# ASSESSMENT OF ASYMPTOMATIC ENDOMETRIAL THICKNESS IN POSTMENOPAUSAL WOMEN AND THOSE WITH MEDICAL DISORDERS AT UNIVERSITY OF ILORIN TEACHING HOSPITAL

**A DISSERTATION SUBMITTED TO THE NATIONAL POSTGRADUATE MEDICAL COLLEGE OF NIGERIA IN PARTIAL FULFILLMENT FOR THE REQUIREMENT FOR THE AWARD OF FELLOWSHIP OF THE COLLEGE.**

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## DECLARATION

I Dr. Tola Yinka Bakare hereby declared that this work is original unless acknowledged. This work has not been submitted in support of an application for a fellowship/diploma of this or any other institution of learning. It has also not been submitted for publication/conference presentation.

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## DEDICATION

This work is dedicated to almighty God for seeing me through the residency program. Also to the memory of one of my supervisor Dr Ibrahim MS who died during the course of this study. Finally to my wife Olubukola Racheal, who stood by me through thick and thin.

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## DEFINITION OF TERMS/ ABBREVIATIONS

| | |
|---|---|
| **BMI** | Body Mass Index |
| **dl** | Decilitre |
| **ET** | Endometrial Thickness |
| **FSH** | Follicular Stimulating Hormone |
| **HRT** | Hormone Replacement Therapy |
| **IGF-1** | Insulin Growth Factor-1 |
| **Kg** | Kilogram |
| K | Kruskal Wallis Test |
| **LH** | Luteinizing Hormone |
| **mg** | Milligram |
| **mm** | Millimetre |
| **mmHg** | Millimetre of Mercury |
| **$m^2$** | Metre square |
| **SPSS** | Statistical Package for Social Science |
| **SD** | Standard Deviation |
| **TVS** | Transvaginal Scan |
| **UITH** | University of Ilorin Teaching Hospital |
| **USA** | United States of America |
| **WHO** | World Health Organization |
| **r** | Spearman correlation coefficient |

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## ABSTRACT

**Background:** Menopause is the time when permanent cessation of menstruation occurs due to loss of ovarian activities. Postmenopausal asymptomatic endometrial thickening is an endometrial thickness of >5mm in the absence of bleeding per vaginal. There is a strong association between endometrial thickness and endometrial disease. Factors influencing endometrial thickness includes parity, postmenopausal years, body mass index and medical illness. These factors exert their influence on the endometrium and resultant chaanges may be picked by transvaginal scan.

**Aim**: This study assessed asymptomatic endometrial thickness in postmenopausal women and those with medical disorders at the University of Ilorin Teaching Hospital, Ilorin using transvaginal scan.

**Objectives**: The objectives of the study were to determine the endometrial thickness among asymptomatic postmenopausal women attending selected out-patient clinics at the UITH, relationship between body mass index and asymptomatic endometrial thickness among postmenopausal women and endometrial thickness in postmenopausal women with diabetes and hypertension.

**Methods**: The study was conducted in the Department of Obstetrics and Gynaecology and other out-patient clinics of the University of Ilorin Teaching Hospital. It was carried out among asymptomatic postmenopausal women who attended the gynaecological, endocrinology, cardiology and general out-patient clinics. It was hospital-based, cross-sectional descriptive study. Participant selection was based on purposive non-probability sampling on the set inclusion criteria. A study proforma sheet was used to obtain information

on age, parity, age at menopause, postmenopausal years and associated medical illnesses. Anthropometric measurements were taken and body mass index was calculated. The participants' blood pressure was measured using a mercury sphygmomanometer and the blood glucose levels using a standardised glucometer. The endometrial thickness was measured using a tranvaginal scan and women with abnormally thickened endometrium were counselled on endometrial biopsy for histo-pathological diagnosis and subsequently referred to the Gynaecology clinic for further investigations and definitive management. Descriptive analysis was performed using SPSS software version 23. The results were presented in tables and charts. P – Value was set as 0.05 as the level of significance.

**Results:** The mean age of participants was 64.90 years ± 8.20 and their mean age at menopause was 48.65years ± 2.67. The mean (SD) of postmenopausal years was 15.65 (6.69) years. There was a documented increase in the mean values of endometrial thickness for participants with the hypertension; 2.82mm ± 4.07 and DM; 2.27mm ± 1.08 when compared with those with no medical disorder; 1.42mm ± 1.16 and this was statistically significant with p values 0f 0.026 and 0.005 respectively while duration of medical illness showed no statistical significant relationship with endometrial thickness. Endometrial thickness of participants increased as BMI increased though not statistically significant. There was an inverse relationship between duration of menopause, parity and endometrial thickness and this was statistically significant (p values = 0.048 and 0.005).

**Conclusion:** This study suggests that parity, duration of menopause, presence of hypertension and diabetes mellitus are related to asymptomatic endometrial thickness in postmenopausal women.

**Recommendation:** Postmenopausal asymptomatic endometrial thickening should be evaluated on a case-by-case basis and risk factors for endometrial cancer including diabetes mellitus and hypertension should be considered in decision making.

# CHAPTER ONE

## INTRODUCTION

The menopause, from the Greek 'Menos' (month) and 'Pausis' (cessation) is defined as the last menstrual period.[1] Retrospectively, menopause is defined clinically as the time of the final menstrual period followed by amenorrhoea of 12 months. Menopause occurs in the human female as a result of two processes. First, oocytes that are responsive to gonadotropins becomes atretic and reabsorbed from the ovary, and secondly, the few oocytes remaining do not respond to gonadotropins. Isolated oocytes can be found in postmenopausal ovaries on very careful histological inspection. Some of them show a limited degree of development, but most reveal no sign of development in the presence of excess endogenous gonadotropins.[2] Thus menopause is the time when permanent cessation of menstruation occurs due to loss of ovarian activity. Post menopause describes the period following the final menses.[3]

It is known that the endometrium irrespective of reproductive or menopausal status contains oestrogen receptors and responds to circulating oestrogens.[4] Abundance of oestrogen results in endometrial overgrowth and low level results in endometrial atrophy. The extent of endometrial thickness thus constitutes a potential biomarker of oestrogen level even in postmenopausal women.[4]

The ovaries are the major source of oestrogen, however peripheral adipose tissue also contributes to its synthesis and this is influenced by medical disorders like metabolic X syndrome.[5] For instance diabetic women who are obese have high insulin resistance with resultant high plasma level of insulin, which increases free oestrogen levels by decreasing the concentration of sex hormone-binding globulin which normally acts as carrier for oestrogen

and other sex hormones in the blood.[6] Also, Insulin growth factor (IGF-1) and its binding protein (IGF binding protein-1) are known to promote endometrial cell growth.[7] Hence, high levels of IGF found in diabetic women and women with higher body mass index may produce endometrial hyperplasia.[7]

According to American Diabetes Association, pregestational diabetes can be diagnosed if the symptoms of diabetes plus random plasma glucose concentration greater or equal to 200mg/dL or fasting plasma glucose of greater or equal to 126mg/dL( fasting is defined as no caloric intake for at least 8 hours) or two hour plasma glucose level of greater or equal to 200mg/dL during an oral glucose tolerance test or glycosylated haemoglobin of greater or equal to 6.5% using a standardized assay.[8]

There is a strong association between the thickness of the endometrial stripe and endometrial disease, with normal endometrium being usually less than 5mm in thickness in postmenopausal women.[9] Transvaginal ultrasonography with or without colour flow imaging has been investigated as a screening technique for endometrial cancer.[9] The measurement of the endometrium is made at its maximal thickness on a midline sagittal image of the uterus obtained by transvaginal ultrasound. It is a measurement of the combined width of the anterior and the posterior layers of the endometrium. It has been suggested that the normal endometrial thickness in a postmenopausal woman is less than or equal to 5mm.[9] There is controversy about the normal measurement in women on hormone therapy, however studies have shown a normal range from 5.4 to 10.8 mm.[10-13] The endometrium may be thicker in the first year after the last menstrual period, reflecting some residual hormonal activity.[14]

Asymptomatic endometrial thickening found on ultrasound examination in postmenopausal women often poses a clinical dilemma.[15,16] Asymptomatic endometrial thickening is defined

as an endometrium of >5 mm discovered on ultrasound in a postmenopausal woman who is not bleeding.[15,17,18]

Endometrial thickness after menopause may indicate malignancy when it is more than 5 mm.[19,20] Nevertheless, there may be other influencing factors such as age, parity, serum estradiol,[4] menopausal years,[21] body mass index(BMI), medical illness like diabetes[21] or hypertension,[23] drugs like tamoxifen[24]or hormone replacement therapy (HRT), myoma, uterine volume and ovarian volume.[25] These factors exert their influence on the endometrium and the resultant changes in the endometrial lining may be picked by sonographic evaluation. Hence, there is a need to describe postmenopausal endometrial thickness and determine how anthropometric measurements and coexisting medical conditions influence it.

# CHAPTER TWO

# LITERATURE REVIEW

## 2.1 Physiology of menstrual cycle

The occurrence of regular, ovulatory menstrual cycle depends on a complex interaction between the hypothalamus, pituitary, ovary and endometrium. The mean age of menarche in Nigeria is 13.50 ± 1.33 years[69] and the mean age of menopause reported in Ibadan was 49.36 ± 5.0 years.[70] The menstrual cycle is divided into an ovarian cycle and an endometrial cycle.

The ovarian cycle involves the development and maturation of ovarian follicles, ovulation and formation of corpus luteum and its degeneration.[28] It is composed of three phases namely; follicular, ovulatory and luteal phases.[29] The development of the oocyte is the key event in the follicular phase of the menstrual cycle. The development of the follicles in the earlier stage is independent of hormonal stimulation up to the pre-antral stage while beyond the pre-antral stage the follicles are stimulated by luteinizing hormone and follicular stimulating hormone. The basis of the hormonal activity in pre-antral to pre-ovulatory follicles is described as two cells, two gonadotrophin hypothesis. LH stimulates thecal cells to produce androgen while FSH stimulates granulosa cells to produce oestrogen from aromatization of androgen produced by the thecal cells. The most advanced follicle at mid follicular phase becomes the dominant follicle. Rising level of oestrogen and inhibin A produced by the dominant follicle inhibits pituitary FSH production. Declining level of FSH causes atresia of all but the dominant follicle.[29]

Ovulation involves the release of the oocytes from the dominant follicle. The LH surge is regarded as the most reliable indicator of imminent ovulation. The LH surge results from high level of oestrogen produced by the granulosa cells which causes a positive feedback effect on the pituitary to produce LH. Also the progesterone produced by the luteinized granulosa cells further amplifies the positive feedback effect of oestrogen on the pituitary gland LH secretion. Macrophages within the follicle produce proteolytic enzymes which cause breakdown of the follicular wall and subsequent release of the oocyte.[29] The luteal phase is characterized by the production of progesterone from the corpus luteum formed from granulosa and theca cells retained after ovulation. In the absence of pregnancy, luteolysis occurs' 14days after ovulation.[29]

Endometrial cycle involves the changes that occur in the endometrium during the menstrual cycle. The changes are mainly as a result of the direct influence of oestrogen and progesterone on the endometrium. The endometrium is made up of two layers; basal and functional layers. Basal layer is relatively unresponsive to hormonal stimulation and remain intact throughout the menstrual cycle. Functional layer consist of two layers namely; the compacta and spongiosa. The functional layer is responsive to hormonal stimulation and most of this layer is lost at the time of menses.[27] The endometrial cycle is divided into three phases namely; menstruation, proliferative and secretory phase.

Menstruation is the visible manifestation of cyclic physiologic uterine bleeding due to shedding of the endometrium following invisible interplay of hormones mainly through the hypothalamo-pituitary-ovarian axis.[28] Menstruation is initiated by the withdrawal of oestrogen and progesterone. In an ovulatory cycle, the endometrium is exposed to oestrogen and progesterone in an orderly manner causing decidualization of the endometrium. If implantation fails to occur programmed cell death (apoptosis) ensues. Thus menstruation is the shedding of the dead endometrium and ceases as the endometrium regenerates.[29]

Proliferative phase involves an increase in growth of the functional part of the endometrial lining and endometrial glands under the influence of oestrogen. During this time, the epithelial lining of the endometrial glands changes from a single layer of low columnar cells to pseudo-stratified epithelium with frequent mitosis. The endometrial thickness increases from 0.5mm at menstruation to 3.5mm to 5mm at the end of the proliferative phase.[29]

The secretory phase is characterized by progesterone induced glandular secretory activity. This results in decidualization of the endometrium in the late luteal phase. Decidualization is an irreversible process and leads to endometrial apoptosis and menstruation unless pregnancy occurs.[29]

### 2.2 Menopause

Menopause means permanent cessation of menstruation at the end of the reproductive life due to loss of ovarian follicular activity. The clinical diagnosis is confirmed following stoppage of menstruation for twelve consecutive months without any other pathology. The age at which menopause occurs is genetically predetermined.[30] The mean age at menopause reported in Ibadan was 49.36 ± 5.0 years.[70]

Climateric is the period of time during which a woman passes from reproductive to the non-reproductive stage. This phase covers 5-10 years on either side of menopause. Post-menopause is the phase of life that comes after menopause.[30] Premature ovarian failure is said to have occurred when menstruation ceases before the age of 40 years and early menopause before the age of 45 years.[1]

Menopause can be divided into two types namely; physiologic menopause which is as a result of progressive loss of oocytes mainly through atresia and a few during ovulation, and artificial menopause which occurs as a result of surgical removal of the ovaries or by radiation therapy.[2]

## 2.3 Reproductive endocrinology of climacteric and menopause

The process of menopause cannot be satisfactorily explained by any single theory. However it is an established fact that with progressive reduction of gonadotrophin responsive ovarian follicle, a stage is reached when suboptimal ovarian oestrogen secretion can neither promote the hormonal interaction of the hypothalamo-pituitary-gonadal axis nor sustain cyclical endometrial growth and normal menstrual cycle ceases.[31]There is a significant fall in serum level of oestradiol which in turn decreases the negative feedback effect on hypothalamo-pituitary axis resulting in increase in FSH. The increase in FSH is also due to diminished inhibin production by the granulosa cells of the ovarian follicles. The increase of LH occurs' subsequently.[30]

## 2.4 Asymptomatic endometrial thickening in postmenopausal women

The endometrium is the lining epithelium of the uterine cavity above the level of the internal os.[28] It is made up of two layers; basal and functional layers. The functional layer is further divided into compacta and spongiosa. [27] During the proliferative phase of the menstrual cycle, the basal layer measures about 1mm in thickness, while the functional layer reaches a maximum thickness of about 3.5-5mm by 14$^{th}$ day. However, the endometrium measures about 8-10mm in the secretory phase. [27]

Concern is raised when an endometrium of > 5 mm is discovered during an ultrasound examination, often one that is undertaken for non-gynaecologic reasons. Subsequent radiologic reports prompt interventions that can be invasive and involve risk.[32]

In the first year after the last menstrual period the normal endometrium is often thicker than it will be several years after menopause, reflecting fluctuating levels of estrogen.[32] Descriptions

of the endometrium on ultrasound examination include global thickening, heterogeneity, focal areas of thickening, fluid collections, increased vascularity, and myometrial associated findings such as myometrial cysts, and sub-mucosal fibroids. After menopause, endometrial thickening may reflect proliferative endometrium, cystic hyperplasia, complex hyperplasia, atypical hyperplasia, or carcinoma of the endometrium. Ultrasound evidence of thickened endometrium may also indicate structural abnormalities such as a uterine septum, sub-mucous myomas, polyps, or adenomyosis. Ultrasound technology, by identifying vascular flow, now allows differentiation of polyps from other abnormalities.[33] Increased vascularity and fluid accumulation in association with endometrial thickening are cause for greater concern than other findings.[34]

Asymptomatic endometrial thickening is defined as an endometrium of greater than 5mm discovered on ultrasound in a postmenopausal woman who is not bleeding.[14,16,17] It has been suggested that normal endometrial thickness in postmenopausal woman is ≤5mm. Current ultrasound literature suggests that asymptomatic endometrial thickness of 8 to 11 mm in a postmenopausal women is not abnormal.[9-11,35,36] In clinical studies, endometrial malignancy is uncommon in women with an endometrial thickness measurement <5 mm. [37,38] The incidence of endometrial thickening in postmenopausal women ranges from 3% to 17% while the incidence of endometrial cancer in an unselected postmenopausal population is 1.3 to 1.7 /1000.[39-41] Goldstein in 2010 recommended that postmenopausal asymptomatic endometrial thickening be evaluated on a case by case basis. The clinician must consider risk factors for endometrial cancer including obesity, polycystic ovary syndrome and diabetes mellitus in their decision making.[19]

## 2.5 Role of transvaginal scan (TVS) in the measurement of endometrial thickness in postmenopausal women

Ultrasonography involves the use of high-frequency sound waves to visualize internal organs and structures. It can be utilized to screen for signs of endometrial carcinoma or precancerous abnormalities. Two types of ultrasonography are available for visualizing the uterine lining: transabdominal, in which the sound waves are directed through the abdomen; and transvaginal, in which the instrument transmitting the sound is inserted into the vagina. In clinical studies, endometrial malignancy is uncommon in women with an endometrial thickness measurement less than 5 mm.[37,38]

The Canadian Cancer Society reports that there is inadequate evidence that screening by ultrasonography or endometrial sampling would reduce the mortality from endometrial cancer.[42] It is unknown how many women who have endometrial cancer are diagnosed in the absence of bleeding. Although diagnosis of cancer in asymptomatic women has been estimated by Smith-Bindman to be 5% to 10% of all cases.[43] Assessment of endometrial thickness using transvaginal scan has proven useful in the diagnosis of pathologic endometrial changes in postmenopausal women. Recently, it has been reported that endometrial thickness measurement performed via TVS can be used as a screening method in terms of premalignant lesions of endometrium cancer[44-47]. The endometrial thickness, which was determined, is also compatible with histo-pathological diagnosis.[44-47] Granberg et al documented that if the cut-off limit for an abnormally thickened endometrium was set at 5 mm, the positive predictive value for identifying pathologic changes was 87.3%.[48] In the Nordic trial, the largest study to date, a cut-off of less than 5 mm was associated with 96 percent sensitivity, 68 percent specificity and an accuracy of 78 percent for detecting histologically abnormal endometrium in patients with postmenopausal bleeding.[49] The

endometrial thickness constitutes a potential biological marker of estrogen status even in postmenopausal women because the endometrium contains estrogen receptors and responds to circulating estrogens..[50]

Chard et al evaluated the usefulness of transvaginal ultrasonography in visualizing endometrial abnormalities, particularly precancerous changes, of 111 postmenopausal women and discovered that all women who had endometrial thickness of >5mm (31%) had endometrial tissue abnormalities.[51] Thus the results confirmed findings from previous studies in which further evaluation for endometrial cancer was recommended if endometrial thickness is >5mm. TVS was found to be very useful; it was simple to perform, was well accepted by the patients, and is a non-invasive technique.[51]

Tsuda et al and Gerber et al conducted similar study on TVS measurement of endometrial thickness in postmenopausal women using a cut off of 3mm and 10mm respectively and concluded that there is no prognostic advantage with symptomatic patients who had bleeding of shorter than 8weeks and that endometrial screening often results in unnecessary operations.[52,53] In 1995, Ciatto et al conducted a study on the feasibility of using TVS to screen for endometrial carcinoma solely on the basis of endometrial thickness and concluded that screening by endometrial sonography is feasible on a practical basis, but its efficacy needs to be proven by prospective controlled studies which would enroll large populations to ensure sufficient statistical power.[54]

Vuento et al focused on the feasibility of TVS to screen for endometrial cancer in asymptomatic postmenopausal women using multiple criteria, one of which was endometrial thickness and the authors concluded that TVS, while sensitive for detecting early endometrial cancer, has a low specificity that precludes its utility as a screening modality.[17] A study by Fleischer et al in which 1926 women underwent ultrasound examination as part of the workup for an osteoporosis prevention trial found that 93 women had an endometrium

thickness of > 6 mm. When endometrial aspiration of 42 of these women was undertaken, there were abnormal findings in only 1 case. A further 1750 of 1833 women with endometrial thickness of < 6 mm underwent sampling, yielding 5 abnormal results (1 of which was endometrial cancer). The sensitivity was 17% for 6 mm and 33% using 5 mm as a threshold. The positive predictive value was 2%. The negative predictive value at <6mm was 99%

In summary, various studies on the role of transvaginal scan (TVS) in the measurement of endometrial thickness in postmenopausal women have yielded conflicting results. Some studies reported that endometrial thickness measurement performed via TVS can be used as a screening method in terms of premalignant lesions of endometrium cancer while others concluded that there is no prognostic advantage.

### 2.6 Effect of BMI on endometrial thickness in post menopausal women

The body mass index (BMI) or quetelet index is a value derived from the mass (weight) and height of an individual. The body mass index is defined as the body mass divided by square of the height, and is universally expressed in units of $kg/m^2$, resulting from mass in kilograms and height in metres. The BMI is an attempt to quantify the amount of tissue mass (muscle, fats, and bone) in an individual, and then categorize that person as underweight, normal weight, overweight, or obese based on that value. The WHO regards a BMI of less than $18.5kgm^{-2}$ as underweight, normal 18.5 – $24.9kgm^{-2}$ while a BMI equal or greater than $25kgm^{-2}$ is considered overweight and $30kgm^{-2}$ and above is considered obese.[56]

The most important study that examined the relationship between BMI and endometrial thickness and suggested the presence of a significant relationship between both is a prospective cross-sectional study conducted by Douche et al on Japanese women. This study, which included 212 cases, found a significant relationship between endometrial thickness and BMI. It was stated that this relationship was not dependent on the age and menopausal age.[57]

Similarly in a study that included 531 healthy postmenopausal women, a high positive correlation between BMI and endometrial thickness was found among the participants.[58] Serin et al, in a study conducted on a total of 182 postmenopausal women investigating the effects of obesity and hypertension on endometrial thickness concluded that only obesity increases endometrial thickness.[59] Similarly Andolf and colleagues stated that there is a relationship between endometrial thickness and BMI[20]

However Van Der Bosch and colleagues observed the opposite as their study revealed that neither BMI nor body weight is related to endometrial thickness.[60] Similarly a study by Berker et al involving 75 postmenopausal women could not find a statistically significant relationship between increased endometrial thickness and BMI. However, compared with the other group, patients having a lower BMI and diagnosed with atrophic endometrium is significant in terms of showing the effect of the peripheral estrogenic conversion.[61] Guven and colleagues on the other hand, assessed the endometrial thickness and correlation with BMI in 97 postmenopausal women. Patients' age, the period after menopause and BMI were compared, and it was found that BMI was associated with age and period after menopause, but no correlation with endometrial thickness was observed.[62]

**2.7 Effect of hypertension on endometrial thickness**

Hypertension is a common medical disorder that affects 20–30% of adults in the United States[63]. Hypertension is defined as a sustained blood pressure higher than 140/90 mm Hg. In the nonpregnant patient, essential hypertension accounts for more than 90% of cases; however, many other conditions must be considered.[63] The prevalence of hypertension in Nigeria observed by Adeloye and colleague was 28.9.[83] Hypertension has been identified as a risk factor for the development of endometrial carcinoma. Assessment of endometrial thickness using transvaginal ultrasonography has proven useful in the diagnosis of pathologic endometrial changes in postmenopausal women. Studies performed outside Nigeria have

shown that, compared with normotensive postmenopausal women, hypertensive postmenopausal women had increased asymptomatic endometrial thickness[76].

A study by Alcazar et al compared the endometrial thickness of asymptomatic postmenopausal hypertensive patients with normotensive patients, and a thicker endometrium was found in hypertensive cases[64]. Altıntaşoğlu et al conducted a study in 2005 which included 27 hypertensive, 24 obese, and 20 healthy postmenopausal women and reported that in hypertensive and obese postmenopausal women, it is necessary to particularly perform endometrial thickness measurements, and pathological examination should be performed for cases whose endometrial thickness is greater than 5 mm.[66] Similarly in a study by Yavuz Yurtsever et al, in which the effect of Body Mass Index on endometrial thickness was compared, it was found that 24.4% of the hypertensive group had endometrial thickness of greater or equal 5mm whereas 11.7% of the non-hypertensive group showed a similar thickness. The average endometrial thickness in hypertensive patients was 4.56±3.04mm, whereas the average endometrial thickness in non- hypertensive group was 3.99±2.38mm ($p=0.043$). Thus, a statistically significantly increased endometrial thickness in hypertensive patients was found.[67] Pardo and colleagues published the ultrasonographic endometrial results of asymptomatic postmenopausal women and determined that patients with hypertension were found to have a thinner endometrium.[65]

**2.8 Effect of diabetes mellitus on endometrial thickness**

Diabetes mellitus is a chronic metabolic disorder due to either insulin deficiency (relative or absolute) or due to peripheral tissue resistance (decrease sensitivity) to the action of insulin.[68] The pathophysiology involved are; decreased sensitivity of skeletal muscles and liver to insulin (insulin resistance) and inadequate secretion of insulin (beta cell dysfunction). The ultimate effect is hyperglycaemia.[68]

According to American Diabetes Association, pregestational diabetes can be diagnosed if the symptoms of diabetes plus random plasma glucose concentration greater or equal to 200mg/dl or fasting plasma glucose of greater than or equal to 126mg/dl ( fasting is defined as no caloric intake for at least 8 hours) or two hour plasma glucose level of greater or equal to 200mg/dl during an oral glucose tolerance test or glycosylated haemoglobin of greater or equal to 6.5% using a standardized assay.[26]

Diabetic women who are obese have high insulin resistance with resultant high plasma level of insulin, which increases free oestrogen levels by decreasing the concentration of sex hormone-binding globulin which normally acts as carrier for oestrogen and other sex hormones in the blood.[6] Also, Insulin growth factor (IGF-1) and its binding protein (IGF binding protein-1) are known to promote endometrial cell growth.[7] Hence, high levels of IGF found in diabetic women and women with higher body mass index may produce endometrial hyperplasia.[7]

A retrospective study on effect of body mass index on endometrial thickness in postmenopausal asymptomatic patients was conducted at the Istanbul research and training hospital menopausal clinic between June 2008 and April 2010 revealed that 23.0% of the study group was diabetic. The endometrial thickness in 74% of diabetic patients was ≤5 mm, whereas the endometrial thickness in 26% of patients was ≥5 mm. The average endometrial thickness of the diabetic and non-diabetic women were 4.80±3.41 mm and 4.18±2.57 mm respectively with a p- value of p=0.007.[67]

In a 1993 study of ultrasonic thickness of the endometrium in 300 asymptomatic postmenopausal women, it was found that endometrial thickness correlated significantly with BMI.[20] In the same study, Andolf and colleagues found a non-significant trend towards a

higher prevalence of predisposing factors (hypertension, nulliparity, DM) in women with a thick endometrium.[20]

# CHAPTER THREE

## 3.1 **AIM**

This study assessed asymptomatic endometrial thickness in postmenopausal women and those with medical disorders at the University of Ilorin Teaching Hospital using transvaginal scan.

## 3.2 OBJECTIVES

1. To measure the endometrial thickness in asymptomatic postmenopausal women attending the out-patients clinics at the UITH.
2. To determine the relationship between body mass index and endometrial thickness among asymptomatic postmenopausal women
3. To measure the endometrial thickness in selected asymptomatic postmenopausal women with diabetes and hypertension in order to determine the relationship between endometrial thickness and duration of medical disorders of hypertension or DM.

## 4.3 HYPOTHESIS

Null hypothesis 1: There is no relationship between the anthropometric measurements of BMI and endometrial thickness in asymptomatic postmenopausal women.

Alternate hypothesis 1: There is a relationship between the anthropometric measurements of BMI and endometrial thickness in asymptomatic postmenopausal women.

Null hypothesis 2: There is no relationship between medical disorders of hypertension, diabetes and endometrial thickness in asymptomatic postmenopausal women.

Alternate hypothesis 2: There is a relationship between medical disorders of hypertension, diabetes, and endometrial thickness in asymptomatic postmenopausal women.

## 4.4 JUSTIFICATION/RELEVANCE OF THE STUDY

Endometrial cancer is the commonest gynaecological cancer in the developed world, third in sub-Sahara and an important cause of morbidity and mortality in women[82]. Endometrial thickness measurement is one of the investigations done for suspected case of endometrial cancer. Obesity, hypertension and diabetes mellitus are identified risk factors for endometrial cancer. The finding of asymptomatic endometrial thickening on ultrasound presents a clinical management dilemma and is a frequent reason for referral by family physicians. The presence of endometrial hyperplasia is associated with risk of progression to endometrial cancer and this is dependent on the histological type.[80] Endometrial thickness constitutes a potential biological marker of estrogen status even in postmenopausal women because the endometrium contains estrogen receptors and responds to circulating estrogens.

The cut-off values for endometrial thickness in asymptomatic postmenopausal woman have been determined. However, studies are few on the relationship between medical disorders, anthropometric measurements and asymptomatic endometrial thickness after menopause. These medical disorders are now prevalent in our society due to westernisation of diet and women with these conditions now live longer due to availability of drugs. Thus there is a need to assess the endometrial thickness in these postmenopausal women using TVS and factors that influence postmenopausal endometrial thickness in them. Those with abnormally thickened endometrium will be counselled on need for further investigations such as endometrial biopsy and transferred to gynaecology clinic.

# CHAPTER FOUR

# METHODOLOGY

## STUDY AREA

The study was conducted at the University of Ilorin Teaching Hospital (UITH), a tertiary health institution located in Ilorin East local government area of Kwara state. Ilorin is the capital of Kwara state which is located in the North-Central geopolitical zone of Nigeria.

The University of Ilorin Teaching Hospital serves as a referral centre for patients not only within Kwara state but also for neighbouring states like Niger, Kogi, Ekiti, Oyo and Osun states. In addition to tertiary health care, it also provides primary and secondary health care services. The subjects for the study will be recruited from the out-patients presenting to the Department of Obstetrics and Gynaecology, UITH and also from other departments for example, Family Medicine Department and Medicine Department.

The Obstetric Unit is housed in a 2 storey building and consists of antenatal and postnatal wards which have 30 beds each, a 25 bed postnatal surgical ward; an 18 bed emergency ward, and a 25 bed gynaecology ward. Also housed in same 2 storey building are the antenatal clinics, labour ward, ultrasound room, family planning unit, an operating theatre with two functional suites and a neonatal intensive care unit adjoining the labour ward. There are four firms that are run by Consultants who supervise the resident doctors and interns.

The Department of Family Medicine represents the primary care unit of the hospital; most patients are expected to pass through the general out-patient clinic for assessment. Majority of these are managed and those that need other forms of specialist care are referred to other units of the hospital. The department is run by six consultant family physicians, residents in

various stages of training, principal and senior medical officers, and other members of the health care team including nurses and the health record staff.

The medical out-patient clinics are run by the cardiology, endocrinology, nephrology, neurology and dermatology units. The medical ward occupies the last floor of a two storey building. It consists of two wards namely the male and female medical wards. A stroke unit is attached to the ward. The medical outpatient clinic is housed in a one storey building and the clinic holds every Mondays to Fridays.

STUDY POPULATION

The study population comprised of asymptomatic postmenopausal women attending the out-patient clinics at the University of Ilorin Teaching Hospital.

**Inclusion criteria**

1. Postmenopausal women whose last menstrual period is more than 12months as at presentation.
2. Postmenopausal women attending diabetes or hypertension clinics and have been diagnosed of such conditions for minimum period of one year.
3. Asymptomatic postmenopausal women with no history of bleeding per vaginam since attainment of menopause.
4. Willingness to participate

**Exclusion criteria:**

1. Women who had hysterectomy or oophorectomy ( surgical menopause)
2. Postmenopausal vaginal bleeding
3. Women diagnosed with female genital malignancy such as endometrial, cervical or vaginal cancer

4. Refusal to participate

## STUDY DESIGN

This study was a cross sectional descriptive study to determine the endometrial thickness of asymptomatic postmenopausal women. Patient selection was based on purposive non probability sampling based on the inclusion criteria. Ethical approval was obtained from the Ethical Research Committee of the UITH. All patients who met the criteria for the study were recruited until the sample size was completed.

## SAMPLING METHOD

The selection of subjects was by purposive non probability sampling based on inclusion criteria. The total number of patients based on the calculated sample size was proportionally allocated to the hypertensive group, diabetic mellitus group and lastly to women that were not diabetic nor hypertensive. None of the participants had both hypertension and DM.

## DATA COLLECTION

Women who satisfied the inclusion criteria were counselled. The study topic and importance was explained in details, benefits of the study was highlighted and stressed in a language that the women understood well. The copy of the consent form was given to the women who participated in the study for their signature or thumb printing. A questionnaire was administered to the women by the investigator. Information was obtained on age, parity, age at menopause, duration of menopause (years since menopause), associated medical illnesses (hypertension or diabetes mellitus), duration since diagnosis, and history of hypoglycaemic drugs, antihypertensive drugs were elicited. Anthropometric measurement was obtained by measuring the weight using a ZT-120 weighing scale and the weight was recorded to the nearest 0.1Kg, with subjects in minimum clothing. Height was measured using a portable

stadiometer and was recorded to the nearest 0.1 meter, with the subjects barefoot. BMI was computed as (weight[Kg]/(height[m]$^2$). A BMI of <18.5kgm$^{-2}$ was regarded as underweight, normal weight as ≥18.5kgm$^{-2}$ while a BMI of ≥25kgm$^{-2}$ was considered overweight and above 30kgm$^{-2}$ was considered obese. Systolic and diastolic blood pressure was measured using a mercury sphygmomanometer. A value of ≥140/90mmHg on two occasions, 4-6hours apart in a previously normotensive individual was taken as hypertension. Blood sample was obtained from all participants and the glucose level was checked using a standardised glucometer. The result obtained was used as the base line glycaemic control and to exclude pre-existing undiagnosed diabetes in the participant. Thereafter, patients were subjected to general and abdominal examinations. This was followed by transvaginal ultrasound scan for endometrial thickness. The researcher was trained by the supervising consultant Radiologist and reliability of his measurement was adjudged as >90%. The supervisor also reviewed and validated measurements of ET of participant during the study. Thus, all the TVS were done by the researcher.

PROCEDURE

The participants were counselled about the study and informed consent was obtained. The measurement of endometrial thickness was done in the presence of a female chaperon. The TVS was done using Aloka SSD-1000 ultrasound machine designed by ALOKA GmbH, Meerbusch, Germany using a frequency of 7.5MHZ. The participants were asked to empty their bladder before the procedure and lie in dorsal position with the knee and hip flexed. She was draped with linen to expose only the perineum. In the presence of a female chaperon, the transvaginal probe was lubricated with the coupling gel and covered with condom, then lubricated with coupling gel before insertion. The lubricated probe was inserted gently into the vagina and with gentle manipulation, the endometrium was measured in the longitudinal (sagittal) plane and this included the measurement between the two basal layers of the

anterior and posterior uterine wall at the thickest point. The probe was removed from the vagina after measurement, condom was removed from the probe and the transvaginal probe cleaned in between usage to prevent cross infections. Participants were subsequently asked to dress up and findings discussed with them. Women with abnormally thickened endometrium were counselled on endometrial biopsy for histopathological confirmation and subsequently transferred to the consultant clinic for further investigations and definitive management.

SAMPLE SIZE ESTIMATION

The sample size was determined by the formula[26]

$$n = \left( \frac{(z\alpha + z\beta)\sigma}{\mu 1 - \mu 0} \right)^2$$

Where

$z\alpha$ = 1.96 (critical value that divides the central 95% of z distribution from 5% in the tails),

$z\beta$ = 1.28 (critical value that separates the lower 10% of distribution from upper 90%),

$\sigma$ = SD,

$\mu 1 - \mu 0$ = difference of two means.

Using a previous study by Hebbar et al,[26] a prospective observational study on 110 asymptomatic healthy postmenopausal women in which their endometrial thickness were measured transvaginally. They reported that mean ET in them was 3.8 mm with a standard

deviation (SD) of 2.3.Sample size was estimated to show the significant difference in means at 1 mm and 1.5 mm, with a desired level of power of 90% and level of significance 0.05.

$$n_1 = \frac{(1.96 + 1.28)^2 (2.3)^2}{(1)^2}$$

$n_1 = 56$ subjects

$$n_2 = \frac{(1.96 + 1.28)^2 (2.3)^2}{(1.5)^2}$$

$n_2 = 25$ subjects

$n = n_1 + n_2$

$n = 81$

Provision for attrition was 10% i.e. 8 subjects

Calculated total sample size = 81 + 8 = 89 subjects

Therefore the minimum sample size for this study was 89 subjects.

Accordingly, it was estimated that 56 patients was required to show the difference of 1 mm from established mean and 25patients was required to show the difference of 1.5 mm.

DATA ANALYSIS

The data was analyzed using the Statistical Package for Social Sciences software (SPSS) version 23. The results were presented in tables and charts. Endometrial thickness was found to be skewed (skewness z score 24.0314), thus it was analyzed using non-parametric methods. It was presented as median with inter-quartile range and analyzed using Mann-

Whitney U test and Kruskal Wallis test. Also, Spearman-rho correlation was used to determine the relationship between endometrial thickness and other variables. Probability (*p*) values less than 0.05 was accepted as statistically significant.

## ETHICAL CONSIDERATION

Approving Authority: An Institutional approval was obtained from the Ethical Review Committee of University of Ilorin Teaching Hospital before the commencement of the study.

Voluntary Participation: Subjects participation in this study was voluntary and they had the liberty to withdraw at any stage if they wish.

Confidentiality: All the data obtained from the study was made confidential and used solely for the purpose of the study and any publication arising from it.

Beneficence: The study contributed to general knowledge. Participant especially those with abnormal endometrial thickness were referred for further investigation and prompt treatment was instituted when necessary. The cost of the transvaginal ultrasound was borne by the researcher.

Non-maleficence: The procedure is generally safe with minimal discomfort to the patient. There was no additional risk due to participation.

Justice: All participants were treated with same degree of respect and equity was ensured.

Dignity: Participants were treated with dignity. Unnecessary exposure of the participants was avoided and a female chaperon was present at all times.

# CHAPTER FIVE

# RESULTS

The study was conducted over a period of 7 months, from 1st May to 30th November 2017.

## 5.1 SOCIO-DEMOGRAPHIC CHARACTERISTICS.

Table 1 shows the socio-demographic characteristics of the participants.

**Age**: All the consenting women were post menopausal and the age range was 51-82years. As shown in table I. The mean age was 64.90years±8.20 of the 89 participants recruited. Majority of the participants fell within the age bracket of 51-70 years, accounting for 75.3% of all the participants recruited for the study. While 38.2% of the participants were in the age group of 61-70 years, 22(24.7%) were more than 70years.

**Marital status**: A total of 72 women were married and this accounted for 80.9% of all participants. The percentage of participants who were never married was 2.2% and the widowed were 15 accounting for 16.9%.

**Occupation**: approximately half (55.1%) of the subjects were traders, 31.5% were civil servants. Artisans and unemployed accounted for 9.0% and 4.5% of all participants respectively.

**Educational status**: Most participants had some form of education (89.9%). Thirty (33.7%) women had tertiary level education. The percentage of women without formal education was 10.1%, those with primary school level of education were 21(23.6%) and secondary school education were 29, constituting 32.6%.

**Ethnicity**: Analysis of the ethnicity of the participants showed that they were predominantly Yoruba. From table I, 67 women (75.3%) were Yoruba. The other ethnicities represented were Igbo (22.5%) and Hausa/Fulani (2.2%).

**Parity**: There were 47(52.8%) women who were para 5 and above. While 37(41.6%) and 2(2.2%) women had 2 - 4 and 1 parous experiences respectively. The participants with no parous experience were 3(3.4%).

## 5.2: DURATION OF ILLNESS AND GYNAECOLOGICAL VARIABLES

The post menopausal years as seen in table II ranged between 1-31 years, and the mean value was 15.65years±6.69. Also shown on table II is the age of participants at attainment of menopause which ranged from 45 – 58years with a mean value of 48.65years ± 2.67. Majority of the participants, 68(76.4%) had no previous menstrual abnormality while 21(23.6%) had previously experienced menstrual abnormality in past which includes menorrhagia, oligomenorrhoea and polymenorrhoea. The mean value for duration of the co-morbidity of the participants was 15.37years±9.94 for hypertension and 12.21years±6.38 for DM.

## 5.3 MEASUREMENTS OF ENDOMETRIAL THICKNESS AND ANTHROPOMETRIC PARAMETERS OF THE STUDY POPULATION

The anthropometric parameters of the participants are shown in table III. They include the BMI, weight and height. The BMI ranged from 19.15 - 41.60kgm$^{-2}$ with a mean value of 29.01kgm$^{-2}$±5.98. Weight of participants ranged from 46.0 - 106.0kg with mean value of 72.24kg±14.60 while the mean value of height was1.58m±0.06 and ranged 1 .48 – 1.80m. Approximately half 43(48.4%) of the participants were obese while those with normal BMI were 41.6% (37). Only 9(10.1%) participants were over-weight. The table also shows the

endometrial thickness of asymptomatic postmenopausal women. The endometrial thickness measurement ranged between 0.10-23.00mm with a mean value of 2.17mm±2.57. Majority of the participants 88(98.9%) had an endometrial thickness of < 5mm while only 1(1.1%) participant had a thickness of >5mm.

## 5.4 RELATIONSHIP BETWEEN ENDOMETRIAL THICKNESS AND SELECTED PARAMETERS

Table IV showed a statistically significant relationship between postmenopausal years and endometrial thickness with a mean endometrial thickness of 2.53mm for duration of less than 5years and 2.06mm for duration of more than 5years (p-value = 0.048). Also, there was a statistically significant relationship between parity and endometrial thickness (p=0.005). Hence, endometrial thickness decreased with increase in postmenopausal years and parity. This also shows that the mean endometrial thickness measurement of participants with hypertension or DM was higher than mean endometrial thickness of those with no medical disorder. The mean value of endometrial thickness for hypertensives was 2.8mm±4.07 (0.20-23.00mm) and the measurement in the diabetic participants ranged between 0.32-4.10mm with a mean value of 2.27mm±1.08. Participants without medical disorder had a mean value of 1.42mm±1.16 (0.10-3.90mm). Table IV Shows the comparison between the endometrial thickness of participants of the various study groups. There was statistically significant difference between the mean values of endometrial thickness of participants with hypertension and those without medical disorders (U = 299.500, p = 0.026). Significant statistical difference was also found between diabetes mellitus and those without medical disorders (U = 256.00, p = 0.005).

## 5.5 RELATIONSHIP BETWEEN BODY MASS INDEX AND ENDOMETRIAL THICKNESS OF THE PARTICIPANTS.

Table V highlights the relationship between BMI and endometrial thickness of the participants. There was no statistically significant relationship between BMI and endometrial thickness ($p = 0.19$). However, there was an increase in endometrial thickness with increasing BMI as evidenced by the increase in the means across the BMI groups, though this was not statistically significant. Kruskal-Wallis test a non parametric test showed that there was no statistically significant difference in the endometrial thickness between the various body mass index groups; $K=4.746$, $p=0.191$, with mean value of endometrial thickness of participants for normal weight=1.58mm±1.21, over weight=1.61mm±1.02, class I obesity=2.33mm±1.64, class II obesity=2.38mm±1.28 and 2.70mm±3.68 for class III obesity.

Table VI shows the anthropometric parameters that correlated positively with endometrial thickness. Only the weight of the participants has a positive but weak correlation with the endometrial thickness ($p = 0.021$, $r = 0.251$). BMI and height did not show any significant correlation using the Spearman correlation coefficient/ test.

## 5.6 THE RELATIONSHIP BETWEEN ENDOMETRIAL THICKNESS AND THE DURATION OF THE HYPERTENSION OR DIABETES MELLITUS.

Table VII shows the relationship between the duration of selected medical disorders and endometrial thickness. They were assessed using the Mann-Whitney U test in relation to duration of medical disorders in the participants. Median duration of illness was used for grouping the duration of illness. The mean value of endometrial thickness of participants with duration of hypertension of ≤ 12years was 3.93mm±5.52 while that of > 12years was

1.81mm±1.07. The mean value of endometrial thickness of participants with duration of DM of ≤ 10years was 2.51mm±1.24 while that of > 10years was 1.85mm±0.89. There was no statistical significance between duration of medical illness and endometrial thickness with p-value of 0.213 and 0.085 for duration of hypertension and DM respectively.

**Figure I:** Distributution of the study population.

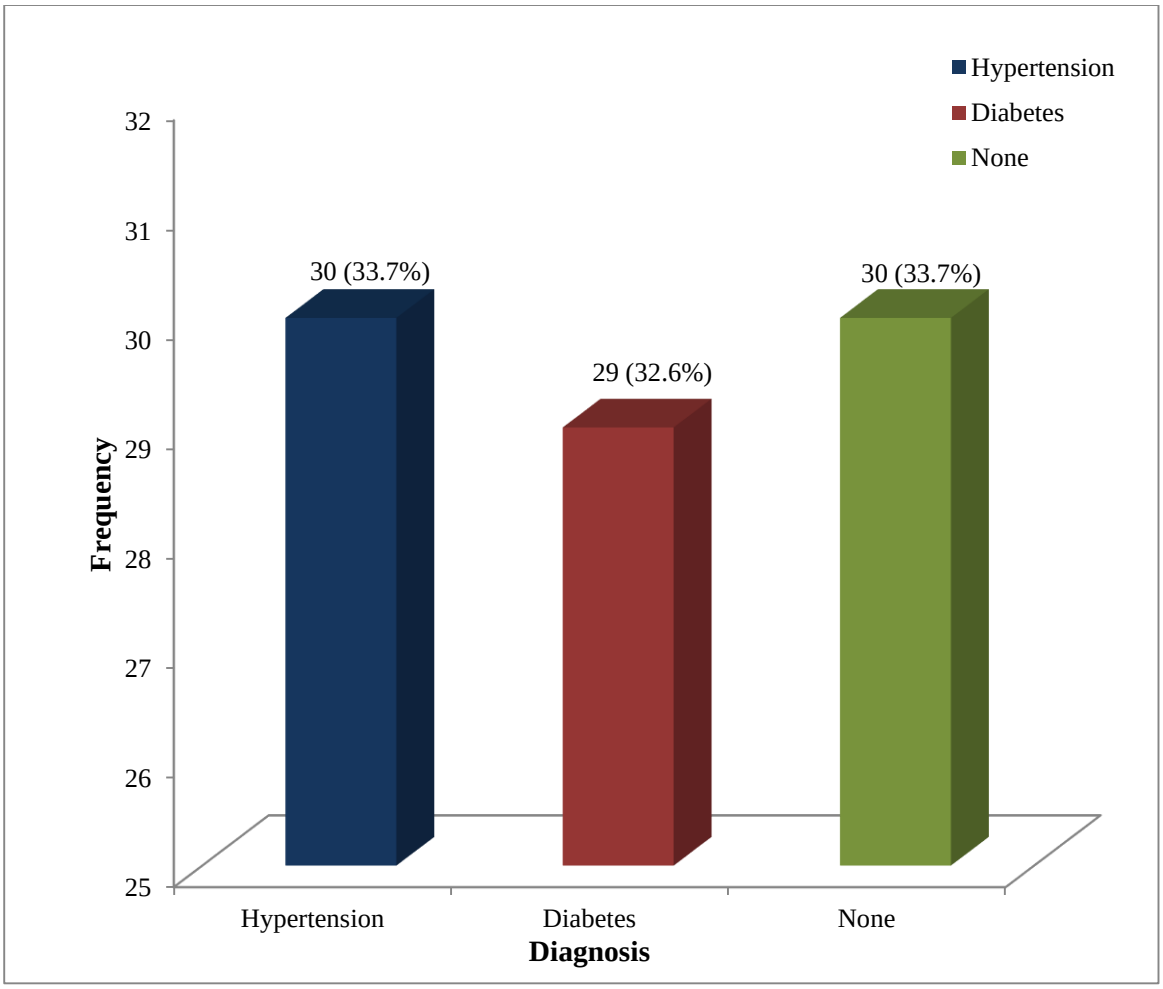

**Table I**: Socio demographic characteristics

| Variables | Hypertension n (%) | Diabetes n (%) | None n (%) | Total n (%) |
|---|---|---|---|---|
| **Age group (years)** | | | | |
| 51 – 60 | 8 (24.2) | 7 (21.2) | 18 (54.5) | 33 |
| 61 – 70 | 14 (41.2) | 12 (35.3) | 8 (23.5) | 34 |
| > 70 | 8 (36.4) | 10 (45.5) | 4 (18.2) | 22 |
| Mean ± SD | 65.67 ± 7.68 | 67.79 ± 8.79 | 61.30 ± 7.34 | 64.89 ± 8.31 |
| Range | 54 – 80 | 54 – 82 | 51 – 75 | 51 – 82 |
| **Marital status** | | | | |
| Single | 1 (50.00 | 1 (50.0) | 0 (0.0) | 2 |
| Married | 24 (33.3) | 22 (30.6) | 26 (36.1) | 72 |
| Widowed | 5 (33.3) | 6 (40.0) | 4 (26.7) | 15 |
| **Occupation** | | | | |
| Unemployed | 2 (50.0) | 0 (0.0) | 2 (50.0) | 4 |
| Artisan | 3 (37.5) | 2 (25.0) | 3 (37.5) | 8 |
| Trader | 16 (32.7) | 16 (32.7) | 17 (34.7) | 49 |
| Civil Servant | 10 (35.7) | 10 (35.7) | 8 (28.6) | 28 |
| **Education** | | | | |
| None | 1 (11.1) | 6 (66.7) | 2 (22.2) | 9 |
| Primary | 9 (42.9) | 6 (28.6) | 6 (28.6) | 21 |
| Secondary | 12 (41.4) | 7 (24.1) | 10 (34.5) | 29 |
| Tertiary | 8 (26.7) | 10 (33.3) | 12 (40.0) | 30 |
| **Ethnicity** | | | | |
| Yoruba | 23 (34.3) | 20 (29.9) | 24 (35.8) | 67 |
| Igbo | 7 (35.0) | 7 (35.0) | 6 (30.0) | 20 |
| Hausa | 0(0) | 2(100) | 0(0.0) | 2 |
| **Parity** | | | | |
| 0 | 1 (33.3) | 2 (66.7) | 0 (0.0) | 3 |
| 1 | 1 (50.0) | 0 (0.0) | 1 (50.0) | 2 |
| 2 – 4 | 15 (40.5) | 9 (24.3) | 13 (35.1) | 37 |
| > 4 | 13 (27.7) | 18 (38.3) | 16 (34.0) | 47 |

**Table II**: Duration of illness and Gynaecology history

| Variables | Hypertension n (%) | Diabetes n (%) | None n (%) | Total n (%) |
|---|---|---|---|---|
| **Age at menopause(years)** | | | | |
| Mean ± SD | 49.27 ± 3.48 | 50.14 ± 3.99 | 48.33 ± 2.29 | 48.65±2.67 |
| Range | 47 – 58 | 45 – 58 | 45 – 55 | 45-58 |
| **Post menopause (years)** | | | | |
| ≤ 5 | 6 (22.2) | 6 (22.2) | 15 (55.6) | 27 |
| 6 – 10 | 16 (42.1) | 13 (34.2) | 9 (23.7) | 38 |
| > 10 | 8 (33.3) | 10 (41.7) | 6 (25.0) | 24 |
| Mean ± SD | 16.40 ± 6.75 | 17.66 ± 7.76 | 12.97 ± 6.69 | 15.65 ± 6.69 |
| Range | 5 – 30 | 7 – 31 | 1 – 25 | 1 – 31 |
| **Previous menstrual abnormalities** | | | | |
| Yes | 6 (28.6) | 11 (52.4) | 4 (19.0) | 21 |
| No | 24 (35.3) | 18 (26.5) | 26 (38.2) | 68 |
| **Duration of hypertension(years)** | | | | |
| Mean ± SD | 15.37±9.94 | | | |
| Range | 1.00-34.00 | | | |
| **Duration of DM(years)** | | | | |
| Mean ± SD | | 12.21±6.38 | | |
| Range | | 3.00-30.00 | | |

**Table III:** Measurements of endometrial thickness and anthropometric parameters of the study population

| Variables | Frequency | Percent |
|---|---|---|
| **Endometrial thickness (mm)** | | |
| < 5 | 88 | 98.9 |
| ≥ 5 | 1 | 1.1 |
| Mean ± SD | 2.17 ± 2.57 | |
| Range | 0.10 – 23.00 | |
| **BMI (kg/m$^2$)** | | |
| 18.5 – 24.9 | 37 | 41.6 |
| 25.0 – 29.9 | 9 | 10.1 |
| 30.0 – 34.9 | 28 | 31.5 |
| 35.0 – 39.9 | 11 | 12.4 |
| ≥ 40 | 4 | 4.5 |
| Mean ± SD | 29.01 ± 5.98 | |
| Range | 19.15 – 41.60 | |
| **Weight (kg)** | | |
| Mean ± SD | 72.24 ± 14.60 | |
| Range | 46.00 – 106.00 | |
| **Height (m)** | | |
| Mean ± SD | 1.58 ± 0.06 | |
| Range | 1.48-1.80 | |

**Table IV**: Relationship between endometrial thickness and selected parameters.

| **Variables** | **Endometrial thickness(mm) Mean ± SD** | **Test** | ***p* value** |
|---|---|---|---|
| **Postmenopause(years)** | | | |
| ≤ 5 | 2.53 ± 1.61 | 488.500[U] | 0.048* |
| > 5 | 2.06 ± 2.79 | | |
| **Parity** | | | |
| 0 | 2.70 ± 1.56 | 12.890[H] | 0.005* |
| 1 | 2.55 ± 0.21 | | |
| 2 – 4 | 2.45 ± 1.26 | | |
| > 4 | 1.89 ± 3.34 | | |
| **Previous menstrual abnormalities** | | | |
| Yes | 2.36±1.21 | 546.500[U] | 0.105 |
| No | 2.10±2.87 | | |
| **Hypertension** | 2.82 ± 4.07 | | |
| Range | 0.20 – 23.00 | | |
| **Diabetes Mellitus** | 2.27 ± 1.08 | | |
| Range | 0.32 – 4.10 | | |
| **Without medical disorders** | 1.42±1.16 | | |
| Range | 0.10-3.90 | | |
| **Hypertension vs Nil medical disorders** | | 299.500[U] | 0.026* |
| **Diabetes vs Nil medical disorders** | | 256.00[U] | 0.005* |

**[U]: Mann Whitney U test,**

**[H]: Kruskal Wallis test,**

***: *p* value < 0.05 (statistically significant).**

**Table V**: Relationship between BMI and endometrial thickness

| | Endometrial thickness (mm) | | | |
|---|---|---|---|---|
| **BMI (kg/m2)** | **Mean ± SD (mm)** | **Median (Inter-quartile range)** | **K** | ***p* value** |
| 18.5 – 24.9 | 1.58±1.21 | 1.35 (0.33 - 2.38) | 4.746 | 0.191 |
| 25.0 – 29.9 | 1.61 ± 1.02 | 1.20 (1.00 – 1.80) | | |
| 30.0 – 34.9 | 2.33 ± 1.64 | 2.45 (0.74 – 3.80) | | |
| 35.0 – 39.9 | 2.38 ± 1.28 | 2.50 (1.45 – 3.45) | | |
| ≥ 40 | 2.70 ± 3.68 | 2.20 (0.85 – 3.60) | | |

K: Kruskal Wallis Test

**Table VI:** Relationship between endometrial thickness and anthropometric measurements

| | Endometrial thickness | |
|---|---|---|
| **Variable** | **R** | ***p* value** |
| BMI | 0.174 | 0.111 |
| Weight | 0.251 | **0.021*** |
| Height | 0.029 | 0.793 |

**r: Spearman correlation coefficient; *: *p* value <0.05 (i.e. statistically significant)**

**Table VII**: Relationship between endometrial thickness and duration of selected medical disorders.

| | Endometrial thickness | | | |
|---|---|---|---|---|
| **Variable** | **Mean ± SD** | **Median (IQR)** | **U** | ***p* value** |
| **Duration of Hypertension** | | | | |
| ≤ 12 years | 3.93 ± 5.52 | 3.50 (0.40 – 4.10) | 76.500 | 0.213 |
| > 12 years | 1.81 ± 1.07 | 1.50 (0.90 – 2.30) | | |
| **Duration of Diabetes** | | | | |
| ≤ 10 years | 2.51 ± 1.24 | 2.75 (1.78 – 3.60) | 70.000 | 0.085 |
| > 10 years | 1.85 ± 0.89 | 1.75 (1.28 – 2.30) | | |

**Median duration of illness was used for grouping**
**U: Mann-Whitney U test**

# CHAPTER SIX

# DISCUSSION

Endometrial cancer is important because it occurs more commonly in the postmenopausal period. It is the commonest gynaecological cancer in the developed world and third commonest gynaecological cancer in sub-Sahara Africa[82]. There is a strong association between endometrial thickness and endometrial disease, with normal endometrium usually less than 5mm in thickness in postmenopausal women[9]. Despite standardizing the cut off value for endometrial thickness in asymptomatic post menopausal women, there is paucity of studies to document how factors such as hypertension, diabetes mellitus and BMI can influence the endometrial thickness especially in the developing world. This study highlights the above mentioned factors and their possible effect on endometrial thickness measured using transvaginal ultrasonography. Eighty nine asymptomatic postmenopausal women were recruited from gynaecology, endocrinology, cardiology and general out- patient clinics of UITH and were proportionally allocated to the hypertensive group, diabetes mellitus group and nil medical disorders group. The mean value of endometrial thickness for this study was 2.17mm and this study suggests that in asymptomatic postmenopausal women, parity, duration of menopause, presences of hypertension, diabetes mellitus are related to endometrial thickness.

The mean age at menopausal of participants in this study was 48.65years ± 2.65. This compared favourably with those reported in Ibadan and Ile-Ife in which the mean menopausal age were 49.36 ± 5.0 years and 48.4 ± 5.0 years respectively[70,71]. These findings are in agreement with those of previous studies that suggest that women world worldwide attain menopause at about 50years[71]. The mean menopausal age of this study is lower than reports from the western world as evidence by a study conducted by Gold et al,McKinlay et al and

Stanford et al in which the mean age at menopause were 51.4years, 51.3yeras and 51.1years respectively[72,78,79]. Beyene in 1989 suggested that low nutritional status due to low socio-economic status may be responsible for reaching menopause early.[73] More than half of the participants had a parity of 5 and above. This compared favourably with the Nigeria Demographic and Health Survey report of 2016 which stated Total Fertility rate as 5.13. The rate of obesity is increasing worldwide. Obesity causes not only cardiovascular problems but also multiple problems in every part of the body. Obesity is a major risk factor for endometrial hyperplasia. Endometrial hyperplasia carries the risk of progression to endometrial cancer[80]. Many participants in the study were obese with a BMI of greater than 30kg/$m^2$ and this accounted for 48.4%. The predominance of obesity in this study was similar to a study by Yurtsever et al on effect of BMI on endometrial thickness in postmenopausal asymptomatic patients in which 42.2% of the participants was obese[67]. The predominance of obesity could be due to menopausal transition which results in reduced resting metabolic rate, lowered energy expenditure, increase in fat mass and central adipose tissue accumulation[81]. In this study there was no statistically significant relationship between BMI and endometrial thickness. However, there was a corresponding increase in endometrial thickness as BMI increases. The finding is similar to study by Nakamura H et al[77] and Berker et al[61] but differs from findings by Douchi et al who observed a statistically significant relationship between endometrial thickness and BMI.[57] This can be attributed to the difference in methodology and BMI classification by Douchi et al in which BMI of $\leq$ 25kg/$m^2$ was considered normal while >25kg/$m^2$ was considered to be obesity. Other studies also showed statistically significant relationship between endometrial thickness and BMI.[59,60] The differences in findings may have be due to differences in methodology and larger sample size of obese women compared to index study. In the first year after the last menstrual period the normal

endometrium is often thicker than it will be several years after menopause, reflecting fluctuating levels of estrogen[32].

The mean endometrial thickness was found to decrease significantly as postmenopausal years increased. The mean value of endometrial thickness of participants in this study with postmenopausal year of ≤5years was 2.53mm and 2.06 mm for >5years. This was probably due to fall in hormone levels particularly oestrogen as age and menopausal year increased. These values are comparable to findings Warming et al[58] but lower than values of endometrial thickness studied by Hebbar S et al. They reported a thickness of 4.7mm in women of ≤ 5years postmenopause.[26] This may be attributed to the fact that the mean age of participants in this study was higher (64.90years vs 55.4years). It was also observed that the endometrial thickness was found to decrease as parity increased, with nulliparous participants having the highest endometrial thickness (2.70mm). Low parity is related to longer period of exposure to unopposed oestrogen without disruption of the normal cycle.[40] Studies have suggested that mechanical shedding of precursor cells of malignant potential at each delivery help to prevent thickened endometrium and related disorders in subsequent years. The antimitotic property of progesterone was also given as an explanation due to growth limiting effect on the endometrium[74,75].

Both hypertension and diabetes mellitus are part of the metabolic X syndrome and usually cause an increase in endometrial thickness in postmenopausal women[26]. This study showed that endometrium of participants with hypertension was thicker than those without hypertension and this was statistically significant. This finding was comparable to earlier studies by Alcazar et al[33] and Yuvuz Yurtsever et al[67] but contrary to other studies by Ayodele et al[76] and Serin et al[59] in which there was no statistically significant difference between the endometrial lining of hypertensive and normohypertensive postmenopausal women. The difference in findings may probably be due to difference in methodology, while

hypertension alone was compared with endometrial thickness, earlier study compared it with hypertension and obesity as a combination.[59] There was no statistically significant difference between the duration of hypertension and endometrial thickness.

Diabetic women especially the obese diabetics have been found to have insulin resistance with resultant elevated level of insulin which in turn causes a fall in the concentration of sex hormone-binding globulin a carrier of oestrogen and other hormones in the blood[6]. The high circulating free oestrogen causes an increase in free oestrogen level and resultant endometrial hyperplasia. The mean value of endometrial thickness of participants with diabetes mellitus in this study was 2.27mm ± 1.08 while that of non diabetic participants was 1.42mm ± 1.16. There was a positive correlation between endometrial thickness and DM. However there was no statistical significance between duration of diabetes mellitus and endometrial thickness of participants. The finding in this study was similar to study by Yavuz Yurtsever in which the mean endometrial thickness of participants with diabetes was higher than those without diabetes mellitus[67]. However this findings differed from study by Andolf et al and Nakmura et al[21,77] . Only one participant had an endometrial thickness of greater than 5mm. She had endometrial biopsy with histopathology report of complex adenomatous hyperplasia and subsequently had total abdominal hysterectomy with bilateral salpingoophoorectomy done.

# CONCLUSION

The mean age at menopause in this study was 48.65years ± 2.67. There was a significant inverse relationship between parity, postmenopausal years and endometrial thickness of asymptomatic postmenopausal women. Furthermore, a positive correlation was found between hypertension, diabetes mellitus and asymptomatic endometrial thickness. There was no significant relationship between BMI, duration of selected medical disorders and endometrial thickness. Thus, asymptomatic endometrial thickness in postmenopausal women may be influenced parity, postmenopausal years, hypertension and diabetes mellitus. These factors should be taken into consideration while evaluating these women.

# RECOMMENDATION

1. Transvaginal ultrasound scan should not be done routinely for all asymptomatic postmenopausal women because the risk of asymptomatic endometrial thickening is low.
2. Postmenopausal asymptomatic endometrial thickening should be evaluated on a case-by-case basis and risk factors for endometrial cancer including diabetes mellitus and hypertension should be considered in decision making.

## STRENGTHS

1. Measurement of endometrial thickness was done solely by the researcher. Thus preventing inter observer error
2. This study is one of the few studies done in this environment on endometrial thickness in asymptomatic postmenopausal women
3. Rigorous methodology used in patient selection with the inclusion and exclusion criteria was strictly adhered to.

## LIMITATIONS

1. There were few studies done in this environment on asymptomatic endometrial thickness in postmenopausal women. This limited comparisons with findings of other researcher.
2. The study was done in only one centre. A multicentre study with a larger number of participants may be more representative.
3. Contact with participants was only once thus long time effects of influencing factors were not studied. Serial measurements would have shown trends in endometrial thickness
4. Histopathologic evaluation of the endometrium was not done to exclude occult endometrial cancer

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## APPENDIX I

## INFORMATION SHEET

**ASSESSMENT OF ASYMTOMATIC ENDOMETRIAL THICKNESS IN POSTMENOPAUSAL WOMEN AND THOSE WITH MEDICAL DISORDERS AT UNIVERSITY OF ILORIN TEACHING HOSPITAL**

BRIEF DESCRIPTION OF THE STUDY

The study is to measure the lining of the uterus of asymptomatic postmenopausal women and to identify possible factors that may influence it. Those with abnormally thickened lining of the uterus will be counselled on the need for further investigation such as endometrial biopsy and treatment will be instituted when necessary. This study is in partial fulfilment of the requirements for the award of fellowship of the faculty of Obstetrics and Gynaecology of the National Postgraduate Medical college of Nigeria.

BENEFITS OF PARTICIPATION

It will contribute to general knowledge and society at large will benefit. It may also be of benefit for the women especially those with abnormal endometrial thickness because they will be referred for further investigation and prompt treatment will be instituted when necessary. The cost of the transvaginal ultrasound will be borne by the researcher.

CONFIDENTIALITY/RESPECT FOR SUBJECT

The information collected about you will be made confidential. The study proforma sheet will be handled and kept by the researcher so as to prevent the leakage of information about the participants. Unnecessary exposure of the participants will be avoided and a female chaperon

Will be present.

WHAT IS REQUIRED FOR THE PARTICIPATION IN THE

You will answer some questions and afterwards you will undergo a transvaginal ultrasound in which an instrument will be inserted into your vagina to assess the womb. The findings will be documented and you will be followed up if endometrial thickness exceeds the normal expected value for postmenopausal women.

RISK OF PARTICIPATION

The procedure is generally safe with minimal discomfort to the patient. There is no additional risk due to your participation. However for those that need further evaluation and treatments, risks and complications will depend on procedures and these would be explained where necessary.

CONSENT TO PARTICIPATE AND RIGHT TO WITHDRAW

Your participation in this study is voluntary and you have the liberty to withdraw at any stage if you wish. You will not be penalized. However, I will appreciate your willingness to participate in this study.

COST OF THE RESEARCH

The cost of the research will be borne by the researcher and no additional cost will be transferred to the participants.

CONFLICT OF INTEREST

I have no conflict of interest to be declared. If you feel you are being coerced in any way please contact the secretary of UITH Ethical Review Committee.

RESEARCHER: DR TOLA YINKA BAKARE

Telephone no: 08034204114

## APPENDIX II

CONSENT FORM

ASSESSMENT OF ASYMPTOMATIC ENDOMETRIAL THICKNESS IN POSTMENOPAUSAL WOMEN AND THOSE WITH MEDICAL DISORDERS AT UNIVERSITY OF ILORIN TEACHING HOSPITAL

I……..of……

…….....

.....

Hereby consent to participate in the above research after proper information on the nature of the study and its benefit has been explained to me.

Date ……

Signed……

OR

Right thumb print……

I confirm that I have explained to you the purpose and nature of the study. All information obtained in this study is strictly confidential. If the study is published, there will be no information that will identify you as a participant.

Date……

Signed……

Witness----------

Signed----------

## APPENDIX III

## STUDY PROFORMA FOR DATA COLLECTION

### (a) SOCIO – DEMOGRAPHIC CHARACTERISTICS

1. Patient Initial_____
2. Hospital Number_____
3. Address _____
4. Phone Numbers_____
5. Age_____
6. Marital Status i. Single ii. Married iii. Divorced iv. Separated
   v. widowed
7. Occupation i. Unemployed ii. Artisan iii. Trader iv Civil Servant
   v. Professional vi. Others – Specify
8. Educational Status i. Primary ii. Secondary iii. Tertiary iv. Others
9. Ethnicity i. Yoruba ii, Igbo iii. Hausa iv Others (specify)}
10. Husband's Occupation i. Unemployed ii. Artisan iii. Trader
    iv. Civil Servant v. Professional vi. Others – Specif
11. Husband's Educational Status i. Primary ii. Secondary iii.Tertiary
    iv. Others
12. Parity
13. Last Menstrual Period
14. Years since last menstrual period
15. Height_____ m, Weight_____ Kg, BMI_____ $Kg/m^2$
16. BP.....mmHg

**(b) PAST OBSTETRIC HISTORY**

i. Number of previous pregnancies

ii. Number of previous deliveries …(a)1 (b)2 (c)3 (d)4 (e)5 or more

iii. Number of living children

**(c)** GYNAECOLOGICAL HISTORY

i. Age at first menstrual bleeding.....

ii. Age at last menstruation.....

iii. Past history of heavy or prolong menstrual bleeding (1) Yes (2) No

**(d)** PAST MEDICAL HISTORY

i. Hypertension (1) Yes (2) No

ii. Diabetes Mellitus (1) Yes (2) No

iii. Others

**(e)** FAMILY AND SOCIAL HISTORY

i. Cancer (1) breast (2) colon (3) endometrium (4) Cervix (5) others.....(specify)

ii. Smoking (1) Yes (2) No

iii. Alcohol (1) Yes (2) No

**(f)** DRUG HISTORY

iv. Antihypertensive

v. Glucose lowering Agent

vi. Others

**(g)** TRANSVAGINAL ULTRASOUND FINDINGS

vii. Endometrial thickness (mm) .....

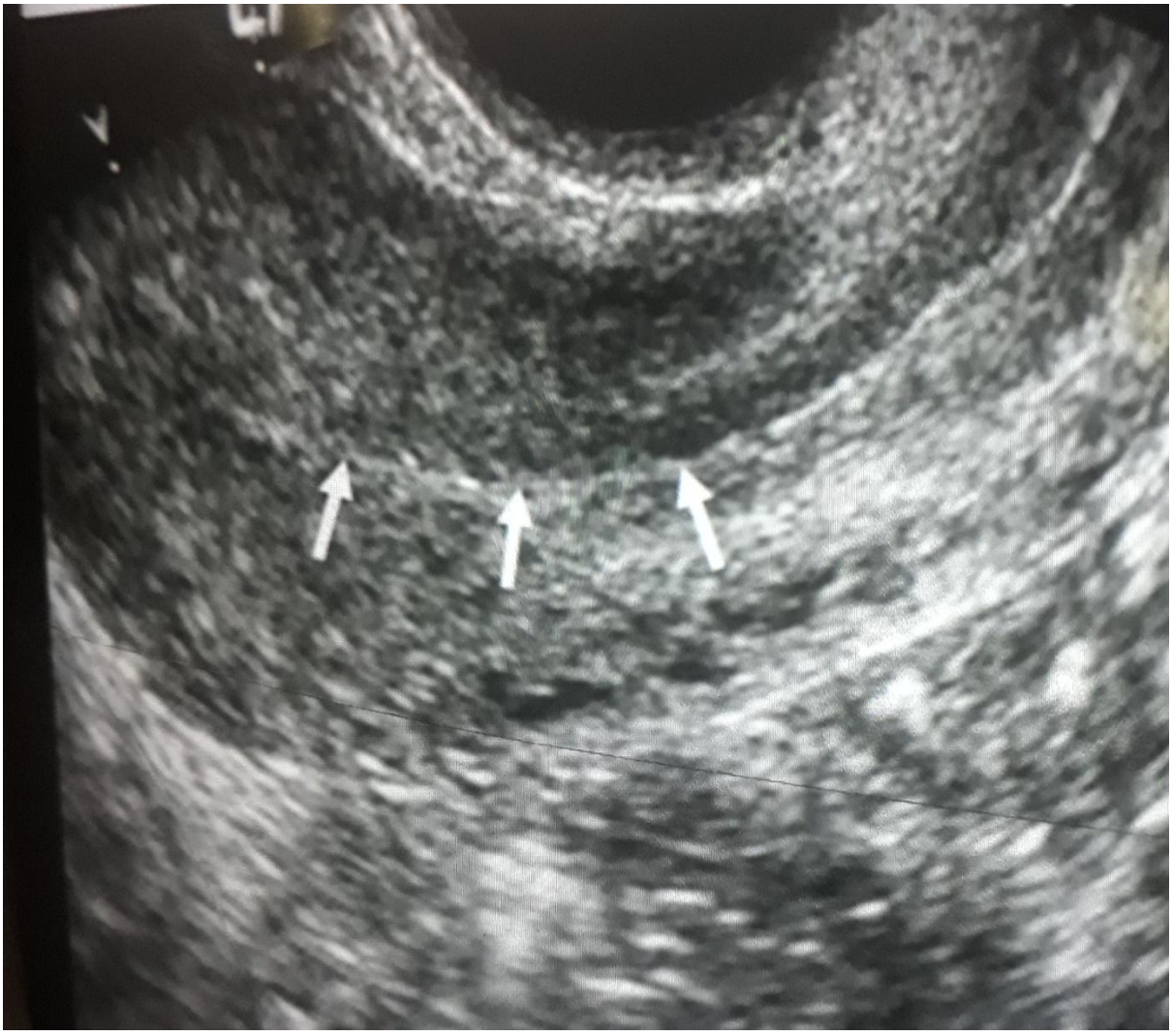
**( h)** BLOOD GLUCOSE LEVEL (MMOL/L) .....

**(f)** BLOOD PRESSURE (mmHg)

## APPENDIX IV

## NORMAL ADULT TRANSVAGINAL ULTRASOUND FINDINGS

Transvaginal ultrasound of the uterus in the sagittal plane shows anteflexion of the uterus in which the uterine fundus directs to the left of the image. Note the normal endometrium appearing as an echogenic line (arrows).[84]



# UNIVERSITY OF ILORIN TEACHING HOSPITAL

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UITH ERC Protocol Number: ERC PIN/2015/11/0861
UITH ERC Approval Number: ERC PAN/2016/02/1492

Our Ref: UITH/CAT/189/19[a]/435

Date: 01/02/2016

## ASSESSMENT OF ENDOMETRIAL THICKNESS IN ASYMPTOMATIC POSTMENOPAUSAL WOMEN ATTENDING CLINICS AT UNIVERSITY OF ILORIN TEACHING HOSPITAL

UITH Ethical Research Committee (ERC) assigned number: NHREC/02/05/2010
Name of Applicant/Principal Investigator: DR. SAKARE T.Y.
Address of Applicant: Dept. of Obst. & Gyn., University of Ilorin Teaching Hospital, Ilorin.
Date of receipt of application: 06/11/2015
Type of Review: Full Committee Review
Date of full Committee Decision on the Research: 24/11/2015
Date of full Committee approval: 01/02/2016

**Notice of full Committee Approval**

I am pleased to inform you that the research described in the submitted protocol, the consent forms and other participant information materials have been reviewed by the UITH Ethical Review Committee (ERC) and given full Committee approval.

This approval dates from 01/02/2016 to 31/01/2017. You are requested to inform the committee at the commencement of the research to enable it appoint its representative who will ensure compliance with the approved protocol. If there is delay in starting the research, please inform the ERC so that the dates of approval can be adjusted accordingly.
Note that no participant accrual or activity related to this research may be conducted outside these dates.

The UITH ERC requires you to comply with all the institutional guidelines and regulations and ensure that all adverse events are reported promptly to the ERC.
No changes are allowed in the research without prior approval by the ERC. Please note that the ERC reserves the right to conduct monitoring/oversight visit to your research site without prior notification.

Notwithstanding above, we will not be responsible for any misconduct on the part of the researcher in the course of carrying out the research.

Thank you.

PROF O.T. ADEDOKUN MBBS (Ib.), FWACP (Paed.), DHCP (Lond), ASN/ISN Fellow, Cert. M&M
Chairman, UITH Ethics Review Committee, (ERC)