CLINICAL, RADIOLOGICAL AND ENDOMETRIAL HISTOPATHOLOGICAL FEATURES IN PERIMENOPAUSAL AND POSTMENOPAUSAL WOMEN WITH ABNORMAL UTERINE BLEEDING AT MOI TEACHING AND REFERRAL HOSPITAL.

BY

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A RESEARCH THESIS SUBMITTED TO THE SCHOOL OF MEDICINE IN PARTIAL FULFILLMENT FOR THE AWARD OF THE DEGREE OF MASTER OF MEDICINE IN REPRODUCTIVE HEALTH AT MOI UNIVERSITY

DECLARATION

Student Declaration

I declare that this thesis is my original work and has not been presented in any other university or institution for the award of the degree or any academic credit. Views expressed herein are my own unless otherwise stated and in such a case, the reference has been cited. No part of this thesis may be reproduced without prior written permission of the author and/or Moi University.

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DEDICATION

I dedicate this study to my beloved mother and father, my dearest wife and daughter, and my three brothers, all of whose unconditional love and relentless support have been the ultimate wind beneath my wings.

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ABSTRACT

Background: Abnormal Uterine Bleeding (AUB) affects 3-30% of peri- and 5-10% of postmenopausal women. While the condition is mostly due to ovulatory/endometrial dysfunction or benign pathologies, peri- and postmenopausal women with AUB are at a higher risk of being diagnosed with endometrial hyperplasia (EH) and cancer (EC). Risk factors for EH and EC include obesity, diabetes mellitus and chronic hypertension. Data on endometrial histologies and factors associated with diagnosis of EH and EC in these women is limited in Kenya.

Objectives: To describe the clinical, ultrasound and endometrial histopathological features, determine the prevalence of and factors associated with diagnosis of EH and EC in peri- and postmenopausal women with AUB at Moi Teaching and Referral Hospital (MTRH).

Methods: A cross-sectional study of women aged ≥40 years with AUB. All women who met the eligibility criteria and consented within a period of 12 months were enrolled (100 participants). Endometrial biopsies were done using a Pipelle. Histological evaluation of samples was done by two pathologists. Data on sociodemographic, clinical characteristics (BMI, chronic illness, bleeding patterns, parity, contraception use) and ultrasound findings were collected using a questionnaire. Associations between these factors and the diagnosis of EH/EC were tested using chi-square or fisher's exact test, significance was accepted at a p value ≤ 0.05. Logistic regression was modeled using factors significantly associated with EH/EC diagnosis on bivariate analysis.

Results: From 64 perimenopausal women, 40 (62.5%) had cyclical or benign patterns, 23 (35.9%) had EH and 1 (1.6%) had EC. EH without atypia was the most seen individual pattern in this group (32.8%). From 36 postmenopausal women, 15 (41.7%) had cyclical or benign patterns, 14 (38.9%) had EH and 7 (19.4%) had EC. EH without atypia was the most seen individual pattern in this group too (25%). The prevalence of EH and EC in the perimenopausal group was 35.9% and 1.6% respectively, and 38.9% and 19.4% respectively in the postmenopausal. None of the clinical characteristics was significantly associated with the diagnosis of EH/EC. Thickened endometrium on ultrasound was the only feature associated with diagnosis of EH/EC ($p = 0.004$) on multivariate analysis.

Conclusions: The histological findings in peri- and postmenopausal women with AUB at MTRH were mostly cyclical patterns/benign endometrial pathologies. However, EH without atypia was the single most commonly seen individual pathology in each group. The prevalence of both EH and EC in these women was significantly higher compared to most studies, with endometrial thickening on ultrasonography noted to significantly be associated with diagnosis of the two conditions.

Recommendations: Performance of pelvic ultrasonography and endometrial biopsies in women aged ≥ 40 years who have AUB is strongly recommended to identify high risk features and rule out EH and EC in these women.

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ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
AUB	Abnormal Uterine Bleeding
BMI	Body Mass Index
CCSP	Cervical Cancer Screening Program
D&C	Dilatation & Curettage
DPE	Disordered Proliferative Endometrium
EC	Endometrial Cancer
EH	Endometrial Hyperplasia
ET	Endometrial Thickness
FIGO	International Federation of Gynecology and Obstetrics
FMP	Final Menstrual Period
GOPC	Gynecology Out-Patient Clinic
HMB	Heavy Menstrual Bleeding
HRT	Hormonal Replacement Therapy
IREC	Institutional Research and Ethics Committee
IMB	Inter-menstrual Bleeding
MBChB	Bachelor of Medicine and Surgery
MMED	Master of Medicine (Degree)
MT	Menopausal Transition
MTRH	Moi Teaching and Referral Hospital
OPD	Out-patient Department
PCOS	Polycystic Ovary Syndrome
PGRH	Post Graduate Reproductive Health
PMB	Postmenopausal Bleeding
RCOG	Royal College of Obstetricians and Gynaecologists

RH	Reproductive Health
RMBH	Riley Mother and Baby Hospital
SOM	School of Medicine
TVS	Transvaginal Sonography
WHO	World Health Organization

OPERATIONAL DEFINITIONS OF TERMS

Women of the reproductive age: Women aged between 15-49 years (WHO).

Menopause: Permanent cessation of menstruation resulting from the loss of ovarian follicular activity (WHO), confirmed after 12 consecutive months of amenorrhea in the absence of other pathological or physiological causes. The period following these 12 months of cessation of menstruation is termed as the **Postmenopausal Period**, and women in this period as **Postmenopausal Women**.

Perimenopause: The period when a woman is transitioning from the reproductive years into menopause, defined in temporal, physiological, biological or symptomatic terms (Derzko, 1997). In this study, the term denotes the period from when a woman turns 40 years to when they are experiencing amenorrhea of not more than 12 consecutive months, in the absence of other pathological or physiological causes. Any woman in this period will be referred to as **perimenopausal**.

Abnormal Uterine Bleeding (AUB): Irregularities in the menstrual cycle involving frequency, regularity, duration, and volume of flow in women of the reproductive age, or any form of uterine bleeding in postmenopausal women (PMB). It could present in the following ways, which will denote clinical patterns of bleeding described in this study:

- **Menorrhagia**: Excessive and/or prolonged (>7 days) bleeding occurring at regular intervals in the reproductive years.
- **Metrorrhagia:** Denotes bleeding that occurs irregularly/erratically that the menstrual phase cannot be determined at all.
- **Menometrorrhagia:** Bleeding that occurs erratically/irregularly and excessively that the menstrual phase cannot be determined at all.
- **Metrotaxis:** Continuous/nonstop bleeding

- **Intermenstrual bleeding:** Bleeding (usually not excessive) that can either occur randomly in a cycle, or in a cyclical/predictable manner between otherwise normal menstrual cycles.
- **Acute AUB:** An episode of heavy bleeding that in the opinion of the clinician is of sufficient quantity to require immediate intervention. Acute AUB may present in the context of chronic AUB.
- **Chronic AUB:** Abnormal uterine bleeding present for the most of the previous 6 months.
- **Postmenopausal Bleeding (PMB):** A form of AUB that occurs at least 12 months after the final menstrual period (FMP) marking the onset of menopause. It can either present as light (menses-like) or heavy vaginal bleeding (more than normal menses in amount), spotting, or a mixture of these.
- **Spotting:** Any bloody vaginal discharge that is not large enough to require sanitary protection.

Lesion: Any pathological or traumatic discontinuity of tissue or loss of function of a part. For the purpose of this study, the following types of lesions on the vulva, vagina and cervix denote gross genital tract lesions:

- friable tissue (soft, eroded, may be bleeding)
- red patchy areas,
- pebbly or nodular growths,
- granular areas,
- white patches,
- ulcerated area
- Polyps.

Histopathological evaluation: The microscopic evaluation of tissue, especially tissue rendered or suspected to be abnormal as a result of a disease process.

Parity: The number of times that a woman has given birth to a fetus with a gestational age of ≥20 weeks (ACOG, WHO), regardless of whether the child was born alive or was stillborn. In Kenya and thus in this study, parity denotes the number of deliveries ≥ 28 weeks of gestation.

Premalignant: A condition that may (or is likely to) become cancer. Also referred to as pre-cancerous. In this study, the term will denote endometrial hyperplasia.

Malignant: A tumor that is not self-limited in its growth, is capable of invading into adjacent tissues, and may be capable of spreading to distant tissues. In this study, the term will denote all forms of endometrial cancers.

Prevalence: the proportion of persons in a population who have a particular disease or attribute at a specified point in time or over a specified period of time. In this study, the proportion will be expressed as a percentage.

CHAPTER ONE: INTRODUCTION

1.1 Background

Abnormal Uterine Bleeding (AUB) is defined as any bleeding that does not correspond with the frequency, duration or amount of blood flow of a normal menstrual cycle (Munro et al., 2018). Its prevalence in women of the reproductive age is reported to range between 3-30%, with adolescent and perimenopausal women being the most affected. Bleeding whose source has been determined to be the uterus in postmenopausal women is termed postmenopausal bleeding (PMB), and is also a form AUB. As high as 10% of postmenopausal women will experience PMB (Breijer et al., 2010). Overall, a third of women will experience AUB sometime in their life, with as high as 70% of gynecologic consultations in the perimenopausal and postmenopausal periods being due to the condition (Desai et al., 2014).

AUB in perimenopausal and postmenopausal women is mostly due to ovulatory and endometrial dysfunction or benign endometrial pathologies such as endometrial polyps and uterine leiomyomas (fibroids). However, it could also be the first and principal symptom of endometrial cancer (EC) or its precursor, endometrial hyperplasia (EH). The gold-standard for the diagnosis of the various causes of AUB is the histological evaluation of samples of the endometrium obtained through an endometrial biopsy (EMB). This is particularly done in women with AUB who are at a higher risk of being diagnosed with endometrial hyperplasia or cancer, such as perimenopausal and postmenopausal women. The primary aim of the histological evaluation of the endometria in these women is to rule out endometrial hyperplasia and cancer (Frederic & Mirza, 2018; Bradley Linda, 2013). Preliminary evaluation of a woman who presents with AUB also includes the performance of a pelvic ultrasound to identify possible structural pathologies that could be the cause of or contribute to the AUB symptom.

Endometrial cancer (EC) is the leading gynecologic malignancy in most developed countries, and the second most common malignancy after cervical cancer in developing countries (Frederic & Mirza, 2018; Forae & Aligbe, 2013). It is predominantly seen in postmenopausal and perimenopausal women, with only 2-5% of cases being detected in women aged <40 years (Pellerin & Finan, 2005). AUB is the most commonly reported symptom in women with EC, with as high as 90% of these women reporting to have the symptom (R. B. Goldstein et al., 2002). Various clinical features such as obesity and diabetes mellitus have been linked to EC and its precursor, endometrial hyperplasia, with women identified to have certain radiological features such as a thickened endometrium reported to be more likely to be diagnosed with the two conditions.

Studies done in perimenopausal and postmenopausal women with AUB in different populations have reported different endometrial histopathological patterns and different prevalence of EH and EC in these women. However, there is a dearth of regional data on the topic, particularly from Sub-Saharan Africa.

1.2 Problem Statement

About a third of women will experience some form of AUB in their lifetime, particularly during the perimenopausal period. While a majority of the underlying causes of the condition are non-malignant, studies done in other populations have shown that endometrial hyperplasia and cancer are most detected in perimenopausal and postmenopausal women with AUB, thus recommending histological evaluation of the endometria in these women. Despite these recommendations, not all of these women undergo endometrial histopathological evaluation in our set-up. This is particularly for those who are radiologically identified to have structural pathologies such as uterine

fibroids and endometrial polyps, in whom AUB is generally assumed to primarily be due to the identified structural cause.

While it is established that cervical cancer is the leading gynecologic malignancy in the country, the true prevalence of endometrial cancer is unknown. It is however estimated that for every 30 cases of cervical cancer, there is one case of endometrial cancer, hence highlighting on the potential burden of the two gynecologic cancers. Conditions such as obesity and non-communicable diseases such as diabetes and chronic hypertension, which have been identified as risk factors for endometrial hyperplasia and cancer in other populations, are significantly on the rise within our country.

There is paucity of local and regional data on the clinical, ultrasound and endometrial histopathological features in peri- and postmenopausal women with AUB, the proportion of these women who are indeed diagnosed with endometrial hyperplasia and cancer, and factors associated with the diagnosis of these two conditions within our set-up.

1.3 Research Questions

1. What are the sociodemographic, clinical characteristics and ultrasound findings in perimenopausal and postmenopausal women with AUB at MTRH?
2. What is the prevalence of endometrial hyperplasia and endometrial cancer in perimenopausal and postmenopausal women with AUB at MTRH?
3. What are the endometrial histopathological patterns in perimenopausal and postmenopausal women with AUB at MTRH?
4. What are the clinical characteristics and ultrasound findings associated with the diagnosis of endometrial hyperplasia and endometrial cancer in perimenopausal and postmenopausal women with AUB at MTRH?

1.4. Justification of Study

Describing the endometrial histopathological patterns in perimenopausal and postmenopausal women with AUB will highlight the various histopathological causes of AUB and the proportion of these women who are indeed diagnosed with EH and EC in our set-up. This will in turn reiterate the importance of performing endometrial biopsies in those presenting with similar symptoms thus creating room for early diagnosis and timely management of these conditions. Moreover, identifying endometrial pathologies co-existing with radiologically identified structural entities such as uterine fibroids will prompt the performing of endometrial biopsies in these women too, thus allowing proper management of both conditions.

Furthermore, identifying possible clinical characteristics and ultrasound features that are associated with the diagnosis of endometrial hyperplasia and cancer will allow us to pay keen attention to women with these characteristics/features thus prompting us to employ primary and secondary preventive measures in the fight against endometrial cancer and its precursor endometrial hyperplasia.

Availability of this data obtained from our local set-up will enable us to formulate and/or strengthen our own protocols for the evaluation and management of perimenopausal and postmenopausal women with AUB.

1.5 Study Objectives

1.5.1 Broad Objective

1. To describe the clinical, radiological and endometrial histopathological features in perimenopausal and postmenopausal women with abnormal uterine bleeding at MTRH.

1.5.2 Specific Objectives

1. To describe the sociodemographic, clinical characteristics and ultrasound features in perimenopausal and postmenopausal women with abnormal uterine bleeding at MTRH.

2. To determine the prevalence of endometrial hyperplasia and cancer in perimenopausal and postmenopausal women with abnormal uterine bleeding at MTRH.

3. To describe the endometrial histopathological patterns in perimenopausal and postmenopausal women with abnormal uterine bleeding at MTRH.

4. To determine clinical characteristics and ultrasound features associated with the diagnosis of endometrial hyperplasia and cancer in perimenopausal and postmenopausal women with abnormal uterine bleeding at MTRH.

CHAPTER TWO: LITERATURE REVIEW

Abnormal Uterine Bleeding (AUB) is defined as any bleeding that does not correspond with the frequency, duration or amount of blood flow of a normal menstrual cycle (Munro et al., 2018; Mishra & Sultan, 2017). It is reported to affect 3-30% of women of the reproductive age, and 5-10% of postmenopausal women in whom it is termed postmenopausal bleeding (Piróg et al., 2019; Smith-bindman et al., 2008). As much as a third of women will experience AUB sometime in their life (Munro et al., 2018), with as high as 70% of gynecological clinic referrals in perimenopausal women being due to the condition (Desai et al., 2014). About one million women in the United Kingdom seek help for AUB per year, making the condition the 4th most common reason for referral of women by the general practitioners to specialist clinics in the country (Narice et al., 2018).

2.1 Normal Menses and Abnormal Uterine Bleeding

Normal menstrual periods (menses) are described using parameters such as frequency, duration, regularity, and volume of flow:

Frequency

The normal frequency of menstrual cycles has been redefined by FIGO to denote a cycle that repeats every 24-38 days, as opposed to the previous definition of 21-35 days. Any cycle that exceeds beyond 38 days is labeled as an '**Infrequent Cycle**' (previously called oligomenorrhea), while a cycle that lasts less than 24 days is labeled as a '**Frequent Cycle**' (previously called polymenorrhea).

Duration of Flow

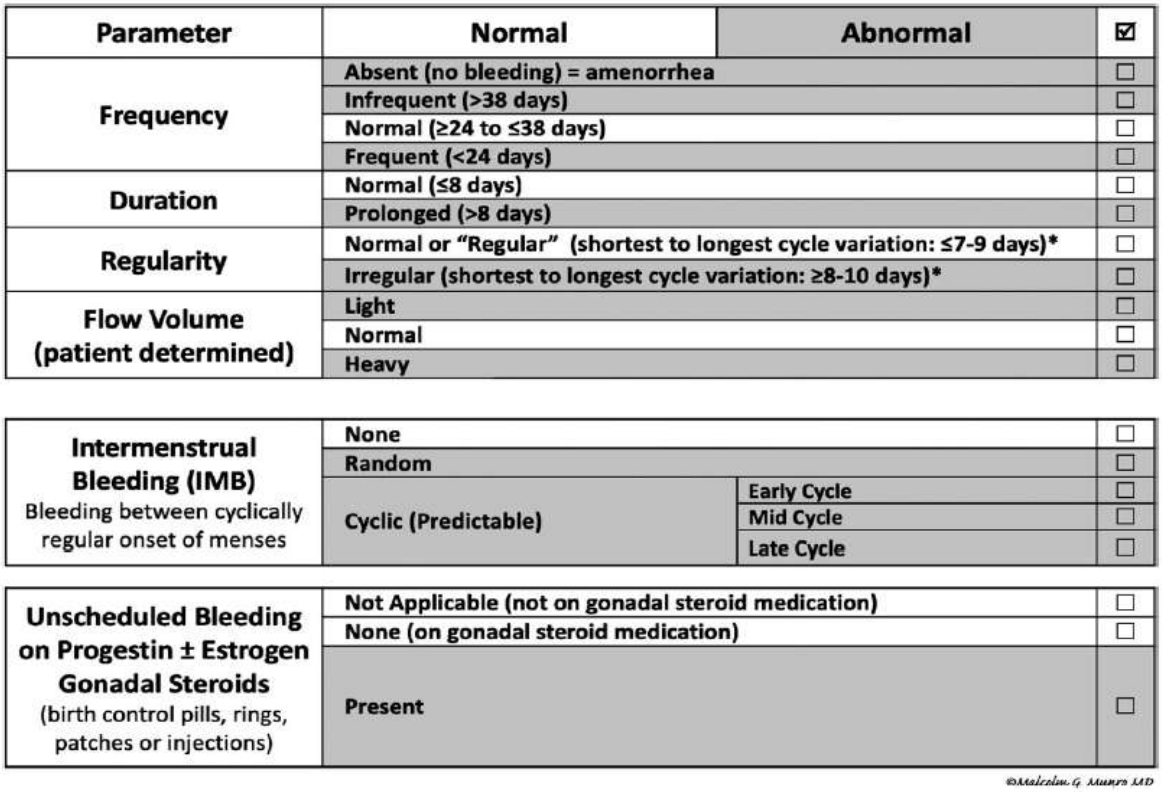
The normal duration of a menstrual flow is 8 days or less, with menses lasting longer than 8 days being termed as '**Prolonged Menses**'.

Regularity of Cycles

A regular cycle is defined as one in which the shortest to longest cycle variation, that is the difference between the shortest and the longest cycle, is equal to or less than 9 days. However, this variation depends on the age of a woman, and is considered normal when ≤9 days in those aged between 18-25 years and those between 42-45 years, and ≤7 days in those between 26-41 years. An irregular cycle, which was previously defined as one in which the difference between the shortest and the longest cycle is 20 days, is currently defined as one in which the shortest to longest cycle variation is ≥8-10 days (Munro et al., 2018).

Flow Volume

Pertaining to volume of blood lost per given menstrual flow, the volume is usually patient determined and is described as either normal or abnormal, which could denote either light or heavy menses. The term **Heavy Menstrual Bleeding** (HMB) is a symptom and not a diagnosis, and is defined as excessive menstrual blood loss, which interferes with a woman's physical, social, emotional and/or material quality of life. Menorrhagia, as is used in this study to denote menstrual bleeding that is > 80mL and prolonged (>8days) occurring at regular intervals, thus would be described as a prolonged menses and/or HMB by the new proposed terms by FIGO.



Parameter	Normal	Abnormal	☑
Frequency	Absent (no bleeding) = amenorrhea		☐
	Infrequent (>38 days)		☐
	Normal (≥24 to ≤38 days)		☐
	Frequent (<24 days)		☐
Duration	Normal (≤8 days)		☐
	Prolonged (>8 days)		☐
Regularity	Normal or "Regular" (shortest to longest cycle variation: ≤7-9 days)*		☐
	Irregular (shortest to longest cycle variation: ≥8-10 days)*		☐
Flow Volume (patient determined)	Light		☐
	Normal		☐
	Heavy		☐

Intermenstrual Bleeding (IMB) Bleeding between cyclically regular onset of menses	None		☐
	Random		☐
	Cyclic (Predictable)	Early Cycle	☐
		Mid Cycle	☐
		Late Cycle	☐

Unscheduled Bleeding on Progestin ± Estrogen Gonadal Steroids (birth control pills, rings, patches or injections)	Not Applicable (not on gonadal steroid medication)	☐
	None (on gonadal steroid medication)	☐
	Present	☐

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Figure 2.1: FIGO AUB System 1. Nomenclature and Definitions of AUB Symptoms; adopted from The FIGO Menstrual Disorders Committee (Munro et al., 2018)

Bleeding patterns that fall outside the parameters of a normal menstrual cycle have historically been defined using terms such as **menorrhagia**, **metrorrhagia**, **menometrorrhagia**, **polymenorrhea**, **oligomenorrhea**, etc. Although these terms are progressively being replaced by the newer terms such as Heavy Menstrual Bleeding (HMB) and Inter-Menstrual Bleeding (IMB), they are still in wide use (Pennant et al., 2016).

According to the Menorrhagia Research Group, menorrhagia can objectively be defined as a total measured menstrual blood loss per cycle that is >80mL, or subjectively as a complaint of excessive regular menstrual bleeding occurring in consecutive cycles in the reproductive years (Gillian et al., 2004). Menometrorrhagia denotes a mixture of menorrhagia and metrorrhagia and usually presents as bleeding that occurs erratically and excessively resulting in the inability to determine the phase of a menstrual cycle.

The Menorrhagia Research Group defined the average menstrual blood loss in a woman's cycle to be 35-50ml without significant blood clots. Population studies on menstrual patterns have shown that about 10% of women experience menstrual blood loss >80mL per cycle (Gillian et al., 2004). Methods of quantifying the amount of menstrual blood loss per cycle have been listed by the research group as:

- Self-estimation by the woman,
- Counting the number of days of menstruation,
- Counting the number of sanitary products used during menstruation,
- Weighing the total number of sanitary products used during menstruation,
- Use of a full blood count,
- Measuring of blood collected from a menstrual cup,
- Chemical analysis using the alkaline haematin technique,
- Use of the Pictorial Blood Loss Assessment Charts (PBACs),
- Use of the Menstrual Pictogram (more recent method).

These methods have varying amounts of accuracy in the estimation of the total menstrual blood loss, some being opted more in research settings than in clinical use.

The International Federation of Gynecology and Obstetrics (FIGO) classifies the causes of AUB using the **PALM-COEIN** classification. PALM-COEIN is a pneumonic that constitutes of two main groups of pathologies that cause AUB:

The **PALM** group constitutes of organic pathologies, namely:

- **P**-polyp
- **A**-adenomyosis
- **L**-leiomyoma
- **M**-malignant and pre-malignant pathologies such as endometrial hyperplasia.

The **COEIN** group constitutes of non-organic pathologies, namely:

- **C**-coagulopathy,
- **O**-ovulatory dysfunction,
- **E**-endometrial dysfunction,
- **I**-iatrogenic,
- **N**-not otherwise classified (Munro et al., 2018).

A woman may have one or more of the entities from the PALM-COEIN classification, either or both of which could be responsible for the AUB. Structural entities such as endometrial polyps, adenomyosis and uterine leiomyoma are often asymptomatic and thus may not always be the cause of the AUB despite being identified through imaging in a woman presenting with the condition (Munro et al., 2011). Women suspected to have these structural causes should thus still be investigated for co-existing conditions- either other structural or non-structural causes from the PALM-COEIN classification, which could be the cause of or contributing to the AUB (Whitaker & Critchley, 2016).

2.2 Investigating a Patient with Abnormal Uterine Bleeding

2.2.1 Physical Examination and Laboratory Investigations

Following a detailed medical history and physical examination that includes a pelvic exam, a patient with AUB is evaluated using a combination of laboratory investigations and radiologic imaging (Hill & Decherney, 2015). A detailed medical history of the patient may lead to the identification of iatrogenic causes of AUB such as use of anti-coagulants or hormonal contraceptives. A family history of certain conditions such as Polycystic Ovary Syndrome (PCOS) may also lead to suspicion of the patient also having the condition, as genetic inheritance has been implied in some cases (Dumesic et al., 2015). From a physical examination, features suggestive of a coagulation abnormality may be identified, with include findings such as ecchymosis or petechiae on the skin or

mucosal surfaces. Physical features suggestive of polycystic ovary syndrome such as acne, hirsutism, acanthosis nigricans and alopecia may also be discovered during a physical examination. A palpable pelvic mass or bulky uterus detected during an abdominal and/or pelvic examination through a bimanual exam, may indicate presence of uterine leiomyoma, adenomyosis or malignancy. Uterine Leiomyoma is the most common tumor seen in women, with almost 80% of black women being said to develop at least one fibroid by the age of 50 (S. R. Goldstein & Lumsden, 2017). A speculum exam during the pelvic examination may aid in the identification of genital tract lesions that could be the cause of the abnormal vaginal bleeding in patients, besides endometrial/uterine causes. Vulvar, vaginal or cervical lesions could cause vaginal bleeding in a woman and should thus be ruled out before labeling the condition as AUB. An Ethiopian study by Ergete et al reported that 84.4% of the cancers diagnosed in women who presented with postmenopausal bleeding were cervical cancer, while only 10.7% of them were endometrial cancer (Ergete & Tesfaye, 2001).

Laboratory investigations done in a patient with AUB include a pregnancy test in women of the reproductive age, complete blood count (CBC) to rule out thrombocytopenia and identify anemia that may have resulted from significant blood loss, and coagulation profile to rule out coagulopathy. Both thyroid dysfunction (hypothyroidism) and hyperprolactinemia can cause anovulatory cycles that manifest as AUB. Measurement of serum thyroid stimulating hormone (TSH) levels and serum prolactin levels is thus prudent in patients with AUB, particularly those with other signs suggestive of these endocrine dysfunctions (Linda & Porter, 2013).

2.2.2 Pelvic Imaging

The imaging modality of choice for investigating pelvic pathologies that could be the cause of AUB is pelvic ultrasonography (Munro et al., 2018). The American College of Obstetricians & Gynecologists (ACOG) recommends the use of either transvaginal sonography (TVS) or endometrial biopsy but not necessarily both, as the first investigation for women with postmenopausal bleeding. Recommendations on the first investigation of choice for perimenopausal women with AUB are not as clear as for the postmenopausal women, thus it is not uncommon to find perimenopausal women undergoing ultrasonographic evaluation first, followed by endometrial biopsy (Bradley & Porter, 2013; Cansino & Catherine, 2009). When pelvic ultrasonography is not adequate or further evaluation of the uterine cavity is needed, sonohysterography (also known as saline infusion sonohysterography) or hysteroscopy (preferably in the office setting) are recommended (Micah & Alan, 2012).

The normal endometrium varies both in appearance and thickness throughout a woman's menstrual cycle and age in general. The endometrium is thinnest during the menstrual phase of the cycle (2-4mm), and is around 5-7mm in the early proliferative phase, 11mm in the late-proliferative/pre-ovulatory phase, and thickest (7-16mm) in the secretory phase in premenopausal women. Interpretation of endometrial thickness in these women should be done while putting into consideration the phase of the menstrual cycle the woman was in when the ultrasound was done. However, this poses a challenge for those women with irregular cycles in whom the phase of the menstrual cycle may be difficult to distinguish. Generally, an endometrial thickness of >16mm discovered in any phase of the menstrual cycle is considered abnormal. The cut-off for normal endometrial thickness in postmenopausal women is <5mm in those with postmenopausal bleeding, and 8-11mm in those without postmenopausal bleeding. An endometrial thickness that is above these

normal cut-off values should raise suspicion of diffuse proliferative endometrium, endometrial hyperplasia or endometrial cancer, among other possible pathologies (Nalaboff et al., 2001)

TVS has been reported to have a high sensitivity and specificity in detecting structural pathologies such as uterine leiomyomas, polyps, and also an abnormally thickened endometrium that could be a sign of endometrial hyperplasia or cancer. The accuracy of TVS in the diagnosis of endometrial pathologies responsible for AUB in women, particularly endometrial hyperplasia and cancer, has been tested by correlating sonographic features to endometrial histopathological findings in these women. One of the most important of these sonographic features is an abnormally thickened endometrium. A multi-center case-control study done in the UK concluded that TVS had good sensitivity and specificity as a screening tool for endometrial cancer in postmenopausal women, with a sensitivity and specificity of 80.5% and 86.2% respectively when a 5mm endometrial thickness cut-off value was assigned to distinguish normal from abnormal endometrium (Jacobs et al., 2011). In another study done in Turkey that aimed at evaluating the accuracy of TVS in the detection of endometrial pathologies, TVS was reported to represent a practical approach for the initial evaluation of uterine pathologies. However, hysteroscopy was noted to have better a diagnostic value for uterine pathologies in general, and uterine polyps in particular (Babacan et al., 2014). A similar study done in India looked at the accuracy of TVS in the detection of endometrial abnormalities in perimenopausal and postmenopausal women presenting with AUB. The objective of this study was to identify endometrial thickness cut-off values that would distinguish normal from abnormal endometrium in these women. From this study, 6mm was identified as the endometrial thickness cut-off value (sensitivity of 87.5%, specificity of 77.3%) for the perimenopausal group, and 4mm as the cut-off value for the

postmenopausal group (sensitivity 92.3%, specificity of 66.67%) that would accurately distinguish normal from abnormal endometrium.

Other less frequently used imaging modalities in a patient presenting with AUB include the magnetic resonance imaging (MRI), which has been reported to be the imaging of choice for patients suspected to be having adenomyosis (Micah & Alan, 2012).

2.2.3 Histological Evaluation of the Endometrium

The primary role of histological evaluation of the endometria in women with AUB is to rule out endometrial hyperplasia (EH) and endometrial cancer (EC), and to identify other possible etiologies that can only be diagnosed histologically, e.g., endometritis, atrophic endometrium, disordered proliferative endometrium etc. This is particularly recommended for perimenopausal and postmenopausal women with AUB, who are at a higher risk of being diagnosed with EH and EC. Different guidelines recommend different ages at or above which women with AUB will require to have an endometrial biopsy done, the ages ranging between 35-45 years. The American College of Obstetricians and Gynecologists (ACOG) recommends histological evaluation of the endometrium as a first line test for any woman 45 years or older who presents with AUB, after ruling out pregnancy (Micah & Alan, 2012). Other recommendations propose histological evaluation of the endometrium for any woman 40 years or older who presents with AUB, due to the risk of malignancy that increases during this period through the postmenopausal period (Narice et al., 2018; Pennant et al., 2016). Endometrial biopsy should also be performed in women with AUB who are younger than 40 years, who have conditions that expose the endometrium to excess and unopposed estrogen, which includes patients with the following conditions: obesity, polycystic ovary syndrome (PCOS), granulosa cell tumors, etc. Women with Lynch Syndrome, and those with

persistent AUB despite adequate medical therapy also qualify to have endometrial biopsies done despite being <40 years in age (Hill & Decherney, 2015).

With the emergence of office-based methods of acquiring endometrial biopsies such as endometrial sampling using the Pipelle device, dilation and curettage (D&C) which has historically been the first choice for endometrial biopsy is now used less often. Pipelle biopsy has gained popularity and acceptance due to it being a minimally invasive procedure with minimum associated complications and high specificity and sensitivity in the detection of both EH and EC. Furthermore, D&C has the disadvantage of requiring the patient to be put under general anesthesia for the procedure to be done. In one meta-analysis, the Pipelle device was noted to perform equally as good as D&C and as well as or better than other endometrial sampling devices in terms of sampling adequacy and sensitivity. It also was relatively better regarding pain/discomfort and costs (Narice et al., 2018). Reported complications of endometrial sampling with the Pipelle are estimated to occur in 1.2-3.8% of cases, and include vasovagal responses, uterine perforation and infections (Belcaro et al., 2020).

In a meta-analysis of 39 studies constituting 7914 premenopausal and postmenopausal women who underwent endometrial histological evaluation using different biopsy devices, the Pipelle device was reported to be more sensitive in detecting EC and EH with atypia than the Vabra device. The detection rate of EC in the study was 99.6% in postmenopausal women and 91% in premenopausal women when global disease was present. The detection rate of EH with atypia was 88% with the Pipelle device, and the overall specificity of the instrument was reported to be 98-100% (Paul et al., 2000). Gungorduk et al compared the accuracy of Pipelle versus that of D&C in the diagnosis of endometrial pathologies, and reported a concordance rate of 62% between Pipelle biopsy findings and hysterectomy results, compared to a rate of 67% by D&C, concluding that

Pipelle biopsy has an accuracy comparable to D&C in the diagnosis of endometrial pathologies (Gungorduk et al., 2014).

One challenge for endometrial biopsies is the ability to obtain adequate and assessable samples, with studies reporting inadequate/insufficient sample rates ranging between 2-60% (Kandil et al., 2014). However, there is a wide variation in the definition of what an adequate sample is and what makes a sample inadequate/insufficient among pathologists, with some pathologists opting to adopt terms such as ‘‘unassessable’’ for those biopsy samples where minimal endometrial tissue is being reported(V Phillips, 2006). There are currently no standard criteria for determining the adequacy of an endometrial biopsy sample. One of the most commonly accepted definition of an adequate sample is one which has one or more pieces of endometrium large enough to determine the gland to stroma ratio and endometrial morphological features, while an inadequate sample is described as consisting only of blood or cervical mucus with fragments of benign endocervix, or a large amount of blood with only small fragments of endometrial glands and stroma. The rate of inadequate samples in other published studies has been reported to range between 4.8% and 33%, although notably in most of these studies, the criteria for adequacy of the samples was not stated (McCluggage, 2005). A study involving 1926 patients who had endometrial biopsies done at a tertiary hospital in South Africa found that as high as 25% of the biopsy samples were reported to have no endometrial tissue, and listed postmenopausal status, obesity and advanced age as factors associated with a higher failure rate of the biopsy. The study revealed that from repeat biopsies following an inadequate/scant biopsy, 10% of the patients had EH and 5% had EC, while 15% had EC detected from hysterectomy specimens (Mohanlal et al., 2010).

In a study of clinicopathological characteristics of 1120 endometrial biopsy samples deemed insufficient for diagnosis, Kandil et al reported that more samples from older women were discovered to be insufficient compared to those from young women (14.6% versus 5.8%). An adequate sample in this study was defined as one with at least one intact tissue fragment containing both glands and stroma for premenopausal patients and 5-10 strips of atrophic endometrial epithelium for postmenopausal patients. Repeat biopsies were done in 38% of the patients in the study on a 12-month follow-up and out of these, 75% had an adequate sample on the repeat biopsy, 10% of which showed malignant tumor (Kandil et al., 2014)

In a meta-synthesis by Narice et al analyzing studies done on the effectiveness of the Pipelle sampler compared to other endometrial sampling devices, the Pipelle was found to have comparable performance to D&C when it came to sample adequacy, with rates of adequacy in studies ranging between 89.7-98%. Rates of sample adequacy were noted to be higher when the samples were taken by a consultant gynecologist (83-96%) compared to when they were taken by a general practitioner (76%). Some of the factors contributing to an unsuccessful endometrial biopsy include cervical stenosis and pelvic organ prolapse which hinder access to the uterine cavity, focal endometrial pathologies such as endometrial polyps and submucosal fibroids, endometrial atrophy, etc. When it comes to pain and discomfort during a biopsy procedure, 15 studies in the meta-analysis reported that most patients experienced minimal discomfort with the Pipelle. The Pipelle device was also noted to be cheaper than other alternative samplers (Narice et al., 2018).

2.3 Sociodemographic and Clinical Characteristics of Perimenopausal and Postmenopausal Women with AUB

The perimenopausal period, also known as the climacteric period or menopausal transition, is defined as the period around the onset of menopause that is often marked by various physical signs such as hot flushes and menstrual irregularities (S. R. Goldstein & Lumsden, 2017). This period spans between 2-8 years prior to and a year after the final menstrual period of a woman (Nargis et al., 2014). Although the period may vary from population to population, with some populations having women entering the transition as early as the mid 30's, numerous studies have identified it to be between 40-50 years (Abid et al, 2014; Sharma et al., 2014; Sudhamani & Sirmukaddam, 2015). By another definition, the perimenopausal period has been defined using temporal, physiological, biological or symptomatic descriptors. In temporal terms, the period starts from about 35 years to menopause, between 1-10 years before to a year after the final menstrual periods (FMP). Physiologically, it is the period when ovulatory function begins to diminish following rapid depletion of functional ovarian follicles and ovulation becomes erratic and less frequent, eventually ceasing altogether. Biologically, it begins when follicle stimulating hormone (FSH) levels rise to 30-50 IU/l. Symptomatically, it is the period when menses range from erratic spotting to heavy and/or prolonged bleeding, and vasomotor and genitourinary symptoms begin to occur, minimally and infrequently at first then increasing both in intensity and severity (Derzko, 1997). While more than 90% of EC is diagnosed in postmenopausal women, about 7% of cases occur in women <50 years, particularly in the perimenopausal period, with only 2% of cases being reported in women <40 years (Narice et al., 2018).

Age is a significant sociodemographic factor in women with AUB. About a third of patients presenting to the gynecologic outpatient clinics in developed countries present with AUB, with the prevalence of AUB in women of the reproductive age being reported to range between 9-14% (Rajagopal et al., 2019). A systematic review of epidemiological studies on menstrual disturbances in developing countries reported a prevalence of 5-15% of AUB in women of the reproductive age, and speculated a higher percent in older age groups (Harlow & Campbell, 2004). Majority of the women from the reproductive age-group who are diagnosed with AUB are adolescent and perimenopausal women (Porwal et al., 2015). About 70% of gynecological consultations in perimenopausal women are also said to be due to AUB (Desai et al., 2014), with a fifth of premenopausal women being reported to have their daily lives interfered by the condition (Pennant et al., 2016). A study done in Canada reported that by the age of 40, about 10% of women seek medical attention due to AUB, with the incidence increasing to as high 50% by 45 years (Derzko, 1997). AUB is one of the most frequent indications for hysterectomy, with no organic pathology being identified in 40% of these patients. Around 6% of women aged between 25-44 years report to the general physician with complaints of excessive menstrual bleeding, 35% of which get referred to a gynecologist for further management, and 60% of them eventually ending up having hysterectomies done in the next 5 years. Consequently, over 75,000 hysterectomies are done every year, 25-30% of them due to AUB (Abid et al, 2014).

Natural Menopause is defined as permanent cessation of menstruation due to loss of ovarian follicular activity. It is a retrospective diagnosis that is made following 12 consecutive months of amenorrhea in the absence of physiologic or pathologic cause. Studies in developing countries generally report a younger age at menopause, while the average age at natural menopause in western countries is estimated to be 51 years

(Cheung et al., 2004). A cross-sectional descriptive study done in rural western Kenya reported the median age at menopause to be 48.28 years, and that almost all women in the region were menopausal by 55 years. The total fertility period in the study averaged 35 years (Noreh et al., 1997).

Postmenopausal bleeding (PMB) is vaginal bleeding occurring after at least 12 consecutive months following the final menstrual period (FMP) of a woman (Breijer et al., 2010). While vaginal bleeding can be of any source along the genital tract, including the vagina and the cervix, the term PMB is used to generally denote bleeding that is exclusively from the uterus, and is thus a form of AUB (Ergete & Tesfaye, 2001). About 5-10% of women in the postmenopausal period experience PMB (Smith-bindman et al., 2008). This proportion reduces with advanced age, while the risk of endometrial malignancy (EC) in the presence of PMB increases from 1% at the age of 50 years to 50% in women aged 80 years. PMB is a common sign of EC, with more than 90% of patients diagnosed with the malignancy in the postmenopausal period presenting with the symptom. AUB accounts for two thirds of all gynecologic visits in the postmenopausal group, with different studies reporting different rates of EC in these women, ranging between 3-25% (Clarke et al., 2018). Although simply referred to as PMB when listing the different clinical patterns of bleeding, it can manifest in the form of heavy or light bleeding, spotting, or a mixture of these. Postmenopausal women with EH or EC commonly have moderate to heavy vaginal bleeding compared to those with atrophic endometrium, who mostly report to have spotting (Deeba & Khan, 2016).

In a cross-sectional study done in Cameroon that evaluated 163 women seeking consultation for AUB, the mean age of the participants was 36 (± 12.27) years, with ages ranging between 11 and 71 years. Perimenopausal and postmenopausal women

constituted 36% of all participants. Out of the 163 the participants, 67 (41.1%) were married and 77 (47.24%) were formally employed. Out of the 163 participants, 63 (40.38%) had secondary and 56 (35.9%) had tertiary education as the highest form of education. When it comes to clinical characteristics, the 163 participants had the following reproductive characteristics: 72 (44.11%) were nulliparous, 20 (12.27%) were primiparous and 71 (43.56%) were multiparous. The most commonly reported bleeding patterns in the 149 premenopausal participants were as follows: 97/149 (65.10%) had irregular bleeding (metrorrhagia), 41/149 (27.51%) had heavy menstrual bleeding (menorrhagia), 14/149 (9.39%) had frequent bleeding (polymenorrhea), 16/149 (10.73%) had infrequent bleeding (oligomenorrhea), 19/149 (12.75%) had prolonged bleeding (menorrhagia). Only 16.5% of the participants used a contraceptive method among which, more than half used injectable progestins. Out of the 163 participants, 109 (66.87%) were either overweight or obese (Marie et al., 2020).

In a study done in Poland, Pirog et al evaluated 57 women with postmenopausal bleeding, the mean age of their participants was 56.6 years. The median BMI of the participants was 25.3kg/m², while the mean age of entry into menopause was 51.1 years. Out of the 57 participants, 10 (17.5%) had diabetes mellitus, 29 (50.9%) had chronic hypertension. Smoking was reported by 4 (7.0%) of their participants, while 8 out of the 57 (14.0%) participants were on hormonal replacement therapy (Piróg et al., 2019).

2.4 Prevalence of Endometrial Hyperplasia and Cancer in Perimenopausal and Postmenopausal Women with AUB.

Endometrial Cancer (EC) is the most frequent gynecologic malignancy in the developed world, and the 6th most commonly occurring cancer in women globally, with an estimated 320, 000 new cases being diagnosed annually. Developed Countries record a higher incidence of EC (5.9%) compared to developing countries (4.0%), which is attributed to a higher prevalence of obesity and extended life expectancy in developed countries, both which are major risk factors for EC (Frederic & Mirza, 2018; Parslov et al., 2000). The prevalence of EC in Kenya is not exactly known, but it is estimated from hospital-based data that for every 30 cases of cervical cancer in the region, there is one case of EC (Ndirangu & Muchiri, 2013).

Based on histologic and metabolic properties, EC is divided into two main types. Type 1 EC (endometrioid type) makes up 80-90% of all EC cases, typically forms in the context of hyperestrogenism, and is thus almost always preceded by endometrial hyperplasia (EH)/endometrial intraepithelial neoplasia (EIN). Type 1 EC usually has a favorable prognosis, and commonly occurs in perimenopausal or women in early menopause. Type 2 EC (non-endometrioid type) which makes up 10-20% of all EC, usually occurs in the presence of an atrophic endometrium and generally has a poor prognosis. It usually occurs in advanced ages (late menopause), and includes histological sub-types such as serous, clear cell, mucinous, squamous, transitional cell, carcinosarcoma, mesonephric, and undifferentiated carcinoma (Frederic & Mirza, 2018).

Endometrial hyperplasia (EH) is the irregular proliferation of the endometrial glands with an increase in gland to stroma ratio when compared with proliferative endometrium. It is the main precursor lesion for EC, specifically type 1 EC, the two pathologies thus sharing similar risk factors. The incidence of EH is reported to be three times higher than EC. The

World Health Organization (WHO) previously classified EH into simple or complex hyperplasia without atypia and simple or complex hyperplasia with atypia. Diagnosis of these lesions was made based on the degree of glandular proliferation, gland to stroma ratio and presence or absence of nuclear atypia. Each of these lesions has a different risk of progression to and co-existence with EC. Simple and complex hyperplasia without atypia have 1% and 3% risk of progression to EC respectively, while simple and complex hyperplasia with atypia have 8% and 29% risk of progression to EC. The different types of hyperplasias were also noted to have different rates of regression, with or without treatment. About 60% of simple hyperplasia without atypia was noted to spontaneously regress, while 84% regressed on progestin therapy. On the other hand, 56% of complex hyperplasia without atypia was noted to regress on follow-up. EH with atypia is reported to have a 36% progression rate, and only 55% of cases will show regression even with progestin therapy. The risk of concurrent EC in EH with atypia is as high as 43% (RCOG Green-top Guideline No.67, 2016). A meta-analysis by Doherty et al showed that the pooled prevalence of concurrent EC in EH with atypia was 32.6%, and that the annual risk of progression of the premalignant pathology to EC was 8.2%, while that of EH without atypia was 2.6% (Doherty et al., 2020). In 2014, the WHO classification was reviewed and updated, and now only classifies EH into two main types- hyperplasia without atypia (non-atypical) and hyperplasia with atypia (atypical) (Emons & Beckmann, 2015).

The essence of histopathological evaluation of the endometria in perimenopausal and postmenopausal women with AUB is to rule out EH and EC due to the increased risk of detection of these pathologies in these groups of women, particularly the postmenopausal. The mean ages for patients with Type 1 and Type 2 EC is 63 and 67 years respectively, with most patients being diagnosed with EC between 50-59 years. Of all the cases of EC,

20-25% will be diagnosed in the premenopausal years, with only 2-5% being detected in patients <40 years (Pellerin & Finan, 2005). Another report indicates that only 7% of all cases of EC occur <50 years (Narice et al., 2018), with 1-14% of postmenopausal women presenting with vaginal bleeding being eventually diagnosed with EC (Cansino & Catherine, 2009; Smith-bindman et al., 2008; R. B. Goldstein et al., 2002).

In a systemic literature review by Pennant et al that aimed at establishing the risk of EC in premenopausal women with AUB, the risk of EC in these women was established to be 0.33%. Heavy menstrual bleeding (HMB) in the study was associated with a lower risk of EC (0.11%) compared to intermenstrual bleeding (IMB), which had a risk of 0.52%. The risk of EC was also noted to be higher with increasing age in premenopausal women (Pennant et al., 2016).

In a meta-analysis and literature review by Clarke et al that aimed at establishing the risk of EC in women with postmenopausal bleeding, the pooled prevalence of PMB as a symptom in postmenopausal women diagnosed with EC irrespective of tumor stage was reported to be 91%. The pooled prevalence of EC in women with PMB on the other hand, was reported to be 9%. The estimates for this prevalence varied by region, with a prevalence as high as 13% being reported in studies from Western Europe, to as low as 5% in studies from North America (Clarke et al., 2018).

Karmarkar et al reported a prevalence of 10.4% of gynecological malignancies in women with PMB, 6.4% of which were cervical cancer and 3.6% EC. EH with atypia was reported in 7.2% of the women in their study (Karmarkar et al., 2014). Qureshi et al on the other hand reported a prevalence of 3.3% and 10% of EH and EC respectively in postmenopausal women with AUB. The prevalence of EH and EC in perimenopausal women with AUB in their study was 25% and 2.86% respectively (Qureshi et al., 2015).

In Devi et al's study of 500 perimenopausal and postmenopausal women with AUB, the prevalence of EH and EC in the perimenopausal group was 20.7% and 0.2% respectively. EH and EC were seen in 8% and 2.6% respectively in the postmenopausal group (Devi & Aziz, 2014). Abid et al on the other hand reported that the prevalence of EH and EC in the perimenopausal women in their study was 6.5% and 1.2% respectively, while that in postmenopausal women was 13.2%, and 9% respectively (Abid et al., 2014).

2.5 Endometrial Histopathological and Bleeding Patterns in Women with AUB

2.5.1 Perimenopausal Women

Pirog et al grouped endometrial histopathological patterns in their study into 3 main categories:

1. Cyclical patterns and benign endometrial pathologies
2. Premalignant pathologies (endometrial hyperplasia)
3. Malignancy (endometrial cancer) (Piróg et al., 2019).

Most studies on endometrial histopathological patterns in perimenopausal women with AUB have identified normal cyclical patterns (proliferative and secretory patterns) and benign pathologies such as benign endometrial polyps, chronic endometritis, disordered proliferative endometrium (DPE), submucosal fibroids, atrophic endometrium, decidual reaction, products of conception (POCs), etc., as the most common histological patterns/findings.

The proliferative pattern is the endometrial pattern during the proliferative/follicular phase of the menstrual cycle which occurs before ovulation, with the endometrium in this phase predominantly being under the influence of estrogen. The secretory pattern on the other hand, is the endometrial pattern during the secretory/luteal phase that occurs after ovulation, with progesterone from the corpus luteum following ovulation being the main

hormone of influence. A woman with AUB and a proliferative pattern as the histological finding on biopsy may be having anovulatory cycles, while a biopsy showing a secretory pattern may indicate the presence of ovulation thus pointing towards an ovulatory dysfunction (Bhat, 2020). A mixed proliferative-secretory pattern is indicative of hormonal imbalance and can also be seen in women with delayed ovulation, anovulation with superimposed progestins, exogenous hormones with hormonal replacement therapy (HRT) or oral contraceptive pills (OCPs), and sometimes malignant conditions (Deligdisch, 2000). Other patterns that could be histologically detected that may indicate hormonal imbalance include disorderly proliferative endometrium (DPE), non-secretory endometrium with stromal and glandular breakdown, luteal phase defect (LPD) and pill effect (Abid et al., 2014).

Abid et al conducted a cross-sectional study of 241 women with AUB, 77 (32%) of which were perimenopausal, 45 (18.67%) postmenopausal, and the rest were women aged <40 years. The most common bleeding patterns in the perimenopausal group were polymenorrhea (30%), followed by metrorrhagia (26%), menorrhagia (22%) and menometrorrhagia (3%). Endometrial histopathological patterns in this group were as follows: 21/77 (27.3%) had normal cyclical patterns (secretory and proliferative), while 56/77 (72.7%) had pathological patterns (both benign, premalignant and malignant). The pathological patterns were as follows: 35/77 (45.5%) had patterns suggestive of hormonal imbalance, 8/77 (10.4%) had benign endometrial polyp, 7/77 (9.1%) had chronic endometritis, 5/77 (6.5%) had endometrial hyperplasia and 1/77 (1.2%) had endometrial carcinoma (Abid et al., 2014).

Azim et al, on the other hand, conducted a retrospective study of 128 patients with AUB who had undergone endometrial curetting. Sixty-six (51.5%) of the study participants

were <40 years, 53 (41.4%) were perimenopausal and 9 (7.1%) were postmenopausal. The most common bleeding pattern in the perimenopausal group was polymenorrhagia (50.9%), followed by menorrhagia (20.7%) and metrorrhagia (9.4%). Normal cyclical patterns were the most seen patterns in the perimenopausal group, with secretory pattern being reported in 18/53 (34.6%), while proliferative pattern in 12/53 (23%). Benign pathological findings in the perimenopausal group were as follows: 4/53 (7.6%) had disordered proliferative endometrium, 4/53 (7.6%) had benign endometrial polyp, 4/53 (7.6%) had chronic endometritis, 2/53 (3.8%) had products of conception, 2/53 (3.8%) had atrophic endometrium, 1/53 (2.1%) had complete hydatiform mole and 1/53 (2.1%) had partial hydatiform mole. Premalignant and malignant patterns in the group were as follows: 3/53 (5.7%) had EC and 1/53 (2.1%) had EH without atypia (Azim et al., 2011).

A cross-sectional study of 100 women with AUB by Qureshi et al involved 70 (70%) perimenopausal and 30 (30%) postmenopausal aged between 40-70 years. All participants in the study had TVS done prior to diagnostic dilatation and curettage (D&C). Histological results were grouped into two- normal endometrial patterns (secretory, proliferative and atrophic patterns) and abnormal endometrial patterns (endometrial polyp, hyperplasia and cancer). The histological patterns in the perimenopausal group were as follows: 18/70 (25.71%) had EH, 17/70 (24.29%) had secretory endometrium, 16/70 (22.86%) had atrophic endometrium, 13/70 (18.57%) had proliferative endometrium, 4/70 (5.71%) had benign endometrial polyp and 2/70 (2.86%) had EC (Qureshi et al., 2015).

Devi et al evaluated curettings and hysterectomy specimens of 500 women with AUB aged between 40-60 years, 425 (85%) of which were perimenopausal and 75 (15%) postmenopausal. Patients with uterine leiomyomas (AUB-L) were notably excluded from

their study. Menorrhagia was identified as the most common bleeding pattern (68.8%) in the study, followed by metrorrhagia (20.39%), polymenorrhea (6.65%) and oligomenorrhea (1.93%). Out of all participants, 352 (70.4%) were diagnosed with AUB from non-organic causes, 114 (22.8%) from organic causes and 34 (6.8%) had inadequate biopsy samples. Proliferative pattern was identified in 127/425 (29.9%) of the perimenopausal women, atrophic endometrium in 124/425 (29.1%) and EH in 88/425 (20.7%). The rest of the patterns in the group were as follows: 23/425 (5.4%) had secretory endometrium, 17/425 (4.0%) had disordered proliferative endometrium, 9/425 (2.1%) had benign endometrial polyp, 9/425 (2.1%) had endometritis, 2/425 (0.5%) had features of hormonal imbalance and only 1/425 (0.2%) had EC. Inadequate samples were reported in 29/425 (6.8%) of the perimenopausal participants (Devi & Aziz, 2014).

In a retrospective study by Nemer et al that involved 43 women with AUB who had undergone endometrial sampling prior to hysterectomy, only 1/43 (2.34%) patient was <40 years, 23/43 (53.48%) were perimenopausal and 19/43 (44.18%) were postmenopausal. The bleeding pattern in the perimenopausal group was mostly menorrhagia (52.17%), while the pattern off bleeding was not documented in the rest. Histological results were grouped into two- the normal or benign group (N/B Group) and endometrial cancer and hyperplasia group (Ca/H Group). In the perimenopausal group, 14/23 (60.9%) had normal cyclical patterns, 5/23 (21.7%) had benign endometrial polyp, 2/23 (8.7%) had EH without atypia, 1/23 (4.3%) had EH with atypia and 1/23 (4.3%) had chronic endometritis. From the normal cyclical patterns detected in the group: 6/23 (26%) were secretory pattern, 6/23 (26%) were shedding/menstrual phase pattern and 2/23 (8.9%) were proliferative pattern. There were no cases of atrophic endometrium or EC detected in the group, with all cases of EC in the study being detected in the postmenopausal group (Nemer et al., 2019).

In a retrospective study by Belcaro et al, 625 women of the reproductive ages with AUB who had undergone office hysteroscopy with targeted endometrial biopsy were evaluated. From these women, 514 (82.3%) were ≥40 years of age. Notably, women with high risk factors for EC (obesity, diabetes, family history of endometrial, ovarian or colon cancer and PCOS) were excluded from the study. Focal structural lesions were detected by ultrasound in 365 (58.4%) participants, while 260 (41.6%) had no structural lesions detected. From histological results, 618 (98.9%) were normal or benign histological patterns, while 7 (1.1%) were premalignant and malignant patterns. Notably, EH without atypia was included in the benign pathologies group and not premalignant group in this study. The histological patterns in the normal/benign pathologies group were as follows: 175/625 (28%) were benign endometrial polyp, 162/625 (26%) were EH without atypia, 100/625 (16%) were uterine myoma, 94/625 (15%) were dysfunctional endometrium, 18/625 (2.8%) were atrophic endometrium and 1/625 (0.16%) was fibrotic tissue. In the premalignant and malignant group, 4/625 (0.64%) were EH with atypia and 3/625 (0.48%) were EC of adenocarcinoma type (Belcaro et al., 2020).

In a prospective study of 143 women with AUB aged ≥40 years, endometrial sampling with a Pipelle followed by diagnostic D&C were performed. Out of the 143 women, 140 had successful biopsies. From these women 45.7% had menorrhagia, 31.9% had polymenorrhagia and 22.4% had metrorrhagia. The histopathological patterns in the normal and benign group were as follows: 37/140 (26.4%) were proliferative endometrium, 33/140 (23.5%) were secretory endometrium, 8/140 (5%) were endometritis and 3/140 (0.7%) were benign endometrium polyp. Normal cyclical patterns and benign pathologies thus constituted 81/140 (57.8%) of the findings. Premalignant and malignant pathologies constituted 59/140 (42.2%) of the findings, and were as follows: 45/140 (32.1%) were EH without atypia, 5/140 (3.6%) were adenocarcinoma, 5/140

(3.6%) were EH with atypia, 2/140 (1.4%) were adenosquamous carcinoma, 1/140 (0.7%) was adenosarcoma and 1/140 (0.7%) was mixed mullerian tumor (Abdelazim et al., 2013).

In a retrospective study of 486 women managed for AUB at a tertiary hospital in Nigeria, 72 (14.8%) of the participants were perimenopausal. Benign endometrial polyp was the most common histological finding in the perimenopausal group, reported in 21/72 (29.1%) of the participants. The rest of the normal/cyclical and benign histological patterns in the group were as follows: 18/72 (25%) were products of conception, 6/72 (8.3%) were proliferative pattern, 2/72 (2.75%) were leiomyoma, 2/72 (2.75%) were secretory pattern, 2/72 (2.75%) were stromo-glandular dissociation, 1/72 (1.4%) was complete mole and 1/72 (1.4%) was acute endometritis. From the premalignant patterns, 13/72 (18%) were EH without atypia and 4/72 (5.5%) were EH with atypia. There were no cases of EC in the group, while 1.4% of the biopsy samples were deemed inconclusive (Asuzu & Olaofe, 2018).

2.5.2 Postmenopausal Women.

Studies on postmenopausal women with AUB in different populations have reported varying endometrial histopathological patterns in these women, most establishing that benign endometrial pathologies and low-risk premalignant pathologies as the most common findings:

In Abid et al's study of 241 women with AUB, 45 (18.7%) of the participants were postmenopausal. The reported histological patterns in these women were as follows: 16/45 (35.5%) had benign endometrial polyp, 15/45 (33.3%) had atrophic endometrium, 6/45 (13.2%) had EH, 4/45 (9%) had features of hormonal imbalance and 4/45 (9%) had EC. EH was observed in 12 (5%) of all 241 participants, 7 (2.9%) of which had

hyperplasia without atypia and 5 (2.1%) had hyperplasia with atypia. EH was seen most frequently in postmenopausal women (46%) followed by perimenopausal (38.5%) and finally women aged <40 years (15.5%) respectively (Abid et al., 2014).

Qureshi et al on the other hand reported the following endometrial histological findings in the 30 postmenopausal women with AUB they evaluated in their study: 12/30 (40%) had atrophic endometrium, 9/30 (30%) had proliferative pattern, 4/30 (13.3%) had secretory pattern, 3/30 (10%) had EC, 1/30 (3.3%) had benign endometrial polyp and 1/30 (3.3%) had EH (Qureshi et al., 2015).

In 75 postmenopausal women with AUB evaluated by Devi et al, the histopathological findings were as follows: 57/75 (76%) had atrophic endometrium, 3/75 (4%) had EH without atypia, 3/75 (4%) had EH with atypia, 2/75 (2.6%) had EC, 2/75 (2.6%) had benign endometrial polyp, 1/75 (1.6%) had disordered proliferative endometrium, 1/75 (1.3%) had chronic endometritis and 1/75 (1.3%) had features of hormonal imbalance. Out of the 75 women, 5 (6.9%) had inadequate biopsy samples (Devi & Aziz, 2014).

A retrospective study by Nemer et al that included 19 postmenopausal women with AUB reported the following histological patterns in these women: 6/19 (31.6%) had benign endometrial polyp, 3/19 (15.8%) had atrophic endometrium, 3/19 (15.8%) had EC, 2/19 (10.5%) had EH without atypia, 2/19 (10.5%) had proliferative pattern, 1/19 (5,2%) had EH with atypia, 1/19 (5.2%) had chronic endometritis and 1/19 (5.2%) had shedding pattern (Nemer et al., 2019).

In a cross-sectional study by Deeba et al, 110 postmenopausal women with AUB were evaluated. The duration of the AUB in these women ranged between 1-10 years (mean of 5.2 years). EH without atypia was the most seen pattern in the study, reported in 60/110 (54.5%) of the women. The rest of the patterns observed were as follows: 27/110 (24.5%)

had atrophic endometrium, 14/110 (12.7%) had EC, 5/110 (4.5%) had EH with atypia and 4/110 (3.6%) had benign endometrial polyp. When data was stratified for age, duration of AUB symptom and parity, the frequency of EH and EC in participants was discovered to be higher with increasing age, duration of AUB and parity (Deeba & Khan, 2016).

In Pirog et al's study that evaluated the risk of EC in 57 postmenopausal women with AUB who had a normal endometrial thickness, 43/57 (75.4%) of the women had benign histological findings. From this benign group, 32/57 (56.1%) were either proliferative pattern, atrophic endometrium or benign endometrial polyp, while 11/57 (19.3%) were EH without atypia, which was considered a benign finding in the study. Ten out of 57 (21.1%) of the women had EH with atypia, and 2/57 (3.5%) had EC. Baseline characteristics between the group with normal and benign findings and that with EH/EC were compared, including endometrial thickness, age, BMI, age of menopause, percentage of patients with diabetes, hypertension, hypercholesterolemia, and those who were on hormonal replacement therapy (HRT) or smoking. From the comparisons, only endometrial thickening was associated with diagnosis of EH/EC (Piróg et al., 2019).

In an older study that is considered one of the landmark studies for women with PMB, Miyazawa evaluated 138 postmenopausal women. Information on age, parity, age at menopause, interval between final menstrual period (FMP) and onset of PMB, type and duration of PMB, use of estrogen, body weight, comorbidities and pelvic examination findings (palpated uterine size and uterine depth on sounding) was obtained. Histopathological patterns of the endometrial biopsies obtained through D&C were divided into 4 groups: 1) Atrophic or inactive endometrium 2) Proliferative endometrium 3) Hyperplastic endometrium 4) Endometrial carcinoma. The mean interval between the final menstrual period (FMP) and onset of PMB was 7 years, with the amount of bleeding

in the women being described as either spotting, moderate flow or heavy flow. Moderate or heavy flow was reported in 70% of patients with EH and EC, while spotting was reported in 70% of patients with atrophic and proliferative endometrium. The histopathological findings in the study were as follows: 82/138 (59%) had atrophic endometrium, 27/138 (20%) had proliferative pattern, 18/138 (13%) had EH and 11/138 (8%) had EC. The study concluded that bleeding from EH and EC was heavier in amount and had a longer duration than in patients with atrophic or proliferative endometrium, that associated medical problems (hypertension and diabetes mellitus) are commonly observed in patients with EC, and that in the presence of EC among patients with PMB, a greater uterine depth seems to correlate with higher tumor grade and disease stage as well as myometrial invasion (Miyazawa, 1983).

It is not unusual for patterns of the different phases of the menstrual cycle that normally exist in reproductive years (proliferative and secretory patterns) to be found during the postmenopausal period. The proliferative endometrium in the postmenopausal years is due to ongoing estrogenic stimulation but without hyperplastic changes or malignancy, and can also be seen in women with pelvic organ (uterine) prolapse or benign endometrial polyps (V Phillips, 2006). Besides the normal cyclical patterns, some of the commonly reported benign organic pathologies in women with PMB include atrophic endometrium and benign endometrial polyps. The histological appearance of the postmenopausal endometrium depends on the hormonal pattern of the final menstrual cycle before entering menopause. When the final cycle ends in deficient proliferation or secretion, simple atrophy will appear as sparse, narrow glands lined by atrophic epithelium within a dense, fibrous stroma. Cystic atrophy occurs when irregular proliferation or cystic glandular hyperplasia occurs prior to the decline in estrogen levels during the menopausal transition years and during menopause. A thickened endometrium (≥4-5mm) during the

menopausal period may be due to a proliferative endometrium, cystic atrophic endometrium, endometrial hyperplasia or malignancy (Otify et al., 2015).

2.6 Clinical Characteristics and Ultrasound Features Associated with Diagnosis of Endometrial Hyperplasia and Cancer in Perimenopausal and Postmenopausal Women with AUB

Studies done in perimenopausal and postmenopausal women have identified various clinical characteristics that are risk factors and are associated with the diagnosis of endometrial hyperplasia and cancer. Some clinical and behavioral characteristics have also been established to reduce the risk of being diagnosed with these two pathologies:

Albers et al identified anovulatory cycles, obesity, nulliparity, age greater than 35 years, tamoxifen use and diabetes mellitus (DM) as risk factors for EC (Albers, 2004). Anovulatory cycles lead to a continuous exposure of the endometrium to estrogen that is unopposed by progesterone, thus creating an unstable thick endometrium that could eventually develop EH, which can progress to or co-exist with EC. Polycystic Ovary Syndrome (PCOS) has also been identified as a risk factor for EH and EC due to the anovulatory cycles common in the condition (Telner, 2007). Endometrial biopsy is recommended in women with PCOS and other conditions that lead to continuous exposure of the endometrium to unopposed estrogen, regardless of age of the woman, particularly when symptomatic and/or with sonographic evidence of a thickened endometrium (Munro et al., 2011).

Obesity is also a proven clinical risk factor for both EH and EC. Renehan et al reported that 57% of EC in the United States is attributable to being overweight or obese (Renehan, 2011). Visceral fat is an endocrine organ that secretes an array of adipokines that exert both local and systemic effects that induce endometrial proliferation and promote tumor formation (Onstad et al., 2016). There is also increased peripheral

conversion of androgens (androstenedione) into estrone by the enzyme aromatase in the excess adipose tissue in overweight and obese women, resulting in continuous exposure of the endometrium to estrogen unopposed by progesterone due to absence of or erratic ovulation (anovulation or oligo-ovulation). Although EC rarely occurs in the premenopausal period, increasing obesity and a rising prevalence of metabolic syndrome in this period have registered a marked increase in the prevalence of the condition, with a 48% increase in age-standardized rates of EC being reported (Whitaker & Critchley, 2016).

Diabetes mellitus (DM), particularly Type 2 diabetes, and chronic hypertension that are commonly associated with obesity, have also been identified as a risk factors for EC (Vălu & Toma, 2017). Type 2 diabetes is characterized by elevated levels of insulin and insulin-like growth factors (IGF-1) which have been linked with the development of EC. An increase of insulin and IGF-1 receptors is observed in EH, which further supports this correlation. Insulin resistance, chronic inflammation, and high free ovarian steroid hormone levels are other possible mechanisms (Onstad et al., 2016). Hypertensive disorder is prevalent in older obese patients but does not appear to be a significant factor by itself, even though 25% of patients with EC have hypertension or arteriosclerotic heart disease. Some theories have suggested that DM and hypertension are frequent sequelae of obesity and an excess estrogen environment and are considered epiphenomena rather than causal for EC. However, a recent systemic review and meta-analysis of published case-control and cohort studies concluded that an association between hypertension and EC was weaker but still significant among studies with adjustment for smoking, BMI, oral contraceptive use, and parity, compared to studies without such adjustment, thus suggesting an increased risk of EC among patients with hypertension (Aune et al., 2017).

Tamoxifen is a selective estrogen receptor modulator used in the treatment and prevention of breast cancer. In the breast, it acts as an estrogen antagonist, whereas in the endometrium it acts as a weak estrogen agonist. Studies have established a link between the use of this medication with development of EH and EC. Vălu et al associated use of tamoxifen with a 6 to 8-fold increase in the incidence of EC (Vălu & Toma, 2017). A large population-based study constituting of 74,280 breast cancer patients in Taiwan showed that tamoxifen use for >3 years or by patients >35 years was associated with a significantly increased risk for developing EC (Chen et al., 2014).

Factors protective against EC include use of combined hormonal or progesterone-only contraceptives and cigarette smoking. A systemic review on the effects of hormonal contraceptives on EC demonstrated a decrease in the risk of EC of about 50% for ever use of combined oral contraceptives (COCs) and noted that this protective effect persisted for over 10-20 years after discontinuation of the COC. The review also reported that non-hormonal uterine devices strongly have protective effects against EC; however, data on oral or injectable progestogen-only preparations (POPs) including the levonorgestrel-releasing intrauterine system, although limited, still suggest similar protective action (Mueck et al., 2010). A review of literature and meta-analysis of studies on the effects of cigarette smoking on EC showed that an increase in smoking of 20 cigarettes per day was significantly associated with 16% and 27% reduced risks of EC in prospective and case-control studies respectively (Zhou et al., 2008). The mechanism suggested for this effect is that smoking stimulates hepatic metabolism of estrogens, leading to a reduced incidence of endometrial abnormalities. Other theories suggest that lower circulating estrogen levels from weight reduction and earlier age at menopause may also be at play.

In a prospective multi-center study that evaluated reproductive risk factors for EC in 302,618 women, reduction in EC risk was observed in women with late menarche, early menopause, history of oral contraceptive use, high parity and a shorter time since last full-term pregnancy (Dossus et al., 2010). A case-control study done in Denmark also highlighted the protective effect of parity by establishing that the risk of EC reduced by 40% the risk in nulliparous women after completion of one term pregnancy (Parslov et al., 2000).

When it comes to ultrasound features associated with diagnosis of endometrial hyperplasia and/or cancer:

A correlation between the mean uterine cavity depth and histological diagnosis was established in one of the earlier landmark studies on women with postmenopausal bleeding. In this study, it was reported that a diagnosis of endometrial hyperplasia and cancer was more likely to be made with greater uterine cavity depths, and that uterine cavity depth was also associated with higher grades of malignancy and deeper myometrial invasion in those eventually diagnosed with malignancy (Miyazawa, 1983).

Endometrial thickness in perimenopausal women has a limited utility for distinguishing normal from abnormal endometrium, due to the various changes it undergoes through the different phases of the menstrual cycles. The endometrial thickness cut-off value beyond which further evaluation is necessary, is still not well established. Thickness over 8 mm confers a high sensitivity – 83.6%, but less specificity – 56.4% to TVUS, while a thickness over 16 mm confers 67% sensitivity and 75% specificity respectively. In a cross-sectional study that evaluated 103 patients with AUB in Romania, 73 patients had abnormal histopathological findings (endometrial hyperplasia and cancer) and had an average endometrial thickness of 13.03mm detected through ultrasonography. Besides measurement of endometrial thickness, assessment of endometrial texture is also

important, as changes in endometrial texture may indicate endometrial pathology. Focal or diffuse heterogeneous endometrial changes noted on ultrasonography require further investigation (Nicula et al., 2017).

In an Iranian study that investigated the accuracy of TVS in screening for endometrial hyperplasia (EH) in pre- and postmenopausal women with AUB, the sensitivity, specificity, PPV, and NPV of TVS detected endometrial thickness in diagnosing EH in pre-menopausal women was 90.7%, 84%, 90.7%, and 84% respectively, while the sensitivity, specificity, PPV, and NPV in postmenopausal women was 100% for each. The accuracy of TVS in diagnosing EH in premenopausal and postmenopausal women was 88.25% and 100%, respectively (Shokouhi, 2015).

In a cross-sectional study that evaluated 382 women aged 40 years and above who had AUB in India, a correlation between endometrial thickness and histological diagnosis was established. Majority (46.86%) of the participants in this study had an endometrial thickness of 5-10mm, 39.01% had an endometrial thickness of 11-15mm while 8.38% had an endometrial thickness measuring 16-20mm. Thickness measuring <5mm and >20mm was reported in 3.66% and 2.09% of the participants respectively. Greater endometrial thickness was associated with the diagnosis of more severe pathologies, with 32 participants who had an endometrial thickness measuring 16-20mm being discovered to have the following pathologies: 11 had hyperplasia without atypia, 8 had endometrial carcinoma, 6 had disordered proliferative endometrium, 4 had endometrial polyp, 2 had atypical hyperplasia and 1 had menstrual endometrium. Out of the 8 participants who had an endometrial thickness of >20mm, 7 (87.5%) were diagnosed with endometrial cancer and 1 (12.5%) was diagnosed with endometrial hyperplasia without atypia (Sujana G et al., 2020).

CHAPTER THREE: METHODOLOGY

3.1 Study Design

This was a cross-sectional study of perimenopausal and postmenopausal women with AUB at MTRH.

3.2 Study Setting

The study was carried out at the Gynecology Unit of Moi Teaching and Referral Hospital (MTRH). MTRH is the second largest National Referral Hospital in Kenya after Kenyatta National Hospital (KNH). It is located along Nandi Road in Eldoret Town, 310 kilometers Northwest of Nairobi, in Uasin Gishu County which is in the North Rift region of Western Kenya. The hospital offers both in-patient and out-patient services and serves both cash paying and corporate clients. Being the main referral hospital in Western Kenya, it has a catchment population of around 20 million people which comprises about 40% of the Kenyan population.

The Gynecology Unit comprises of the Gynecology Out-Patient Clinic (GOPC), Gynecology Ward (Faraja Ward) and the Gynecologic Oncology Division. From the clinic registers of the past 3 years prior to this study, an average of 108 patients with AUB who were ≥40 years were seen at the Gynecology Unit per year (about 2 new patients each week).

3.3 Target Population

The target population was women aged ≥ 40 years who were presenting with the complaint of vaginal bleeding not characteristic of normal menses or vaginal bleeding in the postmenopausal period at the Gynecology Unit at MTRH.

3.4 Study Population

The study population was women aged ≥ 40 years who were diagnosed with AUB at the Gynecologic Unit at MTRH.

3.5 Eligibility Criteria.

3.5.1 Inclusion Criteria.

• Women aged ≥ 40 years, who were diagnosed with AUB.

3.5.2 Exclusion Criteria.

• Women with a positive pregnancy test.

• Women with a gross vulvar, vaginal and/or cervical lesion.

• Women with a bleeding disorder.

• Inability to access the uterine cavity for sampling, due to an obstructing intrauterine pathology or inability of the patient to be positioned for procedure.

3.6 Participant Recruitment

This was a census of all women aged ≥40 years diagnosed with AUB between the months of June 2019 and May 2020, who met the eligibility criteria and consented for enrollment. A total of 100 women were consecutively enrolled in the study within the 12 months period.

3.7 Study Procedure

A pre-test of the data collection tool (questionnaire) was done in the first week of the study. Using Connelly's 10% sample size rule for a pilot study (expected number of patients from previous records being 108 per year), the questionnaire was administered to 11 women aged ≥ 40 years from the gynecology ward and outpatient clinic. The aim of the pre-test was to assess for whether or not the questions being asked in the questionnaire were understood by the interviewees, and if the data obtained were relevant to the study objectives.

After confirming the applicability of the data collection tool, all women ≥ 40 years presenting with the complaint of vaginal bleeding not characteristic of normal menses or postmenopausal bleeding at the Gynecology Unit were thereafter approached and assessed for eligibility. A detailed history and thorough physical examination were conducted. The physical examination included measuring of weight, height, and calculation of body mass index (BMI) for each participant. The women were then provided with general information about the study, including the description of a speculum examination and an endometrial biopsy procedure. Based on the menstrual status and reported history, the patients were grouped into the perimenopausal and postmenopausal groups.

Following the general physical examination, a pelvic exam was done. The pelvic examination included external examination of the perineum/vulva, followed by a speculum examination to inspect the vagina and cervix for possible gross lesions. Cervical cancer screening using visual inspection with acetic acid (VIA) was offered to all patients <65 years who were due for screening. The pelvic examination was concluded with a digital and bimanual exam. Women who were discovered to have gross vulvar, vaginal or cervical lesions were excluded from the study and managed accordingly.

For perimenopausal women who presented without having a pregnancy test done, a urine βHCG test was ordered. For all women, a Complete Blood Count (CBC) was also ordered. Ancillary laboratory investigations routinely done in the work-up of a patient with AUB were ordered selectively depending on the signs and symptoms the woman was presenting with. These tests included: thyroid function tests (TFTs), serum prolactin level, and coagulation profile where necessary. A pelvic ultrasound was also ordered as part of the routine investigations for patients with AUB. Written consents were taken from those eligible for enrollment in the study and an endometrial biopsy taken.

Thereafter, an interviewer administered structured questionnaire (Appendix 3) was filled (Figure 3.1).

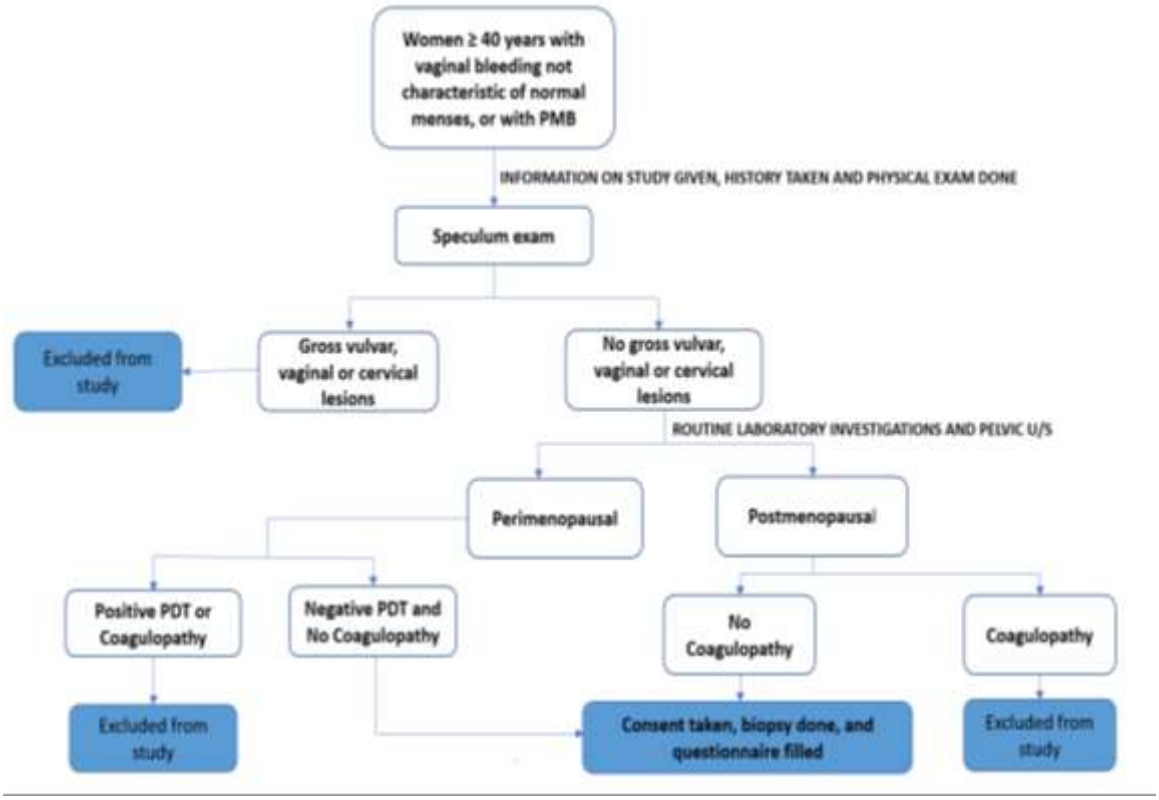

Figure 3.1: Study Procedure

Those patients who had ongoing symptoms at the time of presentation/investigations but remained stable, were managed as outpatients while waiting for the histology results. Biopsy samples were sent to the pathology laboratory at MTRH within 24 hours, and the two consultant pathologists doing the evaluation of the biopsies given details of the samples for tracking. Upon receiving of the biopsy results, which occurred approximately between 10-14 days after the biopsy procedure, patients were called back, and the results explained to them. They were then referred to either the Gynecology Outpatient Clinic (GOPC) or Gynecologic Oncology Clinic for further management. Those patients who were already at the gynecology ward continued to be managed accordingly depending on the biopsy results.

3.8 Sample Collection Procedure

Items for the endometrial biopsy procedure were assembled in the procedure room. They included: Pipelle sampler, bivalve speculum, sponge holding forceps, tenaculum, sterile gauzes, KY gel, a pair of sterile gloves, sample jar (labeled with patient details) with adequate 10% formalin in it.

The patient was placed in lithotomy position on the examination couch, in the presence of a chaperone. She was again given information on the procedure before commencing.

The patient's vulva was cleaned using a normal saline soaked gauze.

The labia minora were then parted and a lubricated speculum gently inserted into the vagina and adjusted for adequate cervical visibility.

Cervical cancer screening using Visual Inspection with Acetic Acid (VIA) was done where necessary.

The Pipelle device was then inserted through the cervical os into the uterine cavity until it reached the uterine fundus, followed by withdrawal of the stylette to create vacuum.

The Pipelle was then gently moved back and forth and in a rotational movement within the endometrial cavity to sample it as much as possible, then withdrawn and the obtained sample placed in a sample jar with 10% formalin.

The procedure was repeated a maximum of three times in patients' whose first samples appeared inadequate (scanty, purely bloody or mucoid).

The speculum blades were then collapsed and the instrument gently withdrawn from the vagina. The average time for the entire procedure was 5-10 minutes.

The patient was then given a sanitary towel to use in case of bleeding, and analgesia prescribed if in considerable amount of pain (oral paracetamol or tramadol).

The sample jar label contained the patient's details (name, year of birth and patient number), date of sample collection, nature of sample and the requested investigation. A request form with the patient's identification details and a brief clinical background was attached to each sample.

The patient was contacted when the histology results came out. The results were explained to the patient and a management plan made. Follow-up of the patients continued at the GOPC and Gynecologic Oncology Clinic depending on the histological diagnosis.

3.9 Sample Processing

Tissue grossing, staining and reporting was done as follows:

Specimens fixed in 10% formalin immediately after removal were submitted to the pathology laboratory in a labeled container within 24 hours, accompanied by a request form.

After accessioning of the sample at the lab, gross description of sample tissue size/volume and appearance of specimen was done.

The specimen was then processed in an Automatic tissue processor STP 120, embedded using the embedding station.

Thereafter, 3 microns thin sections were cut using a rotary microtome.

The sections were then stained with Hematoxylin and Eosin (H&E) following the lab standard operating procedures (SOPs).

Stained slides were thereafter cleared with xylene, then mounted using DPX mountant and cover-slipped, ready for evaluation under a microscope.

Initial interpretation of each of the processed tissues was done separately by each of the two consultant pathologists, and concordant histopathological findings were accepted as the final result. Where there was discordance in the individual results of the two pathologists, the two would reevaluate the processed tissues together and come to a final conclusion.

The histopathological findings were reported as: Proliferative pattern, secretory pattern, menstrual phase, mixed proliferative-secretory pattern, atrophic endometrium, acute or chronic endometritis, disordered proliferative endometrium, decidual reaction, benign endometrial polyp, leiomyoma, hyperplasia without atypia, hyperplasia with atypia, endometrial cancer (histological sub-type and grade reported) and insufficient sample. Patients who were reported to have an insufficient sample had a repeat endometrial biopsy done, and the second results, if conclusive, were accepted as the final results.

3.10 Data Collection and Management

3.10.1 Data Collection

Data was collected using an interviewer administered structured questionnaire (Appendix 3). The questionnaire used included parts for socio-demographic data (age, marital status, level of education, employment status & medical insurance), clinical characteristics (BMI, chronic illness: DM or chronic hypertension), cigarette smoking (previous or current), family history of cancer (breast, colon, ovarian or uterine cancer), menstrual characteristics (menstrual status, age at menarche and menopause, history of AUB in earlier reproductive years, current bleeding pattern, duration of AUB), hormonal contraceptive use (previous and current use), obstetric history (parity, age at first

pregnancy), and pelvic ultrasound findings. Acquisition of consent, collection of the biopsies and administration of the questionnaire were all done by I, the principal investigator in the study.

3.10.2 Data Management

Data collected in the questionnaires was checked for completeness and consistency then entered into MS Access in preparation for analysis. The MS Access database was encrypted using a password that was only available to the principal investigator, who was also the data entry person. Data entry was done, and the database hosted in a password encrypted laptop that was also under the care of the principal investigator. Data entered was backed up at the end of each day of entry to an external hard drive.

3.11 Statistical Data Analysis and Presentation

Descriptive statistics such as mean and the corresponding standard deviation (SD) were used to summarize continuous variables such as age if Gaussian assumptions held. Otherwise, median and the corresponding inter quartile range (IQR) were used. Gaussian assumptions were assessed using Shapiro and Wilk test for normality. Data on sociodemographic, clinical and behavioral characteristics, menstrual and obstetric characteristics, contraceptive use, and ultrasound findings were stratified for the 2 groups of women (perimenopausal and postmenopausal) for comparison of these characteristics between the two groups. Significance was accepted at a p value ≤ 0.05. The endometrial histopathological patterns for each group were described separately to answer specific objectives one and two of the study. Data was described using frequencies and proportions. Associations between clinical, menstrual, obstetric characteristics, contraceptive use, ultrasound findings and the diagnosis of endometrial hyperplasia and cancer (EH/EC) were tested using chi-square or fisher's exact test depending on cell

count. Significance was accepted at p value ≤ 0.05. Logistic regression was modeled using factors that were associated with EH/EC diagnosis on bivariate analysis. Data was analyzed using STATA 16. Results were presented using tables, pie-charts and bar graphs.

3.12 Dissemination of Findings and Impact

A copy of this thesis will remain in the school library, available to other researchers. The study will also be published in medical journals and also presented in local and/or international medical conferences. The information obtained will be used to improve provision of reproductive health services to perimenopausal and postmenopausal women with AUB at MTRH and within the region, and can be used as a baseline for other studies of its nature.

3.13 Ethical Considerations

i. Approval to conduct the study was sought and obtained from the Institute of Research and Ethics Committee (IREC) prior to conducting the research.
ii. Permission to carry out this research at the gynecology unit in MTRH was sought and attained from the hospital's Chief Executive Officer.
iii. Informed and written consent was obtained from each participant.
iv. Participation in this study was voluntary and the participants reserved the right to withdraw from participation at any stage.
v. The participants were not coerced or induced to participate in the research.

CHAPTER FOUR: RESULTS

Between June 2019 and May 2020, a total of 107 women aged ≥ 40 years who were presenting with the complaint of either vaginal bleeding not characteristic of normal menses or postmenopausal bleeding were approached and assessed for eligibility to be enrolled in the study. From the 107 women, 3 were discovered to have gross cervical lesions, 2 could not have the biopsy procedure done (one had a uterine mass occluding the cervix, the other was of advanced age with severe morbidity and could not be positioned for the biopsy procedure), and 2 opted out of the study (Figure 4.1).

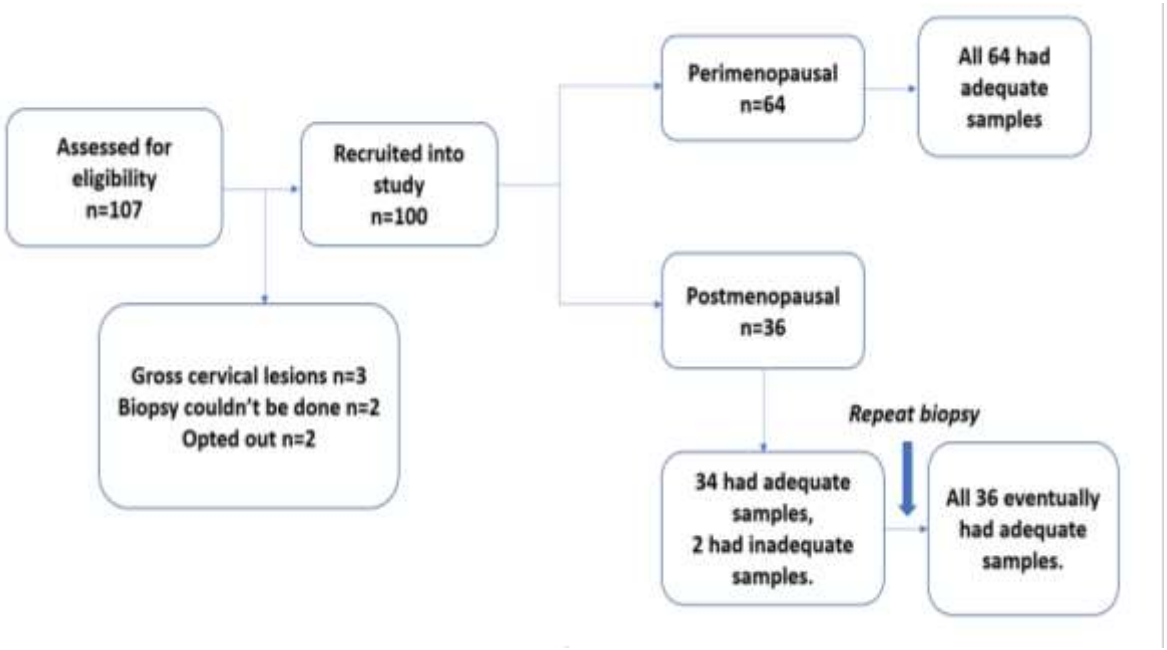

Figure 4.1: Participant Recruitment Process

The histopathological evaluation of each biopsy sample was done separately by two consultant pathologists. The two then compared their findings and where there was discordance in the reported results, they evaluated the samples together and came to a conclusion. The discordance rate of the initial individual results by the two pathologists was 13 out of the 100 samples evaluated (13%). A consensus was reached upon the second evaluation by the two pathologists together for all the 13 samples.

4.1 Sociodemographic, Clinical Characteristics and Ultrasound Features in Perimenopausal and Postmenopausal Participants

4.1.1 Sociodemographic Characteristics

The mean age of the 64 perimenopausal women was 46.05 years (SD: ±3.73). Out of the 64 women, 42(65.63%) were married, 8/64 (12.50%) were widowed and the remaining 14/64 (21.87%) were either divorced, single or separated. From these 64 women, 32 (50%) had primary and 24/64 (37.50%) had secondary education as the highest level of education, while only 8/64 (12.50) had tertiary education.

The mean age of the 36 postmenopausal women was 62.11 years (SD: ±7.96). Out of these, 24/36 (66.67%) were married, 8/36 (22.22%) were widowed and the remaining 4/36 (11.11%) were either single, divorced or separated. Out of these 36 women, 17(47.22%) had primary education as the highest education level, while only 5/36 (13.89%) had tertiary education. Statistically significant differences in age ($p < 0.001$) and education level ($p < 0.002$) were observed between the perimenopausal and postmenopausal groups, while no significant differences were observed in terms of marital status, medical insurance and employment status between the two groups (Table 4.1).

Table 4.1: Sociodemographic Characteristics

Variable	Perimenopausal (N=64)	Postmenopausal (N=36)	P-value
	Mean (SD[1]) or n (% of participants)		
Age (*Years*)	46.05(±3.73)	62.11(±7.96)	<0.001[t*]
Marital Status			
Divorced	5(7.81%)	1(2.78%)	
Married	42(65.63%)	24(66.67%)	0.627[f]
Separated	4(6.25%)	1(2.78%)	
Single	5(7.81%)	2(5.56%)	
Widowed	8(12.50%)	8(22.22%)	
Education Level			
None	0(0.00%)	7(19.44%)	
Primary	32(50.00%)	17(47.22%)	0.002[f*]
Secondary	24(37.50%)	7(19.44%)	
Tertiary	8(12.50%)	5(13.89%)	
Medical Insurance			
Yes	42(65.63%)	30(83.33%)	0.058[c]
No	22(34.38%)	6(16.67%)	
Employment Status			
Casual laborer	8(12.50%)	2(5.56%)	
Formal employment	8(12.50%)	5(13.89%)	0.117[f]
Self-employed	27(42.19%)	9(25.00%)	
Unemployed	21(32.81%)	20(55.56%)	

[1]SD = Standard Deviation
[t] t-test, [c] Chi-square test, [f]Fisher's exact test,
*Statistically significant at $p \leq 0.05$

4.1.2 Clinical Characteristics

Out of the 64 perimenopausal women, 42(65.62%) were either overweight or obese and 11/64 (17.18%) had at least one chronic illness considered a risk factor for endometrial cancer (EC). From the 36 postmenopausal women, 31(86.11%) were either overweight or obese and 20/64 (55.56%) had a history of at least one chronic illness considered a risk factor for EC. Only 1/64 (1.56%) of the perimenopausal and 6/36 (16.67%) of the postmenopausal women reported a family history of a malignancy associated with an increased risk of EC. None of the study participants in both groups reported current or a history of cigarette smoking. Statistically significant differences in BMI ($p = 0.003$),

chronic illness (p = 0.001) and family history of cancer (p = 0.008) were observed between the two groups (Table 4.2).

Table 4.2: Clinical Characteristics 1 (BMI, Chronic Illness, Family History)

Variable	Perimenopausal (N=64)	Postmenopausal (N=36)	P-value
	n (% of participants)		
BMI [+]			
Underweight	2(3.13%)	0(0.00%)	
Normal	20(31.25%)	5(13.89%)	0.003[f*]
Overweight	23(35.94%)	7(19.44%)	
Obese	19(29.69%)	24(66.67%)	
Chronic Illness			
Yes	11(17.18%)	20(55.56%)	0.001[c*]
No	53(82.82%)	16(44.44%)	
Qualifying Illness			
No illness	53(82.82%)	16(44.44%)	
Diabetes	0(0.00%)	5(13.88%)	<0.001[f*]
Hypertension	11(17.8%)	15(41.68%)	
Family History of Cancer [0]			
Yes	1(1.56%)	6(16.67%)	0.008[f*]
No	63(98.44%)	30(83.33%)	

[0]breast, colon, ovarian or uterine cancer.
[+] Body Mass Index: Underweight (BMI <18.5Kg/m²), Normal (BMI 18.5-24.9Kg/m²), Overweight (BMI 25.0-29.9Kg/m², Obese (BMI ≥30Kg/m²)
[c] Chi-square test, [f]Fisher's exact test,
[*]Statistically significant at $p \leq 0.05$

As part of clinical characteristics, obstetric and gynecological characteristics were analyzed. The menstrual characteristics analyzed included age at menarche, menstrual status (whether the woman was perimenopausal or postmenopausal), history of menstrual disturbance in earlier reproductive years, current bleeding patterns and duration of AUB. The mean menarcheal ages of the 64 perimenopausal and 36 postmenopausal women were 14.86 years (SD: ±1.53) and 14.78 years (SD: ±1.12) respectively. The mean age at menopause of the 36 postmenopausal women was 49.31 years (SD: ± 5.0). Out of the 64

perimenopausal women, 10(15.63%) reported a history of AUB in earlier reproductive years (age < 40 years), while 7/36 (19.44%) of the postmenopausal women reported the same. In the perimenopausal group, 40/64 (62.50%) had menometrorrhagia, 12/64 (18.75%) had menorrhagia and 7/64 (10.94%) had metrotaxis as the commonest bleeding patterns. In the postmenopausal group, 21/36 (58.34%) had spotting, 9/36 (25.0%) had both heavy bleeding and spotting and 6/36 (16.67%) had heavy bleeding alone. The median durations of AUB in the perimenopausal and postmenopausal groups were 21 months (IQR:4, 86) and 3 months (IQR:1, 12) respectively. Hormonal contraceptive use was reported in 47/64 (73.44%) of the perimenopausal and 21/36 (58.33%) of the postmenopausal women respectively. Statistically significant differences were observed in duration of symptoms ($p < 0.001$) and parity ($p < 0.001$) between the two groups (Table 4.3)

Table 4.3: Clinical Characteristics 2 (Gynecologic and Obstetric Characteristics)

Variable		Perimenopausal (N=64)	Postmenopausal (N=36)	P-value
		Mean (SD[l]), Median (IQR[2]) or n (% of participants)		
Age at Menarche (*Years*)		14.86(±1.53)	14.78(±1.12)	0.7802[t]
Age at Menopause (*Years*)		N/A	49.31(±5.0)	N/A
History of Menstrual Disturbance	Yes	10(15.63%)	7(19.44%)	0.626[c]
	No	54(84.38%)	29(80.56%)	
Bleeding Patterns				
	Heavy Bleeding	N/A	6(16.67%)	
	Heavy Bleeding + spotting	N/A	9(25.0%)	
	Menometrorrhagia	40(62.50%)	N/A	
	Menorrhagia	12(18.75%)	N/A	N/A
	Metrotaxis	7(10.94%)	N/A	
	Metrorrhagia	5(7.82%)	N/A	
	Spotting	N/A	21(58.34%)	
Duration of AUB (*Months*)		21(4, 86)	3(1, 12)	<0.001[w*]
Hormonal Contraceptive Use[0]	Yes	47(73.44%)	21(58.33%)	0.180[c]
	No	17(26.56%)	15(41.67%)	
Parity Status				
	Nulliparous	1(1.56%)	0(0.00%)	1.000[f]
	Parous	63(98.44%)	36(100%)	
Parity		4(3, 6)	7(5, 9)	<0.001[w*]
Age at 1st Pregnancy (*Years*)		20.14(±3.83)	19.0(±3.50)	0.1437[t]

[l]SD = Standard deviation

[2]IQR = Interquartile range

[t] t-test, [w] Wilcoxon rank-sum, [c] Chi-square test, [f]Fisher's exact test,

*Statistically significant at $p \leq 0.05$

[0]Current use or history of use of contraceptive

4.1.3 Ultrasound Features

Out of the 100 women, 92 (92%) had a pelvic ultrasound done via the transabdominal route, while 8/100 (8.0%) had transvaginal ultrasounds. From the 64 perimenopausal women, a bulky uterus was reported in 33(51.56%), hypoechoic uterine masses in 23/64 (35.93%) and endometrial thickening in 17/64 (26.56%). In the postmenopausal group, 15/36 (41.67%) were reported to have a bulky uterus, 8/36 (22.22%) had a hypoechoic uterine mass and 18/36 (50.0%) had endometrial thickening. Statistically significant differences were observed between the two groups in terms of the number of women reported to have endometrial thickening (p = 0.018) and those with a hyperechoic complex uterine mass (p = 0.035) (Table 4.4).

Table 4.4: Pelvic Ultrasound Features

Variable		Perimenopausal (N=64)	Postmenopausal (N=36)	P-value
		n (% of participants)		
Uterine Size				
	Bulky[0]	33(51.56%)	15(41.67%)	0.342[c]
	Normal	31(48.44%)	21(58.33%)	
Hypoechoic Uterine Mass[+]				
	Yes	23(35.93%)	8(22.22%)	0.155[c]
	No	41(64.07%)	28(77.78%)	
Hyperechoic Complex Mass[+]				
	Yes	1(1.56%)	4(11.11%)	0.035[f*]
	No	63(98.44%)	32(88.89%)	
Endometrial Thickening**				
	Yes	17(26.56%)	18(50.00%)	0.018[c*]
	No	47(73.44%)	18(50.00%)	
Impression of Uterine Fibroids/Polyp				
	Yes	23(35.93%)	8(22.22%)	
	No	41(64.07%)	28(77.78%)	0.155[f]

[0]Bulky Uterus: uterine size ≥ 8.5cm x 4cm x 5cm in nulliparous, ≥10.5cmx6cmx6cm in multiparous, and 5cmx3cmx3cm in postmenopausal

[+] Myometrial or endometrial mass or masses

** Thickened endometrium: >16mm in perimenopausal and 4mm in postmenopausal

[c] Chi-square test, [f]Fisher's exact, [*]Statistically significant at $p \leq 0.05$

Structural pathologies were identified via pelvic ultrasonography in 31/100 (31%) of all the participants in the study, with an impression of uterine fibroids being made in 30/100 (30%), and endometrial polyp in 1/100 (1%). From this sub-group of women (n=31), 11/31 (35.48%) were eventually histologically diagnosed with endometrial hyperplasia without atypia and 1/31 (3.23%) with endometrial hyperplasia with atypia. The rest of the histopathological patterns identified in this sub-group of women are seen in table 4.5.

Table 4.5: Endometrial Histopathological Patterns in Participants with an Impression of Uterine Fibroids/Endometrial Polyp on Ultrasound

Histopathological Pattern	**Women with an Impression of Uterine Fibroids/polyp on U/S* (N = 31)**
	n (% of participants)
1. Endometrial Hyperplasia without Atypia	11(35.48%)
2. Atrophic Endometrium	6(19.35%)
3. Chronic Endometritis	4(12.90%)
4. Secretory Endometrium	4(12.90%)
5. Disordered Proliferative Endometrium	3(9.67%)
6. Mixed Proliferative-secretory Endometrium	1(3.23%)
7. Proliferative Endometrium	1(3.23%)
8. Endometrial Hyperplasia with Atypia	1(3.23%)

*U/S = Ultrasound

4.2 Prevalence of Endometrial Hyperplasia and Cancer in Perimenopausal and Postmenopausal Participants

Endometrial hyperplasia was seen in 23 out of the 64 perimenopausal women, thus having a prevalence of 35.94%. Out of these 23 cases, 21 were hyperplasia without atypia (prevalence 32.82%), while 2/23 were hyperplasia with atypia (prevalence 3.12%). Endometrial cancer was seen in only 1 out of the 64 women, thus having a prevalence of 1.56%.

In the postmenopausal group, endometrial hyperplasia was seen in 14 out of the 36 women, thus having a prevalence 38.89%. Out of these 14 cases, 9 were hyperplasia without atypia (prevalence 25.0%), while 6 were hyperplasia with atypia (prevalence 13.89%). Endometrial cancer was seen in 7 out of the 36 women, thus having a prevalence of 19.44% (Figure 4.2)

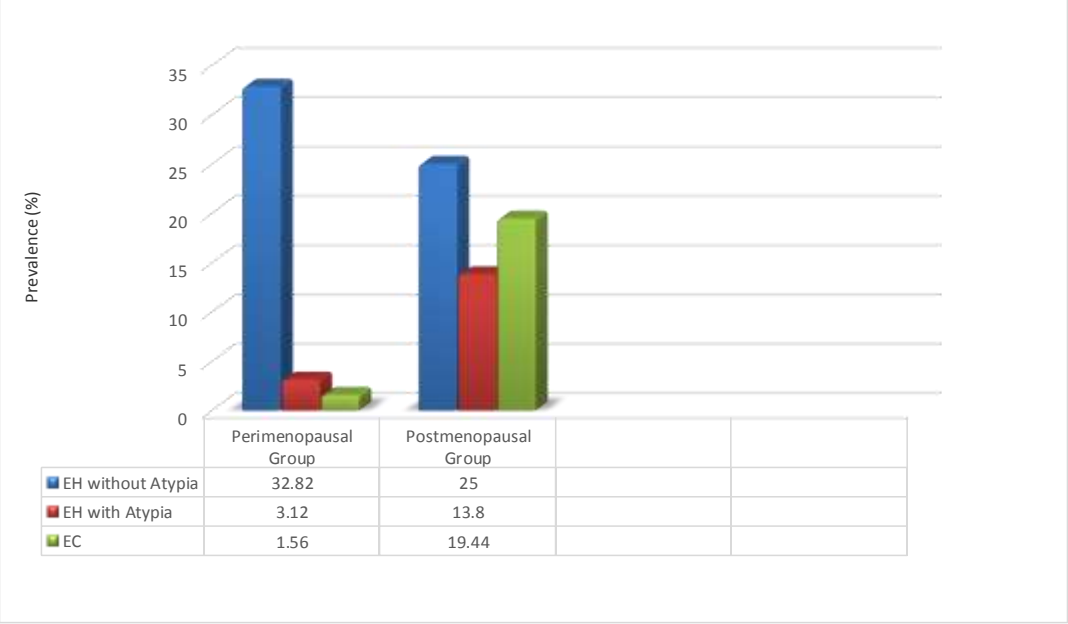

Figure 4.2: Prevalence (%) of Endometrial Hyperplasia and Cancer in Perimenopausal and Postmenopausal Participants

EH = endometrial hyperplasia, EC = endometrial cancer

Out of the 8 detected cases of endometrial cancer in this study, 7 (87.5%) were adenocarcinomas and 1 (12.5%) was endometrial stromal sarcoma (Table 4.8).

Table 4.6: Histological Characteristics of Endometrial Cancers Detected

Tumor Grade and Histological Type	**Endometrial Cancers (N=8)**
	n (% of cancers)
1. Poorly Differentiated Adenocarcinoma	3(37.50%)
2. Moderately Differentiated Adenocarcinoma	3(37.50%)
3. Well Differentiated Adenocarcinoma	1(12.50%)
4. High-grade Endometrial Stromal Sarcoma	1(12.50%)

4.3 Endometrial Histopathological Patterns in Perimenopausal and Postmenopausal Participants

Histological patterns in both groups of women were classified into three groups:

1. Normal endometrium and Benign Pathologies (**N/B Group**)
2. Endometrial hyperplasia with and without atypia- Premalignant Group (**Pre-M Group**)
3. Malignancy Group (**M Group**).

4.3.1 Histopathological Patterns in Perimenopausal Participants

Out of 64 perimenopausal participants, 40 (62.5%) had normal/cyclical patterns and benign endometrial pathologies (N/B Group), 23 (35.94%) had endometrial hyperplasia (Pre-M Group) and only 1 (1.56%) had endometrial cancer (M Group) (Figure 4.3)

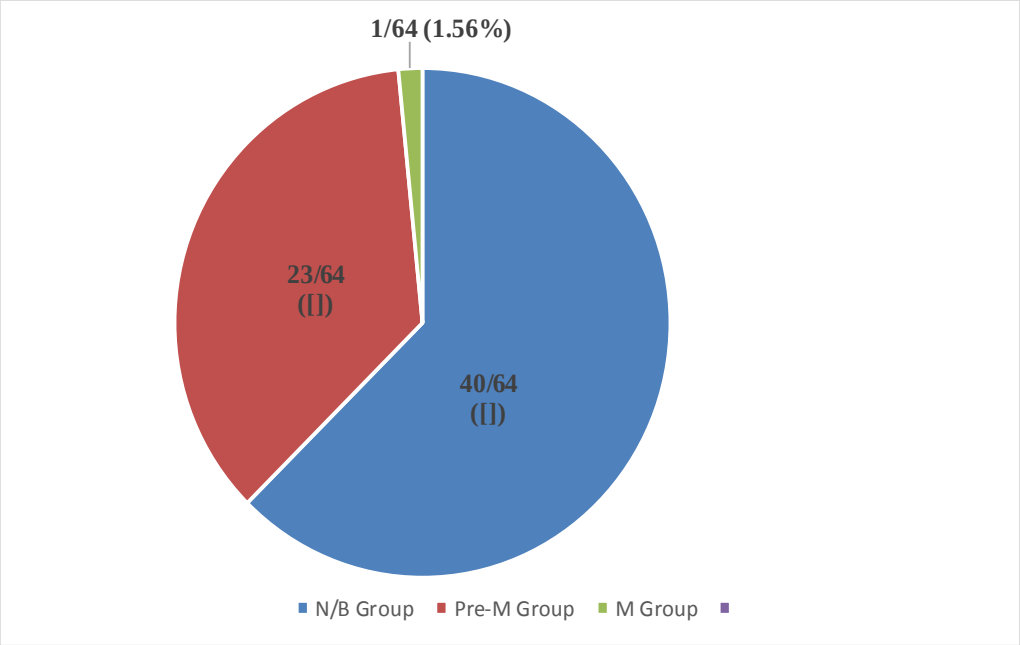

Figure 4.3: Groups of Histopathological Patterns in Perimenopausal Participants
N/B Group = Normal/Benign Group
Pre-M Group = Premalignant Group
M Group = Malignant Group

From the N/B Group, cyclical patterns i.e., secretory and proliferative patterns were the most seen, being reported in 14/64 (21.88%) and 6/64 (9.38%) of the participants respectively. Chronic endometritis and disordered proliferative endometrium (DPE) were the most seen benign pathologies, each reported in 5/64 (7.81%) of the participants. Only 1/64 (1.56%) of the participants was diagnosed with benign endometrial polyp.

From the Pre-M Group, endometrial hyperplasia without atypia, which was the most seen individual pattern in perimenopausal participants, was reported in 21 out of the 64 participants (32.82%). Hyperplasia with atypia was seen in 2/64 (3.12%). Only 1/64 (1.56%) of the participants was diagnosed with endometrial cancer that constituted the M

Group. The rest of the histological patterns in the perimenopausal group are seen in table 4.7 below.

Table 4.7: Histopathological Patterns in Perimenopausal Participants

Histological Pattern	**Perimenopausal Group (N=64)**
	n (% of participants)
1. Endometrial Hyperplasia without Atypia	21(32.82%)
2. Secretory Endometrium	14(21.88%)
3. Proliferative Endometrium	6(9.38%)
4. Mixed Proliferative-Secretory Pattern	5(7.81%)
5. Chronic Endometritis	5(7.81%)
6. Disordered Proliferative Endometrium	5(7.81%)
7. Endometrial Hyperplasia with Atypia	2(3.12%)
8. Atrophic Endometrium	2(3.12%)
9. Endometrial Cancer	1(1.56%)
10. Endometrial Polyp	1(1.56%)
11. Products of Conception	1(1.56%)
12. Decidual Reaction	1(1.56%)

4.3.2 Histopathological Patterns in Postmenopausal Participants

Out of the 36 postmenopausal participants, 15 (41.66%) had N/B Group patterns, 14/36 (38.89%) had Pre-M Group patterns and 7/36 (19.44%) had M Group Patterns (Figure 4.4).

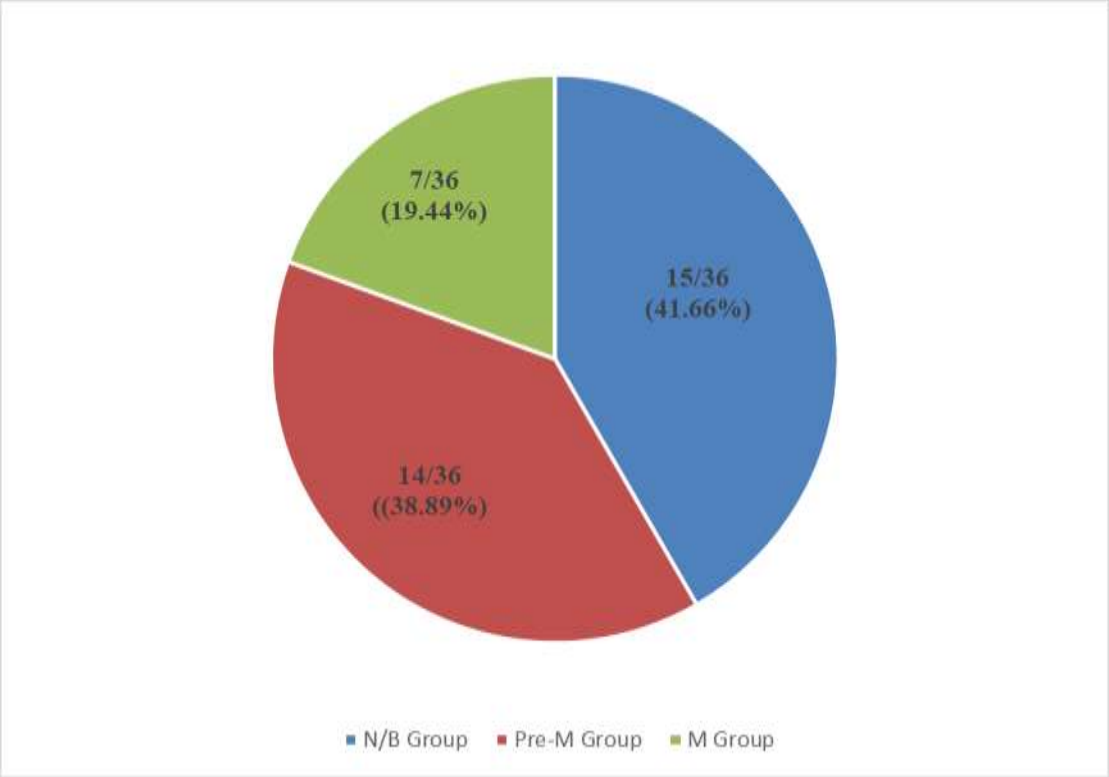

Figure 4.4: Groups of Histopathological Patterns in Postmenopausal Participants

N/B Group = Normal/Benign Group
Pre-M Group = Premalignant Group
M Group = Malignant Group

From the N/B Group, atrophic endometrium was the most seen pattern, being reported in 7/36 (19.44%) of the participants. Chronic endometritis was seen in 3/36(8.33%) and secretory pattern in 2/36 (5.56%). The rest of the N/B findings were proliferative pattern, disordered proliferative endometrium and benign endometrial polyp, each seen in 1/36 (2.78%) of the participants.

From the Pre-M Group, endometrial hyperplasia without atypia, which was the most seen individual pattern in postmenopausal participants, was reported in 9 out of the 36 participants (25%), while hyperplasia with atypia was seen in 5/36 (13.89%). Endometrial

cancer that constituted the M Group, was seen in 7/36 (19.44%) of the participants (Table 4.7).

Table 4.8: Histopathological Patterns in Postmenopausal Participants

Histopathological Patterns	Postmenopausal Group (N=36)
	n (% of participants)
1. Endometrial Hyperplasia without Atypia	9(25.0%)
2. Endometrial Cancer	7(19.44%)
3. Atrophic Endometrium	7(19.44%)
4. Endometrial Hyperplasia with Atypia	5(13.89%)
5. Chronic Endometritis	3(8.33%)
6. Secretory Endometrium	2(5.56%)
7. Proliferative Endometrium	1(2.78%)
8. Disordered Proliferative Endometrium	1(2.78%)
9. Benign Endometrial Polyp	1(2.78%)

4.4 Clinical Characteristics and Ultrasound Features Associated with Diagnosis of Endometrial Hyperplasia and Cancer in Perimenopausal and Postmenopausal Participants

Out of the 100 biopsies done, 55 (55%) were normal or benign (N/B) patterns while 45/100 (45%) were premalignant (EH) and malignant (EC) pathologies. Data on factors that have been reported to be risk or protective factors for EH and EC in literature, including clinical characteristics (BMI, chronic illness, family history of cancer i.e., breast, colon, ovarian or uterine cancer, menstrual characteristics, obstetric history, hormonal contraceptive use) and ultrasound findings of the 100 participants were stratified into the N/B and EH/EC groups to test for associations between these factors and premalignant and malignant (EH/EC) diagnosis.

From the clinical characteristics, neither BMI, chronic illnesses (diabetes and hypertension) or a family history of breast, colon, ovarian or uterine cancer were associated with diagnosis of EH/EC on bivariate analysis (Table 4.9).

Table 4.9: Clinical Characteristics Associated with Diagnosis of EH/EC (BMI, Chronic Illness, Family History)

Variable		N/B[0] Patterns (N=55)	EH/EC[×] (N=45)	P-value
		n (% of participants)		
BMI[+]				
	Underweight	2(3.64%)	0(0.00%)	
	Normal	14(25.45%)	11(24.44%)	0.797[f]
	Overweight	16(29.09%)	14(31.11%)	
	Obese	23(41.89%)	20(44.44%)	
Chronic Illness				
	Yes	16(29.09%)	15(33.33%)	0.648[c]
	No	39(70.91%)	30(66.67%)	
Type of Chronic Illness				
	Diabetes	2(12.50%)	3(20.00%)	
	Hypertension	14(87.50%)	12(80.00%)	0.570[f]
Family History of Cancer**	Yes	4(7.27%)	3(6.67%)	1.000[f]
	No	51(92.73%)	42(93.33%)	

[0]N/B= Normal/Benign Patterns (includes all cyclical patterns and benign pathologies)
[×]EH/EC = endometrial hyperplasia and endometrial cancer
[+] Body Mass Index: Underweight (BMI <18.5Kg/m²), Normal (BMI 18.5-24.9Kg/m²), Overweight (BMI 25.0-29.9Kg/m², Obese (BMI ≥30Kg/m²)
**breast, colon, ovarian or uterine cancer.
[c]Chi-square test, [f]Fisher's exact test

None of the gynecologic and obstetric characteristics were associated with the diagnosis of EH/EC on bivariate analysis (Table 4.10).

Table 4.10: Clinical Characteristics Associated with Diagnosis of EH/EC (Gynecologic and Obstetric Characteristics)

Variable	N/B Patterns[0] (N=55)	EH/EC[×] (N=45)	P-value
	Mean (SD[l]), Median (IQR[2]) or n (% of participants		
Age at Menarche (*Years*)	14.8(±1.51)	14.87(±1.25)	0.813[t]
Menstrual Status			
Perimenopausal	40(72.72%)	24(53.33%)	0.081[c]
Postmenopausal	15(27.28%)	21(46.67%)	
Menopause Age (*Years*)	50.33(±3.2)	48.47(±5.92)	0.303[t]
History of Menstrual Disturbance Yes	10(18.18%)	7(15.56%)	
No	45(81.82%)	38(84.44%)	0.728[c]
Bleeding Patterns			
Heavy Bleeding	3(5.45%)	3(6.67%)	
Heavy Bleeding + spotting	2(3.64%)	7(15.56%)	
Menometrorrhagia	22(40.00%)	18(40.00%)	
Menorrhagia	8(14.55%)	4(8.89%)	0.139[f]
Metrorrhagia	4(7.27%)	1(2.22%)	
Metrotaxis	6(10.91%)	1(2.22%)	
Spotting	10(18.18%)	11(24.44%)	
Duration of AUB (*months*)	11(3,24)	12(3,24)	0.676[w]
Hormonal Contraceptive Use Yes	37(67.27%)	31(68.89%)	0.863[c]
No	18(32.73%)	14(31.11%)	
Pregnancy History			
Nulliparous	0(0.00%)	1(2.22%)	0.450[f]
Parous	55(100%)	44(97.78%)	
Parity	5(3, 7)	5(4, 8)	0.432[w]
Age of first pregnancy (*Years*)	19.65(±3.85)	19.81(3.62)	0.830[t]

[0] N/B= Normal/Benign Patterns (includes all cyclical patterns and benign pathologies)
[×]EH/EC = endometrial hyperplasia and endometrial cancer
[l]SD = Standard deviation
[2]IQR = Interquartile range
[t] t-test, [w] Wilcoxon rank-sum, [c]Chi-square test, [f]Fisher's exact test

When it comes to ultrasound findings, endometrial thickening (p = 0.001) and the finding of hyperechoic complex mass/masses (p = 0.014) were significantly associated with the diagnosis of EH and EC on bivariate analysis (Table 4.11)

Table 4.11: Ultrasound Features Associated with Diagnosis of EH/EC

Variables		N/B Patterns (N=55)	EH/EC (N=45)	P-value
		n (% of participants)		
Uterine Size				
	Bulky[0]	26(47.27%)	22(48.89%)	0.872[c]
	Normal	29(52.73%)	23(51.11%)	
Hypoechoic Uterine Mass[+]				
Yes		20(36.36%)	11(24.44%)	0.125[c]
	No	35(63.64%)	34(75.56%)	
Hyperechoic Complex Mass[+]				
Yes		0(0.00%)	5(11.11%)	0.014[f*]
	No	55(100%)	40(88.89%)	
Endometrial Thickening**				
	Yes	11(20.00%)	24(53.33%)	0.001[c*]
	No	44(80.00%)	21(46.67%)	
Impression of Uterine Fibroids/Polyp				
	Yes	20(36.36%)	11(24.44%)	0.125[c]
	No	35(63.64%)	35(75.56%)	

[0]Bulky Uterus: uterine size ≥ 8.5cm x 4cm x 5cm in nulliparous, ≥10.5cmx6cmx6cm in multiparous, and 5cmx3cmx3cm in postmenopausal
[+] Myometrial or endometrial mass or masses
** Thickened endometrium: >16mm in perimenopausal and >4mm in postmenopausal
[c] Chi-square test, [f]Fisher's exact, *Statistically significant at p ≤ 0.05

Logistic regression was modeled using factors that were significantly associated with the diagnosis of EH/EC on bivariate analysis. While both the finding of endometrial thickening or a hyperechoic complex uterine mass/mass on ultrasound were significantly associated with the diagnosis of EH/EC on bivariate analysis, only endometrial thickening

was determined to be significantly associated with EH/EC diagnosis on the multivariate model (p = 0.004) (Table 4.12).

Table 4.12: Logistic Regression of Factors Associated with the Diagnosis of EH/EC on Bivariate Analysis

Factor		OR[1] (95 CI)	P-value	AOR[2] (95 CI)	P-value
Age		1.04(0.99,1.09)	0.063	1.04(0.96,1.15)	0.331
Endometrial Thickening on U/S	No	Ref			
	Yes	4.31(1.79,10.33)	0.001*	4.17(1.57,11.05)	0.004*
Hyperechoic Complex Mass on U/S	No	Ref			
	Yes	0.64(0.26,1.52)	0.031*	1.03(0.36,2.87)	0.959

[1]OR = odds ratio
[2]AOR = adjusted odds ratio
*Statistically significant at $p \leq 0.05$

CHAPTER FIVE: DISCUSSION

A number of studies have been done internationally with regard to endometrial histopathological patterns in women with AUB, some focusing on either perimenopausal or postmenopausal women, others focusing on all women including those of reproductive age who are younger than 40 years, and some, like this study, focusing on both perimenopausal and postmenopausal women, both groups of women being more likely to be diagnosed with EH or EC. Local/regional data on the subject is limited, with most studies on the subject being done in North and West Africa (Egypt and Nigeria).

5.1 Sociodemographic, Clinical Characteristics and Ultrasound Features in Perimenopausal and Postmenopausal Women with AUB

5.1.1 Sociodemographic Characteristics

The mean ages for the perimenopausal and postmenopausal participants in this study were 46.05 (±3.73) and 62.11 (±7.96) years respectively. These were comparable to findings by Nemer et al in Saudi Arabia and Elkholi et al in Egypt, where the mean ages of the participants were 49 years and 63 years respectively (Nemer et al., 2019; Elkholi & Nagy, 2015). In contrast, the mean ages reported by Asuzu et al in Nigeria and Gunakan et al in Turkey were 33.53 years and 70.3 years respectively (Asuzu & Olaofe, 2018; Günakan et al., 2018). The lower mean age reported by Asuzu et al may be due to the fact that they evaluated women with AUB from all age-groups, and the majority of the study participants (83.5%) were aged between 18-40 years. The mean age reported by Gunakan et al was higher than that in our study due to the fact that they exclusively enrolled postmenopausal women with AUB who were ≥ 65 years.

Majority (66%) of the participants in our study were married, 16% widowed and the rest were either single (7%) or divorced (6%). This is comparable to findings in Pakistan by Abid et al, where 72.6% of the participants were married and 27.3% were unmarried

(Abid et al., 2014). Our findings however, contrast those reported by Marie et al in Cameroon, where 41.6% of the participants were married, and 36.20% were single (Marie et al., 2020). This difference could be due to the fact that women of all ages within the reproductive age group were recruited in their study, thus a younger cohort of women who were more likely to be unmarried.

Only 44% of the participants in our study had secondary school education as the highest level of education, which contrasts findings by Shichenje et al in Western Kenya, in which two thirds of the women were reported to have at least a secondary level education. This could be due to a relatively younger study population recruited in their study, which is likely to be more educated than that in our study. Only 13% of our study participants were employed in the formal sector, which is comparable to the findings by Shichenje et al, who reported that a tenth of their participants were employed in the formal sector (Shichenje et al., 2020).

5.1.2 Clinical Characteristics

Majority (65.63% of the perimenopausal and 86.11% of the postmenopausal) of the participants in our study were either overweight or obese, which is comparable to findings by Elkholi et al, who reported all participants in their study were either overweight or obese (Elkholi & Nagy, 2015). In contrast, Meena et al reported that only 4% of their participants were overweight or obese (Meena Nidhi, 2017). The low proportion of overweight and obesity among the participants in their study could be due to the fact that their participants were relatively of younger age and coming from a predominantly vegetarian population in India. Older age is associated with a relatively more sedentary lifestyle and a lower basal metabolic rate, both which create a propensity for weight gain, while a diet that is mainly plant-based is less likely to be associated with weight gain. Furthermore, the high proportion of overweight and obesity among the participants in our

study keeps in line with the regional trend, as is evidenced in a multi-regional study by Mkuu et al who reported that 1 in 3 women (32.8%) in Kenya were either overweight or obese (Mkuu et al., 2018).

When it comes to chronic illnesses that are proven risk factors for EC, 26% of the participants in this study had chronic hypertension and 5% had diabetes mellitus (DM). This is comparable to findings by Elkholi et al in who reported that 20.6% of their participants had chronic hypertension (Elkholi & Nagy, 2015). Comparable findings were also reported in India by Meena et al, where 21% of the participants in their study had chronic hypertension (Meena Nidhi, 2017). In contrast, Pirog et al in Poland, reported a higher prevalence of hypertension and DM (50.9% and 17.5% respectively) in their study (Piróg et al., 2019). This could be attributed to the fact that the overall prevalence of lifestyle and non-communicable diseases such DM and hypertension in developed countries is higher than in developing countries like ours.

The mean menarcheal ages for the perimenopausal and postmenopausal groups were 14.86 and 14.78 years respectively in this study. This is comparable to an earlier study in the region by Rogo et al which established a mean menarcheal age of 14.4 years (Rogo et al., 1987). Our findings slightly contrast those in Ogeng'o et al's study involving urban Kenyan school girls, which reported a mean menarcheal age of 12.5 years (Ogeng'o et al., 2011). This earlier menarcheal age seen in current adolescent girls could be due to an increase in obesity in the region, which is associated with early menarche.

The mean age at menopause in this study was 49.3 years. This is comparable to an earlier study in the region by J.Noreh et al, which reported the mean age at menopause of women in rural Western Kenya to be 48 years (Noreh et al., 1997). In contrast, the mean age at menopause in Western societies has been reported to be slightly higher, at 51 years

(Cheung et al., 2004). One of the theories that has been used to explain this difference is that in populations like ours where fertility rates are higher and the age of first pregnancies is lower, there generally tends to be a lower age of entry into menopause amongst women (Thomas et al., 2001).

The most common bleeding pattern in the postmenopausal group in this study was spotting (55.56%), followed by heavy bleeding alternating with spotting (25%) and heavy bleeding alone (16.67%). This is in contrast to findings by Elkholi et al who reported light menses-like bleeding as the most common pattern of postmenopausal bleeding (61.15%), followed by spotting (29.89%) (Elkholi & Nagy, 2015). The difference in the bleeding patterns in their study and this study could be due to the fact that they exclusively studied women with postmenopausal bleeding who had an endometrial thickness ≤ 4mm while in this study, all women with postmenopausal bleeding were included, regardless of their endometrial thickness.

5.1.3 Ultrasound Features

Endometrial thickening was reported in 26.56% of the perimenopausal and 50% of the postmenopausal participants in our study. In contrast, endometrial thickening was reported in only 18% of participants with AUB in an Egyptian study (Elsersy, 2017). This difference could be due to the fact that all women of reproductive age were recruited into the study and not just perimenopausal women, with differences in endometrial thickness across the reproductive ages being known. A bulky uterus was on the other hand reported in 51.56% of the perimenopausal and 41.67% of the postmenopausal participants in our study. This contrasts findings by Talukdar and Mahela in India, who reported a bulky uterus in 29.12% of their participants with AUB (Talukdar & Mahela, 2016). However, the specific size of what was regarded as a bulky uterus in their study was not elaborated.

Histopathological evaluation of the 31 women whose ultrasound images gave an impression of structural pathologies (uterine fibroids or endometrial polyps) in this study showed that 35.48% of the women had endometrial hyperplasia (EH) without atypia, and 3.23% had EH with atypia. This is comparable to a study by Merla in which 35.13% of women radiologically diagnosed with fibroids were diagnosed with EH without atypia on histopathological evaluation. However, no case of EH with atypia was reported in their study (Merla, 2013).

5.2 Prevalence of Endometrial Hyperplasia and Cancer in Perimenopausal and Postmenopausal Women with AUB

The prevalence of endometrial hyperplasia (EH) and cancer (EC) in perimenopausal women in this study was 35.94% and 1.56% respectively. This is comparable to a study Abdelazim et al in which the prevalence of EH in perimenopausal women was 35.7% (Abdelazim et al., 2013). However, the prevalence of EC in their study was higher compared to this study (6.4% versus 1.56%), and could be attributed to a relatively older population of participants. Belcaro et al reported a prevalence of 26.64% of EH in their study, which is also comparable to this study's finding. However, the prevalence of EC in their study was remarkably lower than that in our study (0.48% vs 1.56%) (Belcaro et al., 2020). A lower prevalence of EH was reported in perimenopausal women in Nemer et al's study compared to this study (13.0% versus 35.94%), while no perimenopausal women in their study was diagnosed with EC (Nemer et al., 2019). While the prevalence of EC in perimenopausal women in our study may be comparable to that reported in similar studies done in other regions, that of EH was relatively higher. Differences in the prevalence of EH and EC in perimenopausal women in the different studies could be due to genetic differences in the different populations. The differences could also be due to study methodology, including adopted biopsy methods, exclusion of certain groups of

patients who have a higher risk of being diagnosed with these two pathologies such as those with an endometrial thickness of >4mm, etc. (Table 5.1).

Table 5.1: Prevalence (%) of Endometrial Hyperplasia and Cancer in Perimenopausal Women with AUB in Different Studies

Study	Endometrial Hyperplasia * Prevalence	Endometrial Cancer Prevalence
This study (*2020*)	35.94%	1.56%
Abdelazim et al (*2013*)	35.7%	6.4%
Belcaro et al (*2020*)	26.64%	0.48%
Qureshi et al (*2015*)	25.71%	2.86%
Devi et al (*2014*)	20.7%	0.2%
Nemer et al (*2019*)	13.0%	0%
Abid et al (*2014*)	6.5%	1.2%
Azim et al (*2011*)	2.1%	5.7%

* Both endometrial hyperplasia with or without atypia combined.

The prevalence of endometrial hyperplasia (EH) and cancer (EC) in postmenopausal women in this study was 38.89% and 19.44% respectively, which were significantly higher compared to prevalence reported in similar studies done in other populations. Pirog et al reported a prevalence of 40.4% of EH, which is comparable to this study's findings. However, the prevalence of EC in their study was lower compared to ours (3.5% versus 19.44%), which could be explained by the fact that women with an endometrial thickness >4mm were excluded from their study (Piróg et al., 2019). Nemer et al on the other hand reported a lower prevalence of EH compared to ours (15.8% versus 38.89%) and a prevalence of EC that was comparable to this study's (15.8% versus 19.44%) (Nemer et al., 2019). Notably, most studies done in Europe reported a lower prevalence of EC in women with PMB compared to those done in Asia and Africa (Table 5.2).

Table 5.2: Prevalence (%) of Endometrial Hyperplasia and Cancer in Postmenopausal Women with AUB in Different Studies.

Study	Endometrial Hyperplasia * Prevalence	Endometrial Cancer Prevalence
This study (*2020*)	38.89%	19.44%
Deeba et al (*2016*)	59.0%	12.7%
Pirog et al (*2019*)	40.4%	3.5%
Nemer et al (*2019*)	15.8%	15.8%
Abid et al (*2014*)	13.2%	9.0%
Miyazawa et al (*1987*)	13.0%	8.0%
Devi et al (*2014*)	8.0%	2.6%
Qureshi et al (*2015*)	3.3%	10%

* Both hyperplasia without atypia and with atypia combined.

5.3 Endometrial Histopathological Patterns in Perimenopausal and Postmenopausal Women with AUB

5.3.1 Perimenopausal Women

Majority (62.5%) of the histological patterns in the perimenopausal women in this study were either normal/cyclical or benign patterns constituting the N/B Group, which is comparable to findings by Nemer et al, Abdelazim et al and Belcaro et al, who also reported cyclical patterns and benign pathologies to be constituting majority their findings (86.9%, 57.8% and 72.9% respectively) (Belcaro et al., 2020; Nemer et al., 2019; Abdelazim et al., 2013). Secretory pattern was the most seen pattern in the N/B Group in this study (21.8%), which is comparable to findings by Nemer et al (26.0%). In contrast, Belcaro et al reported benign endometrial polyp to be the most seen pattern in the N/B group (28%). This could be attributed to the fact that Belcaro et al used hysteroscopically guided biopsy, which has a higher sensitivity for detecting focal pathologies such as endometrial polyps compared to blind biopsy methods such as the Pipelle biopsy used in this study. The more common use of tamoxifen for both the prevention and treatment of

breast cancer has also been implicated in the higher rates of endometrial polyps in Western populations like theirs (Belcaro et al., 2020).

The premalignant (Pre-M) group made up of EH with or without atypia constituted 35.9% of all findings in the perimenopausal group in this study. This is comparable to findings in a study by Abdelazim et al in which the Pre-M group made up 35.7% of all findings (Abdelazim et al., 2013). Contrasting this, the Pre-M group constituted of only 13% of the findings in a study by Nemer et al (Nemer et al., 2019). The lower proportion in their study could be due to the fact that the perimenopausal group in the study strictly constituted of women aged between 40-50 years while in our study, the upper limit was not defined by a specific age but by whether or not a woman was having a period of amenorrhea of not more than 12 months following the final menstrual period. Thus, the perimenopausal group in our study included women older than 50 years, and with participants with a relatively older age, the prevalence of premalignant pathologies (EH) would naturally be higher, as is also evident in the postmenopausal group compared to the perimenopausal group in this study.

The M group made up of endometrial cancer (EC) constituted 1.56% of all patterns in the perimenopausal group in this study. This is comparable to findings by Abid et al, who reported 1.2% of their findings to be EC. In contrast to this, Abdelazim et al reported a higher proportion of EC, with 6.4% of the perimenopausal participants in their study being found to have EC. This significant contrast could be due to the fact that Abdelazim et al excluded from their study women with a relatively lower risk of EC, such as those with an endometrial thickness < 4mm and those with a history of hormonal contraceptive use. A summary of histopathological patterns in perimenopausal women in this study compared to others is seen in table 5.3.

Table 5.3: Endometrial Histopathological Patterns in Perimenopausal Women with AUB in Different Studies

Histology Group	This Study (2020) N=64 n (% of participants)	Nemer et al (2019) N=23 n (% of participants)	Abdelazim et al (2013) N=140 n (% of participants)	Belcaro et al (2020) N=625 n (% of participants)
N/B[1] Group	*40 (62.5%)* Secretory 14 (21.8%) Proliferative 6 (9.3%) Mixed 5 (7.8%) Endometritis 5 (7.81%) DPE 5 (7.81%) Atrophic E. 2 (3.12%) Polyp 1 (1.56%) POCs 1 (1.56%) Decidual R. 1 (1.56%)	*20 (86.9%)* Secretory 6 (26.0%) Shedding 6 (26.0%) Proliferative 2 (8.6%) Polyp 5 (21.7%) Endometritis 1 (4.3%)	*81 (57.8%)* Proliferative 37 (26.4%) Secretory 33 (23.57%) Endometritis 8 (5.7%) Polyp 3 (2.1%)	*456 (72.92%)* Polyp 175 (28%) Myoma 100 (16%) Mixed P-S 94 (15%) Cyclical 68 (10.8%) Atrophic 19 (3.04%)
Pre-M[2] Group (EH)	*23 (35.9%)* EH without Atypia 21 (32.8%) EH with atypia 2 (3.1%)	*3 (13%)* EH without atypia 2 (8.6%) EH with atypia 1 (4.4%)	*140 (35.7%)* EH without atypia 45 (32.1%) EH with atypia 5 (3.6%)	*166 (26.6%)* EH without atypia 162 (26.0%) EH with atypia 4 (0.6%)
M[3] Group (EC)	*1 (1.56%)* Adenocarcinoma 1 (1.56%)	0 (0%) --	*9 (6.4%)* Adenocarcinoma 5 (3.5%) Adenosquamous 2 (1.4%) Adenosarcoma 1 (0.7%) Carcinosarcoma 1 (0.7%)	*3 (0.5%)* Adenocarcinoma 3 (0.5%)

[1]N/B=normal or benign, [2]Pre-M = premalignant, [3]M = malignant

5.3.2 Postmenopausal Women

Majority (41.66%) of histological findings in the postmenopausal women in this study belonged to the N/B group. This is comparable to studies by Nemer et al and Pirog et al who also reported the N/B group to constitute the majority of the patterns (68.4% and 56.1% respectively) (Nemer et al., 2019; Piróg et al., 2019). In contrast, Deeba et al observed that most findings in their study belonged to the premalignant (Pre-M) group, which constituted 59.0% of all findings. The N/B Group constituted 28.1% of all findings in their study, with the most commonly reported pathology from the group being atrophic endometrium (24.5%) (Deeba & Khan, 2016). From the N/B group, the most commonly seen benign pathology in our study was atrophic endometrium (19.4%), which is comparable to findings by Pirog et al and Deeba et al (29.8% and 24.5% respectively). In contrast, Nemer et al reported endometrial polyp to be the most common benign finding (31.6%) (Nemer et al., 2019). This difference could be due to the relatively younger study population they had (mean age 53.2 years) compared to our study (mean age 62.1 years), as atrophic endometrium is more commonly seen in older and generally hypoestrogenic populations like that in our study.

In the Pre-M (premalignant) group, EH was seen in 38.9% of participants in this study, which is comparable to findings by Pirog et al (40.4%). In contrast, Deeba et al reported a significantly higher proportion of EH in their study (59.0%), which could be due to the fact that dilatation and curettage (D&C) was the biopsy method used in their study instead of endometrial sampling with a Pipelle. From the M (malignant) group in this study, EC cancer in the postmenopausal women was in seen in 19.44% of the women, which is comparable to findings by Nemer et al (15.8%). In contrast, Pirog et al reported a lower proportion of EC in their study (3.5%), which could be due to the fact that their study

only included women who had an endometrial thickness of ≤4mm, who have been proven to generally be less likely to be diagnosed with EC (Table 5.4).

Table 5.4: Endometrial Histopathological Patterns in Postmenopausal Women with AUB in Different Studies

Histology Group	This Study (2020) N=36 n (% of participants)	Nemer et al (2019) N=19 n (% of participants)	Pirog et al (2019) N=57 n (% of participants)	Deeba et al (2016) N=110 n (% of participants)
1)N/B Group	*15 (41.6%)* Atrophic E. 7 (19.4%) Endometritis 3 (8.3%) Secretory 2 (5.6%) Proliferative 1 (2.8%) DPE 1 (2.8%) Polyp 1 (2.8%)	*13 (68.4%)* Polyp 6 (31.6%) Atrophic E. 3 (15.7%) Proliferative 2 (10.5%) Shedding 1 (5.2%) Endometritis 1 (5.2%)	32 *(56.1%)* Atrophic 17 (29.8%) Polyp 10 (17.5%)) Proliferative 5 (8.8%)	*31 (28.1%)* Atrophic 27 (24.5%) Polyp 4 (3.6%)
2)Pre-M Group (EH)	*14 (38.9%)* EH without atypia 9 (25%) EH with atypia 5 (13.89%)	*3 (15.8%)* EH with atypia 2 (10.5%) EH with atypia 1 (5.3%)	23 *(40.4%)* EH without atypia 11 (19.3%) EH with atypia 12 (21.1%)	*65 (59.0%)* EH without atypia 60 (54.5%) EH with atypia 5 (4.5%)
3)M Group (EC)	*7 (19.4%)*	*3 (15.8%)*	*2 (3.5%)*	*14 (12.7%)*

[1]N/B=normal or benign
[2]Pre-M = premalignant
[3]M = malignant

5.4 Clinical Characteristics and Ultrasound Features Associated with Diagnosis of Endometrial Hyperplasia and Cancer in Perimenopausal and Postmenopausal Women with AUB.

None of the clinical characteristics (BMI, diabetes mellitus, Chronic Hypertension, family history of significant malignancy, obstetric and menstrual characteristics) were associated with the diagnosis of endometrial hyperplasia and cancer (EH/EC). This compares to findings by Pirog et al in Poland, who reported that neither BMI, diabetes or chronic hypertension was associated with the diagnosis of EH/EC in women with postmenopausal bleeding (Piróg et al., 2019). However, numerous studies, including systematic reviews, have established an association between BMI, diabetes mellitus and chronic hypertension with the diagnosis of EH/EC (Albers, 2004; Renehan, 2011; Aune et al., 2017). This could possibly be due to the larger study populations/sample sizes used in these studies, which allowed them to test for these associations more accurately.

From the ultrasound findings, endometrial thickening was the only factor significantly associated with the diagnosis of EH/EC on both bivariate and multivariate analysis in our study. This compares to findings by Pirog et al (2019) who reported that EH/EC were less likely to be diagnosed in women with postmenopausal bleeding who had an endometrial thickness of less than 4mm. The role of endometrial thickness is also applied in tools for the assessment of the risk of endometrial cancer in women with AUB, particularly postmenopausal women, including the Risk of Endometrial Cancer (REC) scoring model for EC risk stratification (Stachowicz et al., 2021).

5.7 Study Strengths and Limitations.

5.7.1 Study Strengths

1. All endometrial biopsies were taken by one qualified person, with an overall sample adequacy rate of 100%.

2. Histological evaluation of all biopsies was done by 2 identified consultant pathologists to minimize on inter-observer variations.

3. Women diagnosed with structural causes of AUB were also included in study.

5.7.2 Study Limitations

1. There is a relatively lower accuracy of the Pipelle device in detecting focal pathologies such us endometrial polyps compared to hysteroscopically guided biopsies.

2. The pelvic ultrasounds done were mostly transabdominal and not transvaginal, which has a higher accuracy in detecting pelvic pathologies.

3. Being a hospital-based study, its findings may not be generalizable to the entire population.

CHAPTER SIX: CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions.

Cognizant to the findings in this study discussed in Chapter 4, we conclude the following:

1. Majority of peri- and postmenopausal women with AUB seen at MTRH were either overweight or obese, while more than half of the postmenopausal women had a significant chronic illness, and those who were found to have structural pathologies such as uterine fibroids/endometrial polyps on imaging had other histological findings discovered via biopsy, including endometrial hyperplasia.
2. The prevalence of endometrial hyperplasia (35.94%) in perimenopausal, and that of both endometrial hyperplasia (38.89%) and cancer (19.44%) in postmenopausal women with AUB at MTRH were relatively higher than those reported in most studies done in other populations.
3. Normal cyclical patterns (secretory and proliferative) and benign endometrial pathologies (chronic endometritis in peri- and atrophic endometrium in postmenopausal) constituted majority of the histopathological findings in perimenopausal and postmenopausal women with AUB seen at MTRH. However, the most commonly seen individual pattern in both groups was endometrial hyperplasia without atypia.
4. Endometrial thickening discovered via ultrasonography in peri- and postmenopausal women with AUB seen at MTRH was significantly associated with the diagnosis of endometrial hyperplasia and cancer in these women.

6.2 Recommendations

1. We strongly recommend the performance of endometrial biopsies in peri- and postmenopausal women with AUB whose ultrasound findings show features suggestive of structural pathologies such as uterine fibroids and endometrial polyps, as these pathologies may co-exist with other pathologies such as endometrial hyperplasia.

2. Due to the relatively high prevalence of endometrial hyperplasia in perimenopausal and both endometrial hyperplasia and cancer in postmenopausal women with AUB at MTRH discovered in this study, we reiterate the importance of histological evaluation of the endometria in these two groups of women so as to rule out these two pathologies.
3. We support the use of pelvic ultrasonography for the preliminary investigation of peri- and postmenopausal women with AUB, and reiterate the importance of performing endometrial biopsies in those women discovered to have a thickened endometrium, as they appear to have a higher risk of being diagnosed with endometrial hyperplasia and cancer.
4. Further studies to be done at different facilities in the region, that involve a larger study population so as to adequately assess for possible associations between clinical characteristics and the diagnosis of endometrial hyperplasia and cancer in peri- and postmenopausal women with AUB.

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APPENDICES

APPENDIX 1: CONSENT FORM

My name is Dr. Issa Moshey. I am currently pursuing my master's degree (Mmed) in Reproductive Health at Moi University. A thesis research is a requirement in partial fulfillment of this course. For this, I intend to carry out a research titled "Endometrial Histopathological Patterns of Perimenopausal and Postmenopausal Women Diagnosed with Abnormal Uterine Bleeding at MTRH – Eldoret".

This research will involve the evaluation of biopsies obtained from women aged 40 years or older who have been diagnosed with a condition known as Abnormal Uterine Bleeding (AUB), following routine physical, laboratory and radiological evaluation at MTRH. This form is to inform you on the purpose of the research and invite you to participate in it. You are free to talk to anyone you are comfortable with about this research before you make the decision on whether to participate or not.

During the interview, feel free to stop me at any point in case you need clarification on any aspect of the study. If you have any more questions later on, kindly feel free to contact me using the contact provided on this form.

Purpose of the research:

The purpose of this research is to evaluate and describe the findings of biopsies obtained from the inner linings of the uteruses of women aged 40 years or above, diagnosed with a gynecological condition called Abnormal Uterine Bleeding at MTRH. This will lead to provision of information pertaining to what the various causes of the abnormal uterine bleeding on a histological level are in these women, who have already been diagnosed with the condition through physical, laboratory and/or radiological evaluation, with the ultimate aim being to determine what percentage of them, if any, are eventually diagnosed with pre-cancerous or cancerous lesions of the uterus. The information obtained from this study may be utilized in the formulation of a protocol on the management of women aged 40 years and above, who have been diagnosed with Abnormal Uterine Bleeding at MTRH.

Research intervention, Risks and Benefits:

Following the signing of this consent form, a structured questionnaire will be administered by the principal investigator or by a research assistant. An instrument known as a speculum will be inserted into the vagina to visualize the cervix. A straw-

like instrument known as a Pipelle will then be inserted into the uterine cavity through the cervix, and a sample from the inner lining of the uterus will be collected. You are free to respond or choose not to respond to the questions that you may find inconvenient to you, and you are also free to accept or decline having a speculum exam done or a biopsy sample taken.

Your refusal to participate in the study will not change the treatment plan that your doctors deem fit for you. You may experience mild discomfort during the speculum exam or during the biopsy acquisition process. You may also experience some spotting or bleeding after the procedure, and cramping may occur. You are free to choose to be chaperoned (by a person you are comfortable with) during the procedure.

Information about you will not be shared with anybody. The immediate benefit that will accrue of you is that you will get a histological diagnosis of your condition through the biopsy obtained from the inner lining of your uterus, which will allow us to definitively identify the reason why you are experiencing abnormal uterine bleeding, allowing us to provide you with the appropriate treatment.

Participation and Confidentiality:

In this research, all the women aged 40 years and above in the gynecology inpatient and outpatient units at MTRH diagnosed with abnormal uterine bleeding are invited to participate. The research will be conducted daily for a total period of twelve calendar months. The questionnaire administration will take a total of 10 minutes while the speculum examination and acquisition of the endometrial biopsy will take approximately 5-10 minutes.

The information gathered will be treated with utmost confidentiality: your name will not be used as you will be identified using a serial number only known to me, my biostatitian and research supervisors, hence protecting your identity. The information obtained will be used to improve services in MTRH, to form or strengthen protocols, and may be published in medical journals and/or presented in scientific symposia (both local and international).

Contacts:

In case you have any questions later on, you can contact me on: Telephone: 0704945001, Email address: mosheyissa@yahoo.com . You can also contact the IREC chairperson, MOI TEACHING AND REFERRAL HOSPITAL; P.O.BOX 3-30100, ELDORET.

The Moi University and MTRH Ethics and Research Committee have reviewed and approved this study. This committee is charged with the responsibility of ensuring that research participants are protected from harm.

Respondent's declaration:

I have read the above information/ the above information has been read out to me. I have been given an opportunity to ask questions and seek clarification and my concerns have been satisfactorily addressed. I hereby voluntarily consent to participate in this research.

Name of participant……

Signature of participant……

Date (day/month/year)……

Declaration by the witness for an illiterate participant:

I have witnessed the accurate reading of the consent form to the potential participant, and that she has been given an opportunity to ask questions and seek clarification; and that her concerns have been fully addressed. I hereby confirm that the potential participant willingly consented to participate in this research.

Name of witness……

Signature of witness……

Date (day/month/year)……

Participant's Thumb print:

Declaration by the researcher/research assistant taking the consent:

I have accurately read out the information provided above to the potential participant and have given her an opportunity to ask questions and seek clarification; and that I have fully addressed all her concerns.

This is to confirm that I have not coerced her into consenting and that she has given consent out of her own free will.

Name of researcher/assistant……

Signature of researcher/assistant……

Date (day/month/year)……

APPENDIX 2: FOMU YA IDHINI

Jina langu ni Dr. Issa Moshey. Ninasomea uzamili kwenye Chuo Kikuu cha Moi, katika kitengo cha afya ya uzazi. Ili kuhitimu shahada hii, ninahitajika kufanya utafiti na niliamua kufanya utafiti ili kutathmini matokeo ya sampuli zitakazochukuliwa kutoka kwa nyungu za uzazi za wanawake waliokaribia kufika na waliofika umri wa kikomo cha hedhi wanaotafuta matibabu kwa sababu ya kuvuja damu isiyo ya kawaida; katika kitengo cha huduma ya afya ya wanawake waliolazwa na wasiolazwa katika hospitali ya MTRH, Eldoret.

Utafiti huu unahusu utathmini iwapo wanawake hawa walio na ugonjwa wa kuvuja damu wanayo saratani ya kifuko cha uzazi au la, na kutathmini mabadiliko yoyote katika sampuli zitakazochukuliwa kutoka kwa nyungu za uzazi, kama ni ya kawaida au la. Unao uhuru wa kuongea na yeyote unayemfahamu kuhusu utafiti huu kabla ya kufanya uamuzi wako kuhusu kushiriki au la.

Wakati mahijiano yanaendelea, unao uhuru wa kunikatiza na kuuliza maswali wakati wowote endapo kutakuwa na mambo au vipengee katika hojaji ambayo utakuwa hujayaelewa kikamilifu. Itakuwa furaha kwangu kukueleza. Iwapo maswali mengine yataibuka baada ya kuhojiwa, tafadhali jisikie huru kuniuliza kupitia nambari yangu ya simu ya rununu au anwani ya barua pepe kama ilivyonakiliwa katita kipengee cha mawasiliano.

Lengo la utafiti:

Lengo kuu la utafiti huu ni kutathmini aina ya mabadiliko katika sampuli za nyungu za uzazi za wanawake walio na tatizo la kutokwa na damu isiyo ya kawaida ili kubaini sababu kuu ya tukio hilo na kutumia matokeo hayo kuboresha huduma kwa wanawake walio na shida kama hiyo.

Athari na faida za utafiti huu na jinsi utafiti huu utakavyofanyika:

Nitakuuliza ama msaidizi wangu atakuuliza maswali kuhusu matukio muhimu yanayohusiana na afya yako ya uzazi. Vilevile, nitakufanyia kipimo cha njia ya uzazi nikitumia kifaa cha Spekulamu na hatimaye kuchukua sampuli kukota kwa nyungu ya uzazi kutumia Vibra pipelle. Una uhuru wa kuyajibu au kukosa kuyajibu maswali yoyote ambayo hutakuwa huru kujibu, na pia unao uhuru wa kukataa kushiriki kupimwa njia ya uzazi kwa Spekulamu, au pia kukataa kutolewa sampuli kutoka kwa nyungu ya uzazi.

Kushiriki kwako kwenye utafiti huu hakutaathiri huduma ya matibabu ambayo madaktari wako wanaona yanakufaa. Unaweza kupata adha katika utafiti huu wakati wa kupimwa kwa Spekulamu au wakati sampuli inachukuliwa kutuka kwa nyungu ya uzazi. Upata matokeo ya uchunguzi utakaofanyiwa sampuli ya nyungu yako ya uzazi ambayo huenda yakaelekeza matibabu ya shida yako ya kuvuja damu isiyo ya kawaida. Utafiti huu, hautahusisha kukupa dawa ya aina yoyote.

Jinsi ya kumhusisha muhusika na usiri wa utafiti:

Katika utafiti huu, nitawahusisha wanawake wote ambao wanatafuta matibabu ya utokwaji wa damu isio ya kawaida kutoka kwa nyungu ya uzazi. Utafiti huu utafanyika kila siku na utaendelea kwa muda wa miezi sita baada ya kuanza.

Mahojiano yatachukua muda wa dakika saba na kipimo cha spekulamu pamoja na kutoa sampuli kutoka kwa nyungu ya uzazi kuchukua dakika kumi.

Habari zitakazojitokeza zitawekwa katika mazingira ya faragha ya hali ya juu, na hautatambulishwa. Jina lako litabanwa. Nitakutambua kwa nukuu maalum ambayo nitakupa. Mimi na msaidizi wangu ndio watu pekee ambao watakua na ufahamu kuhusu nukuu hii. Matokeo ya utafiti huu yatatumiwa kuboresha huduma ya uzazi kwa wanawake walio na shida ya kutokwa na damu isiyo ya kawaida kutoka kwa nyungu ya uzazi na huenda yakachapishwa kwa jarida za kimatibabu ama kujadiliwa kwenye vikao vya kisayansi, humu nchini na hata ngambo.

Mawasiliano:

Endapo utakuwa na maswali, unaweza kuniuliza saa hii. Naomba uwe huru kuniuliza maswali ambayo huenda yakaibuka wakati wa utafiti au hata baadaye. Jisikie huru kunipigia simu kupitia nambari yangu ya rununu: 0704945001 au anwani yangu ya barua pepe: mosheyissa@yahoo.com.

Kama utahitaji kuwasiliana na kamati inayosimamia utafiti (IREC), unaweza kufanya hivyo kwa kumuandikia barua mwenyekiti wa kamati kupitia anwani ya posta ifuatayo: Mwenyekiti wa IREC, Hospitali ya Mafunzo na Rufaa ya MOI; Sanduku la Posta 3- 30100, ELDORET.

Kamati inayosimamia utafiti katika Chuo Kikuu cha Moi na Hospitali ya Mafunzo na Rufaa ya Moi (IREC) kushughulikia sheria za utafiti unaohusu binadamu. Kamati hii huhakikisha kwamba wamemlinda mhusika yeyote anayeshiriki katika utafiti wowote dhidi ya madhara ya aina yoyote ambayo huenda yakampata kwa kushiriki katika utafiti. Wanakamati wa IREC wamelisoma na kuidhinisha pendekezo langu la utafiti huu.

Kiapo cha Mhojiwa:

Nimeyasoma maelezo yaliyotangulia/ nimesomewa maelezo yaliyotangulia kisha nikapewa nafasi ya kuuliza maswali na kutafuta uwazi. Maswali yangu yamejibiwa kikamilifu. Kwa hivyo, ninatoa idhini kwa hiari yangu mwenyewe kushiriki katika utafiti huu.

Jina la mhojiwa: ……

Sahihi ya mhojiwa: ……

Tarehe (siku/mwezi/mwaka): ……

Kiapo cha shahidi wa mhojiwa ambaye hawezi kuandika/kusoma:

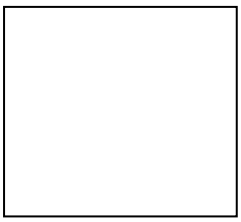
Nimeshuhudia mhojiwa akisomewa kwa usahihi maelezo yaliyomo kwenye nakala hii na akapewa nafasi ya kuuliza maswali na kutafuta uwazi. Maswali yote aliyouliza yalijibiwa kikamilifu. Kwa hivyo, ninadhibitisha kwamba mhojiwa ametoa idhini kwa hiari yake mwenyewe ya kushiriki katika utafiti huu.

Jina la shahidi……

Sahihi ya shahidi……

Tarehe (siku/mwezi/mwaka): ……

Alama ya kidole gumba cha mhojiwa:



Kiapo cha mtafiti/ msaidizi anayechukua idhini ya mhojiwa:

Nimechukua muda kumsomea mhusika maelezo yaliyomo kwenye nakala hii kwa usahihi kasha nikampa nafasi ya kuniuliza maswali na kutafuta uwazi. Ninadhibitisha kuwa nimeyajibu maswali yote aliyoniuliza kwa usahihi na kikamilifu.

Ninathibitisha ya kwamba mhusika ametoa idhini ya kuhusika katika utafiti huu kwa hiari yake mwenyewe.

Jina la mtafiti/ msaidizi: ……

Sahihi ya mtafiti/msaidizi: ……

Tarehe (siku/mwezi/mwaka): ……

APPENDIX 3: QUESTIONNAIRE

Date (dd/mm/yy)…….Serial Number……..

Place of current residence……..…….……

Telephone number……..……

SECTION 1: SOCIO-DEMOGRAPHIC DATA

1.1 Date of birth ……Age……

1.2 What is your marital status? (Tick one that applies).

Single ☐ Married ☐ Divorced ☐ Widowed ☐ Separated ☐ Other ☐

1.3 What is the highest level of your education: (Tick one that applies).

None ☐ Primary ☐ Secondary ☐ Tertiary ☐

1.4 What is your current employment status? (Tick where appropriate)

Formal employment [ ] Casual Laborer [ ] Self-employed [ ] Unemployed [ ]

1.5 Do you have an active Medical Insurance with you?

Yes [ ] No [ ]

SECTION 2: CLINICAL, BEHAVIORAL CHARACTERISTICS & FAMILY HISTORY

2.1 Weight (Kg)……. Height (m)…….. BMI ……..

2.2 Have you been diagnosed with any of the following chronic illnesses/conditions?

Diabetes Mellitus	
Chronic Hypertension	
Polycystic Ovary syndrome	

4.3 Do you currently smoke or have you ever smoked cigarettes before?

Yes [ ] No [ ]

2.3.1 If yes to 2.3, for how long did you smoke or have you been smoking? …….

On average how many packets a day? …….

2.4 Are you currently using any medications? Yes [ ] No [ ]

2.4.1 If yes to 2.4, which one(s), and or how long have you been using?

Drug	Duration of use

2.5 Have you ever experienced any of the following? (tick where appropriate)

Heavy menstrual bleeding since your first period?
Excess bleeding after delivery?
Bleeding after a surgical procedure?
Bleeding after getting dental work?
Bruising, one or two times per month?
Nose bleeding, one or two times per month?
Frequent gum bleeding?
Family history of bleeding symptoms?

2.6 Do you have a family history of any of the following cancers? (Tick where applicable)

Breast, Ovarian or Uterine Cancer	
Colon cancer	

SECTION 3: MENSTRUAL CHARACTERISTICS:

3.1 How old were you when you got your first menstrual period? …….

3.2 When was the first day of your last menstrual period (LNMP)?……..

(Go to question 3.3 if postmenopausal. If perimenopausal, skip to question 3.4)

3.3 How long has it been since you had your last period? ……

3.4 **Menstrual periods prior to the current changes in your menstrual cycles:**

3.4.1 For how many days did your menstrual periods last?.....

3.4.2 How many pads did you use per day?.....

3.4.3 How much blood was usually on your pad prior to a pad change?

Spotting [ ] moderately soaked [ ] fully soaked without clots [ ] fully soaked with clots [ ] flooding negating use of pads [ ]

3.4.4 How many days did you take from the first day of your menstrual period to the first day of your next menstrual period? …….

3.4.5 Were the durations between your menstrual cycles constant? Yes [ ] No [ ]

3.4.6 Did you experience any bleeding between your menstrual periods?

Yes [ ] No [ ]

3.5 For how long have you been experiencing the changes in your menstrual periods/bleeding a year after your final menstrual period? .....

3.6 **Describe your current menstrual periods/bleeding:**

3.6.1 For how many days do your menstrual periods generally last? .....

3.6.2 How many pads do you use per day? .....

3.6.3 Do you in your opinion experience excessive menstrual blood loss that interferes with your physical activities and social life, or put extra financial burden?

3.6.4 How much blood is usually on your pad prior to a pad change?

Spotting [ ] moderately soaked [ ] fully soaked [ ] flooding negating use of pads [ ]

3.6.5 How many days do you take from the first day of your menstrual period to the first day of your next menstrual period? …….

3.6.6 What is the difference in days between your longest and shortest cycles?.....

3.6.7 Do you experience bleeding between your menstrual periods?

Yes [ ] No [ ]

SECTION 4: USE OF CONTRACEPTIVES:

4.1 Are you currently, or have you ever used any form of contraceptives before?

Yes [ ] No [ ]

4.2 If Yes to above, which one? (Tick all that apply).

Method		**Duration of use**
Birth Control Pills (COCs, POPs)		
DMPA		
Implants (Implanon, Jadelle)		
Intrauterine Device (Mirena, Cu-IUD)		

SECTION 5: OBSTETRIC HISTORY:

5.1 Have you ever been pregnant before? Yes [ ] No [ ]

5.1.1 If yes to 5.1, how many times have you been pregnant……..

5.1.2 If yes to 5.1, how old were you when you first got pregnant? ……..

SECTION 6: ULTRASOUND FINDINGS:

6.1 Type of ultrasound (Tick where applicable)

Transabdominal ultrasound [ ] Transvaginal ultrasound [ ]

6.2 Specific Ultrasound findings

6.2.1 Uterine Size: Normal [ ] Bulky [ ]

6.2.2 Myometrial Mass(es): Yes [ ] No [ ]

6.2.3 Endometrial Mass(es): Yes [ ] No [ ]

6.2.4 Endometrial Thickening: Yes [ ] No [ ] Specify E.T ……..

6.2.5 Other Important Ultrasound Findings

SECTION 6: HISTOPATHOLOGICAL PATTERN:

Proliferative Endometrium
Secretory Endometrium
Atrophic Endometrium
Acute or Chronic Endometritis
Menstrual Phase
Disordered Proliferative Endometrium
Decidual Reaction
Endometrial Hyperplasia without Atypia
Endometrial Hyperplasia with Atypia
Mixed Proliferative-Secretory Pattern
Products of Conception
Endometrial Polyp
Uterine Leiomyoma
Endometrial Cancer
Insufficient Sample
Other

APPENDIX 4: IREC APPROVAL

MU/MTRH-INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET

Reference: IREC/2018/297
Approval Number: 0003293

3rd April, 2019

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
03 APR 2019
APPROVED
P. O. Box 4606-30100 ELDORET

Dr. Issa Moshey,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

Dear Dr. Moshey,

RE: FORMAL APPROVAL

The MU/MTRH- Institutional Research and Ethics Committee has reviewed your research proposal titled: -

"Endometrial Histopathological Patterns of Perimenopausal and Postmenopausal Women Diagnosed with Abnormal Uterine Bleeding at Moi Teaching and Referral Hospital".

Your proposal has been granted a Formal Approval Number: ***FAN: IREC 3293*** on 3rd April, 2019. You are therefore permitted to begin your investigations.

Note that this approval is for 1 year; hence will expire on 2nd March, 2020. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date. You will be required to submit progress report(s) on application for continuation, at the end of the study and any other times as may be recommended by the Committee.

Furthermore, you must notify the Committee of any proposal change (s) or amendment (s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. You will also be required to seek further clearance from any other regulatory body/authority that may be appropriate and applicable to the conduct of this study.

Sincerely,

PROF. E. WERE
CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc	CEO	-	MTRH	Dean	-	SOP	Dean	-	SOM
	Principal	-	CHS	Dean	-	SON	Dean	-	SOD

APPENDIX 5: STUDY COSTS

Item	No. of Units	Cost per unit	Total Units Cost	TOTAL COST
Research Proposal Cost				
Book Printing charges	5	400.00	2,000.00	
Questionnaire	120	30.00	3,600.00	
Photocopy consent	120	10.00	1,200.00	
Book binding charges	5	50.00	250.00	
Stationery	10	100.00	1,000.00	
Biostatistician charges	1	15,000.00	15,000.00	
TOTAL				**23,050.00**
Thesis Expenses:				
Book printing charges	8	400.00	3,200.00	
Book binding charges	8	50.00	400.00	
Biostatistician charges	1	15,000.00	15,000.00	
Pipelle device	10	1,200.00	12,000.00	
Pathology lab charges	100	1,500.00	150,000.00	
Other printing charges	10	50	500	
Estimated cost of publishing			60,000.00	**241,100.00**
GRAND TOTAL				**264,150.00**