a single transformative event, which means that leiomyoma tumorigenesis is extremely common (Lobel et al., 2006).

Macroscopically, leiomyomas appear as a round and firm swelling, which has a well-defined demarcation against the adjacent normal myometrium. Leiomyomas are classified clinically according to their location within the uterine cavity, in the simplest way they are divided into submucosal (protruding into the uterine cavity), intramural (confined within the myometrium) or subserosal/pedunculated (distorting the uterine serosa). Some leiomyomas may undergo certain degenerative changes, including haemorrhage, necrosis, cystic changes, and calcifications.

Microscopically, leiomyomas appear as densely packed intersecting bundles of smooth muscle cells.

Despite the benign nature of leiomyomas, they may have several unusual growth patterns, such as diffuse leiomyomatosis, intravenous leiomyomatosis, benign metastasizing leiomyoma and disseminated peritoneal leiomyomatosis (Mulvany et al., 1995, Mulvany et al., 1994, Takemura et al., 1996, Tavassoli and Norris, 1982).

2.6.2 Leiomyosarcoma

Leiomyosarcoma accounts for 1-2% of all uterine malignancies (D'Angelo and Prat, 2010). Like leiomyomas, leiomyosarcoma is also more commonly found in Afro-Caribbean compared to Caucasian women (Brooks et al., 2004).

The commonest presenting symptoms of leiomyosarcoma are postmenopausal bleeding, abdominal swelling, and pelvic pain. In premenopausal women, these symptoms are difficult to distinguish from the symptoms due to leiomyomas. However, the possibility of leiomyosarcoma should always be considered in postmenopausal women with rapidly enlarging uterine swelling.

Macroscopically, leiomyosarcoma usually presents as a single swelling, they are usually intramural and >10cm in size. Compared to leiomyomas, leiomyosarcomas do not have a well-defined demarcation against the adjacent myometrium or the typical whorled appearance. It is common to find evidence of necrosis and haemorrhage.

Microscopically, tumour cell necrosis is a characteristic feature of leiomyosarcoma. The presence of at least two of the following is satisfactory for the diagnosis of leiomyosarcoma – tumour cell necrosis, nuclear atypia or high mitotic rate (Bell et al., 1994).

The mainstay of treatment for leiomyosarcoma is hysterectomy. Routine bilateral salpingo-oophorectomy is not associated with improved survival. There is no clear evidence that adjuvant therapies are helpful. However, radiotherapy may be useful in reducing the risk of local recurrence, while chemotherapy with doxorubicin or docetaxel/gemcitabine is given to women with advanced or recurrent disease (Hensley et al., 2008, Hensley et al., 2009).

The prognosis of leiomyosarcoma is poor even when it is treated at an early stage, the 5-year overall survival rate is 51%; while 53-71% have recurrence disease, of which 40% involve pulmonary metastasis. The reported median survival is only 10 months (Abeler et al., 2009, Major et al., 1993).

2.6.3 Atypical smooth muscle tumours

Atypical smooth muscle tumours or smooth muscle tumours of uncertain malignant potential (STUMP) are tumours that cannot be classified as benign or malignant histologically. Typically, they contain nuclear atypia but the mitotic figures are <10 per 10 HPF and there is no evidence of tumour cell necrosis (Bell et al., 1994). They are further subdivided into 1. Atypical smooth muscle tumour with low risk of recurrence, 2. Atypical smooth muscle tumour with limited experience, and 3. Smooth muscle tumours of low malignant potential. The mainstay of treatment is hysterectomy. The recurrence rate is reported to be between 7-12%, which could include some tumours in the form of leiomyosarcoma (Guntupalli et al., 2009, Ip et al., 2009).

2.6.4 Endometrial stromal sarcoma

Endometrial stromal sarcoma accounts for less than 1% of all uterine malignancies (Harlow et al., 1986). They are subdivided into 1. Endometrial

stromal nodule, 2. Low-grade endometrial stromal sarcoma, 3. High-grade endometrial stromal sarcoma, and 4. Undifferentiated endometrial sarcoma.

Endometrial stromal nodules are benign tumours, which can be found in premenopausal and postmenopausal women, who are asymptomatic or presenting with abnormal uterine bleeding or an enlarging uterus (Dionigi et al., 2002). Macroscopically, they may appear as an intracavitary polypoidal swelling or an intramural tumour. The mainstay of treatment is hysterectomy; however, expectant management can be considered in asymptomatic women.

Low-grade endometrial stromal sarcomas are malignant tumours, they are the second most common uterine sarcoma following leiomyosarcoma, accounting for 6-20% of all uterine sarcomas (Harlow et al., 1986). Most commonly, they are found in perimenopausal women presenting with abnormal uterine bleeding and pelvic pain (Fekete and Vellios, 1984). Macroscopically, they may appear as multiple intracavitary or intramural tumours, within which cystic formation, haemorrhage or necrosis may be present. The prognosis of low-grade endometrial stromal sarcomas is relatively good with a 5-year overall survival rate of 70-84% (Abeler et al., 2009). The mainstay of treatment is a radical hysterectomy and bilateral salpingo-oophorectomy to reduce the risk of any secondary hormonal stimulation of the tumour. Adjuvant chemoradiation therapy is offered to tumours with *t(10;17)* mutation as there is a higher risk of recurrence (Lee et al., 2012).

High-grade endometrial stromal sarcomas are rare tumours that previously may be classified as undifferentiated endometrial sarcomas. They can be found in premenopausal and postmenopausal women with abnormal uterine bleeding or an enlarging uterus. Macroscopically, they most commonly appear as multiple intra-cavitary polypoidal swellings with extensive haemorrhage and necrosis. Compared to low-grade endometrial stromal sarcomas, more women with high-grade endometrial stromal sarcomas have extra-uterine metastatic disease at the time of diagnosis. The prognosis of high-grade endometrial stromal sarcomas is poor;

however, it is not as poor as undifferentiated uterine sarcoma (Lee et al., 2012).

Undifferentiated endometrial sarcomas are rare tumours that are characterised by high-grade cytologic features with no specific type of differentiation. They are typically found in postmenopausal women. The most common presenting complaints are postmenopausal bleeding and symptoms relating to extrauterine metastasis, as approximately two-thirds of women have stage 3 or 4 diseases at the time of diagnosis. Macroscopically, they may appear as a large intracavitary polypoidal swelling with extensive haemorrhage and necrosis. Treatment is radical hysterectomy, bilateral salpingo-oophorectomy, adjuvant radiotherapy +/- chemotherapy; however, the prognosis is very poor with only a small proportion of women surviving more than two years (Kurihara et al., 2008).

2.6.5 Mixed Mullerian tumours

These are an uncommon group of uterine tumours that consist of Mullerian adenofibroma, Mullerian adenosarcoma and malignant mixed Mullerian tumours (carcinosarcomas).

Mullerian adenofibromas are benign tumours. These tumours contain both benign epithelium and mesenchyme. They can be found in both premenopausal and postmenopausal women. Macroscopically, they most commonly appear as intracavitary polypoidal cystic swelling. Treatment includes expectant management or surgical resection depending on the presenting complaint and women's preferences.

Mullerian adenosarcomas account for 5-10% of all uterine sarcomas (Abeler et al., 2009). These tumours contain a benign epithelium, but the mesenchymal component is malignant. Most commonly, they can be found in the endometrial cavity as a large polypoidal cystic swelling; however, they could also be in the myometrium and cervix. Typically, women of premenopausal or postmenopausal ages may present with abnormal

uterine bleeding and pelvic pain (Zaloudek and Norris, 1981). The mainstay of treatment is a hysterectomy and bilateral salpingo-oophorectomy. In early-stage disease, the prognosis is usually good but up to 1 in 4 women may suffer recurrence disease and half of them may die as a result (Clement and Scully, 1989).

Malignant mixed Mullerian tumours are now referred to as carcinosarcomas. They account for 2-5% of all uterine malignancies (Silverberg et al., 1990). They are usually found in postmenopausal women who present with postmenopausal bleeding, an enlarged uterus or raised serum CA125 (Clement and Scully, 1988). One in three women with carcinosarcoma may have a history of previous exposure to pelvic radiotherapy (Zelmanowicz et al., 1998). Macroscopically, they typically appear as a large intracavitary polypoidal swelling with areas of necrosis and haemorrhage (Silverberg et al., 1990). Microscopically, they are usually of serous or endometrioid histological subtypes with a homologous sarcomatous element. The mainstay of treatment involves radical hysterectomy, bilateral salpingo-oophorectomy, and adjuvant chemoradiation therapies. The prognosis of carcinosarcoma is poor, even in women with the early-staged disease; most will experience recurrent disease within the first two years following surgery and the overall survival ranges between 40-60% (Jonson et al., 2006, Garg et al., 2010).

2.6.6 Adenomyosis

Adenomyosis is a benign disease where endometrial glands and stroma are present in the myometrium. Histologically, the diagnosis of adenomyosis requires endometrial tissue to be found in at least 25% of the total myometrial thickness (Parker, 2007).

The prevalence of adenomyosis in hysterectomy specimens is between 5-70% (Bergeron et al., 2006); whereas, in a general gynaecology outpatient clinic, it is diagnosed on ultrasound in approximately 1 in 5 women (Naftalin et al., 2012a). The pathogenesis of adenomyosis is believed to involve a

dysfunction of the endometrial-myometrial junction, which may also be contributed by hormonal and immunological factors (Brosens et al., 1995, Ferenczy, 1998).

Macroscopically, the uterus is diffusely enlarged with a unilateral or bilateral thickening of the myometrium; however, focal myometrial thickening may also occur, mimicking the appearance of a leiomyoma as the adjacent myometrium undergo hypertrophy.

Management of adenomyosis may involve expectant, hormonal therapy, or hysterectomy, which depends mainly on the presenting complaints and women's preferences.

Chapter 3 Importance and clinical significance of endometrial cancer

3.1 Epidemiology and demographics of endometrial cancer

According to Cancer Research UK, between 2015-17, there were approximately 9400 new diagnoses of uterine cancer and 2300 uterine cancer deaths each year (Cancer Research UK, 2020). It is the 4th most common cancer, and it accounts for 5% of all female cancer deaths in the UK. The peak incidence is among women aged between 75-79. Since the early 1990s, the incidence of uterine cancer has increased by about 55%.

In the UK, the lifetime risk of uterine cancer is 1 in 36 women. There is no association between the incidence of uterine cancer with racial backgrounds or household income. The prognosis of uterine cancer is generally good with approximately 70,000 women living in the UK in 2010 following a diagnosis of uterine cancer. The survival rate of uterine cancer has also improved over the past 40 years, from 6 in 10 women surviving beyond 10 years in the 1970s, to 8 in 10 women nowadays.

3.2 Risk factors of endometrial cancer

Oestrogen, both endogenous and exogenous, is the main driving force behind the development of endometrial hyperplasia, which predisposes women to endometrioid EC or carcinosarcoma. In women who have been on unopposed oestrogen therapy for 10 years or more, their risk of developing EC is increased by 10-fold (Crosbie et al., 2010). However, this risk can be reduced to the baseline level if at least 10 days of progestogen therapy is given in each monthly cycle.

Obesity is a significant risk factor for EC. The risk is increased by approximately 6-fold in women with a body mass index (BMI) of over 40 (Calle et al., 2003); nevertheless, the risk can return to baseline following successful weight loss (Adams et al., 2009).

Insulin resistance is an independent risk factor for EC, although it is also commonly found in women who are obese with or without a history of polycystic ovarian syndrome (Cust et al., 2007).

Polycystic ovarian syndrome (PCOS) is characterised by peripheral insulin resistance, oligomenorrhoea and excess androgens (Ehrmann, 2005). As a result, the endometrium is exposed to prolonged oestrogenic stimulation, with an estimated 3-fold increase in the risk of EC (Chittenden et al., 2009). PCOS is commonly found in premenopausal women with EC.

Oestrogen-producing ovarian tumours, such as granulosa cell tumours, can increase the risk of EC due to prolonged unexposed oestrogen stimulation, especially in postmenopausal women. EC is estimated to be found in 9-13% of women with ovarian granulosa cell tumours (Pectasides et al., 2008).

Lynch syndrome (hereditary non-polyposis colorectal cancer) is an inheritable risk factor for EC; women have a 70% lifetime risk of EC (Dove-Edwin et al., 2002). It is characterised by mutations in the mismatch repair genes, including MSH-2, MSH-6, MLH-1 and PTEN (Peel et al., 2000, Zhou et al., 2002). BRCA mutations do not increase the risk of EC significantly (Levine et al., 2001).

Tamoxifen is an anti-oestrogen drug; however, it has a weak oestrogenic effect on the endometrium, especially in postmenopausal women, therefore the risk of EC is increased by approximately 2-3 folds (Cohen, 2004).

Nulliparity is an independent risk factor for EC, but the increased risk is only significant in premenopausal women rather than postmenopausal women (Ali, 2014).

Cigarette smoking is associated with a reduced risk of EC, especially in postmenopausal women; however, the mechanism is unclear (Al-Zoughool et al., 2007).

3.3 Prognosis of endometrial cancer

The histological subtype of the EC is an important prognostic factor. The prognosis is generally more favourable for endometrioid EC and its variants, compared to non-endometrioid EC, such as serous EC, clear cell EC, undifferentiated EC and carcinosarcomas.

Histological grading is only important in endometrioid EC as non-endometrioid EC are all classified as high-grade tumours. A more differentiated low-grade endometrioid EC is associated with a more favourable prognosis.

The stage of EC at the time of diagnosis, for all histological subtypes, is important to the patient's prognosis (Kato et al., 2012).

The presence of lymphovascular space invasion (LVSI) is an independent prognostic factor for EC (Gal et al., 1991). It is associated with an increased risk of recurrence and poorer survival.

Women's age at the time of diagnosis is a prognostic factor for EC (Abeler and Kjørstad, 1991). This is thought to be due to an increased risk of immunosuppression with advanced age. In a case series of 865 women with EC, the 5-year survival rate was 96% among women aged 40-49, compared to only 53% in women aged 70-79 (Connelly et al., 1982).

Progesterone receptors (PR) are more commonly found in well-differentiated endometrioid EC compared to poorly differentiated or non-endometrioid EC (Fukuda et al., 1998). Women with PR-positive tumours may theoretically benefit from hormonal therapy; however, further research is needed on the different subtypes of PR that are present in these tumours.

3.4 Recent advances in genomics and molecular subtyping of endometrial cancer

One of the most significant recent advancements in gynaecological oncology has been the new genomic classification of EC. It is hoped that this will lead to a new era of personalised treatment for EC, given that genomic classification may improve the risk stratification and the use of targeted therapies in EC.

The breakthrough in the genomic classification of EC began with The Cancer Genome Atlas (TCGA) Study (Cancer Genome Atlas Research et al., 2013). This study analysed 373 cases of EC and classified malignancies into three clinical risk groups: 1. Low-risk (polymerase Ɛ (POLE) ultra-mutated), 2. Intermediate-risk (copy number low and MSI-H groups) and 3. High-risk (copy number high/serous-like). Importantly, each group shares similar genomic and molecular features but based on our current risk stratification system they may be classified differently.

The POLE gene encodes for the DNA polymerase epsilon, which has a proofreading function to ensure that DNA replication is accurate (Shinbrot et al., 2014). This proofreading ability is reduced in POLE ultra-mutated tumours and therefore the errors in DNA replication are increased, which in turn predisposes to the development of malignancy. Fortunately, the majority of POLE ultra-mutated EC present at an early stage and they also have a relatively good prognosis even in high-grade tumours. In the PORTEC-2 study, none of the women with grade 3 POLE ultra-mutated EC had a recurrence, compared to 31% in other grade 3 non-POLE ultra-mutated EC (Nout et al., 2010).

Microsatellite instability (MSI) is characterised by defects in the post-replicative DNA mismatch repair (MMR) system (Zighelboim et al., 2007). In the TCGA study, MSI was classified by the presence or absence of several genomic markers (Umar et al., 2004). Tumours with the absence of any of these markers are classified as microsatellite-stable (MSS), the presence of one to two markers is considered low-level MSI (MSI-L), and if

three or more markers are present, they are high-level MSI (MSI-H). A higher level of MSI is associated with more frequent DNA mutations, especially in the PI3K-AKT-mTOR pathway (Campbell et al., 2017). Tumours with MSI-H also typically have a high number of tumour-infiltrating and peritumoral lymphocytes. This favourable tumour microenvironment presents a potential opportunity for cancer immunotherapy, such as the anti-PD-1/PD-L1 antibody (Yamashita et al., 2018).

Copy number low/MSS EC is usually low grade (grade 1 or 2) tumours with few TP53 mutations, whereas copy number high/serous-like EC is commonly serous EC or high grade (grade 3) endometrioid EC with frequent TP53 mutations (Cancer Genome Atlas Research et al., 2013). Loss of the p53 tumour suppressor function is associated with significant genomic instability and a rapid progression of the tumour (Salvesen et al., 2012).

In addition to the TCGA molecular subgroups, other useful molecular markers have also been identified, such as L1CAM. L1CAM is a transmembrane protein that promotes cellular proliferation, migration, invasion, and metastasis; it is over-expressed in various malignancies (Zeimet et al., 2013). In traditionally “low-risk” EC, the 5-year disease-free survival is significantly worse in L1CAM positive tumours compared to L1CAM negative tumours (Kommoss et al., 2017).

The four TCGA molecular subgroups have been combined with other molecular markers, such as L1CAM, to create an integrated molecular risk stratification system for EC (Stelloo et al., 2016). The aim is to improve the management of clinically early-stage EC by reducing the number of overtreatment and undertreatment. PORTEC 4a is the first and ongoing randomised controlled trial, which uses this integrated molecular approach to determine the choice of adjuvant therapy in women with high intermediate-risk EC (Wortman et al., 2018).

The integrated molecular classification system has the potential to revolutionize our future management of EC, such as preoperative planning (whether to perform lymphadenectomy/sentinel lymph node biopsy), choice

of adjuvant therapies, postoperative follow-up strategies, and use of targeted therapies in recurrent or metastatic diseases.

Chapter 4 Principles of ultrasound and its assessment of the endometrium

4.1 Basic principles of ultrasound

Ultrasound is mechanical energy that is transmitted as pressure waves through a medium. In gynaecological ultrasound, the medium could be soft tissue in the pelvis, fluid (blood, urine, or cystic structures) and air.

To generate ultrasound, the ultrasound machine requires a vibrating source, which is usually a piezoelectric crystal, such as quartz. These crystals vibrate when an electric current passes through them, on the contrary, they can also convert sound waves back into electrical energy and thereby allow the creation of an anatomical image.

The basic descriptions of a sound wave include its frequency, wavelength, amplitude, power, intensity, and propagation speed. The frequency of a sound wave is the number of cycles occurring in each second. In diagnostic ultrasound, the range of frequency used is usually between 1 to 15 MHz Amplitude is the size of the sound wave. Power is a measure of the energy created by the sound wave per second, for example, 1 joule per second is equivalent to 1 watt of energy. Therefore, by increasing the voltage applied through the piezoelectric crystal, more power can be transmitted through the ultrasound and hence the diagnostic image can appear brighter on the display screen. The intensity of a sound wave is defined as the concentration of energy applied through the cross-section of a wave. Propagation speed is the time it takes a sound wave to travel through a medium. In general, the propagation speed is fastest if the medium is solid, slower in fluid and slowest in gas.

There are several concepts to consider which can affect the quality of a diagnostic ultrasound image, such as attenuation, reflection, scatter, and absorption of sound waves.

Attenuation is the weakening of a sound wave as it travels through a medium. Different soft tissue mediums in the body may weaken a sound wave differently, which is measured as the attenuation coefficient. Sound waves with a higher frequency tender to suffer more attenuation than those with a lower frequency. Also, the further the sound wave must travel the more of its energy can be lost, therefore, when performing ultrasound examination, the shallowest depth should be used to minimise attenuation.

Reflection occurs when a sound wave travels through the interaction of two mediums, it is the amount of energy that is reflected back to the piezoelectric crystal. This is important in diagnostic ultrasound because the generation of an image relies on the reflection of sound waves. Different medium interfaces and the smoothness of these interfaces can affect the amount of reflection generated.

Scatter is the redirection of sound waves in many different directions, and this occurs more frequently in higher frequency waves than in lower frequency ones. Therefore, although it is preferable to obtain a diagnostic image with the highest frequency possible, it may come with the cost of increased scatter.

Absorption is when sound energy is converted into heat, which increases with a higher frequency sound wave. In performing a clinical ultrasound, it is therefore important to keep scanning time to the minimum and not to increase the power and intensity of ultrasound unnecessarily.

Diagnostic ultrasound creates short pulses of sound waves. In between the transmission of these pulses, the piezoelectric crystal is waiting for the reflected sound waves to create an anatomical image. The shorter the duration of these pulses, the easier it is for the ultrasound machine to discriminate between smaller objects, hence a higher resolution. Pulse repetition frequency (PRF) is the number of pulses being generated each second, a lower PRF allows for more listening time in between the pulses and therefore improves deeper imaging.

4.2 Ultrasound machine

A diagnostic ultrasound machine usually has a master synchronizer, transducer, pulser, receiver, storage device and display monitor.

The transducer is where ultrasound is created and where the reflected sound waves are converted back to electrical energy. It usually has six basic components, which include a case, electrical shield, insulator, wire, matching layer, and damping element.

The receiver converts unprocessed electrical signals from the transducer into data that can be used to create an anatomical image. There are five basic functions of the receiver, these include amplification (receiver gain), compensation, compression, demodulation, and projection. The receiver gain increases all the received signals and therefore increases the brightness of the entire ultrasound image. Compensation makes all received signals identical regardless of the depth. Time gain compensation (TGC) can increase the gain specifically to deeper structures, make them appear brighter, and therefore compensates for absorption.

The ultrasound machine has three main display modes, including amplitude mode (A-mode), brightness mode (B-mode) and motion mode (M-mode).

A-mode has a limited role in diagnostic ultrasound, it is used to measure distance by displaying the wave amplitude against the depth of the reflected waves.

B-mode is most used clinically, it converts received sound waves into dots of varying intensity while maintaining the depth proportional to the time of flight of the pulse. Brighter dots correspond to stronger reflections, whereas weaker reflections are less bright.

M-mode shows the movement of tissues. Stationary tissues are shown as a straight line while moving tissues are represented by sinusoidal lines.

4.3 Doppler ultrasound

In clinical ultrasound, Doppler imaging is usually used to examine the direction, velocity, and pattern of blood flow. The basic principle of Doppler is based on the perceived change in sound frequency or pitch. When the source of the sound is moving towards the receiving transducer, the sound wave will appear to have a higher pitch. On the other hand, when the source of sound is moving away from the receiving transducer, the opposite will occur with the sound wave appearing to have a lower pitch. This difference or shift in frequency is called the Doppler frequency. The frequency shift has a positive correlation with the velocity of the moving object. To optimise Doppler imaging, it is important to use a lower ultrasound frequency and to ensure that the wave beam is perpendicular to the measured blood flow.

There are different types of Doppler imaging; however, the most common types are continuous wave Doppler and pulsed Doppler.

Continuous-wave Doppler uses one piezoelectric crystal to continuously transmit sound waves, while another piezoelectric crystal is used for receiving the reflected waves. It can more accurately measure high velocities compared to pulsed Doppler; however, it cannot reliably determine the location of the blood flow.

Pulsed Doppler uses only one piezoelectric crystal, it receives reflected sound waves in between the pulses. The amount of time for a transmitted sound to return is recorded and thereby allows the depth of the blood flow to be calculated. Its main drawback is the inaccuracies in measuring high-velocity flow, which can lead to a phenomenon called aliasing.

4.4 Endometrial thickness

The endometrial thickness (ET) on ultrasound is measured in the sagittal plane as the maximal diameter across both the anterior and posterior layers

of the endometrium (Leone et al., 2010). The callipers should be placed at the anterior and posterior endometrial-myometrial junctions, respectively (Figure 1). When intracavitary fluid is present, the fluid should be subtracted from the ET measurement or the individual anterior and posterior layers of the endometrium are measured separately, and the sum is reported as the ET. If an intracavitary lesion, such as a polyp, is present, the ET measurement should also include the intracavitary lesion. If the endometrium cannot be clearly defined, then it should be recorded as non-measurable.

4.5 Intracavitary lesions

An intracavitary lesion is defined as anything that protrudes into the uterine cavity (Leone et al., 2010). It can be an endometrial or a myometrial lesion. The percentage of the total endometrial surface involved should be subjectively estimated by the ultrasound operator. The intracavitary lesion is described as “extended” if ≥25% of the total endometrial surface is involved; whereas it is described as “localised” if <25% is involved. Localised lesions are further subdivided into pedunculated or sessile. Pedunculated lesions have a lesion base diameter/maximal lesion diameter ratio of <1, or sessile if the ratio is ≥1. The morphological features of the intracavitary lesion should also be described, including its outline (regular or irregular) and echogenicity (uniform or non-uniform). Intra-cavitary lesions that appear cystic are described as non-uniform (Figure 2).

4.6 Intracavitary fluid

The amount of intracavitary fluid is measured as the largest anterior-posterior diameter in the sagittal plane and the fluid should be described as anechoic, low-level echogenicity, ground glass or mixed echogenicity.

4.7 Echogenicity

The endometrium is described as hyperechoic, isoechoic, or hypoechoic, in comparison to the echogenicity of the myometrium. Furthermore, it may also be described as uniform (the endometrium is homogenous) or non-uniform (the endometrium appears heterogeneous, asymmetrical, or cystic).

4.8 Endometrial-myometrial junction

The endometrial-myometrial junction (EMJ) is the transitional zone between the mucosal layer of the endometrium and the outer smooth muscle layer of the myometrium (Naftalin and Jurkovic, 2009). A layer of inner myometrium encircles the endometrium and various other terms have been used to describe it, such as the uterine junctional zone and sub-endometrial myometrium.

On ultrasound scan, the inner myometrium appears hypoechoic compared to the adjacent endometrium and outer myometrium. This is due to its increased vascularity and more densely packed muscle fibres compared to the outer myometrium (Tetlow et al., 1999).

The EMJ is subjectively described on ultrasound as regular, irregular, interrupted or non-defined. It is best visualised on transvaginal two-dimensional ultrasound in the longitudinal view of the uterus as it allows simultaneous assessment of the anterior and posterior layers of the EMJ. Three-dimensional ultrasound improves the assessment of EMJ by making available the coronal view of the uterus.

It is possible to differentiate between early malignant endometrial lesions from benign lesions, such as endometrial polyps, by carefully assessing the EMJ for breaches of the basal endometrium and morphological changes in

the inner myometrium. Benign endometrial polyps may have a typical single feeder vessel crossing the EMJ on Doppler examination (Timmerman et al., 2003); whereas malignant lesions may show multiple vessels crossing the EMJ with multi-focal origins.

Circulating levels of ovarian sex steroid hormones can affect the visualisation of the EMJ. For example, in postmenopausal women, the average inner myometrium is reported to be thinner (3.6mm +/- 0.03 SD) compared to premenopausal women (4.5mm +/- 0.17 SD) (Kiguchi et al., 2017). Furthermore, in postmenopausal women, the contrast in echogenicity is also less distinct on ultrasound compared to premenopausal women. These observations are thought to be due to postmenopausal fibrous involution of the extracellular part of the outer myometrium, resulting in progressive dehydration of the smooth muscle cells (Tanos et al., 2020).

4.9 Colour and Power Doppler assessment of the endometrium

Doppler imaging of the endometrium should be performed with an ultrasound frequency of at least 5.0 MHz, a pulse repetition frequency of 0.3-0.9 kHz, and a wall filter of 30-50 Hz, and the Doppler gain should be reduced until all artefacts disappear.

The Colour content of the endometrium should be scored using the International Ovarian Tumour Analysis (IOTA) colour score (Timmerman et al., 2000), which is a subjective semiquantitative assessment of the amount of blood flow present. A colour score of 1 represents no colour flow signal detected in the endometrium, a score of 2 is when there is minimal colour, a score of 3 is when there is moderate colour, and a score of 4 is when there is abundant colour detected.

Vascular pattern of the endometrium may be described subjectively as a) single dominant vessel without branching, b) single dominant vessel with

branching, c) multiple vessels with a focal origin, d) multiple vessels with a multi-focal origin, e) scattered vessels, and f) circular flow.

4.10 Sonohysterography

Sonohysterography is performed with saline or gel instillation into the uterine cavity as a contrast medium (Farquhar et al., 2003). The uterine cavity distension can be described as optimal (the cavity is distended), suboptimal (the cavity is barely distended) and failed (there is no distension of the cavity).

4.11 Three-dimensional ultrasound

In routine clinical practice, most ultrasound assessments are performed using two-dimensional (2D) imaging only. However, there is now growing evidence of the benefits of the three-dimensional (3D) ultrasound (Levine et al., 2018), for example, the ability of 3D ultrasound to assess the coronal view of the uterus and volume measurements. In gynaecology, 3D ultrasound has been used to improve the assessment of intrauterine devices in the coronal plane, uterine fibroid mapping, diagnosing uterine anomalies, ectopic pregnancies (especially, interstitial, intramural and cervical), and measuring tumour volumes (Figure 3).

There are various ways to produce a 3D ultrasound image, including mechanical scanning, free-hand scanning with position sensing, free-hand scanning without position sensing, and 2D array scanning for dynamic 3D ultrasound (Fenster et al., 2011).

3D ultrasound machines that are based on the mechanical scanning method utilise a motorized mechanism to mobilise a 2D ultrasound transducer to obtain a series of 2D ultrasound images, the resulting 3D image is created by several computer algorithms. Two of the commonly

used 3D ultrasound display techniques are multi-planar reformatting (MPR) and volume rendering (VR).

Figure 1 – Example of the endometrial thickness being measured in the longitudinal view of the uterus during a transvaginal ultrasound scan (Naftalin and Jurkovic, 2009)

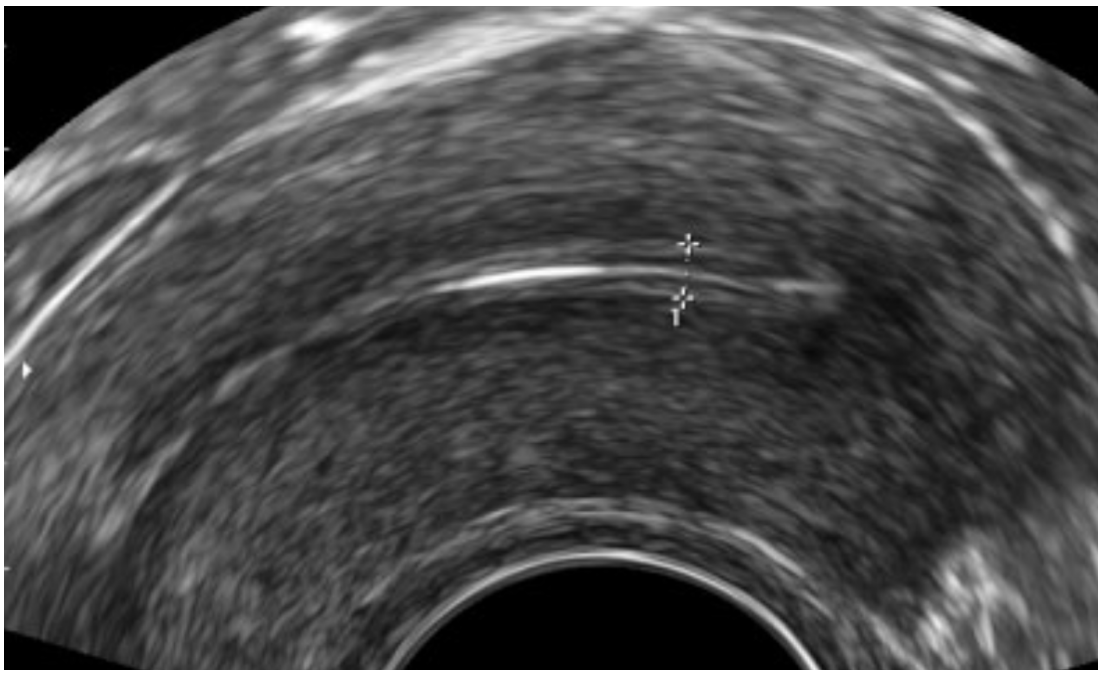


Figure 2 – Example of an intracavitary lesion (benign endometrial polyp) with a regular outline, uniform echogenicity and intra-lesional cystic spaces

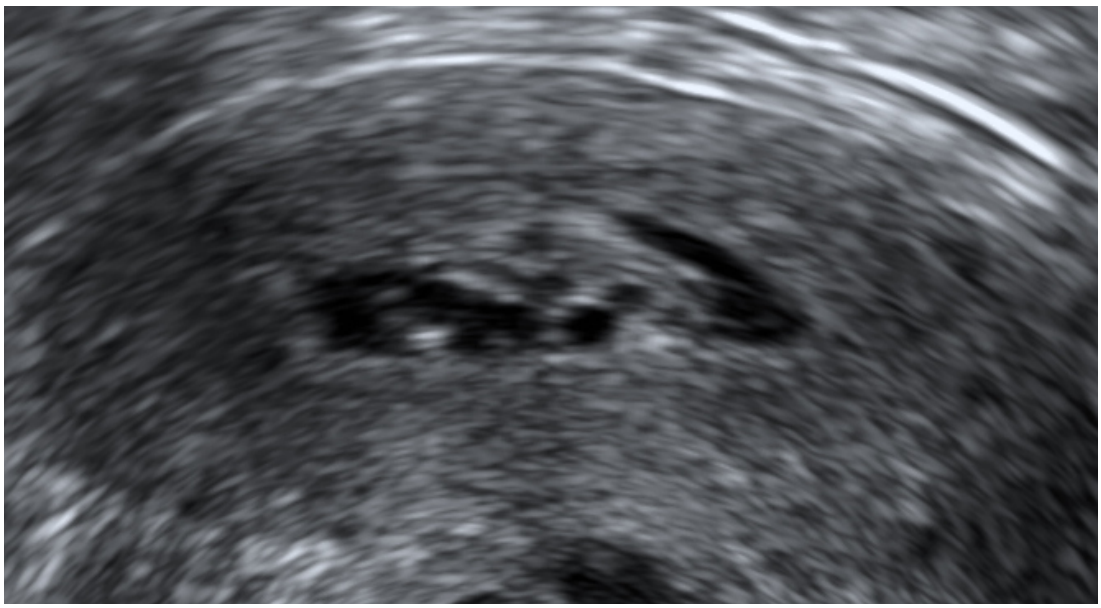
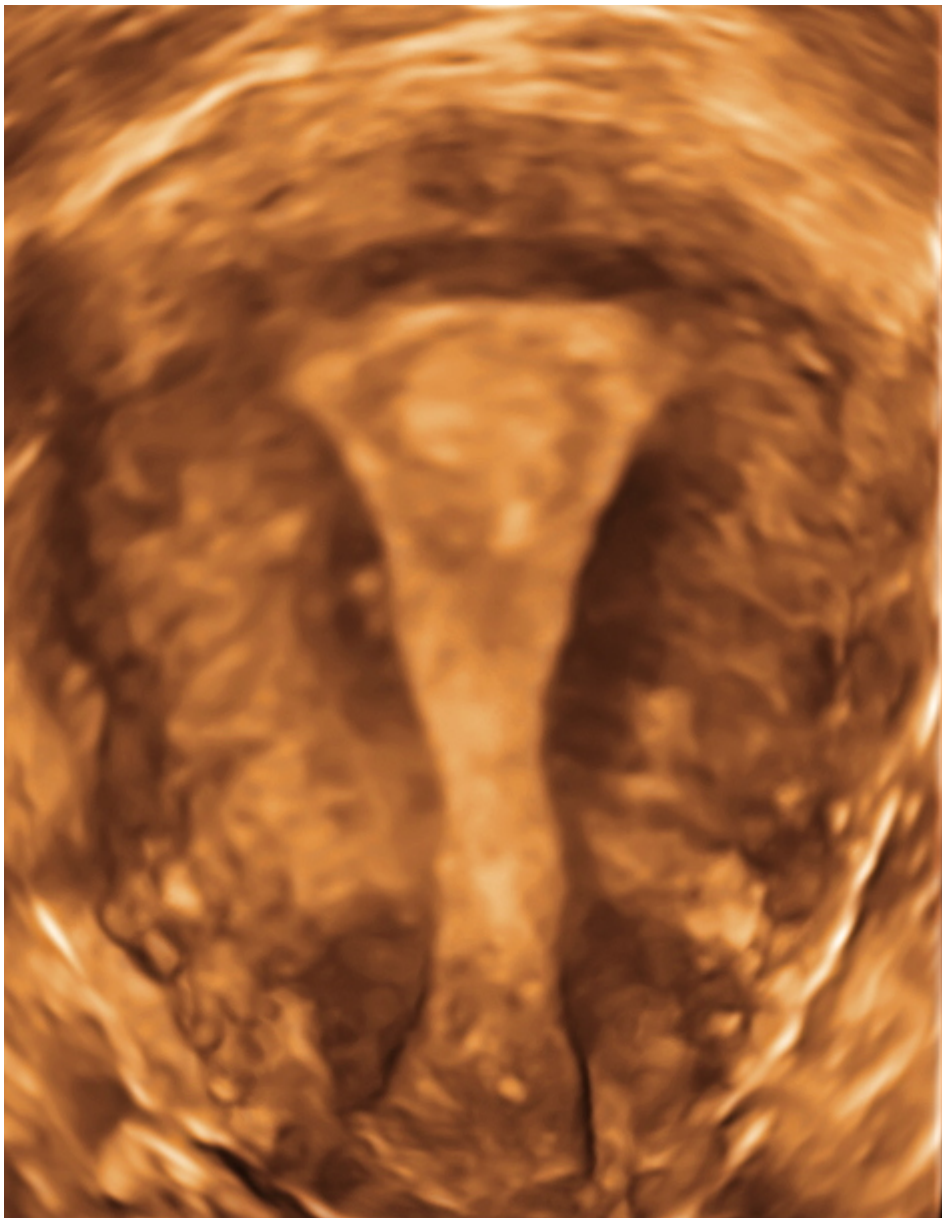


Figure 3 – Example of a three-dimensional ultrasound image in the coronal view of the uterus. There was a well-defined intracavitary lesion (benign endometrial polyp) with a regular endometrial-myometrial junction.



Chapter 5 Current ultrasound-based assessment for women with postmenopausal bleeding

Postmenopausal bleeding (PMB) is defined as vaginal bleeding in women over the age of 45 with at least 12-month history of amenorrhoea, and not on hormone replacement therapy (HRT). PMB is an important clinical symptom because it is the most common presenting complaint in women with endometrial cancer (EC). The risk of EC in women with PMB is between 8-11% (Clarke et al., 2018), which may increase with age and other clinical risk factors.

Abnormal vaginal bleeding in postmenopausal women who are on HRT should be described as unscheduled vaginal bleeding whilst on HRT, rather than postmenopausal bleeding, as their risk of EC is significantly lower compared to women with PMB.

In the UK, women are referred urgently by their general practitioners to a gynaecology rapid access clinic, in accordance with the National Institute for Health and Care Excellence (NICE) guideline, if they experience any PMB, a history of persistent/unexplained vaginal bleeding after 6 weeks of stopping HRT, or if they are on tamoxifen and have abnormal vaginal bleeding (National Institute for Health and Care Excellence, 2015).

5.1 Measurement of the endometrial thickness

Transvaginal ultrasound scan (TVS) with measurement of the endometrial thickness (ET) is the preferred first-line investigation in women with PMB according to the British Society of Gynaecological Oncology guideline (Sundar et al., 2017). However, there is no consensus on the best strategy to manage PMB and other options are also available, such as hysteroscopy or outpatient endometrial biopsies. Some studies reported that in a “low-risk” (<15% risk of EC) population, the most cost-effective strategy is to first

measure the ET on TVS, and if the ET is thickened then women should be offered an outpatient endometrial biopsy. But in the higher-risk (≥15%) population, it may be more cost-effective to carry out an immediate outpatient endometrial biopsy instead (Dijkhuizen et al., 2003).

The BGCS recommends using an ET cut-off of ≥4mm on TVS; however, different cut-offs of 3mm, 4mm, and 5mm have also been suggested by others with reported sensitivities of 98%, 95% and 90% for EC (Timmermans et al., 2010). The BGCS also advises that the measurement of ET alone on TVS is not diagnostically useful in women who are on HRT or tamoxifen.

Women with PMB and an ET of <4mm on TVS do not routinely require further investigations and they can be managed expectantly as their risk of EC is low, unless there is a history of recurrent PMB. In contrast, those with an ET ≥4mm must undergo an endometrial biopsy. The sensitivity of outpatient endometrial biopsy devices, such as the Pipelle endometrial suction curette (Laboratoire CCD, Paris, France), is very good, and the post-test probability of EC with a negative Pipelle biopsy is only 0.9% (Clark et al., 2002).

Outpatient hysteroscopy is usually reserved for those with a history of recurrent PMB despite a negative outpatient endometrial biopsy, ultrasound finding of other abnormalities (e.g., polyps), or women with additional risk factors for EC (e.g., tamoxifen). The post-test probability of EC following a negative hysteroscopy for malignancy is 0.6% (Clark et al., 2002).

Despite the importance of measuring the ET accurately on TVS in women with PMB, a prospective study reported that the endometrium could not be visualised in up to 1 in 8 women with PMB (Epstein and Valentin, 2006). Several factors may make it more difficult to assess the endometrium on TVS, such as an axial uterus, the presence of submucosal fibroids, adenomyosis, obesity or previous uterine surgery (ACOG, 2018).

5.2 Ultrasound subjective pattern recognition and diagnostic mathematical models for endometrial cancer

Several studies have reported on the typical morphological features of endometrial cancer on ultrasound, these include a non-uniform endometrium, an interrupted EMJ, a high colour score on Doppler imaging and a multiple vessels vascular pattern (Figure 4) (Dueholm et al., 2015b, Madkour, 2017, Epstein et al., 2018, Van Den Bosch et al., 2021).

Subjective pattern recognition (SPR) for EC refers to the identification of these typical morphological features of EC, which allow for the diagnosis of EC on ultrasound. In a prospective study, the sensitivity and specificity of SPR for EC were 86% and 90%, respectively (Dueholm et al., 2015b). Compared to the measurement of endometrial thickness alone, SPR appears to offer a better specificity for EC, without a significant sacrifice in sensitivity, and therefore fewer women may undergo further unnecessary invasive tests.

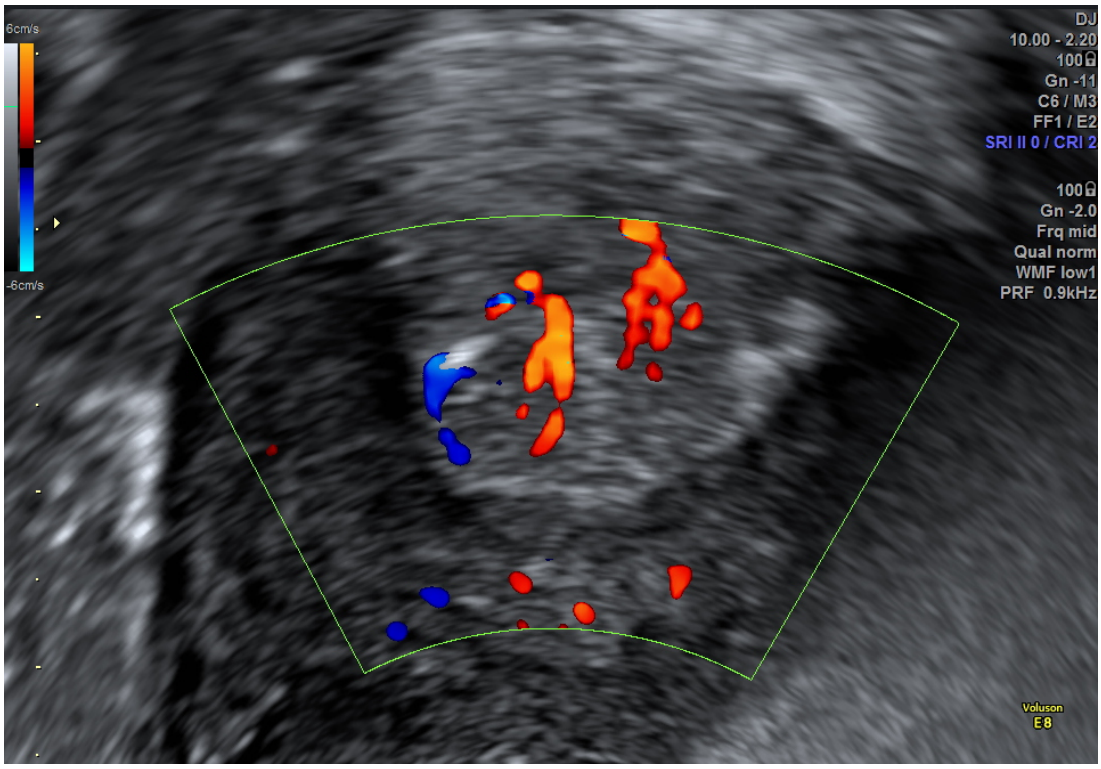
Besides the use of SPR for EC, others have also tried to build mathematical models to predict the presence of EC. Dueholm et al. (2014) proposed the Risk of Endometrial Cancer (REC) score for women with PMB and ET ≥5mm. The scoring system is based on the patient's BMI, Doppler score, ET, interrupted EMJ on unenhanced TVS or irregular surface on GIS. A score of ≥3 has a sensitivity and specificity of 91% and 84% for EC, respectively (or ≥4 if GIS is used, the sensitivity and specificity are 91% and 94%, respectively). Later, Dueholm et al. (2019) also proposed a simplified version of the REC score for women with PMB and an ET ≥8mm. This simplified REC scoring system, when used without sonohysterography, consists of only the Doppler score and whether the EMJ is interrupted. At a cut-off of score ≥2, the sensitivity and specificity for EC or atypical endometrial hyperplasia (AH) were 92% and 84%, respectively. The author proposed that women with PMB can be divided into very low risk

(ET<4mm), low-risk (ET≥4-<8mm), intermediate (ET≥8mm + score <2), or high-risk (ET≥8mm + score ≥2) groups for EC/AH.

Another author prospectively validated 5 mathematical models for EC in women with PMB and ET ≥4.5mm. The area under the curve (AUC) ranged between 0.86-0.90. The model with the best diagnostic performance included ET, heterogeneous endometrial echogenicity, and areas of densely packed vessels on power Doppler. The sensitivity and specificity were 81% and 84%, respectively.

Although the use of SPR and mathematical models has the potential to improve our current risk stratification of women with PMB. The main drawbacks of these studies were that most were developed by ultrasound experts, and few were tested in the hands of less experienced operators; therefore, their reliability and generalisability have not yet been evaluated sufficiently for use in routine clinical practice.

Figure 4 – Example of endometrial cancer on transvaginal ultrasound scan where the endometrium appears heterogeneous, and the endometrial-myometrial junction is interrupted by multiple vessels with multi-focal origins



Chapter 6 Current modalities for the preoperative staging of endometrial cancer

Most EC spread via direct invasion into the myometrium and to the cervix, following which the adnexa and adjacent small bowel may also be involved. In more advanced EC, tumour cells may spread via the lymphatics, this includes the internal iliac, external iliac, common iliac, obturator and para-aortic lymph nodes.

Some EC, such as high-grade endometrioid or serous EC, may spread via the fallopian tubes and into the peritoneal cavity. As a result, there may not be any significant myometrial invasion at the site of the primary tumour (Barlin et al., 2012).

The FIGO staging system for EC is currently the most widely used classification (Creasman, 2009). It requires an accurate preoperative assessment for the myometrial invasion (MI) and cervical stromal invasion (CSI). Women with deep MI (≥50%), stage 1b disease, are at increased risk of lymph node and extrauterine metastases, therefore these women require more extensive treatments, such as lymphadenectomy and adjuvant radiotherapy.

The presence of CSI, FIGO stage II, is also an important clinical finding, as this indicates the need for women to undergo a radical hysterectomy rather than a simple hysterectomy. However, it can be difficult to determine this accurately because of a lack of landmarks between the uterine corpus and the cervix.

Histologically, MI is diagnosed when there is evidence of tumour cells extending beyond the endometrial-myometrial junction (EMJ) and into the underlying myometrium. The maximum depth of MI is measured in millimetres from the EMJ and expressed as a percentage of the total myometrial thickness. In some circumstances, it can be difficult to diagnose MI because the EMJ is poorly defined due to the presence of adenomyosis or leiomyoma. It has been reported that MI is over-estimated in up to 25%

of cases (Silverberg, 2000). Categorizing MI into <50% (superficial) or ≥50% (deep) has made the assessment of MI more straightforward and reproducible. MI can occasionally be found within foci of adenomyosis (Naftalin et al., 2012b); in these women, their prognosis is not worse compared to those who do not have adenomyosis (Hall et al., 1984).

6.1 Magnetic resonance imaging

In most developed countries, preoperative assessment of the myometrial and cervical stromal invasion in EC is performed by magnetic resonance imaging (MRI).

MRI creates multiplanar images with high temporal, contrast, and spatial resolution. It uses radio-frequency waves generated by a scanner with a strong and homogeneous magnetic field. The field strength of the magnet and the type of antenna (called a surface coil) that receives the radio-frequency signal are two important parts of the system for image quality. Most MRI machines have a superconductive 1.5 or 3.0 Tesla magnet.

For pelvic imaging, a phased-array surface coil is used. A phase-array coil is usually composed of 4-32 separate antennas. The signal from each of the coil elements is mathematically converted to one image. The positioning of the coil on the patient is important, as the desired field of view is usually no more than 24cm.

Before placing the women in the centre of the magnetic field, an injection of an anti-peristatic drug is usually given, for example, butylscopolamin IV. The examination begins by obtaining a “localiser” series, these images are usually acquired fast and within a few seconds, with low spatial resolution. They are used to define anatomical positions and planes for the diagnostic images. The standard imaging planes in the pelvis are sagittal, transverse, coronal, and oblique planes. For uterine imaging, oblique images that are parallel and perpendicular to the long axis of the uterine body are of particular interest. At the end of the MRI examination, a contrast agent is

administered, for example, gadolinium-based chelate IV, which will enhance the signal intensity in perfused tissues. Imaging of the same body part after injection is repeated at predefined intervals and is usually referred to as dynamic contrast-enhanced MRI (DCE-MRI). The rationale behind the contrast-enhanced sequence in EC is the improved delineation of the tumour to the myometrium based on a difference in kinetic uptake of the contrast agent between the tumour and healthy myometrium. Diffusion-weighted imaging (DWI) is based on magnetic resonance measurement of the random extra-, intra-, and transcellular movement of water molecules in the body. As some tissues in the body have more restricted diffusion than others, this offers a way of receiving information about tissues on a cellular level. Many solid tumours tend to have more restricted diffusion of water molecules than normal tissues.

The standard MRI sequences that delineate EC include T2-weighted, dynamic T1-weighted gadolinium (early and late) sequences and diffusion-weighted imaging including an apparent diffusion coefficient map. In a recent meta-analysis, the pooled sensitivity and specificity of MRI for deep MI were 81% and 91%, respectively. For the detection of CSI, the pooled sensitivity and specificity were 50% and 95%, respectively (Bi et al., 2020).

6.2 Ultrasound

Preoperative assessment for MI and CSI in EC can also be performed by ultrasound when the expertise is available. This can be particularly useful in women who have contraindications to MRI, such as high BMI, cardiac pacemakers, or claustrophobia.

Both MI and CSI can be assessed by subjective or objective methods on ultrasound.

For the assessment of MI, a large multicentre study recently compared subjective assessment with objective measures (minimal tumour-free margin, tumour/uterine AP diameter ratio) and found that subjective

assessment was superior to objective measures. The objective measures had similar sensitivity for deep MI compared to subjective assessment, but subjective assessment had a significantly higher specificity 76% vs 67% (minimal tumour free margin) and 69% (tumour/uterine AP diameter ratio), respectively (Verbakel et al., 2020).

For the assessment of CSI, subjective assessment also performed better compared to the objective measure (distance from the lower margin of the tumour to the outer cervical os, Dist-OCO). Again, both subjective and objective measures had similar sensitivity, but the specificity of subjective assessment was significantly better at 93% vs 87% (Verbakel et al., 2020).

A previous meta-analysis tried to estimate the accuracy of ultrasound in predicting deep MI and it included 24 studies. Both subjective assessment and objective measurements such as Karlsson's and Gordon's were performed; the pooled sensitivities and specificities were 78%, 84%, 85% and 81%, 82%, 80%, respectively (Alcázar et al., 2015).

Another meta-analysis tried to estimate the accuracy of ultrasound in predicting CSI, the pooled sensitivity and specificity were 63% and 91%, respectively (Alcázar et al., 2018). Heterogeneity was high for both sensitivity and specificity, but no reason was found in the meta-regression analysis. Almost all studies assessed CSI subjectively, and only 1 used objective measurement.

Few previous studies have compared the accuracy of ultrasound and MRI in preoperative staging in EC in the same cohort of patients. In the meta-analysis of Alcazar et al. (2017), only eight studies fulfilled this criterion. It showed that although MRI had a slightly better pooled sensitivity compared to ultrasound, 83% vs 75%, the difference was not statistically significant; while the specificities of MRI and ultrasound were similar, 82% and 86%, respectively.

6.3 Computer Tomography

Computer tomography (CT) does not have a prominent role in the preoperative staging of EC when compared to MRI or ultrasound. In two retrospective studies, the sensitivity of CT for deep MI ranged between 10-83% and specificity 42-100% (Zerbe et al., 2000, Hardesty et al., 2001). For the detection of CSI, the sensitivities were only 20-25% and specificities 70-79%.

Imaging of the chest is important preoperatively to avoid inappropriate surgery in women with pulmonary metastasis. However, a simple chest x-ray (CXR) is usually adequate in low-risk EC and therefore a chest CT scan is not routinely required (Connor et al., 2000).

6.4 Positron emission tomography

Positron emission tomography (PET) is not currently recommended in the NHS for preoperative staging of EC outside of a clinical trial. However, a PET/CT may be considered to exclude distant metastasis before radical pelvic surgery. The reported sensitivity and specificity of PET/CT in detecting metastatic disease were 96% and 93%, respectively (Kadkhodayan et al., 2013).

6.5 Intraoperative frozen section

In the UK, an intra-operative frozen section is rarely performed for EC, unless there is uncertainty regarding the preoperative histological diagnosis or unexpected intraoperative findings of extrauterine lesions or suspicious lymph nodes.

Chapter 7 Current management of endometrial cancer

7.1 Early disease (FIGO stage 1 and 2)

Women with low-risk EC, such as FIGO stage 1a, grade 1 or 2 endometrioid EC, can be managed by hysterectomy and bilateral salpingo-oophorectomy alone. However, some of these women may require further surgery, such as lymphadenectomy or postoperative adjuvant therapy, due to the presence of additional risk factors in the final surgical histological assessment or an underestimation of the disease preoperatively.

The role of lymphadenectomy in EC is controversial, but there is currently no evidence to support the routine practice of lymphadenectomy in women with low-risk EC. A Cochrane review identified two randomised controlled trials comparing routine lymphadenectomy versus palpation for lymph nodes intraoperatively followed by removal of the enlarged lymph nodes only at the surgeon's discretion (Frost et al., 2017, Benedetti Panici et al., 2008, group et al., 2009). They found that there were no significant benefits in survival or the risk of recurrence, between the two approaches. On the contrary, women who received lymphadenectomy were more likely to experience postoperative lymphocysts and lymphoedema.

No randomised controlled trials have previously compared lymphadenectomy versus no surgical removal of lymph nodes in EC.

Sentinel lymph node (SLN) biopsy has become more widely available. A multi-centre prospective study reported a sensitivity and specificity of 84% and 97%, respectively, for the diagnosis of lymph node metastasis by SLN biopsy in low-risk EC (Ballester et al., 2011). Lymph node metastasis was found in 11% of women with low-risk EC, which would have been underdiagnosed if an SLN biopsy was not performed. However, further research is still needed to determine if SLN biopsy is associated with survival benefits.

In women with early staged EC but high-grade endometrioid or non-endometrioid EC, they are usually offered lymphadenectomy and omentectomy.

7.2 Late disease (FIGO stage 3 and 4)

Women with advanced EC who are fit for surgery may benefit from surgical resection of all visible diseases, as there is some evidence from retrospective studies to suggest a survival benefit. Indeed, the presence of any residual disease postoperatively is found to be an independent risk factor for a poorer prognosis. Systematic lymphadenectomy should be performed in all surgically managed late-staged EC as it is associated with a higher detection rate (4-fold) of lymph node metastasis, compared to palpation for enlarged lymph nodes alone (Benedetti Panici et al., 2008).

Neoadjuvant chemotherapy may be offered to women who may not be suitable for upfront surgery.

Surgery can also be offered as a palliative treatment to reduce the symptoms of vaginal bleeding, discharge, and pain (Guimaraes et al., 2011).

7.3 Adjuvant radiotherapy and chemotherapy

Postoperative adjuvant therapy is given to reduce the risk of recurrence.

Adjuvant radiotherapy is given as vaginal brachytherapy and/or external beam radiotherapy (EBRT). Modern radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT) and volumetric modulated arc radiotherapy (VMAT), reduce the side effects of urinary incontinence, diarrhoea, and faecal incontinence, compared to traditional EBRT (Creutzberg et al., 2003).

In low-risk EC, the likelihood of recurrence is low and therefore routine adjuvant radiotherapy is not recommended. For intermediate-risk EC, e.g., in the absence of LVSI, vaginal brachytherapy alone may be adequate. However, in high-risk EC, EBRT is generally required as it reduces the risk of recurrence and it may also confer some survival benefit (Johnson and Cornes, 2007).

Adjuvant chemotherapy (carboplatin and paclitaxel) is usually only offered to women with high-risk EC as it is associated with significant side effects and there is only a 4% absolute risk reduction in death (Johnson et al., 2011).

7.4 Hormonal therapy

There is limited evidence on the outcomes and long-term benefits of progestogen as the primary treatment for EC. It is usually reserved for women who are seeking fertility-sparing management options. The use of oral progestogens and the levonorgestrel-releasing intrauterine system has been reported with no randomised controlled trial comparing the efficacies of these two treatments.

There is no evidence of any survival benefit with postoperative adjuvant progestogen therapy (Martin-Hirsch et al., 2011). Importantly, women taking high-dose progestogens are at increased risk of developing side effects or death from cardiovascular complications (Kokka et al., 2010).

7.5 Molecular markers as determinants for treatment decisions

The new molecular classification of endometrial cancer is currently most relevant in the context of considering postoperative adjuvant therapies for women with high-grade or high-risk EC.

The ESGO/ESTRO/ESP guideline (Concin et al., 2021) recommends that molecular classification can be used to identify a subgroup of women (POLEmut tumours) where the prognosis is excellent and thus omission of adjuvant treatment can be considered in those with stage I-II disease. On the contrary, the prognosis for women with p53abn-tumours is much poorer and therefore adjuvant treatment should be considered in women at all stages of the disease, except where the malignancy is only confined within an endometrial polyp.

More research is now being carried out on how molecular classification of EC could be further introduced into routine clinical practice.

Chapter 8 Summary of background

Measurement of the endometrial thickness (ET) on transvaginal ultrasound scan (TVS) is the most common first-line investigation in women with postmenopausal bleeding (PMB). Nevertheless, the endometrium may not be visualised satisfactorily on TVS in up to 1 in 8 women with PMB. One of the reasons is due to an axial uterus where the ultrasound beam is not at the optimal 90º insonation angle against the long axis of the endometrium; therefore, the resulting quality of the ultrasound images is poor. A transrectal ultrasound scan may potentially reduce the number of unsatisfactory endometrial assessments in women with an axial uterus by altering the angle of insonation and by being closer to the endometrium.

Ultrasound measurement of the endometrial thickness in women with PMB is effective in identifying those who are at low risk of endometrial cancer. However, it has poor specificity and a high false-positive rate for malignancy among those with a thickened endometrium, which leads to inefficient prioritisation of women for endometrial sampling and unnecessary anxiety in women who are without a malignancy. Ultrasound subjective pattern recognition may help to diagnose endometrial cancer more accurately, though its diagnostic accuracy has not yet been adequately evaluated and little is known about its interrater reliability.

Ultrasound and MRI may have similar accuracy in the preoperative staging of endometrial cancer, but few studies have compared the two imaging tests in the same cohort of patients. Furthermore, it may be feasible to simultaneously diagnose and stage EC at women's initial ultrasound scan for PMB, which could reduce the number of hospital visits and delays in surgery.

Endometrial polyps are common, but their natural history is poorly understood and there is no consensus on their treatment, especially in postmenopausal women. Premalignancy or malignancy is only found in a small proportion of polyps and therefore women at low risk of malignancy

or those who are at increased surgical risk may prefer expectant management. More research is needed to help women in making an informed choice about management options.

Given the above, I feel that the aims of this thesis should be to compare the efficacy of transvaginal and transrectal ultrasound scans in assessing the endometrium of postmenopausal women with an axial uterus; to prospectively assess the diagnostic accuracy and interrater reliability of ultrasound subjective pattern recognition for endometrial cancer in women with postmenopausal bleeding; to compare the accuracies of ultrasound and MRI in the preoperative staging of endometrial cancer; to create a model to predict the risk of pre-malignancy or malignancy in postmenopausal polyps, and to assess the growth rates of expectantly managed endometrial polyps.

Part 2 – Materials and Methods

The general methods outlined below apply to all studies that are included in this thesis. Additional methods that are specific to individual studies are included in the relevant study chapters.

Chapter 9 Setting

All studies were carried out at the Gynaecological Diagnostic and Outpatient Treatment Unit (GDOTU) of University College Hospital (UCH) between October 2015 and October 2018.

University College Hospital (UCH) is part of the University College London Hospitals NHS Foundation Trust (UCLH), which was formed in 1994. However, the history of UCLH dates to as early as 1745 with the founding of The Middlesex Hospital. Nowadays, UCLH has an annual turnover of over £1 billion and it employs over 8000 staff.

UCH is situated in the Fitzrovia area of the London borough of Camden. It is a major teaching hospital for the University College London (UCL) medical school, and it is also a major centre for medical research, including being part of the UCLH Biomedical Research Centre and UCL Partners Academic Health Science Centre.

There are 665 in-patient beds and 12 operating theatres at UCH. In 2008, the Elizabeth Garrett Anderson Wing was opened, which allows all women's health services to be provided in one place.

UCH is a tertiary gynaecological oncology centre, and it is part of the North London Cancer Network (NLCN), which serves a population of approximately 1.5 million in the London Boroughs of Camden, Islington, Barnet, Enfield, and Haringey. The annual number of gynaecological malignancies diagnosed is over 360 cases.

Chapter 10 Patient selection

The GDOTU at UCH treats more than 20,000 women each year. The most common presenting complaints are acute early pregnancy complications, general gynaecological problems or suspected gynaecological malignancies via the 2-week wait referral pathway.

Postmenopausal bleeding (PMB) is the commonest symptom in women referred under the 2-week wait pathway, who are assessed in our dedicated rapid access clinic. We define menopause as amenorrhoea lasting over 12 months in women who are over the age of 45. PMB is defined as vaginal bleeding in postmenopausal women who are not on hormone replacement therapy (HRT). Women on HRT with abnormal vaginal bleeding are referred to as unscheduled bleeding whilst on HRT.

All women presenting with PMB undergo a full clinical history taking, abdominal, vaginal and ultrasound examinations in our outpatient clinic. The findings are recorded in our ultrasound clinic database (PIA Fetal Database, version 2.23; Viewpoint Bildverarbeitung GmbH, Munich, Germany).

Chapter 11 Ultrasound examination

Women were examined in the lithotomy position with an empty bladder after informed consent was obtained. The ultrasound examinations were performed systematically. First, the cervix and uterine corpus were identified in the transverse plane. The uterine corpus was then assessed by examining a series of parallel scanning planes, starting from the internal cervical orifice to the top of the uterine fundus. Women with an axial uterus or a suboptimal assessment of the endometrium on a transvaginal scan were offered the option of a transrectal ultrasound examination to improve image quality. And saline infusion sonography or hysteroscopy were also

offered to women with an unsatisfactory transvaginal or transrectal ultrasound examination of the endometrium.

Measurement of the endometrial thickness was performed in the sagittal plane perpendicular to the endometrial midline echo and included both endometrial layers at their thickest point. If there was a presence of intra-cavitary fluid, endometrial thickness was measured by subtracting the size of the fluid from the measurement of the whole uterine cavity in the sagittal plane.

Intra-cavitary lesions, such as endometrial polyps, were measured in three perpendicular planes and their size was represented by the mean of these measurements.

Previous studies have used polyp maximum diameter, mean diameter and volume to describe polyp size (Sasaki et al., 2018). We chose to use polyp mean diameter in our studies because the International Endometrial Tumor Analysis (IETA) group (Leone et al., 2010) recommends that all polyps should be measured in three perpendicular planes. Furthermore, polyp volume is rarely calculated by ultrasound operators in routine clinical practice, while polyp maximum diameter may introduce errors as polyps could be of various shapes.

Assessment of the endometrial morphological features included endometrial echogenicity, midline, and the endometrial-myometrial junction. The endometrial vascularity was assessed using colour Doppler ultrasound with a default setting (pulse repetition frequency – 0.9 kHz, gain – 0.8 and low wall motion filter – 40 Hz) to ensure optimal sensitivity for blood flow. Vascular patterns within the endometrium were assessed subjectively. The examination technique and terminologies used to describe the endometrial morphology were in keeping with the consensus statement by the IETA group (Leone et al., 2010).

Ultrasound scans were performed using an ultrasound system equipped with a 4-9 MHz transvaginal probe and three-dimensional facility (Voluson E8, GE Healthcare Ultrasound, Milwaukee, WI, USA).

All ultrasound scans (except in Study 6 where data were analysed retrospectively) were performed by a single clinical research fellow (MW), a level-II operator, under the indirect supervision of consultant level-III expert operators. As per the Guidelines of the European Federation of Societies for Ultrasonography in Medicine and Biology (Education et al., 2006), a level-II operator is someone who is trained in basic, non-complex gynaecological ultrasonography, and involved in teaching and research in ultrasound.

Chapter 12 Ultrasound diagnosis of endometrial pathologies in women with postmenopausal bleeding

Women with postmenopausal bleeding were categorised into one of the following four groups based on the endometrial morphological features on unenhanced greyscale ultrasound and vascular patterns on colour Doppler examination. The terms and definitions used to describe the endometrium on ultrasound were in keeping with the recommendations of IETA (Leone et al., 2010).

1. Atrophic endometrium – the endometrium appears uniform with no focal lesions, an intact midline echo and an intact endometrial-myometrial junction. On Doppler ultrasound, it appears avascular. The endometrial thickness measures <4.5mm.

2. Uniformly thickened endometrium – the endometrium appears uniform with no focal lesions. The endometrial midline echo and endometrial-myometrial junction are intact. On Doppler ultrasound, it appears avascular or poorly vascularized with a colour score of ≤2. The endometrial thickness measures ≥4.5mm (Figure 5).

3. Benign endometrial polyp – there is a well-defined and localized intracavitary lesion with a regular outline. The surrounding endometrium appears regular with an intact endometrial-myometrial junction. On Doppler ultrasound, there is a single dominant vessel with or without branching, or there is no detectable vascularity (Figure 6).

4. Endometrial cancer – the endometrium appears heterogeneous or there is an irregular intracavitary lesion. The endometrial-myometrial junction could be intact, or it is interrupted, which is suggestive of myometrial invasion. On Doppler ultrasound, multiple vessels are crossing the endometrial-myometrial junction with either focal or multifocal origins (Figure 7).

All ultrasound diagnoses were made based on the ultrasound morphological features and vascular patterns as described above. In some women, endometrial polyps or endometrial cancers were diagnosed in women with an ET <4.5mm.

In previous studies, various ET cut-offs (3-5mm) have been used to define atrophic and non-atrophic endometrium (Timmermans et al., 2010), while the British Gynaecological Cancer Society (BGCS) recommends that a 4mm cut-off should be used (Sundar et al., 2017). However, individual institutions may produce their own guidelines to tailor to their local population and available resources. At our institution, a cut-off of <4.5mm is used to define atrophic endometrium. A meta-analysis by Wong et al. (2016) shows that a lower cut-off improves the sensitivity for detecting EC (the sensitivities for 3-, 4-, and 5-mm cut-offs were 97%, 94.1% and 93.5%, respectively), however, this is at the expense of a lower specificity (45.3%, 66.8% and 74%, respectively).

The Colour score on Doppler ultrasound was assessed as per the IETA consensus opinion (Leone et al., 2010). The operator subjectively

determined the colour score – a colour score of 1 represents no colour flow signal detected in the endometrium, a score of 2 is when there is minimal colour, a score of 3 is when there is moderate colour, and a score of 4 is when there is abundant colour detected.

Women with postmenopausal bleeding were managed according to their ultrasound diagnoses (Figure 8). Those with an atrophic endometrium were managed expectantly with the advice to return for reassessment if postmenopausal bleeding recurred. Whereas women with ultrasound diagnoses of uniformly thickened endometrium or endometrial cancer were offered an immediate outpatient endometrial biopsy, with the latter group of women also being prioritized for histological confirmation and referral to a gynaecological oncologist. Women with suspected benign endometrial polyps were offered a hysteroscopic polypectomy and endometrial biopsy. Follow-up information was recorded from those who returned to the clinic with a recurrence of postmenopausal bleeding within the first 12 months of their initial consultation.

Figure 5 – Example of a uniformly thickened endometrium on a transvaginal ultrasound scan (Wong et al., 2021a)

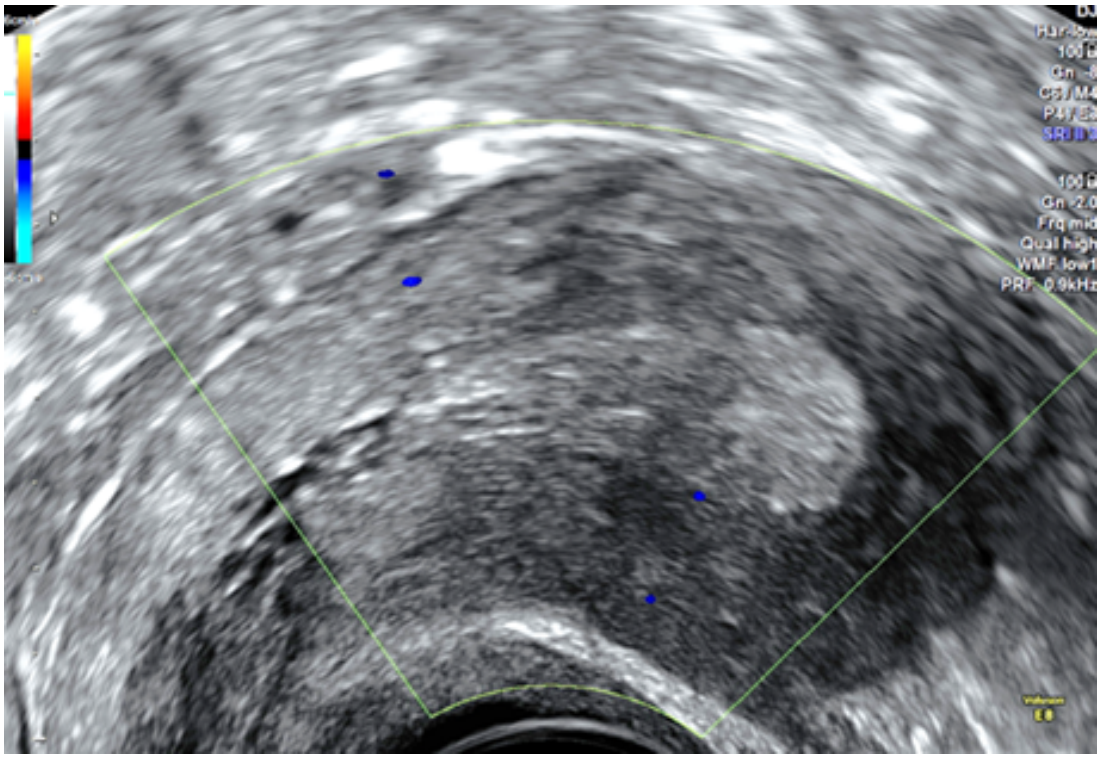


Figure 6 – Example of a benign endometrial polyp on transvaginal ultrasound scan (Wong et al., 2021a)

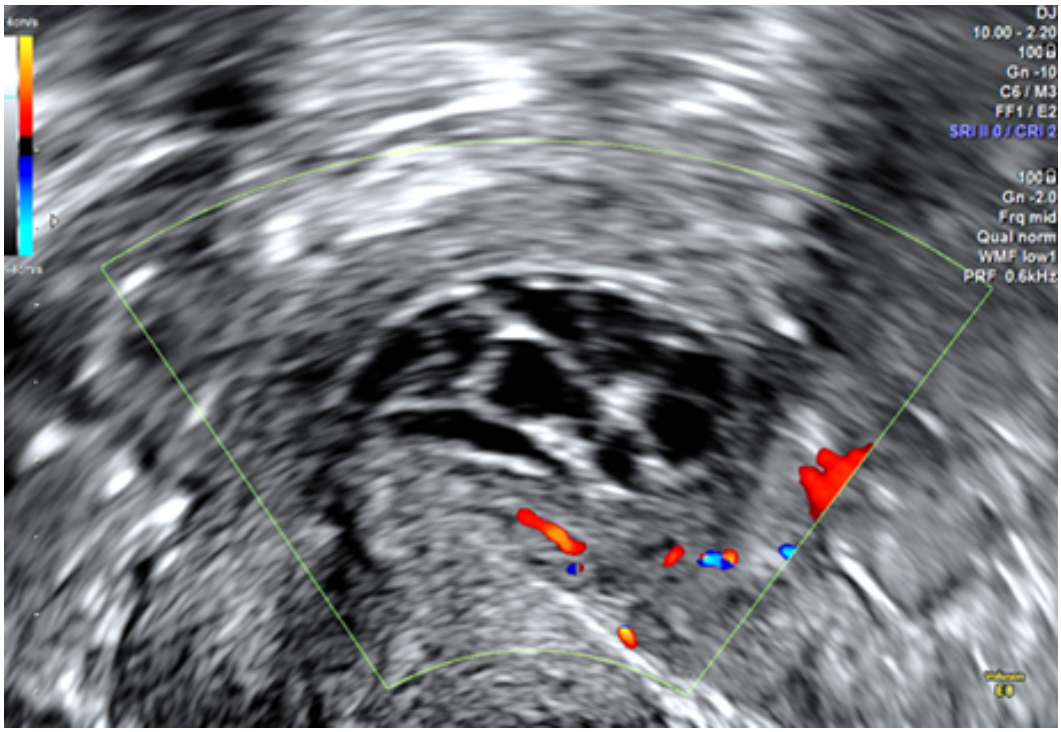


Figure 7 – Example of endometrial cancer on transvaginal ultrasound scan (Wong et al., 2021a)

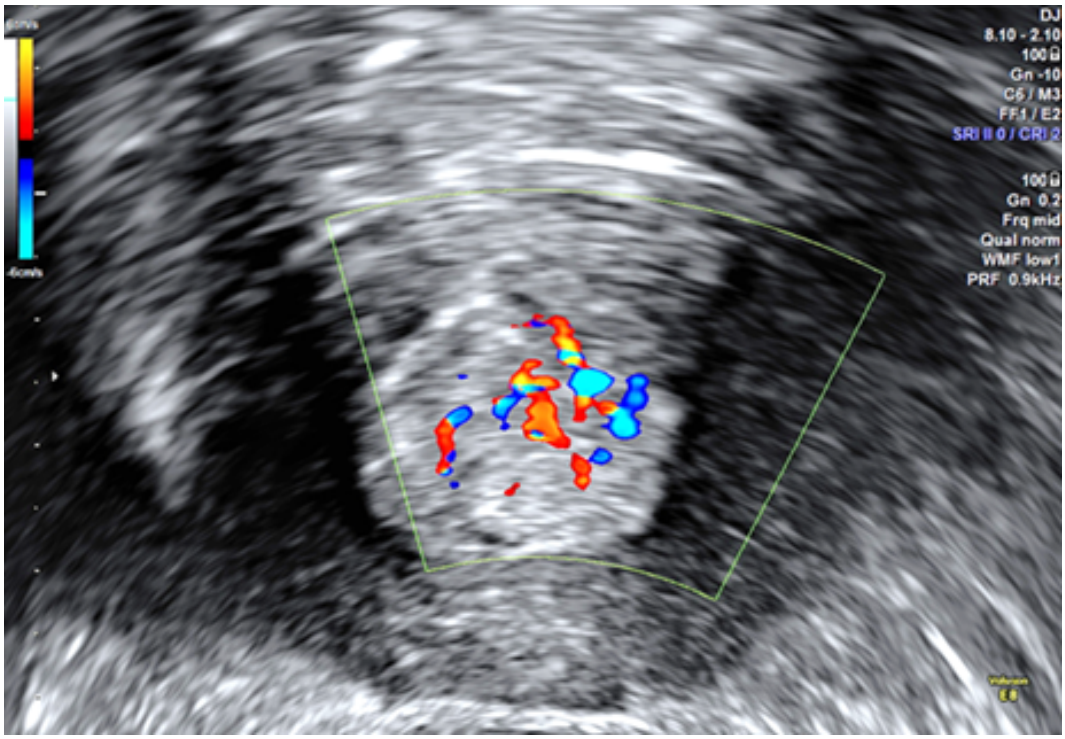
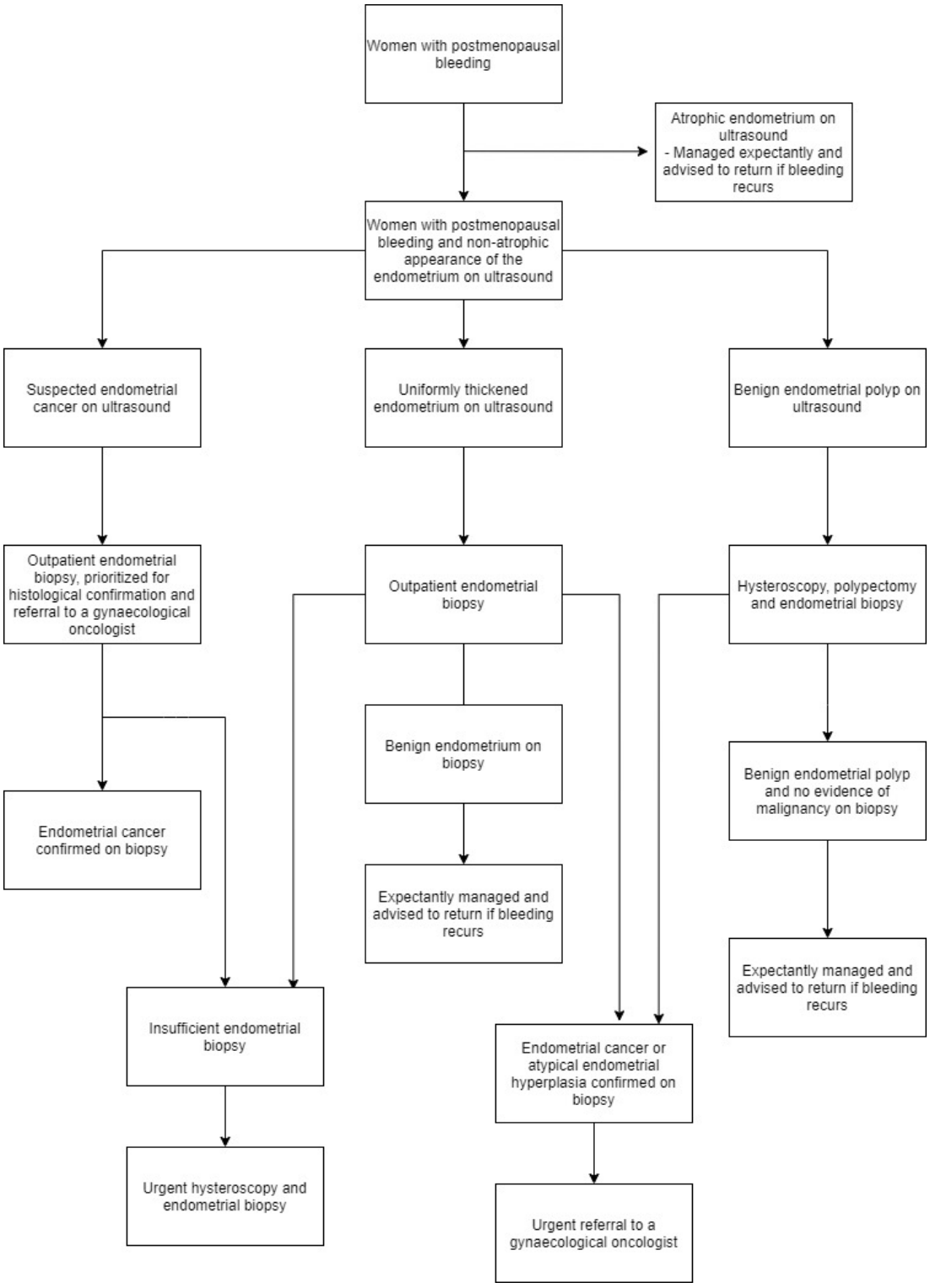


Figure 8 – Management of women with postmenopausal bleeding based on their ultrasound diagnosis by subjective pattern recognition



Chapter 13 Ultrasound preoperative staging of endometrial cancer

In women with suspected endometrial cancer on ultrasound, they were simultaneously assessed for the depth of myometrial invasion and cervical stromal invasion before any endometrial biopsy procedures.

Myometrial and cervical stromal invasion were assessed subjectively on a transvaginal or transrectal ultrasound scan as illustrated in previous studies (Fischerova, 2011, Fischerova et al., 2014, Epstein and Blomqvist, 2014). To estimate the depth of myometrial invasion, the outline of the endometrial-myometrial junction was systemically assessed, scanning in the sagittal plane from cornu to cornu and in the transverse plane from the cervix to the uterine fundus, looking for the point where the tumour appeared to be invading most deeply into the myometrium (this may involve the anterior, posterior, or lateral uterine wall, as well as the uterine fundus). The depth of tumoral invasion into the myometrium was then estimated subjectively. All women were categorised as having either i) no myometrial invasion or myometrial invasion into <50% of the entire myometrial thickness, or ii) ≥50% invasion of the entire myometrial thickness.

The cervical stromal invasion was diagnosed when there was a tumour infiltrating and disrupting the regular outline of the cervical stroma. In some cases, the lower edge of an intracavitary tumour may reach the level of the internal cervical orifice but it does not invade the cervical stroma; to exclude any invasion into the cervical stroma, the ultrasound probe is used to gently push on the cervix to see whether the tumour is sliding off the cervix. If there is a true cervical stromal invasion, there will be no sliding of the tumour (Fischerova et al., 2014, Epstein and Blomqvist, 2014).

All endometrial tumours were measured in the sagittal plane for their maximal diameters in two perpendicular planes (d1 and d2, respectively) and the transverse plane for their width (d3). The mean diameter of the tumour was calculated by d1+d2+d3/3.

Chapter 14 Magnetic resonance imaging preoperative staging of endometrial cancer

All women with a histologically confirmed diagnosis of endometrial cancer underwent a preoperative MRI scan. The standard sequence of MRI scans included T2-weighted imaging (T2WI), dynamic T1-weighted gadolinium sequences (DCE-MRI) and diffusion-weighted imaging (DWI-MRI) with an apparent diffusion coefficient map. On T2WI, endometrial cancer typically has an intermediate signal intensity and is hyperintense compared to the adjacent myometrium. In the absence of myometrial invasion, the endometrial-myometrial junction (EMJ) will appear intact on T2WI and there is a clear sub-endometrial enhancement (SEE) on DCE-MRI. However, when the myometrial invasion is present, the EMJ may appear irregular on T2WI and there is a disruption of the SEE and peritumoral enhancement (PTE) in the DCE-MRI (Fujii et al., 2015). The depth of myometrial invasion in our study was assessed subjectively. Women were categorized into i) no myometrial invasion or myometrial invasion <50% of the entire myometrial thickness, or ii) ≥50% of the entire myometrial thickness.

The cervical stromal invasion was diagnosed subjectively when there was evidence of an intermediate signal intensity tumour disrupting the low signal intensity fibrous cervical stroma on T2WI. On DCE-MRI, the normal enhancement of the cervical stroma may be replaced by a hypo-enhancing tumour. On DWI-MRI, the cervical stroma invasion may have a higher signal intensity on a high b value compared to the lower signal intensity of normal cervical stroma.

All MRI scans were reported by experienced consultant radiologists, who regularly participate in the gynaecological oncology multidisciplinary team meetings, and they were blinded to the ultrasound scan findings.

Chapter 15 Outpatient endometrial biopsies

All outpatient endometrial biopsies were performed by a single clinical research fellow (MW). Women were positioned in the lithotomy position. A plastic disposable Cusco vaginal speculum was used to visualise the cervix. Whenever possible, a vulsellum forceps was not used to secure the cervix, but when it was required a local anaesthetic (1% lidocaine hydrochloride) injection was first applied to the cervix.

The Pipelle endometrial suction curette (Laboratoire CCD, Paris, France) was used in all biopsy procedures. The Pipelle curette was first passed into the cervical canal without any dilatation of the cervix. If there was significant resistance to the Pipelle curette due to cervical stenosis, a disposable Pelican dilator 5/6mm (Eden Medical, Midlothian, UK) was used to gently dilate the cervix to allow the passage of the Pipelle curette into the uterine cavity. The Pipelle curette was inserted to the top of the uterine fundus followed by the withdrawal of the piston to the full length of the instrument, thus creating a negative pressure within the lumen of the curette. The Pipelle curette was slowly removed from the uterine cavity while rotating in a single direction, collecting endometrial tissues within its lumen. The tissue collected was then expelled into a specimen container with 10% formaldehyde and sent for processing in the histopathological department. The biopsy procedure was complete when there was visible endometrial tissue collected in the specimen container.

Pipelle endometrial biopsy is widely performed in the UK, especially in women presenting with PMB. While the incidence of a “failed” Pipelle biopsy could be up to 30% in an unselected population due to cervical stenosis or an “insufficient” sampling (Gordon and Westgate, 1999), other studies have reported that the Pipelle device is highly effective (sensitivity 83-97.5%) in confirming the diagnosis of malignancy in those with a high pre-test probability of EC (Stovall et al., 1991, Guido et al., 1995). False-negative results are mainly due to malignancies affecting <5% of the surface area of the endometrium or if the malignancy is confined within a polyp. In studies

1-3 of this thesis, Pipelle biopsy was used to confirm the ultrasound diagnosis of EC and to further investigate women with a uniformly thickened endometrium. Although we cannot rule out the possibility of a false-negative result in women with a uniformly thickened endometrium and a benign Pipelle biopsy result, we advised women to return immediately if they experience a recurrence of PMB rather than subjecting them to further invasive testing because of their low pre-test probability of EC. During the 1-year follow-up period, none of the women with a recurrence of PMB was found to have EC.

Chapter 16 Histopathology and staging

All histopathological assessments of the endometrial biopsy, endometrial polyps and hysterectomy specimens were performed by experienced consultant histopathologists, who regularly participate in the gynaecological oncology multidisciplinary team meetings.

The pathological assessment of endometrial cancer uses a structured report, which is in keeping with the guideline of RCPath. Important information included the histological type, grade, myometrial invasion, cervical stromal invasion, serosal breach and lymph node involvement.

Endometrial cancers were classified according to the World Health Organisation (WHO) guidelines and staged according to the classification of the International Federation of Gynaecology and Obstetrics (FIGO) (Pecorelli, 2009, Cree et al., 2020).

Chapter 17 Statistical analyses

Clinical data from the research studies were stored in electronic databases (Microsoft Excel 365, Redmond, WA, USA). Statistical analyses were

performed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA).

In general, descriptive methods were used to describe the study population. Comparisons of the population characteristics were unpaired, and all tests of significance were two-tailed. Continuous variables were compared using the independent samples t-test (data of normal distribution) or Mann-Whitney U test (data of non-parametric distribution). Categorical variables were compared using Pearson's chi-square or Fisher's exact test. A significance level of <0.05 was used without multiple comparison adjustments.

Details of the specific tests used, and sample size calculations are outlined in the relevant study chapters.

Chapter 18 Ethical approvals

Study 4 was granted formal ethical approval from the Central London REC2 committee (REC reference: 10/H0713/66 and IRAS reference: 42603), as well as local R&D sponsorship from UCH (Project ID: 10/0316, see Appendix). The approvals were obtained by Dr Joel Naftalin in 2011 and the research was carried out by Dr Michael Wong in 2015 as the principal investigator under the supervision of Prof Davor Jurkovic as chief investigator.

In the other studies, full ethical approvals were deemed not necessary by the local research ethics committee, as the ultrasound assessments in our study were not different from our standard clinical practice.

We followed the guidelines of STARD (Standards for Reporting of Diagnostic Accuracy Studies) and STROBE (Strengthening The Reporting of Observational Studies in Epidemiology) in the conduct and reporting of our research (Vandenbroucke et al., 2007, Cohen et al., 2016).

Part 3 – Results

Chapter 19 Study 1 – Efficacy of transrectal ultrasound scan in assessing the endometrium of postmenopausal women with an axial uterus

19.1 Introduction

In women with an axial uterus who are undergoing transvaginal ultrasound scans (TVS), the ultrasound beam is not at the optimal 90º insonation angle against the long axis of the endometrium, and therefore the resulting quality of the ultrasound images is poor (Goldstein, 2004). Where the endometrium cannot be examined satisfactorily on TVS, the International Endometrial Tumour Analysis (IETA) group recommends that saline infusion sonography (SIS) should be considered (Leone et al., 2010); however, SIS may not be available in some clinical settings and it may also be difficult to perform in women with severe vulvovaginal atrophy.

Transrectal ultrasound scan (TRS) is usually offered to women where the avoidance of TVS is preferred, such as in adolescents, virgins, women with vaginal agenesis or those with severe genital organs atrophy which can make the examination very painful (Sun and Fu, 2007, Lee et al., 2015, Guducu et al., 2013, Martire et al., 2020). We hypothesized that in women with an axial uterus the proportion of satisfactory endometrial assessment could be improved by TRS over TVS. During a TRS, the ultrasound probe is placed posteriorly at the level of the cervical internal os, and retroflexion of the uterus could be achieved by gently pushing down on the uterine fundus abdominally. This manoeuvre alters the angle between the ultrasound beam and the long axis of the endometrium and therefore potentially improves the quality of the ultrasound images. In addition, the

probe could be advanced above the level of the internal os and placed near the uterine corpus and the endometrium to further optimize the image quality.

This study aimed to prospectively evaluate the efficacy and acceptance of TRS in satisfactorily assessing the endometrium in postmenopausal women with an axial uterus. We also compared the measurements of endometrial thickness and the subjective diagnosis of endometrial cancer by TVS and TRS in women with postmenopausal bleeding and an axial uterus.

19.2 Methods

Inclusion and exclusion criteria

Between Oct 2015 and Oct 2018, consecutive postmenopausal women who were referred by their general practitioners for a gynaecological ultrasound scan at our general gynaecology outpatient clinic were eligible for the study. We included women with an axial uterus on TVS and excluded women with a known diagnosis of gynaecological malignancy. On TVS, an axial uterus is where the long axis of the endometrium is in continuation and parallel to the long axis of the endocervical canal.

Study outcomes and follow-up

The primary outcome of the study was the proportion of satisfactory endometrial assessment in postmenopausal women with an axial uterus on TVS, in comparison to TRS. The secondary outcomes were the measurements of endometrial thickness and subjective diagnoses of EC by TVS and TRS.

All women received a TVS first and those with an axial uterus were then offered a TRS in the same clinical consultation without prior bowel preparation. During a TRS, the ultrasound probe was placed posteriorly at the level of the internal cervical os or above, following which the uterus was gently retroflexed by pushing down on the uterine fundus abdominally. This manoeuvre altered the angle between the long axis of the endometrium and the beam of the ultrasound until they were approximately perpendicular to each other.

The ultrasound operator subjectively determined whether the endometrium was satisfactorily visualised or not. If the woman declined a TRS or if the endometrium could not be satisfactorily assessed on TRS, they were offered either an SIS or hysteroscopy instead. Measurement of the endometrial thickness on TVS and TRS is as described in the Methods section of this thesis (chapters 11 and 12) and women with postmenopausal

bleeding were divided into one of the following groups based on ultrasound subjective pattern recognition: atrophic endometrium, uniformly thickened endometrium, benign endometrial polyp, or endometrial cancer.

Women with a non-atrophic endometrium on ultrasound and symptoms of PMB underwent an outpatient pipelle endometrial biopsy or hysteroscopy, with the histology results as the gold standard. Women with an atrophic endometrium on ultrasound or asymptomatic of PMB were managed expectantly with the advice to return immediately if they experienced a recurrence/symptom of PMB.

19.2.1 Statistical analysis

Our final statistical analysis included the acceptance and success rate of TRS in assessing the endometrium in postmenopausal women with an axial uterus. McNemar's test was used to compare the proportions of satisfactory endometrial assessments on TVS and TRS.

Among women who underwent both TVS and TRS for postmenopausal bleeding, we compared the measurements of the endometrial thickness using the Wilcoxon signed-rank test. We did not proceed with the Bland Altman analysis to assess the reliability of the two methods as there was a statistically significant difference in the measurements between TVS and TRS. We compared the agreement of TVS and TRS in the categorisation of the endometrium as malignant or non-malignant by subjective pattern recognition by calculating Cohen's kappa coefficient (κ).

For sample size calculation, according to Abramson and the WINPEPI computer statistical programme (Abramson, 2011), this study required a minimum of 65 women to undergo both TVS and TRS, to detect a difference of 20% in the number of unsatisfactory endometrial assessments, with a power of 80% and a significance level of 0.05.

19.3 Results

A total of 1686 postmenopausal women underwent a gynaecological ultrasound examination during the study period. We excluded 110 women with a previous hysterectomy and 23 with a known diagnosis of gynaecological malignancy. In the remaining women, 886/1553 (57%) presented with PMB or unscheduled vaginal bleeding whilst on hormone replacement therapy; other indications for ultrasound examination are summarised in Table 1.

The prevalence of an axial uterus was 103/1553 (6.6%). Among them, 76/103 presented with PMB, 12/103 with abdominal pain or bloatedness, 6/103 with ovarian cysts, 3/103 with urinary symptoms, 3/103 with an incidental finding of a thickened endometrium on CT scan, 1/103 with a raised serum CA125 and 1/103 was under ultrasound surveillance due to the use of tamoxifen. On univariate analysis, women with an axial uterus were more likely to be older and nulliparous compared to women with an anteverted or retroverted uterus (Table 2). We did not find that women's body mass index, the presence of fibroids or adenomyosis were associated with an axial uterus.

Transrectal ultrasound scan was accepted by 66/103 (64%, 95% CI 55-73) women with an axial uterus (Figure 9); whereas 11/103 women preferred SIS, 8/103 preferred hysteroscopy (all women had endometrial polyps suspected on TVS), 1/103 preferred an outpatient endometrial biopsy (endometrial cancer was suspected on TVS), and 17/103 preferred no further tests (none had presented with PMB).

Transrectal ultrasound scan was successful in 60/66 (91%, 95% CI 84-98) women. It failed in 6 women, of which four were due to a faecally loaded rectum, one was abandoned due to pain, and the remaining one was due to the presence of a submucosal fibroid. In comparison, the endometrium was satisfactorily assessed on TVS in 41/66 (62%, 95% CI 50-74) women (Table 3) and the difference against TRS was statistically significant (X^2 = 14.1, p = <0.001).

We compared the efficacy of TVS and TRS in 50 women with PMB and an axial uterus who underwent both ultrasound examinations. TVS provided inadequate images of the endometrium in 15/50 (30%) women, whereas the endometrium was satisfactorily visualised in all cases on TRS. Among the women with unsatisfactory ultrasound examinations on TVS, 13/15 had an atrophic endometrium, 1/15 had a uniformly thickened endometrium and 1/15 had a benign endometrial polyp on TRS. In 35/50 women, where the endometrial thickness (ET) was successfully on both TVS and TRS, it was significantly thinner on TRS when compared to TVS [median difference was -1.2mm (IQR: -3 to -0.4); $Z = 3.87$, $p = <0.001$] (Figure 10). Using ET<4.5mm as a cut-off for an atrophic endometrium, 11/20 (50%) women with a thickened endometrium on TVS would be reclassified as atrophic on TRS; contrarily, none of the thirteen women with an atrophic endometrium on TVS was found to have a thickened endometrium on TRS.

Table 4 summarises the endometrial assessments by subjective pattern recognition in women who underwent both TVS and TRS. The overall agreement of TVS and TRS on the presence or absence of endometrial cancer was 30/35 (86%, 95% CI 74-97). The reliability of the two methods was moderate ($\kappa = 0.48$, 95% CI 0.06-0.90).

Table 5 summarises the ultrasound diagnoses of TRS in women with PMB and a non-atrophic endometrium against the final histological diagnoses. All cases of histologically confirmed endometrial cancer were detected on TRS; however, there was one case of false-positive diagnosis of endometrial cancer.

Table 1 – Indications for an ultrasound scan (n=1553)

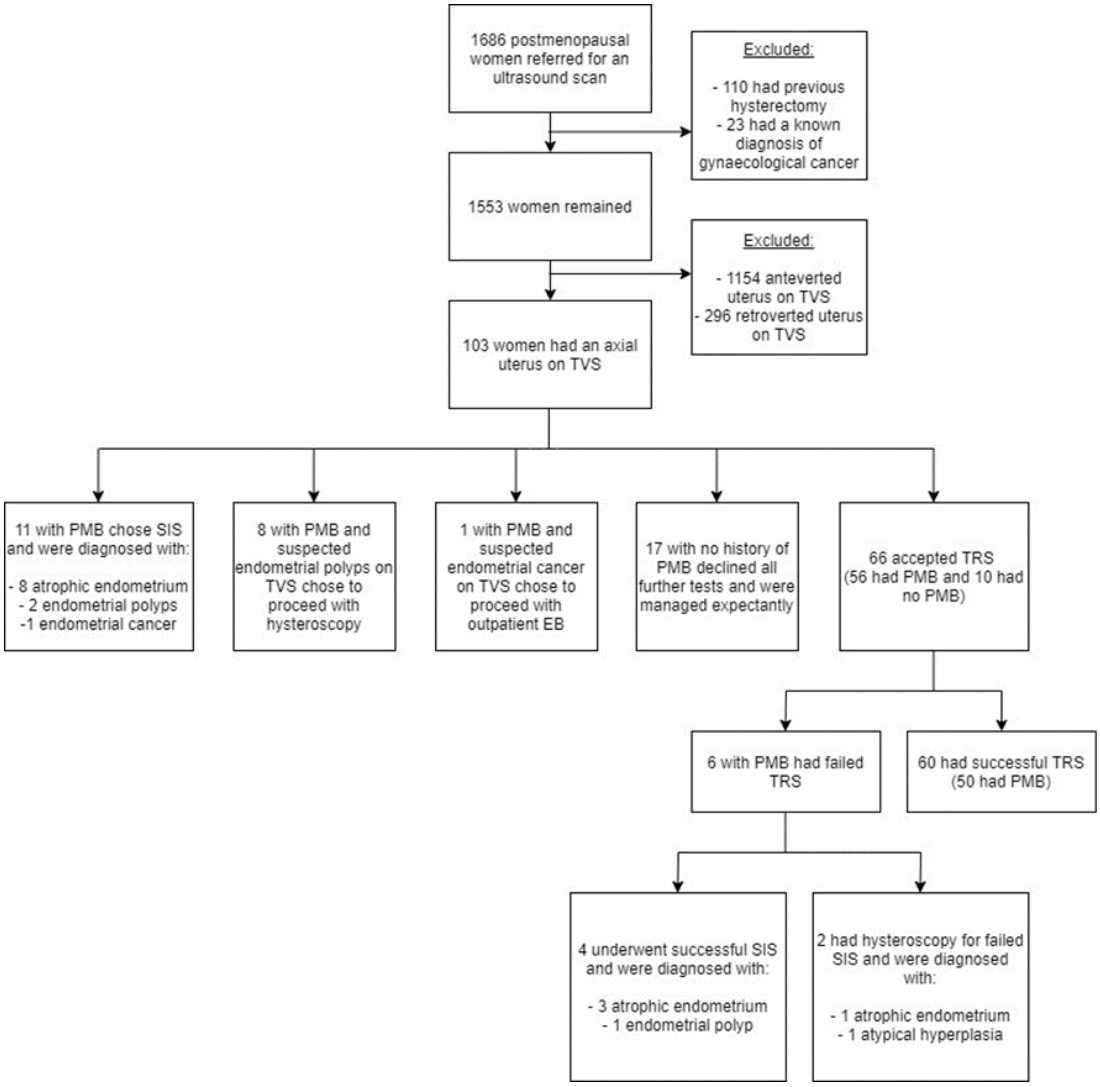
Indications	n (%)
Postmenopausal bleeding	886 (57)
Abdominal or pelvic pain	209 (14)
Abdominal or pelvic swelling	146 (10)
Bowel or urinary symptoms	63 (4)
Incidental finding of a thickened endometrium on ultrasound	63 (4)
Raised serum CA125	52 (3)
Ovarian cancer screening	52 (3)
Endometrial surveillance due to the use of tamoxifen	19 (1)
Other	63 (4)

Table 2 – A univariate analysis to compare the clinical characteristics between postmenopausal women with an axial uterus against those with a non-axial uterus

Clinical characteristics	Women with an axial uterus (n=103)	Women with a non-axial uterus (n=1450)[+]	Test statistics	p-value
Age[1]	65 (57-73)	58 (54-67)	Z = -4.00	<0.001
Body mass index[1] (kg/m^2)	27.3 (22.9-33.8)	26 (22.5-31)	Z = -1.19	0.236
Nulliparity[2]	39 (38)	290 (20)	X^2 = 18.38	<0.001
Adenomyosis[2]	16 (16)	201 (14)	X^2 = 0.22	0.636
Uterine fibroids[2]	27 (26)	464 (32)	X^2 = 1.49	0.222

[1]median (interquartile range), [2]n (%), Z = Mann Whitney test statistic, X^2 = Chi square test statistic, [+]1154 anteverted and 296 retroverted uterus

Figure 9 – Acceptance of transrectal ultrasound scan in postmenopausal women with an axial uterus on transvaginal ultrasound scan



TVS = transvaginal ultrasound scan, TRS = transrectal ultrasound scan, PMB = postmenopausal bleeding, EB = endometrial biopsy, SIS = saline infusion sonography

Table 3 – Endometrial assessments of postmenopausal women with an axial uterus by transvaginal and transrectal ultrasound scans (n=66)

		Transrectal ultrasound scan		
		Successful endometrial assessment	Unsuccessful endometrial assessment	Total
Transvaginal ultrasound scan	Successful endometrial assessment	39	2	41
	Unsuccessful endometrial assessment	21	4	25[†]
	Total	60	6[‡]	66

[†]20 was due to poor ultrasound images, 4 were due to patient discomfort, 1 was due to a submucosal fibroid; [‡]4 was due to a faecally loaded rectum, 1 was due to patient discomfort, 1 was due to a submucosal fibroid

Figure 10 – Histogram of the difference in measurements of the endometrial thickness (mm) by transvaginal and transrectal ultrasound scans in women with postmenopausal bleeding and an axial uterus (n=35)

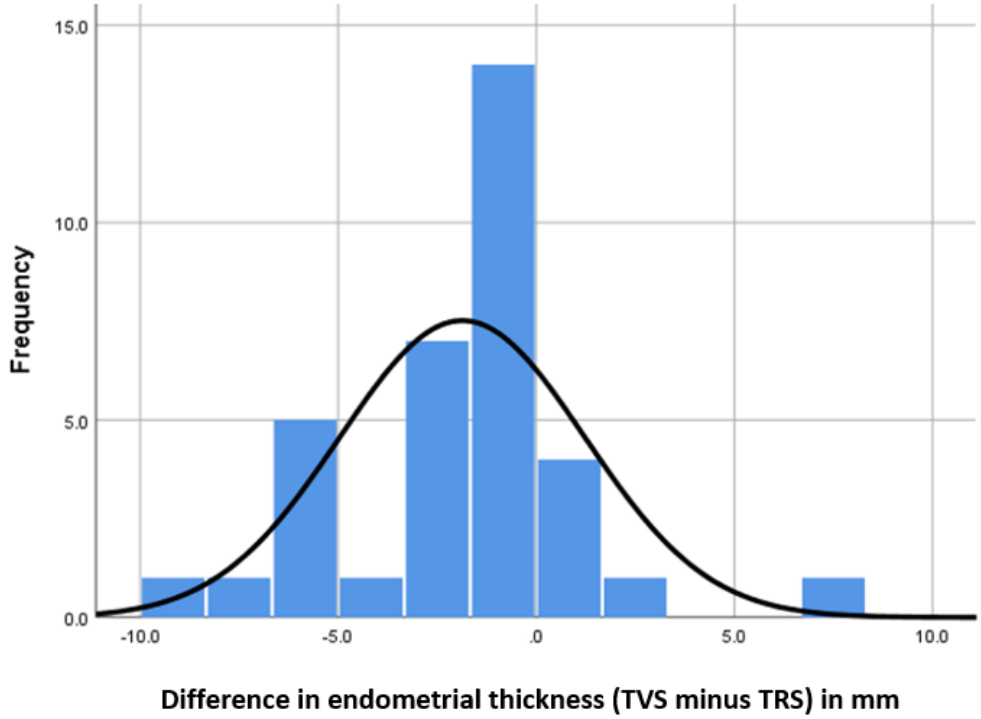


Table 4 – Ultrasound diagnoses based on subjective pattern recognition in women with postmenopausal bleeding and an axial uterus who underwent both transvaginal and transrectal ultrasound examinations (n=50)

		Transrectal ultrasound examination				
		Atrophy	Uniformly thickened endometrium	Endometrial polyp	Endometrial cancer	Total
Transvaginal ultrasound examination	Atrophy	12	0	1	0	13
	Uniformly thickened endometrium	8	1	1	2	12
	Endometrial polyp	2	0	2	3	7
	Endometrial cancer	0	0	0	3	3
	Inconclusive	13	1	1	0	15
	Total	35	2	5	8	50

Table 5 – A comparison of diagnoses on transrectal ultrasound scan and final histology in women with postmenopausal bleeding, a non-atrophic endometrium, and an axial uterus (n=15)

		Final histology[1]			
		Benign endometrium	Endometrial polyp	Endometrial cancer	Total
Transrectal ultrasound examination	Uniformly thickened endometrium	2[+]	0	0	2
	Endometrial polyp	0	5	0	5
	Endometrial cancer	1[*]	0	7	8
	Total	3	5	7	15

[1]final histology was obtained from samples of 6 hysterectomies, 6 hysteroscopies and 3 outpatient endometrial biopsies, [+]two atrophic endometrium, [*]disorganised proliferation of the endometrium

Chapter 20 Study 2 – Interrater agreement and reliability of ultrasound subjective pattern recognition in diagnosing endometrial cancer

20.1 Introduction

Earlier studies have assessed whether endometrial cancer (EC) can be diagnosed accurately on ultrasound based on the morphological features and vascular patterns of the endometrium (Conoscenti et al., 1995, Weigel et al., 1995, Weber et al., 1998, Sheikh et al., 2000, Randelzhofer et al., 2002, Alcázar et al., 2003, Epstein and Valentin, 2006, Opolskiene et al., 2007, Epstein et al., 2001). Regrettably, their findings were difficult to compare as different terminologies were used to describe the endometrium. As a result, in 2010, the International Endometrial Tumour Analysis (IETA) group published a consensus opinion on the terms, definitions and measurements of the endometrium (Leone et al., 2010). Using the IETA terminologies, EC is most commonly described as an endometrium with heterogeneous echogenicity, irregular or ill-defined endometrial-myometrial junction, and multiple vessels with focal or multifocal origins on Doppler ultrasound (Kabil Kucur et al., 2013, Madkour, 2017, Epstein et al., 2018). Subjective pattern recognition refers to the identification of all these ultrasound features, to predict the presence or absence of EC.

It is estimated that three-quarters of EC can be diagnosed on ultrasound by subjective pattern recognition in women with postmenopausal bleeding (Dueholm et al., 2015b). However, there are concerns about its reproducibility and some suggest that it should only be reserved for experts in centres of excellence (Angioli et al., 2014). Indeed, the interrater reliability and accuracy of subjective pattern recognition may be poorer in the hands of less experienced operators (Alcázar et al., 2006, Eriksson et al., 2015, Green et al., 2018). Furthermore, the reliability of using the IETA terminology to describe the endometrium was also found to be poor

(Sladkevicius et al., 2018). Notwithstanding these potential limitations of subjective pattern recognition, some advocate that more resources should be spent on ultrasound training and we should consider limiting our use of terminologies to those that are most reproducible (Neto, 2018).

Few studies in the literature have evaluated the reproducibility of subjective pattern recognition. This study aimed to prospectively assess the interrater reliability of using subjective pattern recognition to diagnose endometrial cancer in women with postmenopausal bleeding, between an experienced and a less experienced operator.

20.2 Methods

Inclusion and exclusion criteria

Between Oct 2016 and Dec 2017, consecutive women who presented to our gynaecological outpatient clinic with a history of postmenopausal bleeding and an endometrial thickness of ≥4.5mm on transvaginal ultrasound scan were included. We excluded women who were on hormone replacement therapy, tamoxifen or if they have a known history of gynaecological malignancy. Saline infusion sonography (SIS) or hysteroscopy were offered to women with an unsatisfactory view of the endometrium on ultrasound scan, and they were excluded from the study because it was not practical to subject women to more than one SIS examination to assess the interrater reliability.

Study outcomes and follow-up

The study outcome was the interrater reliability of subjective pattern recognition in diagnosing endometrial cancer in women with postmenopausal bleeding, between an experienced and a less experienced operator.

All women were examined by both Rater A and Rater B during a single clinic visit. Rater A was a second-year clinical fellow in gynaecological ultrasound scan who had performed a total of approximately 2400 examinations before starting the study. This included assessments of over 200 women for postmenopausal bleeding. Rater B had over 30 years of experience in ultrasound and is a recognised expert in gynaecological ultrasound. The two raters independently performed their assessments in the absence of each other and they were also blinded to each other's findings. Each rater spent up to 10 minutes completing their assessment. Their ultrasound findings and final diagnosis were recorded by an independent healthcare assistant who did not take part in the study.

All ultrasound examinations were performed as described in the Methods section of this thesis (chapters 11 and 12). Women were categorized into one of the following groups based on subjective pattern recognition: uniformly thickened endometrium, benign endometrial polyp, or endometrial cancer; and their management was dependent on their ultrasound diagnosis.

Women with a non-atrophic endometrium on ultrasound underwent an outpatient pipelle endometrial biopsy or hysteroscopy, with the histology results as the gold standard. Women with an atrophic endometrium on ultrasound were managed expectantly with the advice to return immediately if they experienced a recurrence of PMB.

20.2.1 Statistical analysis

The primary outcome of this study was the interrater reliability of ultrasound subjective pattern recognition in the diagnosis of endometrial cancer in women with postmenopausal bleeding.

The first analysis was to determine the agreement and reliability between the two raters on the ultrasound diagnoses of uniformly thickened endometrium, polyp, and cancer. Then a second analysis was performed with the categories combined as either EC or no endometrial cancer. Due to the categorical nature of the measurements, the interrater reliability was assessed using Cohen's kappa (ƙ) statistic, which represents the consistency of the raters in their diagnoses. The ƙ statistic is measured on a scale ranging up to a maximum agreement of 1. We adopted the classification in which a ƙ value of ≤0.2 represents a very poor agreement between the two raters; 0.21-0.40 poor agreement; 0.41-0.60 moderate agreement; 0.61-0.80 good agreement; and 0.81-1.00 very good agreement (Kottner et al., 2011).

Our sample size calculation was based on a previous study that reported interrater reliability of ƙ = 0.5 in the ultrasound diagnoses of uniformly

thickened endometrium, polyp, and cancer by subjective pattern recognition in women with postmenopausal bleeding (Dueholm et al., 2015a). According to Bujag (2017), a minimum sample of 18 women was required if we assume there is no agreement between the two raters in the first place and pre-specifying the power and alpha at 80% and 5%, respectively. As the proportions of women with uniformly thickened endometrium, endometrial polyp and cancer were not expected to be equal, we multiplied the minimum sample size by two to accommodate for this variation. Hence, the required minimum sample size was 36 women.

20.3 Results

There were 52 eligible women with an endometrial thickness of ≥4.5mm on transvaginal ultrasound scan during the study period, twelve of whom were excluded as they were on hormone replacement therapy, tamoxifen or had a history of gynaecological malignancy. The remaining 40 women were included; their clinical characteristics and final histological diagnoses are presented in Table 6. Histological specimens for the final diagnoses were obtained from 16 women who underwent a hysterectomy, 17 hysteroscopies and 7 outpatient endometrial biopsies.

The ultrasound diagnoses of uniformly thickened endometrium, endometrial polyp, and cancer by the two raters are shown in Table 7.

Between the two raters, a total of 80 independent ultrasound diagnoses were made on the 40 women included in this study. Their agreements on uniformly thickened endometrium, endometrial polyp and cancer were 14/16 (87.5%), 22/30 (73.3%) and 28/34 (82.4%), respectively. Overall, the interrater reliability of the ultrasound diagnoses was good with a ƙ statistic of 0.69 (95% CI 0.49-0.88).

When the three categories of ultrasound diagnoses were dichotomised into either cancer or no cancer, i.e., where the no cancer group included both women with uniformly thickened endometrium and endometrial polyp, the two raters agreed on 68/80 (85%) occasions. Both raters agreed on the diagnosis of endometrial cancer in 14 women but disagreed on 6 others. In 4 of these 6 disagreements, Rater A diagnosed an endometrial polyp, whereas Rater B diagnosed cancer. In the other 2 cases, the opposite occurred. There were no cases of uniformly thickened endometrium being diagnosed when the other rater suspected cancer. Overall, the interrater reliability of ultrasound subjective pattern recognition in diagnosing endometrial cancer was good with a ƙ statistic of 0.78 (95% CI 0.61-0.95).

The ultrasound diagnoses by Rater A and Rater B against the final histological diagnoses are summarized in Tables 8 and 9, respectively.

Rater A correctly identified 14/16 women with endometrial cancer and Rater B identified 15/16. Rater A misdiagnosed two cases of cancer as benign polyps, whereas Rater B misdiagnosed one case of cancer as a benign polyp. Rater A had two false-positive diagnoses of endometrial cancer, which were subsequently proved to be a benign polyp and a case of disorganised proliferative endometrium. Rater B had three false-positive diagnoses of endometrial cancer; two of these were benign polyps and the other was a disorganised proliferative endometrium. Overall, the diagnostic accuracies of Rater A and Rater B in diagnosing endometrial cancer using subjective pattern recognition were 90% and 85%, respectively.

Table 6 – Patient characteristics and the final histological diagnoses (n=40) (Wong et al., 2021a)

Patient characteristics	n (%)
Age (years)[1]	61 (57-69)
Time since menopause (years)[1]	9.5 (5.0-19.5)
Nulliparity	12 (30)
Caucasian ethnicity	30 (75)
BMI (kg/m^2)[1]	29.3 (24.2-34.4)
Endometrial thickness (mm)[1]	11.0 (6.2-20.3)
Uterine fibroids	19 (48)
Adenomyosis	11 (28)
Endometrial cancer	16 (40)
- Stage IA	6 (37.5)
- Stage IB	4 (25)
- Stage II	0 (0)
- Stage IIIA	1 (6.3)
- Stage IIIB	1 (6.3)
- Stage IIIC1	2 (12.5)
- Stage IIIC2	1 (6.3)
- Stage IV	1 (6.3)
Histological subtype	
Endometrioid	10 (62.5)
- Grade 1	5 (50)
- Grade 2	3 (30)
- Grade 3	2 (20)
Non-endometrioid	6 (37.5)
- Serous	2 (33.3)
- Carcinosarcoma	2 (33.3)
- Undifferentiated	1 (16.7)
- Neuroendocrine	1 (16.7)
Benign endometrial pathologies	24 (60)
- Endometrial polyp	16 (66.7)
- Atrophic endometrium	4 (16.7)
- Proliferative endometrium	3 (12.5)
- Endometrial hyperplasia	1 (4.2)
Results are presented as median (interquartile range)[1]	

Table 7 – A comparison of the ultrasound diagnoses by both raters (n=40) (Wong et al., 2021a)

		Rater B			
Rater A		Uniformly thickened endometrium	Polyp	Cancer	Total
	Uniformly thickened endometrium	7	2	0	9
	Polyp	0	11	4	15
	Cancer	0	2	14	16
	Total	7	15	18	40

Table 8 – Ultrasound diagnoses by Rater A and the final histological diagnoses (n=40) (Wong et al., 2021a)

		Ultrasound diagnoses by Rater A			
		Uniformly thickened endometrium	Polyp	Cancer	Total
Histological diagnoses	Atrophic endometrium	4	0	0	4
	Disorganised proliferative endometrium	2	0	1	3
	Endometrial hyperplasia	1	0	0	1
	Benign polyp	2	13	1	16
	Cancer	0	2	14	16
	Total	9	15	16	40

Table 9 – Ultrasound diagnoses by Rater B and the final histological diagnoses (n=40) (Wong et al., 2021a)

		Ultrasound diagnoses by Rater B			
		Uniformly thickened endometrium	Polyp	Cancer	Total
Histological diagnoses	Atrophic endometrium	3	1	0	4
	Disorganised proliferative endometrium	2	0	1	3
	Endometrial hyperplasia	1	0	0	1
	Benign polyp	1	13	2	16
	Cancer	0	1	15	16
	Total	7	15	18	40

Chapter 21 Study 3 – Diagnostic accuracy of ultrasound subjective pattern recognition for endometrial cancer in women with postmenopausal bleeding

21.1 Introduction

Postmenopausal bleeding (PMB) is the most common presenting complaint in women with endometrial cancer, the risk is approximately 6-11%, which may increase with additional risk factors, such as older age and obesity (Gredmark et al., 1995).

The clinical priority in assessing women with PMB is to diagnose endometrial cancer early while avoiding unnecessary invasive tests in women at low risk of malignancy. The current practice of measuring endometrial thickness (ET) on transvaginal ultrasound has enabled us to classify women into low-risk (ET <3-5mm) or high-risk (ET ≥3-5mm) of malignancies. In low-risk women, expectant management could be an option (Karlsson et al., 1995, Ferrazzi et al., 1996, Timmermans et al., 2010), on the contrary, endometrial sampling is mandatory in women with a “thickened” endometrium (high-risk). Nevertheless, the specificity for endometrial cancer is poor with measurement of the ET alone and therefore no malignancy is found in approximately two-thirds of women with a thickened endometrium. This creates unnecessary anxiety for women with a thickened endometrium who are awaiting the results of their endometrial biopsy and it is not an effective way to prioritise women for histological confirmation and surgery.

We hypothesized that ultrasound subjective pattern recognition may improve the specificity for endometrial cancer, while not reducing the sensitivity significantly. This study aimed to prospectively evaluate the

diagnostic accuracy of ultrasound subjective pattern recognition for endometrial cancer in women with postmenopausal bleeding.

21.2 Methods

Inclusion and exclusion criteria

Between October 2015 and October 2018, consecutive women referred by their general practitioners to our gynaecology outpatient clinic with a history of postmenopausal bleeding were included. We excluded women who were on hormone replacement therapy, tamoxifen, or those with a known history of gynaecological malignancy.

Study outcomes and follow-up

The study outcome was the diagnostic accuracy of ultrasound subjective pattern recognition for EC in women with PMB.

All women underwent a transvaginal or transrectal ultrasound scan as described in the Methods section of this thesis (chapters 11 and 12) by a single operator. If the endometrium could not be satisfactorily visualised on ultrasound, women were offered either saline infusion sonography or hysteroscopy and they were excluded from the study.

Women were categorized into one of the following groups based on ultrasound subjective pattern recognition: atrophic endometrium, uniformly thickened endometrium, benign endometrial polyp, and endometrial cancer; their management was dependent on their ultrasound diagnosis.

Women with a non-atrophic endometrium on ultrasound underwent an outpatient pipelle endometrial biopsy or hysteroscopy, with the histology results as the gold standard. Women with an atrophic endometrium on ultrasound were managed expectantly with the advice to return immediately if they experienced a recurrence of PMB.

21.2.1 Statistical analysis

The primary outcome of this study was the diagnostic accuracy of ultrasound subjective pattern recognition for endometrial cancer in women with postmenopausal bleeding.

Our final statistical analysis included only women with a satisfactory ultrasound examination. Women with atrophic endometrium were excluded as they did not undergo endometrial sampling and therefore do not have a histological diagnosis. In the remaining women, the diagnostic accuracy (sensitivity, specificity, positive and negative likelihood ratios, false positive and negative rates, and overall accuracy) of subjective pattern recognition for endometrial cancer was assessed with histology as the gold standard. The final histological diagnoses were made on samples obtained from outpatient endometrial biopsy, hysteroscopy, or hysterectomy.

For sample size calculation, we used the method proposed by Buderer et al. (1996). Accordingly, 243 women with postmenopausal women and an endometrial thickness ≥4.5mm were required to estimate the sensitivity and specificity of ultrasound subjective pattern recognition within +/- 10%, in a population with a 19% prevalence of endometrial cancer (Clarke et al., 2018); assuming that the sensitivity and specificity were 86% and 90%, respectively, as reported in a previous study (Dueholm et al., 2015b). Given approximately 47% of women with postmenopausal bleeding would have a thickened endometrium (≥5mm) (Karlsson et al., 1995), the minimum number of women presenting with postmenopausal bleeding required was therefore 517. Also, to account for approximately 20% of women where the endometrium may not be satisfactorily assessed on ultrasound and 10% of women who may not have a final histological diagnosis due to medical co-morbidities or loss to follow-up, the final number of women planned for this study was 739 women.

21.3 Results

A total of 1686 women were examined during the study period, of which 763 were eligible for the study (Figure 11). The ultrasound and final histological diagnoses of these women are shown in Figure 12.

The endometrium could not be satisfactorily assessed in 127/763 (17%, 95% CI 14-19) women, this included 54/127 (43%) women where the endometrium could not be identified and 73/127 (57%) where the endometrium could be identified but the assessment was suboptimal and therefore the diagnosis on ultrasound was uncertain. The presence of uterine fibroids was the most common cause of difficulty in identifying the endometrium in 43/54 (80%) women, whereas 32/73 (44%) suboptimal ultrasound assessments were due to uncertainty regarding the presence of endometrial polyps.

Saline infusion sonography (SIS) was offered to all women with an unsatisfactory ultrasound scan; however, in 20/127 (16%) women SIS was not performed as 17 women (6/17 were virgo intacta) preferred hysteroscopy under general anaesthesia, 2 women preferred expectant management as they had significant medical co-morbidities and one woman proceeded with hysterectomy directly for clinically suspected endometritis. In the remaining 107/127 (84%) women, SIS was successful in 93/107 (87%, 95% CI 81-93) women. Failure of SIS was due to cervical stenosis in 6/14 women, pain in 4/14 women and poor distension of the uterine cavity in 4/14 women; failure was more common if the endometrium could not be identified during the initial ultrasound assessment compared to those in whom the images were suboptimal (26.3% vs 5.8%, $X^2 = 9.1$, $p = 0.003$).

In 636/763 (83%, 95% CI 81-86) women where it was possible to make a diagnosis on ultrasound subjective pattern recognition, 384/636 (60%, 95% CI 57-64) had an atrophic endometrium and they were managed expectantly. Their median endometrial thickness was 2.2mm (range 0.7-4.4mm). In 12 months following their ultrasound assessment, 44/384

women returned with a recurrence of postmenopausal bleeding, of which 10/44 women underwent diagnostic hysteroscopy and 2/44 had a hysterectomy, while the remaining women had no change to the ultrasound appearance of their endometrium, and they were managed expectantly. The final histological diagnoses in the 12/44 women who underwent hysteroscopy or hysterectomy were 7/12 cases of endometrial atrophy, 4/12 cases of a benign polyp and one case of endometrial hyperplasia without atypia.

The endometrium appeared non-atrophic in 252/636 (40%, 95% CI 36-43) women. The ultrasound diagnoses and final histological diagnoses of these women are shown in Table 10. In 12/252 women, a histological diagnosis was not available, this included 6 women who were managed expectantly due to significant medical co-morbidities, 3 did not attend their follow-up appointments, 2 declined any further investigations and 1 managed expectantly following a failed hysteroscopy. The final histological diagnoses in the remaining 240 women were obtained by a total of 117 hysteroscopies, 63 outpatient endometrial biopsies and 60 hysterectomies.

The clinical characteristics of the 240 women who were included in our final analysis for the diagnostic accuracy of ultrasound subjective pattern recognition are summarised in Table 11. The prevalence of endometrial cancer in our study cohort was 65/240 (27%, 95% CI 22-33). The diagnostic performance of ultrasound subjective pattern recognition for endometrial cancer in women with postmenopausal bleeding is presented in Table 12; the sensitivity was 87.7% (95% CI 77.2-94.5) and specificity 97.1% (95% CI 93.5-99.1).

There were 8/178 (5%, 95% CI 2-8) false-negative ultrasound diagnoses of endometrial cancer. Seven of these were endometrial polyps with focal areas of malignancy which were misdiagnosed as benign polyps; all these malignancies were confirmed histologically following hysteroscopic polypectomies. One woman had stage 1a grade 1 endometrioid adenocarcinoma which was misdiagnosed as having a uniformly thickened

endometrium, the diagnosis of malignancy was made histologically on the outpatient endometrial biopsy.

There were 5/62 (8%, 95% CI 1-15) false-positive ultrasound diagnoses of endometrial cancer. In two of these women, the outpatient endometrial biopsies obtained were insufficient and they were referred for diagnostic hysteroscopy where the presence of benign polyps was confirmed. In the other three women, both outpatient endometrial biopsy and hysteroscopy confirmed only benign endometrial pathologies, including disorganised proliferative endometrium, endometrial hyperplasia without atypia and pseudo-decidualised endometrium.

Figure 11 – Study 3 flowchart

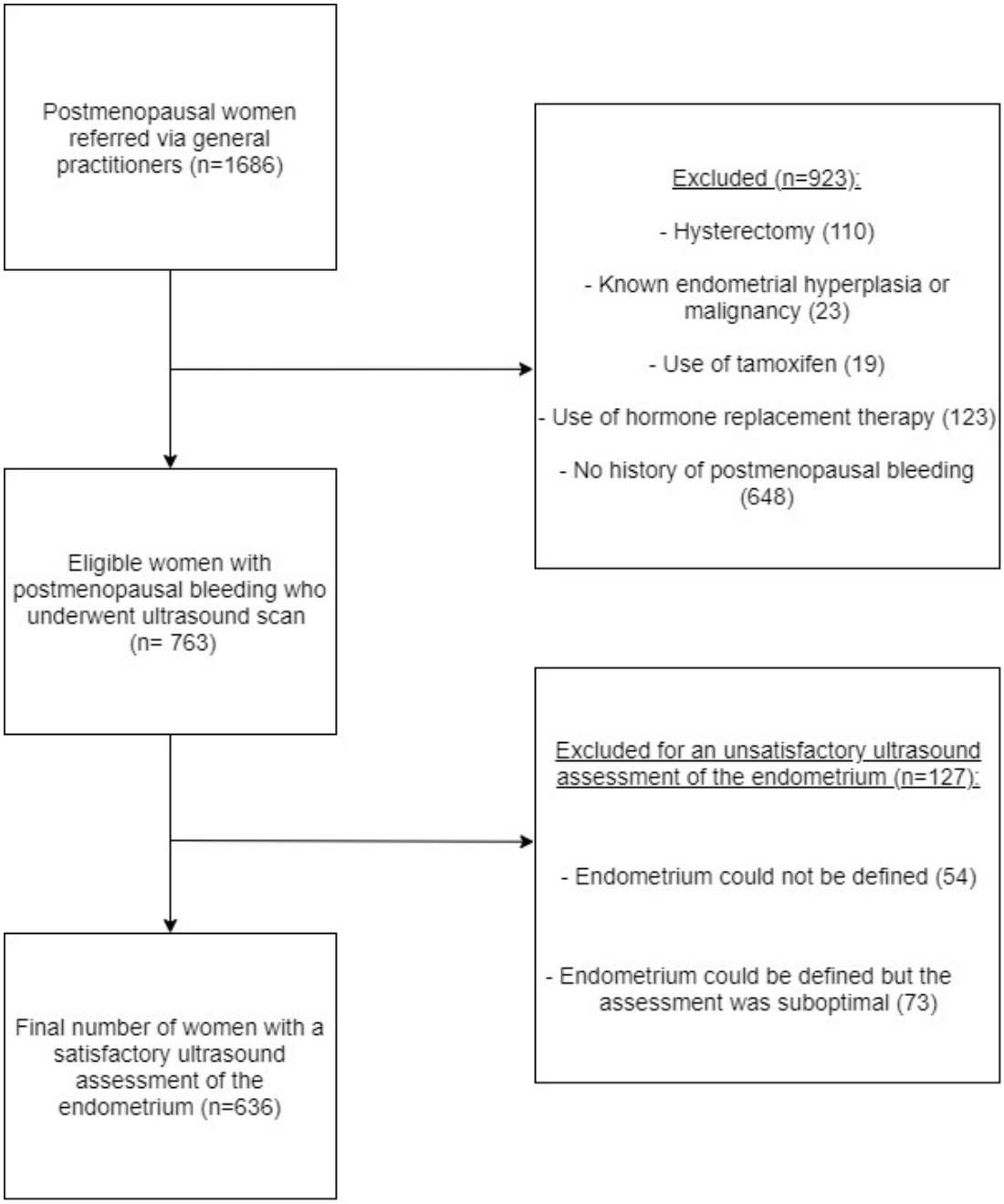
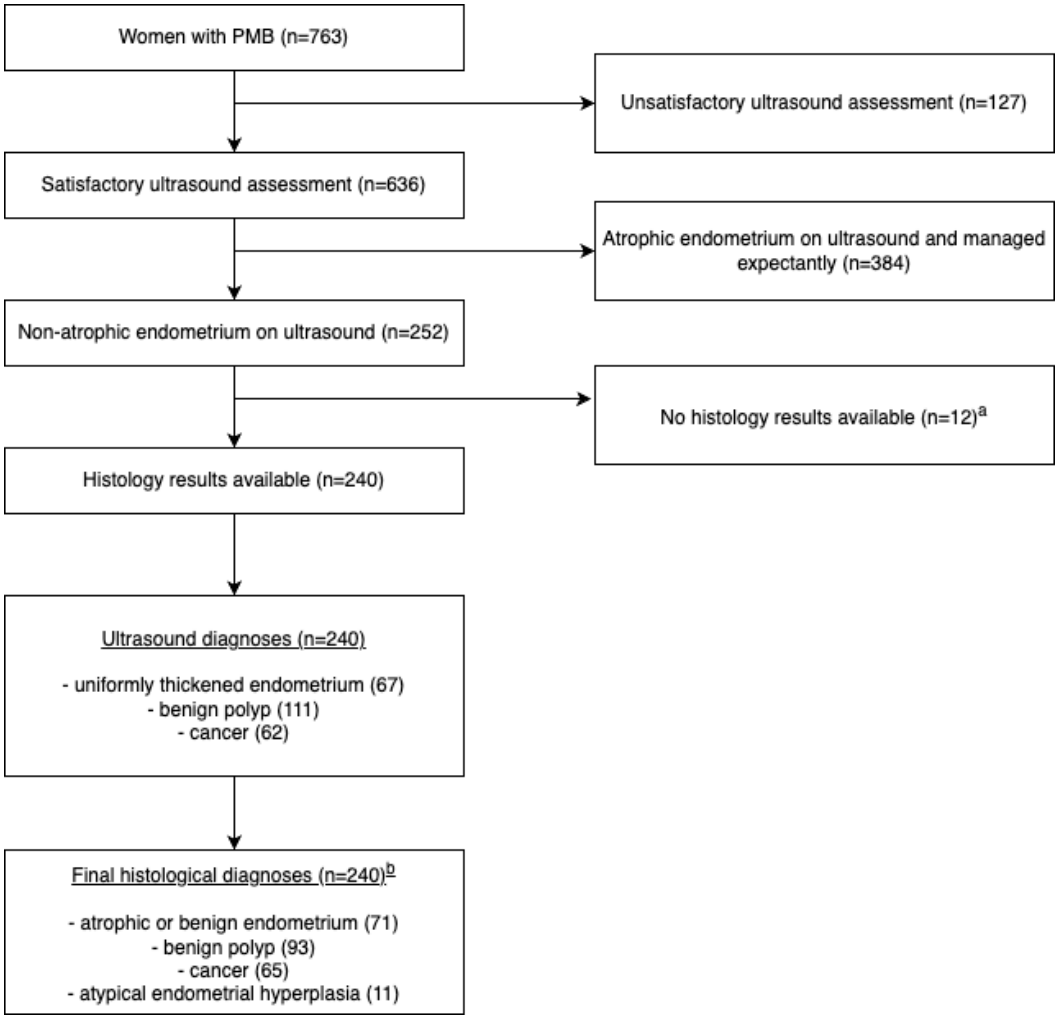


Figure 12 – Eligible women with postmenopausal bleeding who underwent a transvaginal or transrectal ultrasound examination (n=763)



[a]10 benign polyps and 2 uniformly thickened endometrium were diagnosed on ultrasound; women were managed expectantly due to significant medical co-morbidities (n=6), the patient did not attend follow-up appointments (n=3), the patient declined further tests (n=2) and failed hysteroscopy (n=1); [b]based on 117 hysteroscopies, 63 outpatient endometrial biopsies and 60 hysterectomies.

Table 10 – Ultrasound diagnoses in women with a non-atrophic appearance of the endometrium (n=252)

Ultrasound diagnoses	Final histological diagnoses						No histological diagnosis (n=12)
	Cancer (n=65)	Atypical hyperplasia (n=11)	Hyperplasia without atypia (n=14)	Endometrial polyp (n=93)	Proliferative endometrium (n=35)	Atrophic endometrium (n=22)	
Cancer (n=62)	57	0	1	2	2[d]	0	0
Endometrial polyp (n=121)	7[a]	7[b]	4[c]	87	1	5	10[e]
Uniformly thickened endometrium (n=69)	1	4	9	4	32	17	2[f]

[a]all cases were confined within polyps; [b]6 cases were confined within polyps; [c]all cases were confined within polyps; [d]one case of pseudo-decidualised endometrium; [e]6 patients were unfit for surgery, 3 did not attend a follow-up appointment, 1 failed hysteroscopy; [f]both women declined endometrial sampling

Table 11 – Clinical characteristics and histological diagnoses of the women included in the final analysis (n=240)

Characteristics	n (%)
Age[a]	60 (55-69.5)
Nulliparous	65 (27)
Body mass index (kg/m^2)[a]	28.5 (24.4-34.4)
Time since menopause[a]	8 (2-20)
Hypertension	95 (40)
Diabetes mellitus	34 (14)
Oral anticoagulants	8 (3)
Fibroids (total)	106 (44)
Fibroids (submucosal)	14 (6)
Adenomyosis	39 (16)
Spontaneous uterine intracavitary fluid	21 (9)
Endometrial thickness (mm)[a]	8.3 (5.6-12.3)
Final histological diagnoses	
Endometrial cancer[b]	65 (27)
- Stage 1a	28 (51)
- Stage 1b	10 (18)
- Stage 2	4 (7)
- Stage 3a	1 (2)
- Stage 3b	4 (7)
- Stage 3c$_1$	4 (7)
- Stage 3c$_2$	2 (4)
- Stage 4	2 (4)
Histological subtypes	
Endometrioid	42 (65)
- Grade 1	22 (52)
- Grade 2	18 (43)
- Grade 3	2 (5)
Non-endometrioid	23 (35)
- Serous	8 (35)
- Carcinosarcoma	7 (30)
- Undifferentiated	3 (13)
- Neuroendocrine	2 (9)
- Mixed serous/endometrioid	2 (9)
- Clear cell	1 (4)
Benign endometrial pathologies	175 (73)
- Endometrial polyp	93 (53)
- Atrophic endometrium	22 (13)
- Endometrial hyperplasia with atypia	11 (6)
- Endometrial hyperplasia without atypia	14 (8)
- Proliferative endometrium	35 (20)

[a]median (interquartile range); [b]55/65 had surgical staging of endometrial cancer

Table 12 – Diagnostic accuracy of subjective pattern recognition for endometrial cancer in women with postmenopausal bleeding (n=240)

Statistic	Value	95% CI
Sensitivity	87.7%	77.2 – 94.5%
Specificity	97.1%	93.5 – 99.1%
Positive likelihood ratio	30.7	12.9 – 73.2
Negative likelihood ratio	0.13	0.07 – 0.24
Disease prevalence	27.1%	21.6 – 33.2%
Positive predictive value	91.9%	82.7 – 96.5%
Negative predictive value	95.5%	91.7 – 97.6%
Accuracy	94.6%	90.9 – 97.1%

Chapter 22 Study 4 – Comparison of ultrasound and magnetic resonance imaging in the preoperative staging of endometrial cancer

22.1 Introduction

The mainstay of treatment for endometrial cancer is surgery. However, the radicality of surgery and the need for adjuvant therapy depend on the risks of lymph node metastasis and disease recurrence. Endometrial cancers are considered to be “high-risk” of metastasis and recurrence if there are features of deep (≥50%) myometrial invasion (DMI), cervical stromal invasion (CSI), lymphovascular space invasion, poorly differentiated (grade 3) or non-endometrioid histological subtypes (Amant et al., 2005).

The depth of myometrial invasion is clinically important because it is an independent predictor for lymph node metastasis in endometrial cancer. For example, lymph node metastasis is only found in 2% of women with a myometrial invasion of <50% and a well to moderately differentiated tumour; whereas, it is 18% in women with all other “high-risk” endometrial cancers (Luomaranta et al., 2015). If lymph node metastasis is present at the time of diagnosis, the 5-year disease-free survival drops from 90% to 54% (Lurain et al., 1991).

The presence of cervical stromal invasion is also an important clinical finding because it is an indication for radical rather than simple hysterectomy and women will usually require adjuvant radiotherapy.

Magnetic resonance imaging (MRI) is the imaging test most commonly used to assess endometrial cancer for DMI and CSI preoperatively, though ultrasound is an acceptable alternative option (Concin et al., 2021). The advantages of ultrasound over MRI are its wider availability, lower cost, shorter examination time and no requirement for intravenous contrast. The avoidance of intravenous contrast is particularly relevant in elderly patients

with renal impairment (GFR <30 ml/min/1.73m^2), who are at an increased risk of nephrogenic systemic fibrosis with gadolinium-based contrast media (Thomsen et al., 2013). Furthermore, in regions with limited resources, ultrasound is recommended over MRI for the preoperative staging of endometrial cancer (Ribeiro et al., 2020).

When women present with postmenopausal bleeding, endometrial cancer can be accurately diagnosed by ultrasound by subjective pattern recognition, with a false positive rate of less than 10% (Dueholm et al., 2015b). This allows for malignancies to be simultaneously staged at women's initial ultrasound examination. Previous studies have reported good diagnostic accuracy of ultrasound in staging endometrial cancer (Alcázar et al., 2015); however, few of them have compared ultrasound with MRI in the same cohort of women (Alcázar et al., 2017).

The primary aim of this study was to compare the diagnostic accuracies of ultrasound and MRI for the deep myometrial invasion in women with endometrial cancer. The secondary aim was to compare their respective diagnostic accuracies for cervical stromal invasion.

22.2 Methods

Inclusion and exclusion criteria

Between Oct 2015 and Oct 2018, consecutive women with a history of postmenopausal bleeding or unscheduled vaginal bleeding whilst on hormone replacement therapy (HRT) were assessed as described in the Methods section of this thesis (chapters 11 and 12). Women with suspected endometrial cancer on transvaginal or transrectal ultrasound scans based on subjective pattern recognition were eligible for the study. Only endometrial cancers with epithelial or mixed epithelial and mesenchymal histological types were included, i.e., endometrioid, mucinous, serous, clear cell, mixed, undifferentiated and carcinosarcoma. We excluded women with a previously diagnosed gynaecological malignancy.

Study outcomes and follow-up

The primary outcome was the diagnostic accuracies of preoperative ultrasound and MRI for DMI. The secondary outcome was their respective diagnostic accuracies for CSI.

All women with suspected endometrial cancer on ultrasound were simultaneously assessed for the depth of myometrial invasion and cervical stromal invasion as described in the Methods section of this thesis (Chapter 13). The depth of myometrial invasion was categorized into i) no myometrial invasion or myometrial invasion <50% of the entire myometrial thickness, or ii) ≥50% of the entire myometrial thickness. While CSI was either absent or present.

After the ultrasound examination, women were offered endometrial sampling by Pipelle suction curette (Laboratoire CCD, Paris, France) or hysteroscopy. MRI scan was requested for women with a histologically confirmed malignancy, which included the T2-weighted imaging (T2WI), dynamic T1-weighted gadolinium sequences (DCE-MRI) and diffusion-

weighted imaging (DWI-MRI) with an apparent diffusion coefficient (ADC) map.

All MRI scans were performed on a 3T MRI scanner (Achieva or Ingenia, Philips Healthcare, Best, Netherlands) with the patient lying supine on the table, with the arms along her body. The patient was asked to fast 6 hours before the examination and to void 1 hour before it, furthermore, 20mg of butylscopolamine bromide (Buscopan, Boehringer Ingelheim, Germany) was administered intramuscularly just before the examination to reduce bowel motion. T2WI and DCE-MRI images were acquired along three orthogonal planes (para-sagittal, para-axial and para-coronal), whereas DWI-MRI images were acquired on two planes only (para-axial and para-sagittal). B-values of 0, 500, 800 and 1000 s/mm^2 were used for DWI. ADC maps were generated from isotropic DWI using software (Syngo, Siemens, Erlangen, Germany). DCE-MRI was acquired after an intravenous bolus injection of 0.1mmol/kg of gadobutrol (Gadovist, Bayer, Berlin, Germany), followed by a 20ml saline flush, starting 60 seconds after contrast material injection. The standard acquisition protocol included a slice thickness of 4 mm, interspace gap of 1mm, and Field of vision of 20cm (extended from the renal hilar through the pelvis on T1W images to detect nodal involvement).

The assessment of DMI and CSI on MRI is described in the Methods section of this thesis (Chapter 14).

MRI scans were interpreted by experienced consultant radiologists in gynaecological oncology, who were blinded to the ultrasound findings. Similarly, all ultrasound examinations were performed before patients underwent MRI scans.

22.2.1 Statistical analysis

In our final statistical analysis, we included only women who underwent both ultrasound and MRI examinations. We excluded women who did not undergo a hysterectomy following the imaging tests. The diagnostic

accuracies (sensitivity, specificity, positive and negative likelihood ratios, false positive and negative rates, and overall accuracy) of ultrasound and MRI were calculated with the final histology from hysterectomy as the gold standard.

For sample size calculation, we focused on the sensitivity of ultrasound and MRI for deep myometrial invasion because a high sensitivity is important to reduce the risk of women having incomplete surgical staging procedures due to false-negative results. According to Liu et al. (2002), this study required a minimum of 49 women to undergo both the ultrasound and MRI examinations, to detect a difference of 10% in sensitivity, with a power of 80%, a significance level of 5% and the assumption that the expected percentage of a discrepancy between ultrasound and MRI is 5% (DelMaschio et al., 1993).

Reliability between ultrasound and MRI in the preoperative staging of endometrial cancer was assessed using Cohen's kappa (ƙ) statistic.

22.3 Results

During the study period, 1009 women underwent ultrasound examination for postmenopausal bleeding or unscheduled vaginal bleeding whilst on HRT; 144 were excluded as the endometrium could not be satisfactorily assessed (Figure 13). Of the remaining women, 68 were suspected of endometrial cancer on ultrasound and they were simultaneously assessed for the presence of DMI and CSI. Later, we excluded five women who had no evidence of malignancy on endometrial biopsy and hysteroscopy: two of them were diagnosed with benign endometrial polyps, two with proliferative endometrium and one with endometrial hyperplasia without atypia. A further five women were also excluded as they did not undergo MRI due to claustrophobia, presence of a cardiac pacemaker or morbid obesity. And finally, seven more women were excluded as they did not undergo hysterectomy due to significant medical co-morbidities or patients moved abroad. Table 13 summarises the clinical characteristics of the remaining 51 women who were included in our study. The median time between the ultrasound and MRI scan was 20 days (IQR 13-29); whereas the median time between ultrasound and hysterectomy for endometrial cancer was 37 days (IQR 27-50).

Most of the endometrial cancers (38/51, 75%) included in our study were of endometrioid histological type and of which 37/38 (97%) were well to moderately differentiated (grade 1 or 2). The prevalence of DMI and CSI were 22/51 (43%) and 7/51 (14%), respectively. Most malignancies were diagnosed at FIGO stage 1 or 2 (40/51, 78%).

The diagnoses of ultrasound and MRI for DMI and CSI against the final histology are shown in Tables 14 to 17; their respective diagnostic accuracies are summarised in Table 18.

Ultrasound correctly identified more women with DMI compared to MRI (19/22, 86% vs 17/22, 77%); however, the difference was not statistically significant. The respective false-positive rates were 10/29 (34%, 95% CI 17-52) and 7/29 (24%, 95% CI 9-40). The proportion of women with DMI who

were under-staged by ultrasound but correctly staged on MRI was 2/51; whereas, in 4/51 women, it was the opposite.

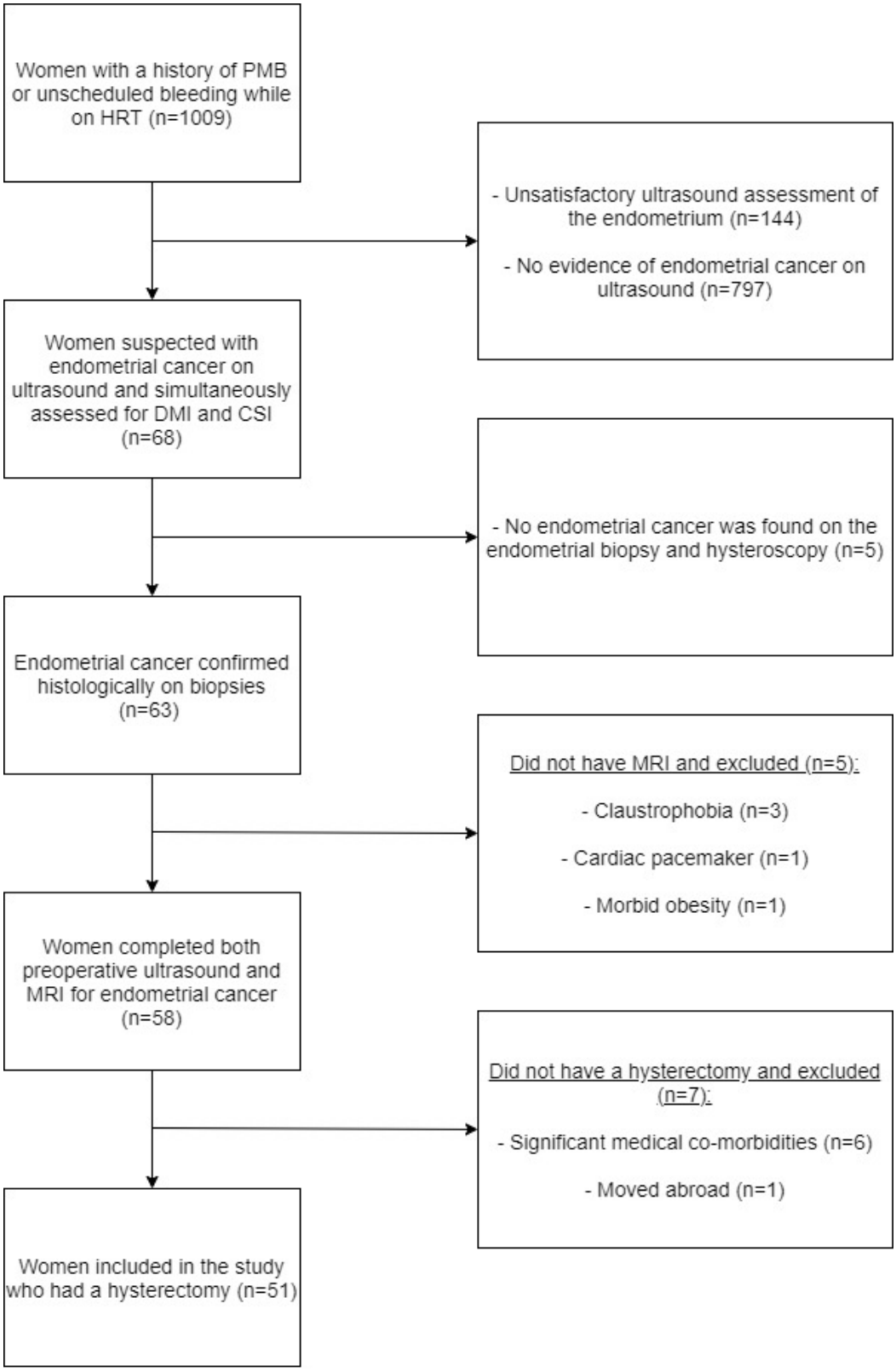
Both ultrasound and MRI correctly identified the same number of women with CSI (5/7, 71%). The respective false-positive rates were both low, 0/44 (0%) and 1/44 (2%).

Ultrasound and MRI agreed on 38/51 (75%, 95% CI 63-87) diagnoses of DMI (Table 19). A ƙ statistic of 0.49 (95% CI 0.26-0.73) means that the agreement was moderate. For the assessment of CSI, ultrasound and MRI agreed on 48/51 (94%) diagnoses (Table 20). A ƙ statistic of 0.69 (95% CI 0.36-1.00) means that the agreement was substantial.

We carried out a subgroup analysis for women with “low risk” endometrial cancers, i.e., low-grade (grade 1 or 2 endometrioid) and clinically stage 1 tumours. This is because, from the gynaecological oncologists’ perspective, the depth of myometrial invasion is most relevant in these women, who may not require more invasive surgeries such as lymphadenectomy or sentinel lymph node biopsy.

The results of our subgroup analysis are presented in Tables 21 and 22, which show that ultrasound detected more women with DMI (8/9, 89%) compared to MRI (6/9, 67%); however, the difference was not statistically significant (Table 23). There were only 2 women with CSI in the subgroup and therefore we did not carry out a comparison between ultrasound and MRI in the detection of CSI.

Figure 13 – Study 4 flowchart



PMB = postmenopausal bleeding, HRT = hormone replacement therapy, MRI = magnetic resonance imaging

Table 13 – Patient clinical characteristics and the final histological diagnoses (n=51)

Characteristics	n (%)
Age[a]	66 (57-76)
Nulliparous	15 (29)
Body mass index (kg/m^2)[a]	28.8 (25.6-32.7)
Time since menopause[a]	12 (5-27)
Hypertension	18 (35)
Diabetes mellitus	5 (10)
Fibroids (total)	14 (27)
Fibroids (submucosal)	1 (2)
Adenomyosis	5 (10)
Anteverted positioned uterus	36 (71)
Retroverted positioned uterus	9 (18)
Axial positioned uterus	6 (12)
Endometrial thickness (mm)[a]	16.5 (11.4-30)
Tumour mean diameter (mm)[a]	25 (18-41)
Final histological diagnoses	
Endometrioid histological subtype	38 (75)
- Grade 1	19 (50)
- Grade 2	18 (47)
- Grade 3	1 (3)
Non-endometrioid histological subtype	13 (25)
- Carcinosarcoma	5 (38)
- Serous	4 (31)
- Neuroendocrine	2 (15)
- Clear cell	1 (8)
- Mixed serous/endometrioid	1 (8)
Stage of endometrial cancer	
- Stage 1a	25 (49)
- Stage 1b	11 (22)
- Stage 2	4 (8)
- Stage 3a	2 (4)
- Stage 3b	3 (6)
- Stage 3c$_1$	4 (8)
- Stage 3c$_2$	0 (0)
- Stage 4	2 (4)
[a]median (interquartile range)	

Table 14 – Ultrasound preoperative diagnosis of deep (≥50%) myometrial invasion against the final histology (n=51)

		Final histology		Total
		DMI present	DMI absent	
Ultrasound	DMI present	19	10	29
	DMI absent	3	19	22
Total		22	29	51
DMI = deep myometrial invasion (≥50%)				

Table 15 – Ultrasound preoperative diagnosis of cervical stromal invasion against the final histology (n=51)

		Final histology		Total
		CSI present	CSI absent	
Ultrasound	CSI present	5	0	5
	CSI absent	2	44	46
Total		7	44	51
CSI = cervical stromal invasion				

Table 16 – MRI preoperative diagnosis of deep (≥50%) myometrial invasion against the final histology (n=51)

		Final histology		Total
		DMI present	DMI absent	
MRI	DMI present	17	7	24
	DMI absent	5	22	27
Total		22	29	51
DMI = deep myometrial invasion (≥50%)				

Table 17 – MRI preoperative diagnosis of cervical stromal invasion against the final histology (n=51)

		Final histology		Total
		CSI present	CSI absent	
MRI	CSI present	5	1	6
	CSI absent	2	43	45
Total		7	44	51
CSI = cervical stromal invasion				

Table 18 – Diagnostic accuracies of ultrasound and MRI for deep (≥50%) myometrial invasion and cervical stromal invasion in endometrial cancer (n=51)

		Sensitivity % (95% CI)	Specificity % (95% CI)	+LR (95% CI)	-LR (95% CI)	Accuracy % (95% CI)
Ultrasound	DMI	86 (65-97)	66 (46-82)	2.5 (1.5-4.3)	0.2 (0.1-0.6)	75 (60-86)
	CSI	71 (29-96)	100 (92-100)	n/a	0.3 (0.1-0.9)	96 (87-100)
MRI	DMI	77 (55-92)	76 (56-90)	3.2 (1.6-6.3)	0.3 (0.1-0.7)	76 (63-87)
	CSI	71 (29-96)	98 (88-100)	31.4 (4.3-231)	0.3 (0.1-0.9)	94 (84-99)

DMI = deep (≥50%) myometrial invasion, CSI = cervical stromal invasion, CI = confidence interval, LR = likelihood ratio, n/a = not available

Table 19 – Agreement between ultrasound and MRI on the preoperative assessment of myometrial invasion with final histology as the reference standard (n=51)

		MRI			Total
		Correctly staged	Over-staged	Under-staged	
Ultrasound	Correctly staged	32	2	4	38
	Over-staged	5	5	0	10
	Under-staged	2	0	1	3
Total		39	7	5	51

Table 20 – Agreement between ultrasound and MRI on the preoperative assessment of cervical stromal invasion with final histology as the reference standard (n=51)

		MRI			Total
		Correctly staged	Over-staged	Under-staged	
Ultrasound	Correctly staged	47	1	1	49
	Over-staged	0	0	0	0
	Under-staged	1	0	1	2
Total		48	1	2	51

Table 21 – Preoperative diagnosis of deep myometrial invasion by ultrasound in women with "low-risk" endometrial cancer against the final histology (n=31)

		Final histology		Total
		DMI present	DMI absent	
Ultrasound	DMI present	8	6	14
	DMI absent	1	16	17
Total		9	22	31
DMI = deep myometrial invasion (≥50%)				

Table 22 – Preoperative diagnosis of deep myometrial invasion by MRI in women with "low-risk" endometrial cancer against the final histology (n=31)

		Final histology		Total
		DMI present	DMI absent	
MRI	DMI present	6	5	11
	DMI absent	3	17	20
Total		9	22	31
DMI = deep myometrial invasion (≥50%)				

Table 23 – Diagnostic accuracies of ultrasound and MRI for deep myometrial invasion in women with "low-risk" endometrial cancer (n=31)

		Sensitivity % (95% CI)	Specificity % (95% CI)	+LR (95% CI)	-LR (95% CI)	Accuracy % (95% CI)
Ultrasound	DMI	89 (52-100)	72 (50-89)	3.3 (1.6-6.7)	0.15 (0.02-1.0)	77 (59-90)
MRI	DMI	67 (30-93)	77 (55-92)	2.9 (1.2-7.2)	0.43 (0.2-1.12)	74 (55-88)

DMI = deep myometrial invasion (≥50%), CSI = cervical stromal invasion, CI = confidence interval, LR = likelihood ratio

Chapter 23 Study 5 – Risk of pre-malignancy or malignancy in postmenopausal endometrial polyps: a CHAID decision tree analysis

23.1 Introduction

Endometrial polyps are common and the pathophysiology is unclear as many are undiagnosed in asymptomatic women (Dreisler et al., 2009).

There is currently no consensus on the management of endometrial polyps in postmenopausal women. Some advocate for the removal of all polyps as pre-malignancy or malignancy has been reported in both symptomatic and asymptomatic women (Golan et al., 2010). While others may consider expectant management as the risk of pre-malignancy or malignancy is low in asymptomatic women (AAGL, 2012). Furthermore, expectant management may also be considered in women who are at increased risk of surgery, such as those with significant medical co-morbidities or a previously failed hysteroscopy due to cervical stenosis.

The estimated risk of pre-malignancy or malignancy in postmenopausal polyps is about 5% (Uglietti et al., 2019). Risk factors for pre-malignancy or malignancy include older age, obesity, hypertension, diabetes mellitus, a history of abnormal uterine bleeding or tamoxifen use (Sasaki et al., 2018). Clinically, it is important to offer all women an individualised discussion about their management options. In a study on women's preference, 59% of women with postmenopausal bleeding would like 100% certainty that malignancy has been ruled out, while 36% of women would accept expectant management if the risk of malignancy is ≤5%, and a small proportion of women (5%) may choose expectant management even if the risk of malignancy is >5% (Timmermans et al., 2007).

We hypothesized that the patient's clinical characteristics and ultrasound morphological features of the polyp may help improve the risk prediction of pre-malignancy or malignancy in postmenopausal polyps.

This study aimed to carry out a decision tree analysis to identify the predictive patient characteristics and ultrasound features of polyps for pre-malignancy or malignancy in postmenopausal polyps.

23.2 Methods

Inclusion and exclusion criteria

Between October 2015 and October 2018, we included consecutive postmenopausal women who were diagnosed with endometrial polyps on transvaginal or transrectal ultrasound scan and underwent hysteroscopic polypectomy or hysterectomy within three months of the ultrasound diagnosis. We excluded women who were on tamoxifen or with a known history of gynaecological malignancy or endometrial hyperplasia.

Endometrial polyps were diagnosed on ultrasound as per the IETA consensus (Van Den Bosch et al., 2021). Accordingly, a benign endometrial polyp appears as a well-defined focal lesion with a regular outline within the endometrial cavity. The surrounding endometrium appears morphologically normal. On Doppler ultrasound, there is either a single feeder vessel or there is no detectable vascularity (Timmerman et al., 2003) (Figure 14).

Study outcomes and follow-up

The study outcome was to create a decision tree model to predict the presence of pre-malignancy or malignancy in postmenopausal endometrial polyps.

On ultrasound, we measured each polyp in three perpendicular planes (d1, d2, d3) in the longitudinal and transverse views of the uterus. Polyps mean diameter (dm) was calculated from these measurements, i.e., dm = (d1+d2+d3)/3 and expressed in millimetres. If multiple polyps were present, only the largest polyp was included in our final analysis. Also, each polyp was assessed for the presence of intralesional cystic spaces (Figure 15). Polyps were described as either cystic, if they contained any intralesional cystic spaces, or solid if they did not contain any visible cystic spaces. In cases where the endometrium could not be assessed adequately, saline infusion sonography was performed. Endometrial lesions with an irregular surface, a multi-vessel vascular pattern on Doppler ultrasound or abnormal

adjacent endometrium, were diagnosed as suspected endometrial cancer (Dueholm et al., 2014) and they were excluded from the study.

For each patient, we recorded their clinical risk factors for endometrial hyperplasia or malignancy, which included age, body mass index (BMI), parity, use of hormone replacement therapy (HRT), history of hypertension and diabetes mellitus (Jenabi and Poorolajal, 2015, Schonfeld et al., 2013, Aune et al., 2017, Byrne et al., 2020).

Following hysteroscopic polypectomy or hysterectomy, all surgical specimens were examined by pathologists who were blinded to the ultrasound assessments. The final histological diagnosis was used as the gold standard. We divided women into two categories for our analysis: 1. Benign polyps, which included polyps with hyperplasia but no evidence of atypia, and 2. Polyps with atypical hyperplasia or malignancy.

Women with endometrial polyps diagnosed on ultrasound and who chose expectant management were advised to return immediately if they experienced symptom/recurrence of PMB.

23.2.1 Statistical analysis

We used the Chi-squared automatic interaction detection (CHAID) algorithm (Kass, 1980, Song and Lu, 2015) to perform our decision tree analysis with the dependent variable defined as the presence or absence of atypical hyperplasia or malignancy in endometrial polyps. Our independent variables were the patient's age, BMI, parity, history of hypertension, diabetes mellitus, use of HRT, number of polyps, polyp mean diameter, presence, or absence of a feeder vessel to the polyp, and whether the polyp appeared cystic or solid on ultrasound. The CHAID algorithm is a non-parametric procedure and therefore it required no assumptions to be made of the underlying data. Multiple 2x2 contingency tables between the dependent variable and each independent variable were created, the most significant independent variable in a chi-square test was then selected to

branch out the decision tree. The categories of each independent variable were merged if they were not significantly different from the dependent variable (IBM, 2020). The decision tree was set to have a maximum of three levels, a minimum of 20 cases in each parent node and any given split should not generate a child node with less than 10 cases, the significance level (α_{merge}, α_{split}, and p-value) was set at ≤0.05. The resulting subgroups created by the decision tree model were divided into three classification groups according to the risk of pre-malignancy or malignancy in endometrial polyps as low-risk (≤5%), intermediate-risk (>5% to ≤20%) or high-risk (>20%).

We used the 10-fold cross-validation method to internally validate our decision tree model (IBM, 2020). In this method, the original study cohort was randomly partitioned into ten subsets of equal sizes. One of the subsets was used as the validation set, while the other nine were used as the training set. The cross-validation process was repeated ten times, in which each of the ten subsets was used only once as the validation set. The average value of the ten results from the folds was estimated as the misclassification risk value.

23.3 Results

During the study period, 1686 postmenopausal women underwent ultrasound examination as illustrated in Figure 16. Of the 1534 eligible women, 886/1534 (58%) women presented with postmenopausal bleeding. Other indications for an ultrasound scan in the remaining 648/1534 women are summarised in Table 24.

We diagnosed 308 endometrial polyps on ultrasound. The proportions of women diagnosed with polyps were similar in those presenting with or without postmenopausal bleeding (192/886 (22%) vs 116/648 (18%); X^2 = 3.3, p = 0.07).

All women with endometrial polyps were offered surgery; however, 68/308 (22%) were managed expectantly due to the woman's preference, the presence of medical co-morbidities or a failed hysteroscopy. In women with postmenopausal bleeding, 11/192 (6%) polyps were managed expectantly, compared to 57/116 (49%) in women without postmenopausal bleeding. On univariate analysis, expectantly managed asymptomatic women were significantly older (median 70 (IQR 62-78) vs 63 (IQR 56-73), p = 0.01)) and they were more likely to have a single polyp (98.2% vs 83.1%, p = 0.01)) of a smaller size (median 10mm (IQR 7.0-12.7) vs 13.3mm (IQR 9-17), p = 0.01)), with no detectable vascularity on Doppler examination (66.7% vs 45.8%, p = 0.03), when compared to asymptomatic women who were managed surgically.

A final 240 women with polyps who underwent surgery in the form of hysteroscopic polypectomy or hysterectomy were included in our decision tree analysis. Patient characteristics are summarised in Table 25. There were 5/240 (2%, 95% CI 0.7-4.8) polyps with hyperplasia without atypia, 8/240 (3%, 95% CI 1.4-6.1) with atypical hyperplasia and 10/240 (4%, 95% CI 2.0-7.5) with malignancy. Overall, the prevalence of pre-malignancy or malignancy was 18/240 (8%, 95% CI 4.5-11.6). Among the malignant polyps, six were of endometrioid histological subtype and the other four were serous adenocarcinomas. On univariate analysis, premalignant or

malignant polyps were significantly larger, more likely to appear solid rather than cystic and less likely to appear avascular on colour Doppler imaging (Table 26). The number of polyps on ultrasound did not appear to be associated with the risk of pre-malignancy or malignancy.

23.3.1 Decision tree analysis and internal validation

In our decision tree analysis, the three most significant predictive variables for premalignant or malignant polyps were polyp size, women's BMI and whether the polyp appeared cystic or solid on ultrasound. The model concluded with a total of five subgroups, which divided women into low-risk, intermediate-risk or high-risk for pre-malignancy or malignancy (Figure 17).

Polyps mean diameter was selected as the first splitting variable in our model. For women with a polyp mean diameter of ≤13mm, their risk of pre-malignancy or malignancy was 4/166 (2%, 95% CI 0.7-6.1); whereas, in polyps >13mm, their risk was 14/74 (19%, 95% CI 10.7-29.7).

Among women with a polyp mean diameter of >13mm, whether the polyp appeared cystic or solid was selected as the second splitting variable. Polyps that appeared cystic had a 1/37 (3%, 95% CI 0.1-14.2) risk of pre-malignancy or malignancy and they were classified as low risk. Polyps that appeared solid were further divided with women's BMI as the third splitting variable. In women with a BMI >28.2, their risk of pre-malignancy or malignancy was 9/14 (64%, 95% CI 39.2-89.4) and they were classified as high-risk; compared to those with a BMI ≤28.2, their risk was 4/23 (17%, 95% CI 1.9-32.9) and they were classified as intermediate risk.

The risk of pre-malignancy or malignancy in women with a polyp mean diameter of ≤13mm was generally low; however, our model further divided these women according to their BMI as the second splitting variable. In those with a BMI >28.4, their risk of pre-malignancy or malignancy was 4/48 (8%, 95% CI 0.5-16.2) and they were classified as an intermediate risk;

while women with a BMI ≤28.4, there were no cases of pre-malignancy or malignancy, and they were classified as low risk.

Using our decision tree model to counsel women in the high-risk and intermediate-risk groups for surgery, where the risk of pre-malignancy or malignancy is >5%, results in 85/240 (35%, 95% CI 29-42) women having hysteroscopic resection of polyps. The overall accuracy of our model for correctly identifying women with premalignant or malignant polyps was 94%. For internal validation, a misclassification risk of 8% ± 1.8% (standard error) was calculated using the 10-fold cross-validation method. This result means that our model may correctly prioritise 92% (95% CI 86.0-97.4) of women with premalignant or malignant polyps; the corresponding sensitivities and specificities of our model were 94.4% (95% CI 72.7-99.9) and 69.4% (95% CI 62.9-75.4).

Figure 14 – Example of a benign endometrial polyp with a regular outline and homogeneous echogenicity on B-mode greyscale ultrasound. On Doppler examination, the polyp had a single feeder vessel (Wong et al., 2021b)

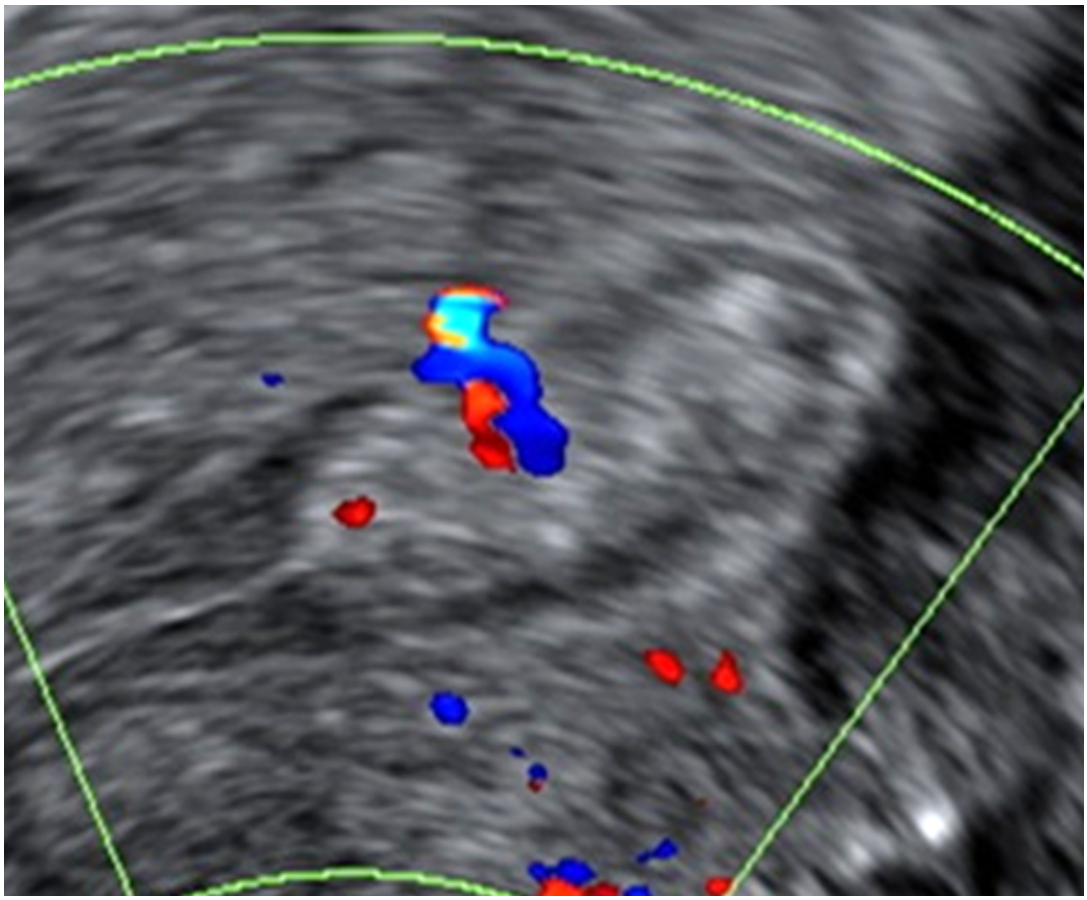


Figure 15 – Example of a benign endometrial polyp with intra-lesional cystic spaces on B-mode greyscale ultrasound (Wong et al., 2021b)

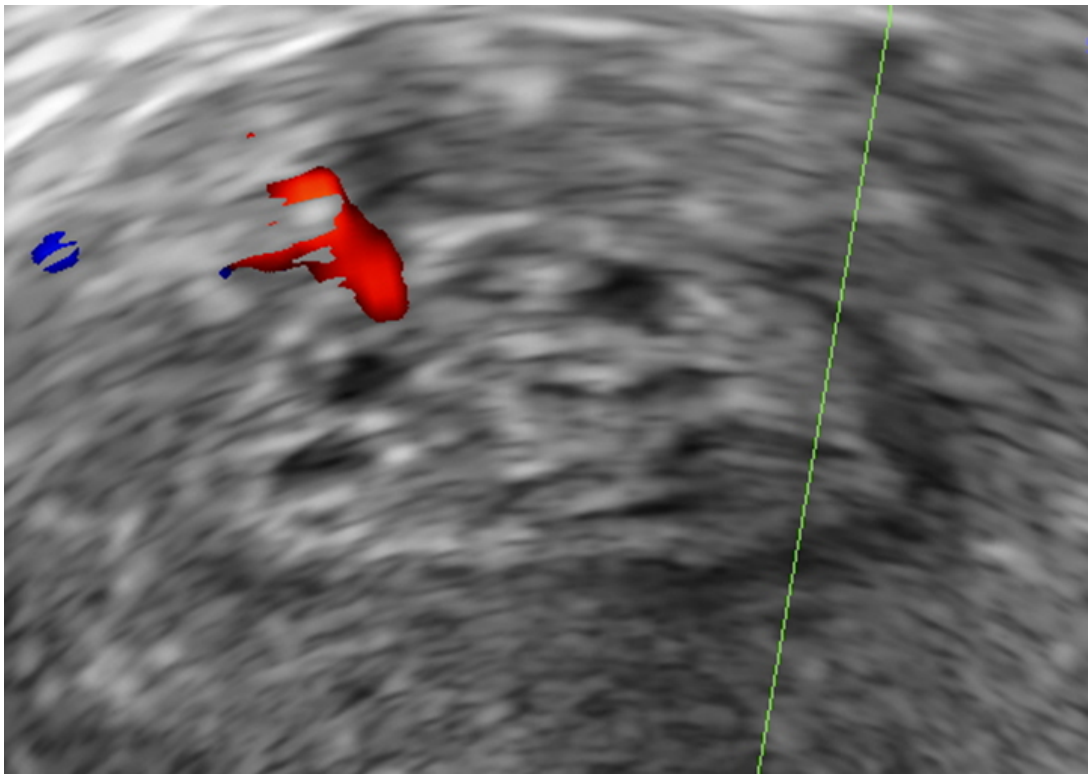


Figure 16 – Study 5 flowchart (Wong et al., 2021b)

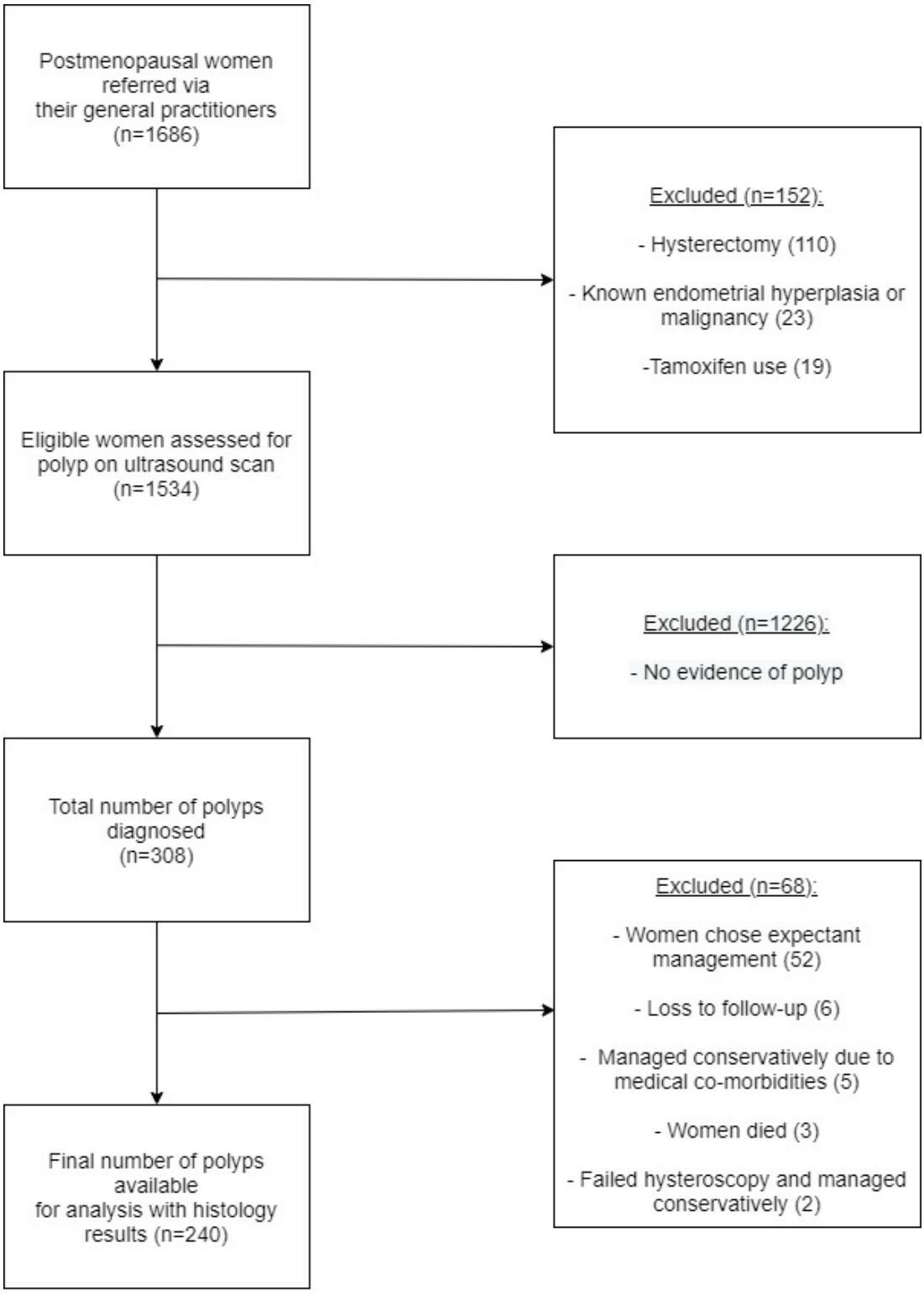


Table 24 – Indications for an ultrasound scan (n=1534) (Wong et al., 2021b)

Indications	N (%)
Postmenopausal bleeding	886 (57.8)
Abdominal or pelvic pain	209 (13.6)
Abdominal or pelvic swelling	146 (9.5)
Bowel or urinary symptoms	63 (4.1)
Incidental finding of a thickened endometrium on ultrasound	63 (4.1)
Raised serum CA125	52 (3.4)
Ovarian cancer screening	52 (3.4)
Other	63 (4.1)

Table 25 – Patient characteristics of the study cohort (n=240) (Wong et al., 2021b)

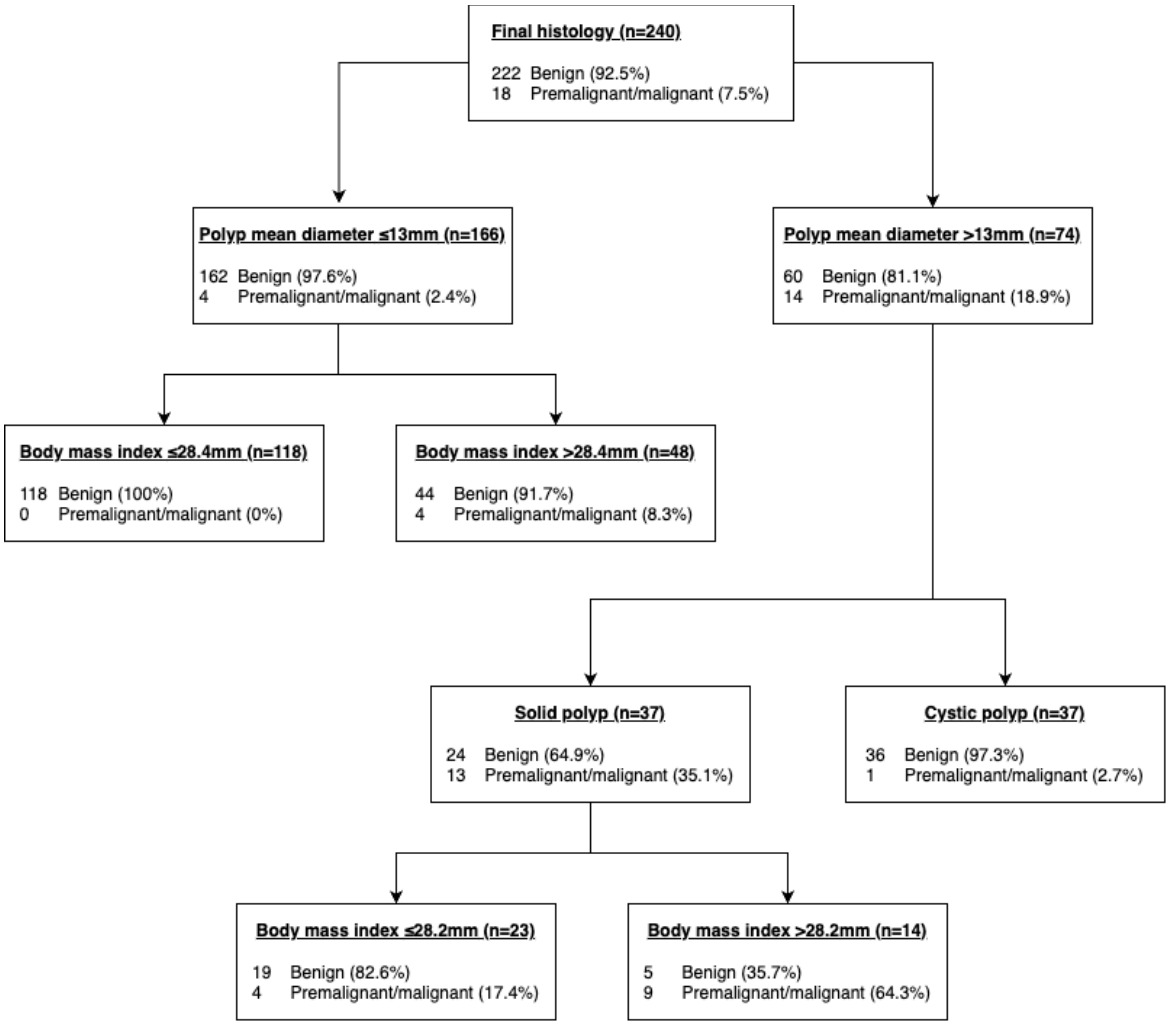
Characteristic	Benign polyps (n=222)	Premalignant or malignant polyps (n=18)
Age[a]	60 (45-94)	65.5 (52-82)
BMI (kg/m^2)[b]	26.6 (18.5-52.3)	30.4 (21.6-40.8)
Nulliparity[b]	63 (28.4)	6 (33.3)
Hypertension[b]	75 (33.8)	10 (55.6)
Diabetes mellitus[b]	22 (9.9)	3 (16.7)
Use of HRT[b]	75 (33.8)	2 (11.1)
Symptoms of PMB[b]	166 (74.8)	15 (83.3)
[a]Median (range), [b]n (%), HRT = hormone replacement therapy PMB = postmenopausal bleeding		

Table 26 – Ultrasound morphological features of the endometrial polyps (n=240) (Wong et al., 2021b)

Characteristic	Benign polyps (n=222)	Premalignant or malignant polyps (n=18)	Test statistic	p-value
Polyps mean diameter (mm)[a]	10.0 (4.0-28.0)	13.3 (7.0-35.0)	U = 862.5	<0.001[c]
Presence of a pedicle vessel[b]	92 (41.4)	12 (66.7)	n/a	0.048[d]
Presence of intra-lesional cystic spaces[b]	82 (36.9)	1 (5.6)	n/a	0.008[d]
Multiple polyps[b]	49 (22.1)	4 (22.2)	n/a	1.000[d]

[a]median (range), [b]n (%), [c]Mann-Whitney U test, [d]Fisher's exact test, n/a = not applicable

Figure 17 – CHAID decision tree analysis on the risk of pre-malignancy or malignancy in women with postmenopausal polyps (Wong et al., 2021b)



Chapter 24 Study 6 – Natural history of endometrial polyps: a retrospective cohort study

24.1 Introduction

Endometrial polyps are localized overgrowths of the endometrial gland and stroma around a vascular core that arise from the surface of the endometrium. They are most commonly found in postmenopausal women and are rarely seen in women younger than the age of 30; however, the exact prevalence of endometrial polyps is unknown as they do not always cause symptoms and therefore may remain undetected (Dreisler et al., 2009). In a retrospective review of polyps that were removed surgically, 44% and 36% of polyps were diagnosed in asymptomatic premenopausal and postmenopausal women, respectively (Hassa et al., 2006).

Most of the diagnosed endometrial polyps are removed surgically, but in some women, expectant management may be preferred because of the presence of medical co-morbidities or when the risk of a malignant polyp is low. However, little is known about the natural history of endometrial polyps when they are managed expectantly.

This study aimed to evaluate the change in polyp size when they are managed expectantly. We also tried to identify predictive factors for polyps' growth rate, spontaneous regression of polyps and women becoming symptomatic of abnormal uterine bleeding during the follow-up period.

24.2 Methods

Inclusion and exclusion criteria

We retrospectively searched our ultrasound clinic database at University College London Hospitals (PIA Fetal Database, version 2.23; Viewpoint Bildverarbeitung GmbH, Munich, Germany) between July 1997 and September 2015 to identify women aged 18 years or older with endometrial polyps that were managed expectantly for a minimal period of 6 months. All women were examined on at least two occasions by a single expert ultrasound operator with a minimum interval of 6 months between the examinations. We excluded women who were using hormonal contraception, hormone replacement therapy or medications that could affect the endometrium, such as tamoxifen. Furthermore, we also excluded women who fell pregnant during the follow-up period.

Endometrial polyps were diagnosed on ultrasound by subjective pattern recognition as described in the Methods section of this thesis (Chapter 12).

Study outcomes

The primary study outcome was the growth rate of endometrial polyps that were managed expectantly. We also analysed for factors that are associated with polyp growth rate, spontaneous regression, and symptoms of abnormal uterine bleeding.

The patients' indications for an ultrasound scan, demographic data, gynaecological, obstetric, and medical history are all routinely recorded at our institution, which enabled us to do this retrospective review. Abnormal uterine bleeding was defined as women's subjective reporting of heavy menstrual periods, irregular periods, intermenstrual bleeding, or postmenopausal bleeding. Women were considered symptomatic if they experienced any abnormal uterine bleeding.

Polyp size, position and vascular pattern on Doppler examination are routinely recorded in our database. We defined the position of the polyp only when the single pedicle vessel could be seen rising from the uterine wall. We measured each polyp in three perpendicular planes in the longitudinal and transverse views of the uterus; the maximum diameter in each plane was recorded and the mean diameter was then calculated from these measurements. If there were multiple polyps, we included only the largest polyp for each woman in our study. We used saline infusion sonography selectively to confirm the diagnosis of polyps if there was any diagnostic uncertainty.

All ultrasound follow-up scans were performed in the same way as the initial examination. Complete spontaneous regression was reported when the previously diagnosed endometrial polyp was no longer detectable on a follow-up ultrasound scan in women who did not undergo any medical or surgical treatments that could result in the removal of the polyp.

24.2.1 Statistical analysis

We used the measurements as recorded in our database at the time of examination to calculate the mean diameter (d_m) of polyps, $dm = (d_1 + d_2 + d_3)/3$. Percentage change in polyp size (r) was calculated as $r = (dm_2 – dm_1/dm_1) \times 100\%$ (where dm_1 and dm_2 are the mean diameters measured at times of t_1 and t_2, respectively), and annual percentage change in size (r_y) was calculated as r_y = (r/interval in months) x12.

The distribution of polyp mean diameter and annual percentage growth in polyp size were examined using the Kolmogorov-Smirnov test for normality. The null hypothesis of the sample distributions being normal was rejected ($p < 0.01$); therefore, non-parametric tests were used. To detect differences in polyp growth rate between two independent ordinal clinical variables, the Mann-Whitney rank-sum test was used; whereas the Kruskal-Wallis test was used when there were more than two variables. Age as an independent variable was normally distributed and therefore the Student’s t-test was

used. Categorical data displayed in the contingency tables were analysed using Fisher's exact test. To correct for multiple significance tests, we used the Bonferroni method, giving the level of probability at which findings were considered significant as $p < 0.0029$, as 17 significance tests were performed.

24.3 Results

A total of 3008 women were diagnosed with endometrial polyps during the study period, of which 163 women were examined at least twice by a single operator. Among them, 51/163 women were excluded (19/51 due to the use of hormone replacement therapy/contraception, 12/51 had polypectomy, 6/51 had a <6-month interval between the initial and follow-up scans, and 4/51 took tamoxifen). The indications for an ultrasound scan in the remaining 112 women who were included in our study are shown in Table 27. Four (4/112) women were found to have no evidence of polyps in their follow-up scans and therefore 108/112 women were available for the analysis of polyps' growth.

The mean age of women at the initial scan was 54.1 years (range 25-93); 67/112 (60%) women were postmenopausal. The median follow-up period between the initial and final follow-up scans was 22.5 months (range, 6-136). Most women (104/112, 93%) had a single polyp at presentation rather than multiple polyps. Most women were diagnosed with polyps for the first time; however, 21/112 (19%) were recurrences of polyps after a previous polypectomy.

There was no significant difference in the median diameter of polyps between women who presented with abnormal uterine bleeding (median 7.3mm, IQR 5.4-9.9) and women who did not have abnormal bleeding (median diameter 6.7mm, IQR, 5.1-9.3).

The median polyps' size at the initial scan was 7.0mm (IQR 5.3-9.6), compared to 7.3mm (IQR 5.3-9.6) at their final follow-up scan. The corresponding median yearly percentage change in polyps' size was 1.0% (IQR, -6.5 to 14.3). On univariate analysis, polyps' growth rate was not associated with women's age, menopausal status, parity, presence of a pedicle vessel on ultrasound scan, polyp's position, or size (Table 28).

Seventy-five (75/108, 69%) women did not have abnormal uterine bleeding at their initial presentation, of which, 11/75 (15%) subsequently developed

abnormal bleeding during the follow-up period. On univariate analysis, women's age, menopausal status, presence of a pedicle vessel on ultrasound scan, polyp size, or growth rate were not predictive of women who would become symptomatic during the follow-up period (Table 29).

Spontaneous regression of polyps occurred in 7/112 (6.3%, 95% CI 1.8-10.7) women. On univariate analysis, polyps appeared to regress more frequently in premenopausal women ($p = 0.016$) and those who presented with abnormal uterine bleeding ($p = 0.004$); however, after Bonferroni correction, these differences were not statistically significant (Table 30).

We repeated all statistical tests using polyps' volume instead of polyps' mean diameter when polyps were assumed to be ellipsoid in shape (polyp's volume = $4/3 \times \pi \times d_1 \times d_2 \times d_3$). However, the results were not significantly different whether polyps' mean diameter or volume was used. We decided to present our findings in polyps' mean diameter as it is more widely used in routine clinical practice.

Histology was available in 9/105 (9%) women with persistent polyps who underwent hysteroscopic polypectomy at the end of the study period and benign polyps were confirmed in all these cases.

Table 27 – Primary indications for an ultrasound scan (n = 112) (Wong et al., 2017)

Indication	n (%)
Ovarian cancer screening	22 (19.6)
Irregular menstrual bleeding	21 (18.8)
Pelvic pain	18 (16.1)
Suspected ovarian cyst	17 (15.2)
Postmenopausal bleeding	12 (10.7)
Suspected fibroid/other pelvic masses	9 (8.0)
Menorrhagia	4 (3.6)
Abdominal bloating	3 (2.7)
Subfertility	2 (1.7)
Others	4 (3.6)
Total	112 (100)

Table 28 – The effects of patients' demographics and polyps' morphological features on polyps' growth rates (n=108) (Wong et al., 2017)

Patient/polyp characteristics	n (%)	Polyp's mean diameter (mm), median (IQR)		Growth rate (%/yr), median (IQR)	p-value
		At presentation	Final		
Age (years)					
≤45	28 (26)	8.0 (5.5 to 11.5)	8.9 (5.7 to 11.2)	0.2 (-11.2 to 18.4)	0.589
>45	80 (74)	6.3 (5.0 to 8.7)	7.0 (5.0 to 9.3)	1.0 (-5.4 to 12.2)	
Menopausal status					
Premenopausal	41 (38)	7.3 (5.5 to 10.4)	9.0 (5.9 to 11.2)	2.2 (-5.9 to 19.7)	0.373
Postmenopausal	67 (62)	6.3 (5.0 to 8.7)	7.0 (5.0 to 9.0)	0 (-6.6 to 11.3)	
Parity					
0	50 (46)	6.7 (5.0 to 9.0)	7.7 (5.3 to 10.3)	3.4 (-4.9 to 19.8)	0.150
≥1	58 (54)	7.2 (5.3 to 10.0)	7.0 (5.3 to 9.3)	-0.7 (-7.0 to 10.0)	
Previous history of polyp					
Yes	21 (19)	7.3 (6.0 to 9.0)	7.3 (5.9 to 9.2)	-2.8 (-7.1 to 14.9)	0.401
No	87 (81)	7.0 (5.0 to 9.7)	7.7 (5.0 to 11.0)	1.6 (-5.7 to 14.7)	
Pedicle vessel on ultrasound					
Present	81 (75)	7.3 (5.7 to 9.9)	8.0 (5.7 to 11.0)	1.0 (-6.6 to 16.5)	0.944
Absent	27 (25)	6.0 (4.7 to 7.3)	5.3 (4.3 to 8.0)	0 (-6.6 to 12.5)	
Polyp position					
Fundal	26 (32)	7.0 (5.7 to 9.7)	8.0 (5.7 to 11.0)	0.5 (-5.7 to 19.8)	0.603
Anterior	22 (27)	8.2 (6.3 to 12.3)	9.2 (6.0 to 11.7)	-1.2 (-8.8 to 10.9)	
Posterior	15 (19)	7.0 (4.7 to 11.7)	9.3 (5.7 to 11.3)	5.9 (-2.7 to 18.5)	
Others	18 (22)	6.7 (5.3 to 9.0)	6.7 (5.3 to 9.0)	1.3 (-7 to 12.6)	
Polyp size at diagnosis					
≤10mm	84 (78)	6.0 (5 to 7.3)	6.5 (5 to 8.7)	1.0 (-6.4 to 15.9)	0.542
>10mm	24 (22)	12.3 (11.3 to 15)	12.9 (9.5 to 14.9)	0 (-7.2 to 13.8)	

Table 29 – Comparison of patients' demographic and polyps' morphological features between women who remained asymptomatic and those who became symptomatic of abnormal uterine bleeding during the follow-up period (n = 75) (Wong et al., 2017)

Patient/polyp characteristics	Remained asymptomatic (n = 64)	Became symptomatic (n = 11)	p-value
Age	56.6 (53.3 to 59.9)[+]	50.5 (43.8 to 57.3)[+]	0.167
Menopausal status			
Premenopausal (%)	19 (30)	6 (55)	0.164
Postmenopausal (%)	45 (70)	5 (45)	
Pedicle sign on ultrasound			
Present (%)	45 (70)	10 (91)	0.269
Absent (%)	19 (30)	1 (9)	
Polyps mean diameter at presentation (mm)	6.3 (5.0 to 9.5)*	7.7 (6.3 to 9.3)*	0.252
Polyp growth rate (%/yr)	1.9 (-5.8 to 19.8)	-4.0 (-6.2 to 12.6)	0.397

[+]mean (95% confidence interval), *median (interquartile range)

Table 30 – Comparison of patients' demographic and polyps' morphological features between polyps that persisted during the follow-up period and those which underwent complete spontaneous regression (n = 112) (Wong et al., 2017)

Patient/polyp characteristics	Polyp persisted (n = 105)	Polyp regressed (n = 7)	p-value[a]
Age	54.8 (52.2 to 57.3)[+]	43.7 (39.0 to 48.4)[+]	0.017
Menopausal status			
Premenopausal (%)	39 (37)	6 (86)	0.016
Postmenopausal (%)	66 (63)	1 (14)	
Parity			
0 (%)	48 (46)	4 (57)	0.703
≥1 (%)	57 (54)	3 (43)	
Symptomatic of abnormal uterine bleeding at presentation			
Symptomatic (%)	30 (29)	6 (86)	0.004
Asymptomatic (%)	75 (71)	1 (14)	
Mean diameter of polyp at presentation (mm)			
≤10 mm (%)	82 (78)	6 (86)	1.000
>10 mm (%)	23 (22)	1 (14)	

[a]After Bonferroni correction for 17 comparisons, the threshold for statistical significance is $p < 0.0029$.

[+]mean (95% confidence interval)

Part 4 – Discussions

Chapter 25 Study 1 – Efficacy of transrectal ultrasound scan in assessing the endometrium of postmenopausal women with an axial uterus

25.1 Discussion

In our study, a transrectal ultrasound scan (TRS) was successful in assessing the endometrium in over 90% of postmenopausal women with an axial uterus and an unsatisfactory endometrial assessment was significantly less common compared to TVS. This suggests that TRS has the potential to reduce the number of women undergoing further tests such as SIS or hysteroscopy for inconclusive endometrial assessment due to an axial uterus.

The prevalence of axial uterus was approximately 1 in 15 (6.6%) postmenopausal women in our study, and it was more common in older or nulliparous women. Among women who presented with postmenopausal bleeding 76/886 (8.6%) had an axial uterus. This is in keeping with Sanders et al. (2014) who retrospectively reviewed the transvaginal ultrasound images of 641 consecutive pre- and postmenopausal women (mean age 38, range 17-74) and reported a 5% prevalence of axial uterus.

Our study also showed that two-thirds of postmenopausal women with an axial uterus would accept TRS to further evaluate the endometrium. The acceptance rate was higher among women with postmenopausal bleeding compared to those without bleeding [56/76 (74%) vs 10/27 (37%), $X^2 = 11.6$, $p = <0.001$]. In our study, saline infusion sonography (SIS) was an alternative option to TRS, we suspect that in clinical settings where SIS is not available, the acceptance rate of TRS could be higher. For example, in

a previous study of 65 pre- and postmenopausal women, the acceptance rate of TRS for urethral assessment was 92% (Umek et al., 2001).

Although TRS failed in 4/66 women due to a faecally loaded rectum, our results suggest that routine bowel preparation is not necessary to achieve a high success rate with TRS. This is in contrast to some studies where a routine rectal enema is given before TRS (Alcazar et al., 2015). Nevertheless, women should be encouraged to attend internal ultrasound scans with empty bowel, if possible, to facilitate both TVS and TRS.

Another common concern regarding TRS is patient discomfort or pain. We did not measure pain objectively in our study; however, we found that only 1/66 women could not complete the examination due to pain, and in our experience, very few women decline TRS due to a previous painful experience. In the study by Nam et al. (2017), 80 women who were over the age of 15 and virgo intacta were asked to rate the intensity of pain on a visual analogue scale (0 = no pain to 10 = worst imaginable pain) at 4 different time points during TRS. The reported mean pain score and standard deviation at baseline were 0.38 ± 0.71, at the time of probe insertion 4.85 ± 2.98, during probe manipulation 4.21 ± 2.79, and 5-minute after the examination 2.33 ± 2.65. To the best of our knowledge, no previous studies have compared the degree of pain between TVS and TRS, especially among postmenopausal women, who may experience increased pain during TVS due to vaginal atrophy.

Most women are less familiar with TRS than TVS and therefore could be more anxious or concerned about the pain associated with TRS. In a survey by Nam et al. (2017), over 80% of Korean women were willing to make additional payments for measures to avoid pain during TRS if they had the choice. The same research group also conducted a randomised control trial to compare the use of lidocaine gel and plain lubricating gel in women undergoing TRS, but they did not find the use of lidocaine gel was associated with a lower pain score. A written information leaflet about TRS before the procedure may help to alleviate some of the women's anxiety about the examination.

We found that measurements of the endometrial thickness (ET) on TVS and TRS were significantly different in women with postmenopausal bleeding and an axial uterus. The ET measured thicker on TVS than on TRS, the median difference was 1.2mm which could be of clinical significance in women with postmenopausal bleeding. Using the conventional cut-offs of an ET ≥3-5mm to indicate the need for endometrial biopsy, more women with an axial uterus may have to undergo an unnecessary invasive test if the ET is measured on TVS alone.

Despite the small number of endometrial cancers in our study, we showed that the accuracy of TRS in diagnosing endometrial cancer subjectively among those with a thickened endometrium was good. Seven cases of endometrial cancer were correctly diagnosed on TRS, but importantly, 4 of them were initially misdiagnosed on TVS as benign polyps or uniformly thickened endometrium. This suggests that the typical morphological features of endometrial cancer may be more difficult to elicit on TVS when the uterus is axial. Our findings support the routine offer of TRS or SIS to women with an axial uterus and postmenopausal bleeding so that the risk of missing a malignancy is reduced.

The main limitation of our study is that both TVS and TRS were performed by the same operator, which did not allow for the possibility of blinding. Also, our subgroup analysis included a relatively small number of women and future studies are needed to confirm the improved diagnostic accuracy of TRS over TVS in women with postmenopausal bleeding and an axial uterus.

In conclusion, a transrectal ultrasound scan is an acceptable and effective way to assess the endometrium of postmenopausal women with an axial uterus. It reduces the chance of an unsatisfactory endometrial assessment on ultrasound and its use should be more widely considered in routine clinical practice. Clinicians should be aware of the potential risks of transvaginal ultrasound scans to misdiagnosis and overestimate the endometrial thickness in women with postmenopausal bleeding and an axial uterus.

Chapter 26 Study 2 – Interrater agreement and reliability of ultrasound subjective pattern recognition in diagnosing endometrial cancer

26.1 Discussion

Our study showed good interrater reliability (ƙ = 0.69, 95% CI 0.49-0.88) in the ultrasound diagnoses of uniformly thickened endometrium, polyp, and cancer by subjective pattern recognition, between an experienced operator and a less experienced operator. A kappa statistic of 0.69 meant that the raters accounted for 69% of the agreement over and above what would be expected by chance alone.

A previous study by Dueholm et al. (2015a) has also investigated the interrater reliability of subjective pattern recognition in diagnosing endometrial cancer in women with postmenopausal bleeding and endometrial thickness ≥5mm. In their study, two experienced raters independently assessed 122 recorded videotapes of ultrasound scans. Each woman was categorized as having no endometrial pathology, hyperplasia, polyp, or cancer. Their interrater reliability was moderate (κ = 0.47, 95% CI 0.30-0.63). However, when the authors repeated their analysis by including videotapes of “high-quality” only, the interrater reliability was instead good (κ = 0.73, 95% CI 0.56-0.90). It is difficult to compare our findings directly with those of Dueholm et al. (2015a); because, firstly, our study utilized real-time scanning rather than recorded videotapes, therefore operators had the freedom to optimize the image acquisition which mimics routine clinical practice more closely. Secondly, we included only three possible ultrasound diagnoses and did not classify endometrial hyperplasia as a separate category; this is because we routinely offer women an endometrial biopsy if they have a uniformly thickened endometrium. Therefore, an additional attempt to differentiate between endometrial hyperplasia and benign proliferative endometrium on

ultrasound would not have made a clinical difference to their initial management. Furthermore, by reducing the number of diagnostic categories, we aimed to improve the interrater reliability as concluded in another study by Sladkevicius et al. (2018).

Although reproducibility studies are paramount before a test can be introduced into clinical practice, a systematic review found that only 14% of published studies were considered to be well designed and had interpreted their results appropriately (Coelho Neto et al., 2015). The author criticized that most reproducibility studies lacked independent acquisitions, blinded analysis and correct statistical analysis. In particular, half of the reproducibility studies in ultrasound techniques in O&G were performed using only static images or video recordings acquired by a single rater. As a result, it is difficult to comment on how interrater reliability could be affected by having different raters performing the ultrasound scans.

The strength of our study is that each rater performed their independent ultrasound scan, and they were blinded to each other's findings. To the best of our knowledge, this is the first reported study where interrater reliability of ultrasound subjective pattern recognition for endometrial cancer has been tested with independent acquisitions.

There are several limitations to our study. Firstly, both raters came from the same tertiary academic unit, used the same high-end ultrasound machine, and performed the ultrasound scans in the same routine and environment. These conditions may vary as ultrasound operators tend to use a wide range of machines and are trained to perform their examinations in various routines. Ultrasound scans that are performed by less experienced operators in a community setting may have lower interrater reliability compared to our study. Secondly, it was not possible to blind the raters to the fact that they were taking part in a clinical study, therefore we cannot exclude the potential bias of the Hawthorn effect. Thirdly, we excluded all women with an unsatisfactory or suboptimal view of the endometrium as they were offered SIS or hysteroscopy instead. Therefore, our results may not apply to women with a distorted endometrial cavity due to submucosal

fibroids, severe adenomyosis or other uterine pathologies. Fourthly, our study included a 40% prevalence of EC which is higher than expected; given that a recent meta-analysis reported a pooled prevalence of only 19% (Clarke et al., 2018). This could be due to our small sample size, a higher prevalence of malignancy at a tertiary gynae-oncology centre or selection bias as we excluded some women with benign endometrial pathologies who underwent SIS.

In conclusion, there was good interrater reliability in diagnosing endometrial cancer on ultrasound by subjective pattern recognition in women with postmenopausal bleeding.

Chapter 27 Study 3 – Diagnostic accuracy of ultrasound subjective pattern recognition for endometrial cancer in women with postmenopausal bleeding

27.1 Discussion

Our results show that ultrasound subjective pattern recognition has good diagnostic accuracy for endometrial cancer in women with postmenopausal bleeding (PMB). By identifying the typical ultrasound morphological features and vascular patterns, we found that 9 out of 10 endometrial cancers could be diagnosed on ultrasound, which allows for the prioritisation of histological confirmation and referral to a gynaecological oncology centre. Compared to the measurement of endometrial thickness alone, subjective pattern recognition had a significantly lower number of false-positive diagnoses of endometrial cancer, 5/62 vs 175/240 (8%, 95% CI 1-15 vs 73%, 95% CI 67-79, $X^2 = 86.1$, p = <0.001), respectively.

The prevalence of endometrial cancer in our study (27%) was in keeping with those reported in other studies (Opolskiene et al., 2011, Sladkevicius et al., 2017, Opolskiene et al., 2010). The proportion of endometrial cancer of endometrioid histological subtype was also not significantly different compared to a recently published multi-centre study, where consecutive women with PMB were recruited, 65% vs 75%, $X^2 = 2.1$, p = 0.15 (Van Den Bosch et al., 2021). Overall, 70% of the endometrial cancers included in our study were of the International Federation of Gynaecology and Obstetrics (FIGO) stage 1.

The diagnostic accuracy of ultrasound subjective pattern for endometrial cancer in our study was similar to those reported by Dueholm et al. (Dueholm et al., 2015b), the sensitivity and specificity were 88% (95% CI 77-95) vs 86% (95% CI 76-93) and 97% (95% CI 94-99) vs 90% (95% CI

83-95), respectively. However, the prevalence of endometrial cancer in their study was significantly higher, 72/174 vs 65/240 (42%, 95% CI 34-49 vs 27%, 95% CI 22-33, X^2 = 9.3, p = 0.002). The author explained that their high prevalence of malignancy was due to 56% of their referrals being made directly to their gynaecological oncology centre, which contained women with a confirmed diagnosis of endometrial cancer before their ultrasound assessment. Unlike their study, we excluded all women with a known diagnosis of gynaecological malignancy.

Another prospective study on the diagnostic accuracy of ultrasound subjective pattern recognition for endometrial cancer was performed by Epstein et al. (2001). In contrast to our findings, they reported a lower sensitivity of ultrasound subjective pattern recognition for endometrial cancer. In their study, 105 women with PMB and endometrial thickness ≥5mm were included. Both conventional ultrasound examination and saline infusion sonography (SIS) were performed. The sensitivity, specificity, positive and negative likelihood ratios of conventional ultrasound were 60%, 90%, 6 and 0.44, respectively; and in SIS (78/105 women), the respective values were 44%, 94%, 7 and 0.6 (45% of the SIS were considered suboptimal). Notably, Epstein et al. (2001) included atypical hyperplasia in their “malignancies” group, which accounted for 5/25 (20%) of all “malignancies”. This difference likely contributed to their lower sensitivity for “malignancies” reported in their study. For example, Alcázar et al. (2003) reported that the “typical” scattered-vessel pattern of endometrial hyperplasia on power Doppler ultrasound was not only found in endometrial hyperplasia but was also present in 63% of endometrial cystic atrophy. Furthermore, in the study by Dueholm et al. (2015b), the sensitivity and specificity of ultrasound subjective pattern recognition for endometrial hyperplasia were only 19% and 92%, respectively.

There were 8/240 cases of false-negative diagnoses of endometrial cancer by ultrasound subjective pattern recognition in our study, the corresponding false-negative rate was 8/65 (12.3%, 95% CI 4-20). In the majority (7/8) of these cases, the misdiagnoses occurred when malignancies were confined focally within endometrial polyps. This finding is not uncommon as up to

12% of endometrial polyps in women with PMB may harbour pre-malignant or malignant cells (van Hanegem et al., 2017). On ultrasound, it can be very difficult to rule out the presence of malignancy in polyps as the malignancy may only be confined to a very small area of the polyp. Our results show that the typical ultrasound features of endometrial cancer are absent in some malignant polyps. Previous studies have suggested that an irregular surface of the endometrial polyp on saline infusion sonography (SIS) may help predict the presence of malignancy (Opolskiene et al., 2009); however, Epstein et al. (2001) found that 38% of malignancies could still be misdiagnosed as benign polyps on SIS. More research is needed to improve the risk prediction of malignancy in postmenopausal polyps. Meanwhile, routine surgical removal of all polyps is recommended in women with PMB.

The findings of our study are only applicable to women where the endometrium could be satisfactorily visualised on an unenhanced transvaginal or transrectal ultrasound scan. We found that the endometrium could not be visualised on unenhanced ultrasound in up to 1 in 5 women with PMB. The commonest cause of difficulty in identifying the endometrium was the presence of uterine fibroids and therefore women with fibroids should consider the options of SIS or diagnostic hysteroscopy as their first-line test. In the study of Epstein and Valentin (2006), they also reported that the endometrial thickness could not be accurately measured on ultrasound in 13/95 (14%) women with PMB, the most common cause was an ill-defined endometrial-myometrial junction.

Our study showed that SIS could be performed successfully in approximately 9/10 women with an unsatisfactory assessment of the endometrium on an unenhanced ultrasound scan. Therefore, in addition to outpatient hysteroscopy, SIS should also be made more widely available in our clinical settings.

Saline infusion sonography is reported to be more accurate than conventional ultrasound in the diagnosis of endometrial polyps (Vroom et al., 2019); however, there is no evidence to support that it improves the

diagnosis of endometrial cancer when the typical morphological features of malignancy are present (Epstein et al., 2001). Besides, several prospective studies have confirmed the presence of malignant cells in 6-8% of transtubal fluid following SIS in women with endometrial cancer (AlcÁZar et al., 2000, Dessole et al., 2006, Berry et al., 2008). Nonetheless, these malignant cells appeared to be non-adherent and non-viable; therefore, SIS and hysteroscopy are not considered to be contraindicated even in the presence of endometrial cancer.

To the best of our knowledge, our study was the first study where the diagnostic accuracy of ultrasound subjective pattern recognition for endometrial cancer was tested in the hands of a non-expert operator. As a result, our findings may be more generalisable compared to other studies where ultrasound examinations were only performed by expert operators.

There are some limitations to our study. Firstly, our histological reference standards included endometrial biopsies obtained by a mixture of outpatient endometrial biopsy, hysteroscopy, and hysterectomy. Although this limitation can also be found in other studies (Opolskiene et al., 2011, Raouf et al., 2011, Sladkevicius and Valentin, 2016, Sladkevicius et al., 2017, Dueholm et al., 2019), it makes it more difficult to compare the results of diagnostic studies where different histological reference standards were used. Secondly, our study was conducted in a tertiary teaching hospital with high-quality ultrasound equipment. More research is needed to confirm the diagnostic accuracy of ultrasound subjective pattern recognition in other clinical settings. Thirdly, we excluded women who did not have a final histological diagnosis or were lost to follow-up. Given the prevalence of EC in our population and the fact that over half the women had endometrial polyps, it is likely that 2-3 of these women had EC.

In conclusion, ultrasound subjective pattern recognition has good diagnostic accuracy for endometrial cancer. It has the potential to diagnose endometrial cancer earlier on ultrasound and improve the prioritisation of women for histological confirmation and surgery.

Chapter 28 Study 4 – Comparison of ultrasound and magnetic resonance imaging in the preoperative staging of endometrial cancer

28.1 Discussion

Our results show that ultrasound and MRI have comparable diagnostic accuracy for DMI and CSI in women with endometrial cancer. Their agreement and reliability were higher in the diagnosis of CSI (κ = 0.69) when compared to DMI (κ = 0.49). In the subgroup of "low-risk" endometrial cancers, ultrasound performed equally well in detecting DMI in comparison to the main cohort of women (89% vs 86%).

Our prevalence of DMI (43%) and the proportion of low-grade endometrial cancers (73%) are in keeping with a previous prospective study where consecutively diagnosed endometrial cancers were included (Savelli et al., 2008).

A recent meta-analysis, which included 560 women, reported that the diagnostic accuracy of ultrasound and MRI in detecting DMI were not significantly different, their pooled sensitivities were 75% and 83%, respectively (Alcázar et al., 2017). In keeping with their findings, we also found that the sensitivity of ultrasound and MRI for DMI were similar (86%, 95% CI 65-97 vs 77%, 95% CI 55-92). Our sensitivity of ultrasound for DMI was higher, this may be because we only included EC where the ultrasound examination was satisfactory. Among the 144 women with an unsatisfactory ultrasound assessment, three were diagnosed with EC and their preoperative MRI correctly identified one of the two women with DMI.

Two recent prospective studies have compared the accuracies of ultrasound and MRI for DMI in women with "low-risk" (grade 1 or 2 endometrioid) endometrial cancer (Cubo-Abert et al., 2021, Gaston et al., 2021). Cubo-Abert et al. (2021) measured the depth of myometrial invasion

on ultrasound objectively with the formula, (1 - the minimal distance between the tumour and the serosa/depth of healthy myometrium) x 100%; whereas, Gastón et al. (2021) used both objective (Karlsson's ratio) and subjective assessments. Cubo-Abert et al. (2021) concluded that the sensitivities and specificities of ultrasound and MRI for DMI were not significantly different, 69% vs 51% and 87% vs 91%, respectively. On the contrary, Gastón et al. (2021) reported that MRI has a higher specificity for DMI than ultrasound, but only when assessed subjectively, 87% vs 74%, respectively (the corresponding sensitivities were 80% vs 75%, respectively).

We found that both ultrasound and MRI had a high false-positive rate for DMI, which is in keeping with previous studies (Alcázar et al., 2017). The most common cause of over-staging is the presence of a large polypoid tumour (Fleischer et al., 1987, Gordon et al., 1989, Cacciatore et al., 1989). A large polypoid tumour may cause distension of the uterine cavity and result in thinning of the myometrium. And when the echogenicity of the tumour is like the myometrium, it can be very difficult to distinguish between the tumour and the surrounding myometrium (Savelli et al., 2012). Furthermore, over-staging of myometrial invasion is more common in tumours with a high colour score and in those with multiple vessels of multifocal origins crossing the endometrial-myometrial junction (Fischerova et al., 2014). Contrarily, under-staging of myometrial invasion is more likely in women with fibroids (Fischerova et al., 2014).

It has been reported that the presence of adenomyosis may also make it more difficult to assess the depth of myometrial invasion in women with endometrial cancer, as adenomyosis reduces the sonographic contrast between the tumour and the surrounding myometrium (Utsunomiya et al., 2004). Also, there is an increased risk of DMI when endometrial cancer extends into pre-existing adenomyosis (Ismiil et al., 2007a, Ismiil et al., 2007b). In our study, the prevalence of adenomyosis was 5/50 (10%), which is in keeping with previous studies (8-16%) (Savelli et al., 2008, Epstein et al., 2018, Zhang et al., 2018). We did not find any cases of over-staging or under-staging in women with adenomyosis.

In our study, we assessed the depth of myometrial invasion and CSI on ultrasound subjectively as there is no consensus on whether a subjective assessment or objective measure is more accurate. In a recent multi-centre prospective study, IETA-4, the performance of subjective assessment was compared against objective measures (such as the tumour/uterine anterior-posterior diameter ratio (Karlsson's ratio) and minimal tumour-free margin), in 1275 measurable tumours (Verbakel et al., 2020). They found that subjective assessment had similar sensitivity for DMI compared to objective measures, but importantly, subjective assessment had a significantly better specificity (76%) against Karlsson's ratio (69%) or minimal tumour-free margins (67%). In another prospective study of 210 women with endometrial cancer, subjective assessment also had better accuracy (76%) when compared to Karlsson's ratio (68%) and Gordon's ratio (67%) (Fruhauf et al., 2017). The author suggested that subjective assessment performed better because more ultrasound morphological features could be considered against the more rigid system of objective measures. This additional information available on subjective assessment may include the size of the tumour, the vascular patterns on Doppler examination and dynamic tests, such as the sliding sign of tumour against the uterine wall or endocervical canal; as it is known that "high risk" tumours are more likely to be larger, have a non-uniform endometrial echogenicity, multifocal vessel pattern across the endometrial-myometrial junction and a moderate/high colour score on Doppler studies (Epstein et al., 2018).

Although we did not utilize three-dimensional ultrasound (3D-US) in our preoperative staging of endometrial cancer, it has been reported that 3D-US may have some advantages over conventional two-dimensional ultrasound (2D-US). These include the option of offline analysis in any plane, such as the reconstruction of the coronal plane, more accurate measurement of the tumour volume, automated quantification of the vascular indices and 3D display of the tumour vascular tree (Green et al., 2018). The reported sensitivities and specificities of 3D-US in detecting deep myometrial invasion are 84-89% and 86-91%, respectively (Yildirim et al., 2018, Yang et al., 2019). However, some studies have compared

objective measures on 3D-US, such as 3D tumour volume and shortest myometrial tumour-free distance to the serosa, against subjective assessment on 2D-US, and they did not find that 3D-US improved the accuracy of preoperative staging (Alcázar et al., 2009, Mascilini et al., 2013). Furthermore, the addition of 3D-US also did not appear to improve the diagnostic accuracy of 2D-US in detecting cervical stromal invasion (Christensen et al., 2016, Green et al., 2018).

Previous studies on the accuracy of ultrasound for DMI or CSI in endometrial cancer were mostly carried out by expert operators (Alcázar et al., 2017, Verbakel et al., 2020). This is supported by Eriksson et al. (2015) who reported that the accuracy for CSI and interrater reliability were higher among expert operators compared to general gynaecologists, though no difference was found regarding the assessment for DMI. In contrast, a recent prospective study by Dueholm et al. (2021) showed that the specificity for DMI was significantly lower in non-expert operators (resident trainees in obstetrics and gynaecology) compared to experts, 37% vs 72%, respectively (the corresponding sensitivities were 96% and 81%, respectively). These findings could be due to non-experts being specifically instructed to classify all uncertain cases as suspected DMI.

The learning curve to reach proficiency in staging endometrial cancer on ultrasound is unknown. In a study involving only a single operator, spanning over 20 years, the sensitivity for DMI using ultrasound subjective assessment improved significantly after the first 50 cases and thereafter maintained at a stable level (Pineda et al., 2016). In the UK nationwide audit on the accuracy of MRI in staging endometrial cancer, there was also evidence showing that the accuracy of assessing myometrial invasion increased with the institution's workload (i.e. >50 cases per year) (Duncan et al., 2012).

The main strength of our study is that the diagnostic accuracy of ultrasound and MRI were tested in the same cohort of women, which is not commonly carried out in previous studies (Alcázar et al., 2017). Secondly, this was the only study where ultrasound diagnosis and staging of endometrial cancer

were carried out simultaneously at women's initial assessment. As the ultrasound examination was carried out before any endometrial biopsies were taken, it avoided any potential iatrogenic disruption to the endometrial-myometrial junction, which may affect the accuracy of ultrasound assessment. In some studies, following invasive diagnostic procedures, such as dilatation and curettage, no residual tumour is found in 2-11% of final hysterectomy specimens (Ortoft et al., 2013, Alcázar et al., 2016, Christensen et al., 2016, Verbakel et al., 2020).

The main limitation of our study is the inclusion of both "high-risk" and "low-risk" endometrial cancers. We attempted to perform subgroup analysis by including women with "low-risk" endometrial cancers only; however, due to the small sample size, our comparison of diagnostic accuracies between ultrasound and MRI was not adequately powered. Regrettably, this is also a common limitation in other studies (Savelli et al., 2012, Mascilini et al., 2013, Fischerova et al., 2014, Fruhauf et al., 2017, Verbakel et al., 2020). Furthermore, the ultrasound and MRI examinations were carried out on different days, therefore, the measurement and interpretation of myometrial invasion could be affected by organ motion of the uterus due to inflation and deflation of the bladder and rectum (Jadon et al., 2014).

The recent ESGO/ESTRO/ESP guideline has reported on the potential benefits of molecular classification over the traditional models of risk classification in EC. Therefore, in the future, it may be possible that preoperative assessment for the depth of myometrial invasion or cervical stromal invasion may play a lesser role in the clinical management of patients. However, more research is needed before molecular classification of EC could be introduced into routine clinical practice.

In conclusion, endometrial cancer can be simultaneously diagnosed and assessed for myometrial and cervical stromal invasion at women's initial ultrasound scan for postmenopausal bleeding. The diagnostic accuracy of ultrasound in the preoperative staging of endometrial cancer is comparable to MRI.

Chapter 29 Study 5 – Risk of pre-malignancy or malignancy in postmenopausal endometrial polyps: a CHAID decision tree analysis

29.1 Discussion

In our study, we carried out a decision tree analysis to classify postmenopausal polyps into low-risk (≤5%), intermediate-risk (>5% to ≤20%) or high-risk (>20%) for pre-malignancy or malignancy. We found that polyp size, patient's BMI and intralesional cystic spaces on ultrasound were the best discriminators between benign and premalignant/malignant polyps. There were no cases of pre-malignancy or malignancy in women with BMI ≤28.4 presenting with polyps measuring ≤13mm in mean diameter. On the other hand, two-thirds of women with high BMI >28.2 and solid polyps >13mm in size were diagnosed with pre-malignancy or malignancy on histological examination.

As our model advocates for prioritized polyp resection for women in the high-risk or intermediate-risk groups, only 1/18 (95% CI 1-16%) malignant polyps were incorrectly classified into the low-risk group. This misdiagnosis occurred in a 58-year-old woman who had a BMI of 34.2 and an endometrial polyp measuring at 22mm in mean diameter. This case highlights that although the presence of intralesional cystic spaces was useful in predicting benign polyps in women with a polyp >13mm, false-negative diagnoses can occur in a small number of premalignant/malignant polyps that appear cystic rather than solid.

Few prospective studies have reported on the prevalence of pre-malignancy or malignancy in postmenopausal endometrial polyps; nonetheless, the prevalence of 4% in our study is in keeping with the pooled estimate of 5.1% (95% CI 3.5-6.8) in a recent meta-analysis (Uglietti et al., 2019).

Traditionally, larger polyps are thought to have an increased risk of malignancy, which has been confirmed by our findings. We found three previous studies that have assessed polyp size in postmenopausal women and the risk of pre-malignancy or malignancy (Ferrazzi et al., 2009, Godoy et al., 2013, Cavkaytar et al., 2014). All these studies reported a larger polyp size was associated with an increased risk of pre-malignancy or malignancy. Various cut-offs were recommended by these studies, which included ≥18mm, ≥19.5mm and ≥30mm, respectively. In contrast, a recent meta-analysis reported that polyp size was not associated with the risk of pre-malignancy or malignancy when a cut-off of ≥2cm was used (Sasaki et al., 2018). In their analysis, four studies with a total of 1770 polyps were included; however, three of these studies included both premenopausal and postmenopausal women (Fernandez-Parra et al., 2006, Gregoriou et al., 2009, Gambadauro et al., 2015); while one study only estimated the polyp size subjectively during hysteroscopy (Fernandez-Parra et al., 2006). Furthermore, the statistical power to detect a difference could be reduced by dichotomising polyp size into <2cm or ≥2cm, rather than analysing it as a continuous variable (Altman and Royston, 2006).

Obesity (BMI ≥30) is a well-known independent risk factor for endometrial hyperplasia and type 1 endometrial cancer. A recent study also found that obesity is significantly associated with endometrial polyps in postmenopausal women (Kaya et al., 2019). This is in keeping with immunohistochemical studies which showed that obese postmenopausal women have a higher proportion of oestrogen receptor (ER) positive cells in the glands and stroma of their polyps, which is in contrast to the low ER expression in atrophic endometrial cells, suggesting steroid receptors have a crucial role in the pathophysiology of postmenopausal polyps (Belisário et al., 2006, de Carvalho et al., 2011). In a meta-analysis of 3612 women, obesity was significantly associated with an increased risk of pre-malignancy or malignancy in polyps (Sasaki et al., 2018). Using a cut-off of BMI ≥32.5, Ghoubara et al. (2018) reported that the sensitivity and specificity for hyperplasia or malignancy in postmenopausal polyps were 77% and 52%, respectively. In our study, we confirmed that a raised BMI

was useful to identify subgroups of women with an increased risk of premalignant/malignant polyps.

Intralesional cystic spaces on ultrasound are thought to represent the dilated glands of endometrial polyps histologically and they could be lined by atrophic, inactive, or proliferative endometrium. In a study of focal endometrial lesions in premenopausal and postmenopausal women, 58.6% of the benign polyps had intralesional cystic spaces (Baldwin et al., 1999). In postmenopausal polyps, the prevalence of these cystic spaces was reported to be even higher at 72.4% (Hulka et al., 1994). Goldberg et al. (2016) compared the greyscale morphological features of benign and malignant endometrial lesions and found that intralesional cystic spaces were more common in benign than malignant lesions (62% vs 6%, respectively). Our results are in keeping with previous studies that intralesional cystic spaces can be used to identify a subgroup of polyps at low risk of pre-malignancy or malignancy.

Endometrial polyps are considered a cause of abnormal uterine bleeding. Some studies suggested that aberrant angiogenesis in the polyp plays a significant role, it causes the endometrial vessels over the polyp to dilate and become fragile; consequently, they are more prone to bleeding (Lockwood, 2011). However, it is less certain whether polyps in women symptomatic of abnormal uterine bleeding have an increased risk of malignancy, as some suggested that the seemingly higher prevalence of pre-malignancy or malignancy amongst symptomatic women could be due to detection bias (Perri et al., 2010). In our study, we found that symptoms of postmenopausal bleeding did not improve the risk prediction of pre-malignancy or malignancy in polyps when other patient characteristics and polyp morphological features were considered.

There are some limitations to our study. Firstly, a significant proportion of polyps (49%) in women without postmenopausal bleeding were managed expectantly and excluded from our analysis. Therefore, we cannot exclude the possibility of a selection bias given that expectantly managed polyps were smaller in size and less likely to have detectable vascularity on

Doppler examination. Therefore, the risk of pre-malignancy or malignancy in incidentally diagnosed polyps could be lower than those reported in our study. Secondly, polyp's size measurement and subjective assessment of intralesional cystic spaces in polyps could be affected by intra- and interrater variability. Thirdly, our decision tree model needs to be externally validated for its accuracy.

In conclusion, polyp size, women's BMI and whether polyps appeared cystic or solid on ultrasound were helpful in a decision tree model to predict the risk of pre-malignancy or malignancy in postmenopausal polyps. Our decision tree model may aid the discussion between women and their clinicians on the benefits and risks of surgery to remove endometrial polyps. It may also help to prioritize women with a high risk of pre-malignancy or malignancy for surgery over those in whom the risk of malignancy is lower.

Chapter 30 Study 6 – Natural history of endometrial polyps: a retrospective cohort study

30.1 Discussion

Our study showed that endometrial polyp growth rate varied considerably among women who were managed expectantly; while some polyps increased in size, others spontaneously regressed over time. Women's age, menopausal status, polyp size, and location within the uterine cavity were not predictive of individual polyp growth.

Prolonged and unopposed oestrogen exposure is a known risk factor for the development of endometrial polyps, which is supported by immunohistochemistry studies showing that there is an increased expression of oestrogen receptors in the endometrial polyps (Maia et al., 1998). However, we did not find that women's age or menopausal status were significantly associated with polyps' growth rate. Some studies reported that polyps could also arise from a dysregulation of apoptosis and therefore these polyps are less dependent on hormones (McGurgan et al., 2006). Multifactorial pathogenesis of polyps is likely responsible for the difficulty in predicting an individual polyp's growth (Indraccolo et al., 2013).

Current management of endometrial polyps is centred on whether women are symptomatic of abnormal uterine bleeding. Hassa et al. (2006) reviewed 155 women retrospectively and found that there was no association between symptoms and polyp size, site or number in both pre-and postmenopausal women. In our study, we analysed 75 women who were initially asymptomatic of abnormal uterine bleeding but subsequently, 11/75 (15%) women became symptomatic over a median follow-up period of 21 months (range, 10-59). We also found no association between polyps' growth rate and the development of abnormal uterine bleeding. In other words, routine ultrasound scans to monitor polyps' growth could not be used to predict the onset of symptoms. This finding supports the clinical rationale

to encourage women with asymptomatic polyps to report symptoms rather than offering them routine ultrasound scans to monitor polyp's growth.

Spontaneous complete regression of endometrial polyps has previously been reported. In a prospective study of 7 women with asymptomatic polyps, saline infusion sonography was performed at the time of diagnosis and after a 2.4-2.7-year interval (DeWaay et al., 2002). The author found that 4/7 (57%) of polyps had spontaneously regressed and could not be detected on the subsequent scan. In another prospective study of 31 perimenopausal women with symptomatic and asymptomatic polyps, saline infusion sonography was performed 12 months apart and a complete spontaneous regression rate of 27% was reported (Lieng et al., 2009). Furthermore, smaller-sized polyps (mean diameter, 10.7 mm) were more likely to regress compared to larger polyps (mean diameter, 15.1 mm).

Spontaneous regression of polyps is not only observed on ultrasound. Three polyps, measured between 5-8mm in size, "vanished" in women who attended repeat hysteroscopies (Haimov-Kochman et al., 2009). However, this observation may be partly related to the trauma caused by the hysteroscopy procedure.

Our study presented the largest series of spontaneously regressed polyps in the literature, and we found that 6.3% (95% CI 2-11) of polyps may regress over a median follow-up period of 28 months (range, 9-56). Although we found that polyps tended to regress more frequently in premenopausal women ($p = 0.016$) and in those who presented initially with abnormal uterine bleeding ($p = 0.004$), due to the small sample size, they did not reach statistical significance following Bonferroni correction.

When symptomatic polyps were examined microscopically, ischaemic tissue necrosis was observed more frequently at the apical portion compared to the same area of asymptomatic polyps. This is thought to be due to thrombosis in subsurface terminal vessels or the feeding vessel (Ferenczy, 2003). This histological observation may explain why some symptomatic polyps may be more likely to regress compared to asymptomatic polyps.

In contrast to Leing et al. (2009), we did not find that the size of polyps was associated with spontaneous regression. Our overall rate of spontaneous regression in polyps was also lower than those reported by DeWaay et al. (2002) and Lieng et al. (2009); one possible explanation for this is that we included an older study population with a higher proportion of postmenopausal women.

The strength of our study is its large cohort size of women and the long follow-up period. All ultrasound scans were also performed by a single, expert operator, which reduces the risk of error due to interrater variability.

There are several limitations to our study. Firstly, as our study was retrospective, it may be prone to selection and information bias. For example, those who chose to be followed up in another institution or those who could not provide a full medical history were excluded from our study. Secondly, a lack of histological confirmation of the polyps is also another limitation. However, we showed that 84/112 (75%) of our polyps had the positive pedicle sign which is known to have a high positive predictive value for polyps (Timmerman et al., 2003). In a prospective study that compared the performance of transvaginal ultrasound with colour Doppler (TVCD) versus SIS, TVCD had an equal positive predictive value compared to SIS when the typical appearance of a polyp and the pedicle artery sign were both present. In 9/105 (9%) of women who eventually underwent surgery, it was reassuring that all polyp diagnoses on ultrasound were confirmed histologically.

In conclusion, the growth pattern of endometrial polyps cannot be accurately predicted; however, a small proportion of polyps do regress spontaneously. The use of ultrasound to routinely monitor polyp size does not inform whether women would become symptomatic of abnormal uterine bleeding. Future research should focus on the predictive factors of polyp regression and the role of expectant management, especially, in premenopausal women who are symptomatic of abnormal uterine bleeding.

Chapter 31 Conclusions and suggestions for future research

Ultrasound subjective pattern recognition was accurate in identifying 9 out of 10 cases of endometrial cancer in women with postmenopausal bleeding (PMB) and a thickened endometrium. Compared to the measurement of endometrial thickness alone (using a threshold of ≥4.5mm), subjective pattern recognition reduced the number of false-positive diagnoses from 73% to 8%, without a significant drop in sensitivity. The improved diagnostic accuracy of endometrial cancer may facilitate the prioritisation of women for histological confirmation and surgery. Future studies should assess the cost-effectiveness and patient satisfaction with ultrasound subjective pattern recognition.

The interrater reliability of ultrasound subjective pattern for endometrial cancer was good. The strength of our study is that we compared independently acquired real-time ultrasound scans, which to the best of our knowledge, has not been done in previous studies. Future studies should focus on training strategies and the assessment for competencies in ultrasound subjective pattern recognition.

Compared to transvaginal ultrasound scan (TVS), there were significantly less unsatisfactory endometrial assessments on transrectal scan (TRS) in postmenopausal women with an axial uterus. Moreover, TRS was more accurate in the subjective diagnosis of endometrial cancer compared to TVS. Therefore, in women with PMB and an axial uterus, clinicians should be aware of the potential risk of missing a diagnosis of malignancy on routine TVS. Future studies should compare the diagnostic accuracies of TVS, TRS and saline infusion sonography in women with PMB and an axial uterus.

We have shown that it is feasible to simultaneously diagnose endometrial cancer and assess for the myometrial and cervical stromal invasion at women's initial ultrasound scan for postmenopausal bleeding. The accuracy

of ultrasound in the preoperative staging of endometrial cancer was comparable to MRI. This streamlined ultrasound-based approach may benefit women by reducing the number of hospital visits, delays in surgery and cost of MRI scans. Future studies should further evaluate the cost-effectiveness and patient satisfaction with this streamlined pathway.

We have presented a model to predict the risk of pre-malignancy or malignancy in postmenopausal polyps, which is based on the polyp size, women's BMI and the presence or absence of intralesional cystic spaces. The model has an accuracy of 92% after internal validation and it may serve as a guide for the individual counselling between women and their clinicians. It may also be used to prioritise women for surgery according to their risk of malignancy. Future studies should validate the accuracy of our model externally.

We found that the growth pattern of endometrial polyps could not be predicted by the patient's clinical characteristics or polyp's morphological features. Furthermore, in asymptomatic women, routine monitoring of polyp size on ultrasound scans did not predict the onset of abnormal uterine bleeding. Some polyps regressed spontaneously, and they occurred more frequently among premenopausal women or those who were symptomatic of abnormal uterine bleeding. Future studies should focus on the role of managing endometrial polyps expectantly, especially, in premenopausal women.

Some of our studies were reliant on the availability of histology as the gold standard and therefore women who were managed expectantly or lost to follow-up were excluded in the final analysis. This is a major limitation, and it may potentially introduce bias. Future studies could overcome this by having alternative gold standards, such as the absence of malignancy at 1-year follow-up or the use of mathematical techniques, such as interval modelling of incomplete data, uncertaintification of classical models and aggregation of incomplete results.

Although more work is needed to improve on our current assessment and management of postmenopausal bleeding and endometrial polyps; we have

shown that the ultrasound-based strategies and other clinical models presented in this thesis may benefit women with a more accurate and earlier diagnosis of endometrial cancer.

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Appendix 1

University College London Hospitals NHS
NHS Foundation Trust

Joint UCLH/UCL/RoyalFree Biomedical Research (R&D) Unit

Office Location:
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07/07/2011

Elizabeth Garrett Anderson Wing
University College London Hospital

Dear Dr Naftalin,

Project ID: 10/0316 (Please quote in all correspondence)
REC Ref: 10/H0713/66
Title: A comparison of transvaginal ultrasound versus magnetic resonance imaging in the pre-operative assessment of myometrial invasion of endometrial cancer

Thank you for registering the above study (non-IMP) with the UCL/UCLH/RF Joint Biomedical Research Unit (UCLH Site). I am pleased to inform you that your study now has local R&D approval to proceed and recruit participants at University College London Hospitals NHS Foundation Trust.

Please note that this approval is granted on the basis of the key documents provided:

- All documentation as listed in the REC notice of favourable opinion dated 31st May 2011
- Sponsorship details, roles and responsibilities, and financial details

As Chief/Principal Investigator you are required to ensure that your study/clinical trial is conducted in accordance with the Department of Health's Research Governance Framework for Health and Social Care (2nd edition 2005) and that all members of the research team are aware of their responsibilities under the Framework.

Please note that you are also required:

- To comply with the Data Protection Act, Caldicott Principles and Trust Information Governance Policy.
- To ensure all researchers taking part in this study have up-to-date and appropriate honorary contracts.
- To ensure that a signed and dated copy of the consent form is kept in the study/trial file and a copy also given to the participant.
- To maintain an investigator file to store all study/trial documentation to be made available for audit.
- Where applicable to acknowledge NIHR/CBRC funding and support and collaboration with the BioStatistics Group.

If applicable to the methodology and conduct of the proposed study:

- There is a legal obligation to abide by the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments as well as any other applicable regulations.

- Medical Devices research regulated by the MHRA should be conducted in accordance to the Device Regulations.

- Tissue research must be conducted in accordance to the Human Tissue Act 2004 and the Codes of Practice issued by the Human Tissue Authority, with special relevance to Code 9 Research. Where tissue is used for human application please ensure that you abide by the Human Tissue (Quality and Safety for Human Application) Regulations 2007.

This R&D approval is conditional upon you complying with all requirements of the Research Ethics Committee notice of favourable opinion and notifying the UCL/UCLH/RF Biomedical Research Unit of the following as they arise:

- Amendments (including a request to extend the study/clinical trial)
- Annual Progress Reports
- Any change in staff, their duties and their time on the study/trial
- End of or suspension of study/trial notification
- Planned audits by the Sponsor
- Publications

For all studies, all serious research related incidents should be reported to the sponsor. In addition, all serious research incidents should be also reported through the relevant Trust incident procedure. For UCLH, research related incidents should be reported through DATIX. The R&D office should also be informed.

Please do not hesitate to contact a member of the team with regards to assistance and guidance for your research.

Yours sincerely

[redacted]

Professor Monty Mythen
Director of Research and Development
UCL/UCLH/Royal Free Biomedical Research Unit

Appendix 2

This thesis has resulted in the following publications:

WONG, M., AMIN, T., THANATSIS, N., NAFTALIN, J. & JURKOVIC, D. 2022. *A prospective comparison of the diagnostic accuracies of ultrasound and magnetic resonance imaging in preoperative staging of endometrial cancer*. J Gynecol Oncol, 33, e22.

WONG, M., AMIN, T., THANATSIS, N., FOO, X. & JURKOVIC, D. 2022. *Efficacy of transrectal ultrasound in assessing endometrium of postmenopausal women with an axial uterus*. Ultrasound Obstet Gynecol, 60, 414-419.

WONG, M., THANATSIS, N., NARDELLI, F., AMIN, T. & JURKOVIC, D. 2021. *Risk of Pre-Malignancy or Malignancy in Postmenopausal Endometrial Polyps: A CHAID Decision Tree Analysis*. Diagnostics, 11, 1094.

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WONG, M., CRNOBRNJA, B., LIBERALE, V., DHARMARAJAH, K., WIDSCHWENDTER, M. & JURKOVIC, D. 2017. *The natural history of endometrial polyps.* Hum Reprod, 32, 340-345.