A PROSPECTIVE OBSERVATIONAL STUDY TO DETERMINE THE AETIOLOGY OF POSTMENOPAUSAL BLEEDING AND CORRELATION OF ENDOMETRIAL THICKNESS IN ENDOMETRIAL CARCINOMA IN OUR POPULATION.

A dissertation submitted to the Tamil Nadu Dr. M. G. R. Medical University, Chennai in partial fulfilment of the requirement for the M.S (Obstetrics and Gynaecology) degree examination to be held in April, 2017.

CERTIFICATE

This is to certify that this dissertation,

"A PROSPECTIVE OBSERVATIONAL STUDY TO DETERMINETHE AETIOLOGY OF POSTMENOPAUSAL BLEEDING AND CORRELATION OF ENDOMETRIAL THICKNESS IN ENDOMETRIAL CARCINOMA IN OUR POPULATION" is the bonafide work of Dr. Carolin Solomi. V. under my supervision in the Department of Obstetrics and Gynaecology, Christian Medical College Vellore in partial fulfilment of the requirements for the award of M.S, Obstetrics and Gynaecology Examination of the Tamil Nadu Dr. M.G.R Medial University to be held in April 2017 and no part thereof has been submitted for any other degree.

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CERTIFICATE BY THE HEAD OF THE DEPARTMENT/ PRINCIPAL

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"A PROSPECTIVE OBSERVATIONAL STUDY TO DETERMINE THE AETIOLOGY OF POSTMENOPAUSAL BLEEDING AND CORRELATION OF ENDOMETRIAL THICKNESS IN ENDOMETRIAL CARCINOMA IN OUR POPULATION" is the bonafide work of Dr. Carolin Solomi .V. under the supervision of Dr. Jessie Lionel, Professor and HOU in the Department of Obstetrics and Gynaecology Unit 1, Christian Medical College Vellore in partial fulfilment of the requirements for the award of M.S, Obstetrics and Gynaecology Examination of the Tamil Nadu Dr. M.G.R Medial University to be held in April 2017 and no part thereof has been submitted for any other degree

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DECLARATION

I, Carolin Solomi .V. , do hereby declare that the dissertation titled "A PROSPECTIVE OBSERVATIONAL STUDY TO DETERMINE THE AETIOLOGY OF POSTMENOPAUSAL BLEEDING AND CORRELATION OF ENDOMETRIAL THICKNESS IN ENDOMETRIAL CARCINOMA IN OUR POPULATION" is a genuine record of research done by me under the supervision and guidance of Dr Jessie Lionel, Professor and HOU of Department of Obstetrics and Gynaecology Unit 1, Christian Medical College, Vellore and has not previously formed the basis of award of any degree, diploma, fellowship or other similar title of any university or institution.

Vellore Dr. Carolin Solomi. V.

Date

Acknowledgement

I acknowledge my dependence and gratitude to GOD Almighty in successful completion of my dissertation.

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Yours sincerely,

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Dear Dr.CarolinSolomi.V,
The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Etiology of postmenopausal bleeding and correlation of endometrial thickness in endometrial carcinoma in our population" on October 20th 2015.

The Committee reviewed the following documents:

1. IRB Application format
2. Proforma
3. Information Sheet and Informed Consent Form (English, Tamil, Telugu, Hindi
4. Cvs of Drs. CarolinSolomi.V, Elsy Thomas, Jessie Lionel,
5. No. of documents 1 - 4

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on October 20th 2015 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

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We approve the project to be conducted as presented.

Kindly provide the total number of patients enrolled in your study and the total number of withdrawals for the study entitled: "Etiology of postmenopausal bleeding and correlation of endometrial thickness in endometrial carcinoma in our population" on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in)

Yours sincerely,

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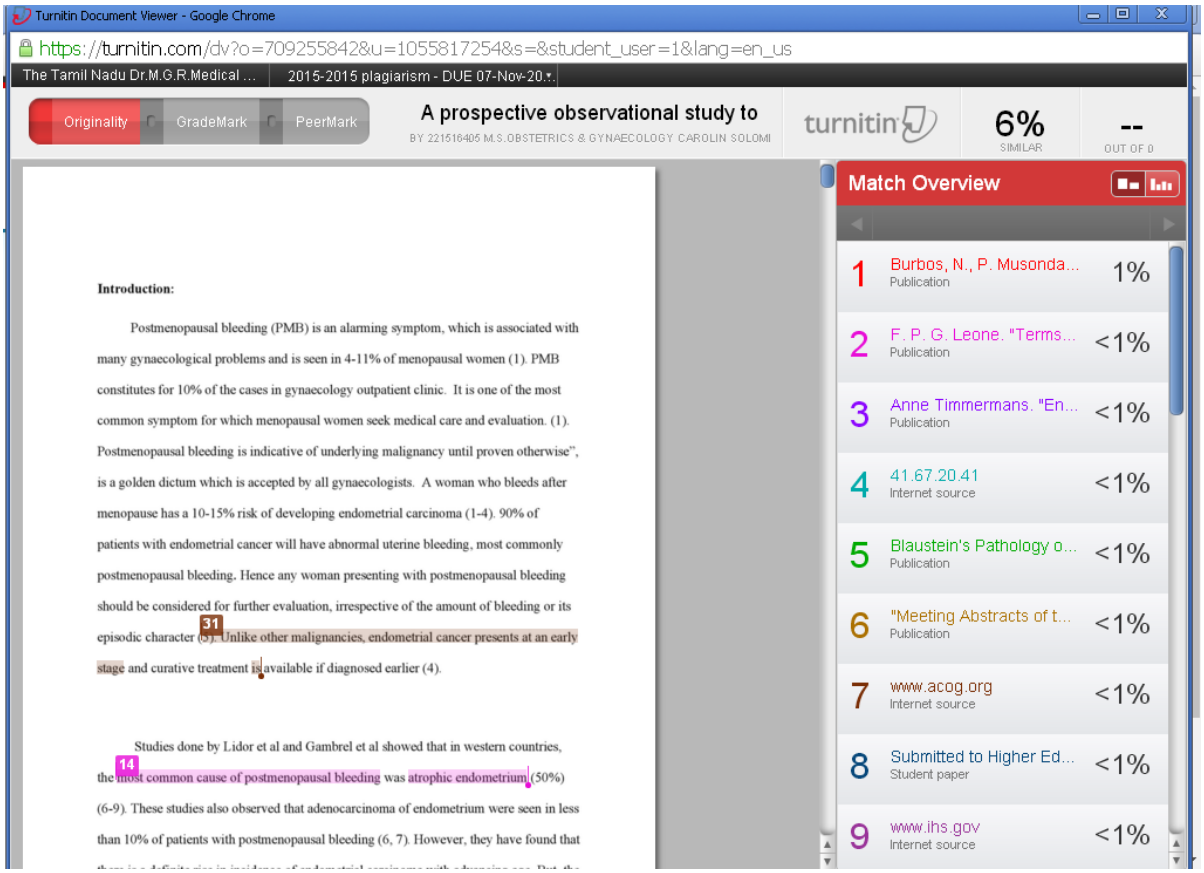

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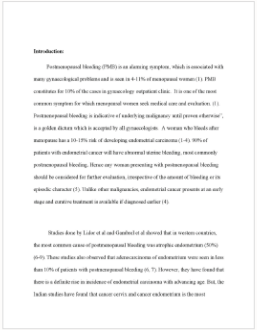


CONTENTS

INTRODUCTION

Introduction:

Postmenopausal bleeding (PMB) is an alarming symptom, which is associated with many gynaecological problems and is seen in 4-11% of menopausal women (1). PMB constitutes for 10% of the cases in gynaecology outpatient clinic. It is one of the most common symptom for which menopausal women seek medical care and evaluation. (1). Postmenopausal bleeding is indicative of underlying malignancy until proven otherwise", is a golden dictum which is accepted by all gynaecologists. A woman who bleeds after menopause has a 10-15% risk of developing endometrial carcinoma (1-4). 90% of patients with endometrial cancer will have abnormal uterine bleeding, most commonly postmenopausal bleeding**.** Hence any woman presenting with postmenopausal bleeding should beconsidered for further evaluation, irrespective of the amount of bleeding or its episodic character (5). Unlike other malignancies, endometrial cancer presents at an early stage and curative treatment is available if diagnosed earlier (4).

Studies done by Lidor et al and Gambrel et al showed that in western countries, the most common cause of postmenopausal bleeding was atrophic endometrium (50%) (6-9). These studies also observed that adenocarcinoma of endometrium were seen in less than 10% of patients with postmenopausal bleeding (6, 7). However, they have found that there is a definite rise in incidence of endometrial carcinoma with advancing age. But, the Indian studies have found that cancer cervix and cancer endometrium is the most commonly encountered causes for postmenopausal bleeding among Indian women.

(9).Hence this study is done to determine the commonest cause of postmenopausal bleeding in our population.

The primary goal in the diagnostic evaluation of postmenopausal bleeding is to exclude endometrial carcinoma (10). The initial evaluation of the uterine cavity in a woman with postmenopausal bleeding can be done by Trans vaginal ultrasound (10). Endometrial cancer can be excluded when the endometrium is thin and homogeneous and endometrial biopsy can be deferred for them (10). Studies done by various study groups including, Tabor et al, Osmers et al, Nasri et al, have showed variable endometrial thickness cut-off viz 4mm, 5mm, 6mm as significant for having endometrial carcinoma(11-13)

ACOG Committee Opinion has stated that endometrial thickness more than or equal to 4mm is considered as significant in postmenopausal women who present with postmenopausal bleeding and thereby warrants endometrial sampling / biopsy (10). In our institution, all patients who present with postmenopausal bleeding, irrespective of the endometrial thickness, office endometrial sampling is being done. The second aim of this study is also to confirm whether the 4mm cut-off given by ACOG can be extrapolated to our population.

AIMS AND OBJECTIVES

AIMS ANDOBJECTIVES:

1. To determine the most common cause of postmenopausal bleeding in our menopausal women.
2. To determine the correlation of endometrial thickness in endometrial carcinoma and to set a cut-off for endometrial thickness.

REVIEW OF LITERATURE

REVIEW OF LITERATURE:

Definitions:

Menopause

WHO defines Menopause as permanent cessation of menstruation due to loss of ovarian follicular activity (14).

According to The International Menopause Society Menopause is defined as a period after 12 consecutive months of amenorrhea where there is no obvious pathological/ physiological cause. (15)

The International Menopause Society also defines menopause as a period known in certainty only after one year from the Final menstrual period (FMP).(15)

Post menopause:

WHO defines post menopause as dating from the FMP, regardless of whether the menopause was induced or spontaneous. (14)

Postmenopausal bleeding:

Postmenopausal bleeding is defined as bleeding from the genital tract that occurs 12 months after the final menstrual period (FMP). (14)

Introduction:

Menopause is a normal age related physiological transition that occurs in all women due to the decrease in circulating levels of estragon (16). In India the average age of

menopause is 47.5 years (16). It isfound in the recent past decades that the lifeexpectancyof Indian women is increasing, and they spend about one third of their life in the menopause period. During this period of life, the menopausal women experience a wide range of menopausal symptoms starting from the menopausal transition period .The distressing menopausal symptoms include hot flushes, urogenital symptoms, mood swings, osteoporosis, postmenopausal bleeding. In addition, menopause perse itself contributes few health risks for these women like cardiovascular problems, cancers etc. Of all these menopausal symptoms explained above, the one which is of major concern is postmenopausal bleeding (PMB) (16).

Global epidemiology:

Gynaecological malignancies are of majorconcern in women in their menopausal phase of life. Among them, the most common malignancy is endometrial cancer (17). Endometrial malignancies have their highest incidence in developed countries than in the developing world due to the influence of certain risk factors like late child bearing, intake of exogenous hormones, lack of breast feeding, lack of exercise, increased intake of fat and increased prevalence in obesity and diabetes. It is reported that, there is highest prevalence of endometrial cancer in North America, Europe and Scandinavia. The prevalence rate reported is more than 15/1, 00,000 populations in these countries (17). In developing countries like South East Asia and Africa the prevalence is very less. According to the American Cancer Society, Cancer facts and Figures 2015, endometrial cancer is the most common malignancy in United States accounting for 6% of all cancers

in women (18). The life time risk of developing endometrial cancer among whites is 2.4% and among blacks is 1.3 %(18).

Cervical cancer is the second most common malignancy worldwide (17). In comparison with developed countries, there is disproportionate increase in the incidence of cervical cancer in developing countries. The mortality related to it is mainly due to lack of infrastructure which is required to screen and detect the pre invasive lesions of Cervix (17).

The third most common malignancy is ovarian malignancy; its prevalence is the same in developing and developed world (17).

Vaginal and Vulval cancers contribute to less than 5% of gynaecologicalmalignancies (17).

Choriocarcinoma accounts for less than 1% in the group of gynaecologicalmalignancies (17).

Indian Epidemiology:

The number of people living with cancer in India is estimated to be approximately 2.5 million (19). Among Indian women breast cancer is the most common cancer accounting for 27 %(19). Cervical cancer ranks as second at 22.8 %(19). It is estimated that for every 8 minutes one woman dies due to cervical cancer. Cervical cancer is more common among the rural women when compared to the urban population (19).

Endometrial cancer is not very common in India when compared to its prevalence in Western countries. In India, data suggest a prevalence rates of 4.3/1, 00,000 in hospital based population in Delhi, 4.2/1, 00,000 and 2.8/1, 00,000 in Bangalore and Mumbai respectively (20).

Aetiology of Postmenopausal bleeding:

Postmenopausal bleeding is bleeding from any part of the genital tract, the uterus, cervix, vagina, vulva, fallopian tubes, or due to ovarian pathology. Uterine source is the most common cause of postmenopausal bleeding. The origin of bleeding can also involve non gynaecologic sites, such as urethra, bladder, rectum and bowel. Hence, the causes of postmenopausal bleeding can be classified on the basis of the origin of the bleeding as, non-genital, genital, uterine or extra uterine (6).

As per the literature, studies done by Bani et al, has shown that the commonest aetiology of postmenopausal bleeding is atrophic endometrium which accounts for 60-80%, followed by oestrogen replacement therapy by 15-25%, endometrial polypswhich constitute about 2-12%, endometrial hyperplasia by 5-10% and lastly the endometrial carcinoma by another 10%(8).

In Indian and South East Asian population, we find the most common cause of postmenopausal bleeding as cervical or endometrial malignancy rather than atrophic endometrium. A study done in Singapore by Lee at al, to assess the aetiology of postmenopausal bleeding in their population found that malignancy is the most common

cause. In their study, endometrial carcinoma accounted for 12.5% and cervical carcinoma for 11.5%. Other benign aetiologies included cervicitis (12.9%), atrophic vaginitis (12.3%), cervical polyp (6.7%), hyperplasia (3.1%), urethral caruncle (2.5%) and oestrogen replacement therapy (1.8%) (9).

Endometrial Atrophy:

Atrophic endometrium contributes to 60-80% of women with postmenopausal bleeding (8). Bleeding in atrophic endometrium is attributed to the decreased production and circulating levels of oestrogen in menopause (21). Due to low oestrogen levels, blood vessels which are lining the endometrial cavity become very thin and fragile. These blood vessels break spontaneously causing postmenopausal bleeding. Another mechanism by which atrophic endometrium causes bleeding is thought to be due to the hypo estrogenic state which causes collapse in the endometrial surface and micro erosions over the epithelium of endometrial cavity. These micro erosions sets in a chronic inflammatory reaction leading to a chronic endometritis stage which causes postmenopausal spotting or bleeding (21). This same effect occurs in senile vaginitis as well, due to the lack of oestrogen the vaginal epithelium becomes thin and the blood vessels close to the surface are exposed causing bleeding.

Endometrial Cancer:

Of all the women with postmenopausal bleeding, approximately 10% of women will have endometrial cancer (8). All women with endometrial cancer presents with postmenopausal bleeding but the vice versa is not true. Hence, every woman with postmenopausal bleeding should be evaluated to rule out endometrial cancer.

Endometrial Polyps:

Endometrial polyps are seen in women at their late reproductive and early menopause age (22-24). 2-12% of women with endometrial polyp presents with postmenopausal bleeding. Endometrial polyps are outgrowths from the endometrial lining in localized areas due to excessive stimulation of oestrogen (24, 25). The exact aetiology of endometrial polyps is unknown but polyps generally arise due to exogenous hormone replacement therapy or tamoxifen therapy (26, 27).

Polyps are usually benign although few may be precancerous or malignant (23). About 0.5% of endometrial polyps will have adenocarcinoma cells.

Endometrial hyperplasia:

Endometrial hyperplasia is considered as a precursor for endometrial cancer. It contributes to 5-10% of women with postmenopausal bleeding (8). Endometrial hyperplasia develops as a result of unopposed oestrogen exposure in women who have anovulation (28). The endometrium grows and gets crowded due to excessive oestrogen exposure and becomes abnormal leading to hyperplasia. Endometrial hyperplasia may

manifest clinically as abnormal uterine bleeding in perimenopausal and post-menopausal women. Endometrial hyperplasia in postmenopausal women can be attributed to endogenous production of oestrogen from either ovarian or adrenal tumours or exogenous oestrogen therapy or tamoxifen therapy (28). Obese postmenopausal women also have high levels of endogenous oestrogen which contribute to endometrial hyperplasia (29).

Types of endometrial hyperplasia are (28):

1. Simple hyperplasia without atypia

2. Complex hyperplasia without atypia

3. Simple hyperplasia with atypia

4. Complex hyperplasia with atypia.

Histopathologically, endometrial hyperplasia is considered when the following features are present (30):

1. Disordered or irregular proliferation of endometrial glands.
2. Increase in gland to stromal ratio. Even though proliferative endometrium also has increased gland to stromal ratio, it is more pronounced in endometrial hyperplasia.

Postmenopausal hormone therapy:

Postmenopausal women on menopause hormone therapy (MHT) can experience postmenopausal bleeding. This accounts for 15-25% of postmenopausal bleeding (8).

Menopausal hormone therapy is given in two forms as, Sequential hormone therapy or continuous combined hormone therapy.

Sequential hormone therapy:

Normal menstrual cycle is characterized by oestrogen predominance during follicular phase and progesterone dominance during secretory phase. Sequential pills are pills which contain oestrogen alone during the first half of cycle (15 pills) and the rest (6 pills) containing both oestrogen and progesterone.

According to K Freely et al, among the postmenopausal women who are using sequential hormone therapy, the endometrium showed weak secretory activity in 70% of cases and proliferative activity in 15% of cases. About 5% of women showed atrophic endometrium (31).

Sequential hormone therapy in postmenopausal women converts the proliferative endometrium to secretory endometrium and thereby decreases the chance of endometrial hyperplasia and malignancy.

The duration of progesterone exposure in a sequential pill remains controversial. In a prospective study done by Sturdee et al, when the progesterone duration in the pill was 10 days, there was 5.3% prevalence of complex hyperplasia and 0.7% of atypical hyperplasia and no adenocarcinoma (32). Hence, it was concluded that longer the duration of progesterone in the pill it is protective for the endometrium. The current recommendation according to the American Cancer Society Consensus is that the

progesterone duration in the sequential pill should be at least 12-14 days to prevent endometrial hyperplasia or malignancy (33-35).

Continuous Combined Hormone therapy:

Large prospective study done by Wells et al on usage of continuous combined hormone therapy in postmenopausal women has shown that there is no evidence of hyperplasia or malignancy after five years of itsusage (36). The mechanism by which the continuous combined hormone therapy prevents endometrial hyperplasia and malignancy is by arresting the mitosis in the glands and leading to atrophic endometrium (34). However, in literature there are anecdotal reports of endometrial malignancy in postmenopausal women using continuous combined hormone therapy (37). The reasons attributed are (37-40):

1. Prior use of unopposed oestrogen,

2. Inadequate dose of Progestin in the pill,

3. Use of less effective Progesterone,

4. Poor compliance,

5. Continuous use of progesterone alone which causes the endometrium to build up leading to cancer.

Endometrial effects of SERMS:

Another important cause of postmenopausal bleeding is the usage of tamoxifen for breast cancers. Selective oestrogen receptor modulators (SERMS) are group of drugs that act on the oestrogen receptors as competitive partial agonists (41). Different tissues have different degrees of sensitivity to the oestrogens, thus having agonist on some and antagonist on others (41).

CLASSIFICATION OF SERMS (41):

I Generation: Triphenylethylenes (Tamoxifen)

II Generation: Benzothiophenes (Raloxifene)

III Generation: Nafoxidene, Lasofoxitene, Ospemifene.

The commonly used and better known SERMS are Tamoxifen and Raloxifene. It is a well-known fact that exposure to oestrogen has a very important role in the development of endometrial cancer /hyperplasia. Results from Early Breast Cancer Trialist's Collaborative group has shown that when tamoxifen, used as an adjunctive treatment inbreast cancer women whose hormonal receptor status is positivehas significantly improved the ten year survival rate. On the other hand, the incidence of endometrial cancer in these women has doubled after 1-2 years of treatment and quadrupled when treated for five years (41, 42). Tamoxifen, one among the SERM acts as an oestrogen agonist in the endometrium by direct stimulation of the oestrogen receptors in the

endometrium. Several large trials found an increased incidence in endometrial carcinoma among users of Tamoxifen for breast cancer. The risk of endometrial cancer in women treated with tamoxifen is dose and time dependent (42). According to ACOG, when used in the standard doses of tamoxifen, it causes endometrial hyperplasia, polyp formation and carcinoma (42). According to the study done by National Surgical Adjuvant Breast and Bowel Project, the endometrial cancer among women with tamoxifen users was 1.6/1000(41).

Uterine sarcomas account for only 8% of all uterine cancers as compared to the women treated with tamoxifen, in whom sarcomas accounted for 17% of cases (41).

Mechanism of action of Tamoxifen in endometrium:

Tamoxifen has proliferative action on the endometrium. It causes hyperplasia of the endometrial glands and hypertrophy of the stroma (41). The molecular mechanisms behind the action of Tamoxifen on endometrium are (41, 43-44):

1. Endometrium of women who are on Tamoxifen has been consistently found to have increased oestrogen and progesterone receptors.

2. Following receptors including oestrogen receptors, c-fos and glyceraldehyde phosphate dehydrogenase mRNA will be upgraded by Tamoxifen.

3. The bromo - deoxyuridene index, which is an indicator of cell mitogenesis is also increased in tamoxifen treated endometrium.

Ultrasound findings in Tamoxifen treated endometrium:

1. There is an increase in the thickness in tamoxifen treated endometrium. It is found that the endometrial thickening in these patients is due to the sub endometrial stromal oedema and enlargement of stromal cells (41, 46).

2. Few patients on Tamoxifen may also develop cysts (7%) and endometrial polyps (12-25%). (41, 46)

Herbal and dietary supplements: There are few case series to state that soya and other phyto oestrogens in large doses may cause estrogenic stimulation of the endometrium (47). One series reports the association of soya with polyp and leiomyoma growth (48). A randomized trial on 376 postmenopausal women who received soya versus placebo showed a significant increase in endometrial hyperplasia over a five-year period (48).

Pathogenesis of endometrial cancers:

The status of normal postmenopausal endometrium:

During the early years of menopause, even though there is decline in the ovarian function, the endometrial glands will retain certain amount of weak proliferative activity (49, 50). As menopause progresses, due to further decrease in the oestrogen secretion from ovaries, the endometrium becomes atrophic and finally develops cystic atrophy changes (51).

From the pathological point of view, a normal postmenopausal endometrium will have only 50% of inactive/atrophic glands and the rest have weak proliferative glands. These proliferative glands will be either focal or diffuse but, will be exerting a low level of effective estrogenic stimulation on the endometrium (49, 50).

Mechanism of Hormonal feedback system:

In response to the decrease in oestrogen levels, the hypothalamus releases GnRH pulses which trigger the anterior pituitary to secrete FSH (52). FSH executes its action in the ovaries by stimulating the ovarian stroma and aids in androgen production. The androgens produced are converted to oestrone by peripheral aromatization and this result in continuous estrogenic stimulation of the endometrium which makes the endometrial glands to switch from their inactive state to a weak proliferative state (52).

Endometrial cancers in menopausal women are most often well differentiated endometriodadenocarcinomas (86%), which arise from the weakly proliferative type of endometrial glands (53).

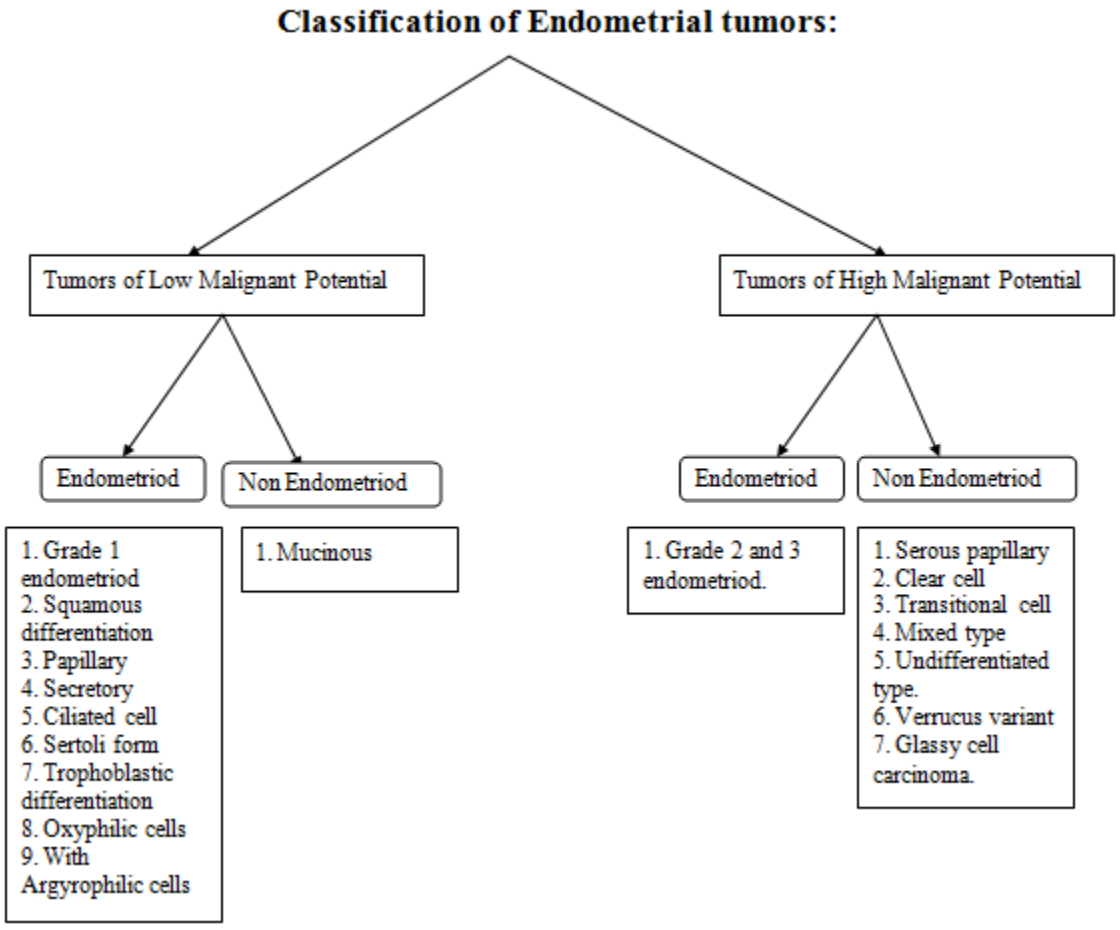
These weak proliferative glands in addition to the presence of oestrogen and progesterone receptors, they also express epidermal growth factor receptors and high MIB-1 (Ki-67) activity on angiogenesis and proliferation (53). These additional factors cause intense proliferation of the endometrium there by leading to endometriod type of adenocarcinoma.

In the past, endometrial cancers in menopausal women were grouped as: (53)

1. Grade 1 Endometriod adenocarcinoma (55%).
2. Grade 2, 3 Endometriod adenocarcinoma (20%)
3. Mosaic of serous papillary and clear cell carcinoma (15%)
4. Non endometriod carcinoma (10%)

The characteristics, prognosis, and survival rate are all similar in grade 1 endometriod adenocarcinoma arising from atrophic endometrium in menopausal women and those arising from hyperplastic endometrium in premenopausal women. These grade 1 endometriod cancers have very good prognosis and the 5 year survival rate is estimated to be 95%, whereas the other types of endometrial cancers like grade 2, 3 endometriod, serous papillary, clear cell and non-endometriod cancers are highly aggressive with poor 5 year survival rate.

The current classification of endometrial tumours is by their histological type and by their degree of tumour differentiation (Low grade vs. high grade).



The molecular level expressions are also different between the two groups of tumours. In low level malignant potential tumours there is (53):

1. Inactivation of PTEN function,

2. Deletion of tumour suppressor genes like EMX2,

3. K-ras proto-oncogene mutation,

4. Microsatellite instability.

In high level malignant potential tumours there is:

1. Mutations in p53 tumour suppressor gene,

2. Reduced expression of epithelial cadherin (E-cadherin).

Risk factors for endometrial cancer:

Risk factor is defined asany characteristic of a person that increases the chance of developing a disease or cancer. The risk factors can be modifiable or non-modifiable. Factors like age, family history, age of menarche, menopause, etc. are non-modifiable. Some factors like obesity, diabetes, drug intake, etc. are modifiable riskfactors.The various risk factors which influence the risk of developing endometrial cancer are as follows.

1. Obesity
2. Increasing age
3. Early menarche and late menopause
4. Anovulation- Polycystic ovarian disease.
5. Diabetes and hypertension
6. Family history of endometrial, breast, colorectal cancer

Obesity:

Obese postmenopausal women have increased risk for developing endometrial cancer (54, 55). It is associated with 2-5 fold increase in the risk of endometrial cancer (55). They develop cancer mainly due to the excess production of oestrone and to a lesser extent due to the decreased levels of sex hormone binding globulin (SHBG) in them(55,56).

The presence of excess fat cells in obese women increases the peripheral conversion of androgens (androstenedione) from ovaries and adrenals to oestrone. Moreover, the concentration of SHBG is decreased in obese women leading to excess unbound oestrone causing endometrial changes (56).

Age:

The risk of developing endometrial cancer increases as age advances. The median age at which endometrial cancer develops is between 60-65 years of age (57). The conversion of androgens to oestrogen is via cytochrome P 450 aromatase. As body weight and age increases, this reaction of peripheral aromatization increases. On literature review, it is found that peripheral aromatization is seen in 15% of patients in the age group of less than 45 years whereas in women of more than 45 years the reaction is seen in 47% of patients. Hence, obesity and age are addictive risk factors in the development of endometrial cancers (57).

Exogenous hormone therapy:

Unopposed exogenousoestrogen administration is another important risk factor. It is associated with 8-15 fold increase in endometrial cancer. When combined contraceptive pills are used instead of oestrogen alone, the risk of developing endometrial cancer is decreased (53).

Long term usage of Tamoxifen has 6 fold increase in risk of endometrial cancer. The risk is increased drastically when it is used for more than 5 years (53).

Reproductive factors:

Early menarche, late menopause, nulliparity, history of polycystic ovarian disease is associated with prolonged oestrogen exposure to endometrium, making them high risk for developing endometrial cancer (53).

Lifestyle factors:

Less physical activity and diet containing excess fat indirectly increase the risk of endometrial cancer by increasing the BMI (58).

Medical comorbidities:

Diabetes mellitus is associated with 2 fold increase in the risk of endometrial cancer in obese women (59).Hypertension, as single factor is not associated with endometrial cancer. But, when hypertension is associated with diabetes and obesity it increases the risk (60).

Miscellaneous:

Cervical stenosis, Pyometra and Ichthyosis uterus are taken as risk factors for developing squamous cell variant of endometrial cancer.

Prior radiation therapy can cause endometrial cancer (Secondary carcinoma).

Genetic causes-Lynch Syndrome.

Factors with reduced risk for developing endometrial cancer (61-63):

1. Cigarette smoking.

2. Coffee intake

3. Intrauterine contraceptive device usage.

Diagnostic Workup and Evaluation:

Endometrial evaluation:

Women with postmenopausal bleeding should be assessed initiallyeitherwith endometrial biopsy orwith Transvaginal ultrasonography. Evidences suggest that the initial diagnostic evaluation does not require performing both the transvaginal ultrasonography and endometrial biopsy (64).

Ultrasound in evaluation of Postmenopausal bleeding:

Over the past years, it is found that transvaginal ultrasound is used to accurately diagnose endometrial pathologies. In women with postmenopausal bleeding measurement of endometrial thickness helps in differentiating those who are at risk for endometrial cancer.

TVS which is used as the initial investigation to evaluate the endometrium in women with postmenopausal bleeding is less invasive and has excellent high negative predictive value. TVS is also used in women whom endometrial sampling was performed but tissue was insufficient for diagnosis (64).

The International Endometrial Tumour Analysis (IETA) group has come forward with the following recommendations for an universal standardized technique in measuring the endometrial thickness and determining intracavitrarylesions (65, 66).

Technique of measuring Endometrial Thickness:

Generally in women, ultrasound pelvis should be done in the order of Trans abdominal ultrasound followed by transvaginal scan. Every assessment and evaluation of the pelvic organs especially the uterus should begin with the identification of the bladder and cervix. The uterus is scanned first in sagittal plane from one cornua to the other followed by in the transverse plane from cervix to the fundus and the uterine measurements are noted (66). Subsequently, endometrial cavity is magnified and the endometrial thickness is measured (66). Endometrial thickness is measured in sagittal

plane as maximum anteroposterior thickness of the endometrial echo (64, 66). It is the maximum measurement between the two endometrial layers (double endometrial layer) (66). The callipers should be placed in the endometrial-myometrium interface in a magnified image (64, 66).

While measuring the endometrial thickness if the angle of insonation between the endometrium and the ultrasound beam is 90 degrees, the quality of the image will be better (66). The endometrial thickness measurement should be reported in millimetres.

In cases where the endometrium is asymmetrically thickened, the endometrial thickness is reported as the sum of the largest anterior and posterior endometrial thickness (66).

Terms and Definition in interpretingendometrialthickness (66):

The IETA group in the World Congress of Ultrasound in Obstetrics and Gynaecology has recommended standard terms and definitions in interpreting ultrasound reports (66).They are as follows:

1. **Echogenicity:**

The echogenicity of the endometrium is described as hyper echogenic, iso echogenic, and hypo echogenic with reference to the myometrialechogenicity (66). It should be reported as either uniform (or) non-uniform (66). Uniform echogenicity denotes a homogeneous and symmetrical endometrium. Examples for uniform echogenicity are trilaminar endometrium and monolayer endometrium which is seen in

cases of atrophic endometrium (66). If the endometrium appears heterogeneous, asymmetrical or cystic it is reported as non-uniform echogenicity.

2. Endometrial – myometrial Junction:

The endometrial –myometrial junction should be reported as regular, irregular, interrupted, (or) not defined (65).

In 10% of cases, where the endometrium is not visualized clearly, the report should be interpreted as 'non-measurable' (66).

Radiological appearance of postmenopausal endometrium:

The normal postmenopausal endometrium is thin, homogeneous and echogenic. Generally, a uniform, thin homogeneous endometrium of <4 mm without focal thickening excludes malignancy and is suggestive of atrophy. Any endometrial thickness of > 4 mm or non-uniform endometrium with focal thickening should be further investigated by endometrial biopsy or hysteroscopy. The presence of postmenopausal bleeding with endometrial thickness >5mm is 92% sensitive and 57% specific for endometrial cancer (67,). ACOG Committee Opinion also supports the above statement (64).

Study done by Gerber et al have shown that in patients with postmenopausal bleeding, if the endometrial thickness is < 5mm, the risk of endometrial cancer is < 1 %(68). Hence further sampling is not required in these patients (68). However, ACOG recommends that endometrial sampling is mandatory in postmenopausal women with

persistent postmenopausal bleeding even if endometrial thickness is less than 4mm (64). The supporting evidence behind this is, a thin, homogeneous endometrium does not reliably exclude type 2 endometrial cancer (69, 70).

A study done by Wang et al reviewed the preoperative ultrasound reports of 52 postmenopausal women who were diagnosed to have type 2 endometrial cancer. Out of the fifty two postmenopausal women, 9 (17%) had endometrial thickness less than 4mm and another 9 (17%) had indistinct endometrium. In these 18 women, in addition to the thin endometrium there were additional ultrasound findings such as adnexal mass, intracavitary growth /fluid etc. Hence, it was concluded that any women with postmenopausal bleeding despite a thin endometrium when associated with other ultrasound abnormalities will require an endometrial sampling (69).

Ferrasi et al and Karlson et al have shown that using 4mm as the cut off for endometrial thickness, the transvaginal ultrasound has 96-98% sensitivity and 36-68% specificity in detecting endometrial cancer. The false positive rates are between 44 and 66%. However, the same studies have picked up 4 cases of endometrial cancer when the endometrial thickness was less than 3.5mm (71, 72).

Wong et al did a retrospective analysis to estimate the accuracy of transvaginal ultrasound in measuring the endometrial thickness in the diagnosis of endometrial cancer. The results of this study showed that the median endometrial thickness in those with endometrial cancer when compared with benign conditions were 15.7 versus 3.2 with a p value <0.001. It was also found that, using an endometrial cut off of 3mm the sensitivity

of ultrasonography in detecting endometrial carcinoma was as high as 97%. Hence, it was concluded that women with postmenopausal bleeding with endometrial thickness of less than 3mm are less likely to have endometrial cancer and further investigations can be avoided on them (73).

Invasive methods for endometrial evaluation in women with postmenopausal bleeding (74):

1. Dilatation and curettage.
2. Office endometrial sampling.
3. Hysteroscopy directed biopsy.
4. Saline sonosalphingography.

Dilatation and curettage:

Dilatation and curettage is traditionally the standard invasive method of choice to evaluate the endometrium in women with postmenopausal bleeding. Its diagnostic accuracy in detecting endometrial pathologies is debatable (74). The endometrial tissue obtained after a good dilatation and curettage is less than 50% (75). The ideal method of dilatation and curettage is complex. It requires general anaesthesia and has complications like uterine perforation, infection, pain, bleeding etc. (76, 77). In a large critical review comparing D&C and office endometrial sampling it was found that, D&C had more complications but the histopathological results in both the groups are the same (74).

Hence, to avoid all these complications newer endometrial sampling methods have come into practice.

Office Endometrial sampling (74):

First Generation methods:

1. Vabra aspirator

2. Novak curette.

Second Generation methods:

1. The Pipelle device

2. The Pipette

3. The Z-Sampler

4. The Tis- U- Trap.

Technique of endometrial sampling:

Endometrial sampling using first generation devices requires no anaesthesia, but the disadvantage in these sampling devices is that they use a motorized pump to create negative pressure for suction which causes discomfort/ pain in few patients (78). Second generation sampling devices like Pipelle, Z- Sampler have a flexible plastic piston in the

inner core which on withdrawing outwards helps to create negative pressure to aspirate tissue(78).

It is found that, of all the newer sampling devices, Pipelle is better, safe, accurate and economical in sampling the endometrial tissue in detecting endometrial pathologies. (74).

The Pipelle:

The Pipelle sampling device was first devised by Cornier.E in 1984(79). It is a 23 cm long flexible, plastic polypropylene sheath with the outer sheath diameter 3.1mm and a piston in the inner sheath with diameter 2.6mm. The outer sheath of the Pipelle has graduated markings from 4cm to 10cms from the extreme distal rounded tip of the device. The tip of the device has a small opening of 2.2mm in diameter through which the endometrial tissue will get aspirated when the proximal end of the piston is pulled outwards(79).

It is said that the office endometrial sampling by Pipelle, samples adequate endometrial tissue as compared to the traditional dilatation and curettage. The diagnostic accuracy in detecting endometrial pathologies by Pipelle was found to be 95.5 %.(76, 77)

Kavak et al did a prospective study in 78 premenopausal and postmenopausal women who were scheduled for traditional D&C had transvaginal ultrasound and endometrial sampling using Pipelle prior to the curettage. It was found that, the

histopathological results from curettage and Pipelle sampling coincided in 87% of women. Hence, it was estimated that endometrial sampling by Pipelle had 75% sensitivity and 100% specificity in diagnosing endometrial pathologies. When ultrasound is used along with Pipelle, its sensitivity increased to 90 %(84). Goldschmidt et al in their analysis also supported that in 90% of cases the results from endometrial sampling by Pipelle correlated with D&C results (85). Using transvaginal ultrasound along with Pipelle sampling increases the sensitivity but decreases the specificity in detecting endometrial disease.

Even though endometrial sampling by Pipelle has excellent outcomes, a recent study done by Rezk et al contradicts this. This prospective observational study was done to assess the safety and acceptability of Pipelle endometrial sampling in postmenopausal women when compared to Pipelle sampling in premenopausal women. Primary outcomes taken were safety and adequacy of the Pipelle sampler. The conclusions of this study were endometrial sampling by Pipelle is more painful, lessacceptable and less adequate in postmenopausal women (86).

There is certain amount of false negativity in any method of endometrial sampling used. Feldmann et al followed for two years 263 pre and postmenopausal patients with negative biopsy by office endometrial sampling / Dilatation and curettage for abnormal uterine bleeding and found that approximately 2% of patients had uterine malignancy which was missed by the initial biopsy. (87)

Gudio et al found that, when 65 women with known endometrial cancer underwent Pipelle endometrial sampling cancer was missed in 11 out of 65 women. Endometrial cancer can be a focal disease involving 25% or 50% of the endometrial cavity. Hence, blind sampling can cause errors (88).

3. Hysteroscopic guided Biopsy:

Dilatation and Curettage and endometrial sampling methods, being blind procedures can miss cases of endometrial polyps, myomas, focal hyperplasia and neoplasia. In view of all these constraints hysteroscopy is considered as the preferred method in evaluating the endometrium in women with postmenopausal bleeding (74). It has high sensitivity and specificity in detecting endometrial pathology (74). It visualizes the focal endometrial abnormalities and thereby directed biopsies can be taken in the same sitting (89). In the recent years, due to the advancements in the technology and surgical expertise hysteroscopy is considered as a safe, simple out-patient procedure which is easily performed without any discomfort to the patient (89). Hysteroscopy along with endometrial biopsy helps in accurately diagnosing the endometrial pathology in a woman who is presenting with postmenopausal bleeding. Office based hysteroscopy except in being a diagnostic tool, it is also used in surgically treating the cause of bleeding in the same setting (89, 90).

Sonja et al have conducted a prospective study to investigate the diagnostic accuracy, sensitivity, specificity, positive predictive and negative predictive of hysteroscopy in detecting endometrial pathology in 148 women with postmenopausal

bleeding and concluded them to be 95.1%, 100%, 81%, 92% and 100% respectively(90). In 69% of patients the cause of bleeding was also removed hysteroscopically in the same sitting thus facilitating treating with diagnosis (90).

Even though hysteroscopy has high sensitivity, specificity and excellent diagnostic accuracy in detecting endometrial pathologies, it is not cost effective and easily applicable as transvaginal ultrasound (89). Hysteroscopy is not superior to D&C and other sampling methods in its sensitivity to detect endometrial hyperplasia and malignancy (89). Even though, hysteroscopy is superior to other diagnostic modalities in detection of endometrial polyps, it should be used with caution in women suspected to have endometrial cancer because of the possibility of retrograde spilling of malignant cells into the peritoneum during hysteroscopy (89, 90).

Therefore, in developing countries like India where there is lack of infrastructure, hysteroscopy is not considered as first line gold standard modality in the evaluation of postmenopausal bleeding. When endometrial polyps is suspected and in grossly thickened endometrium the routine endometrial sampling procedure can be bypassed and diagnostic hysteroscopy followed by biopsy can be performed (74).

4. Saline infusion sonohysterography:

Saline infusion sonography (SIS) is an out-patient procedure which is used one among the different methods in investigating a woman with postmenopausalbleeding(92). The technique of SIS consists of intrauterine infusion of saline through a catheter with an

inflating balloon placed in the cervix (92). The expansion of uterine cavity is directly observed through the transvaginal ultrasound. In an out-patient setting, the feasibility of saline infusion sonography is similar to diagnostic hysteroscopy (93). It helps in discriminating high risk patients who need further evaluation (93). Abeera Choudry et al, did a cross sectional study on 77 women with postmenopausal bleeding to estimate the diagnostic accuracy of saline infusion sonography in them and concluded that saline infusion sonography along with endometrial biopsy can be used as a standard procedure in the evaluation of women with postmenopausal bleeding because of its excellent sensitivity (92%), specificity (79%) and good patient acceptability (93).

Farquhar et al, in their analysis have recommended SIS in patients with irregular endometrial appearance suspecting polyps, sub mucous fibroids etc. (92). Society of Radiologists in Ultrasound Consensus suggested that SIS can be used in conditions where there is focal endometrial thickening in ultrasound, so that SIS can confirm the presence of a focal thickening and the nature of it (92). SIS is helpful when there is discrepancy between the findings of ultrasound and biopsy. Moreover, SIS is more sensitive than ultrasound and biopsy in detecting focal endometrial abnormalities. On concluding, even though SIS cannot replace transvaginal ultrasound in all cases it is useful in certain cases were added information can be obtained by performing it.

MATERIALS AND METHODS

Materials and Methods:

Thestudy was a prospective observational study which was conducted in Christian Medical College Hospital, Vellore between February 2016 to July 2016 in the department of Obstetrics and Gynaecology after the Institutional EthicsCommitteeclearance. We included all postmenopausal women who presented any time after one year of menopause with postmenopausal bleeding. Detailed history, clinical examination, per speculum and per vaginal examination was done systematically to evaluate the clinical diagnosis of postmenopausal bleeding. A structured proforma was made and details of the patient including her age, age of menarche, age of menopause, parity, body mass index, amount of bleeding, number of episodes of postmenopausal bleeding, associated co morbidities and any drug intake like hormone therapy, and anticoagulants are noted, following which, the diagnostic evaluation for postmenopausal bleeding is done by using transvaginal ultra sonogram and the endometrial thickness was determined. Endometrial biopsy is done after ultrasound and the histopathological report was correlated.

The results were analysed to determine the commonest cause of postmenopausal bleeding. The endometrial thickness was correlated with the histopathological reports to set a cut off value for endometrial thickness below which, further intervention including endometrial biopsy is not necessary.

Participants:

Eligibility Criteria:

Inclusion criteria:

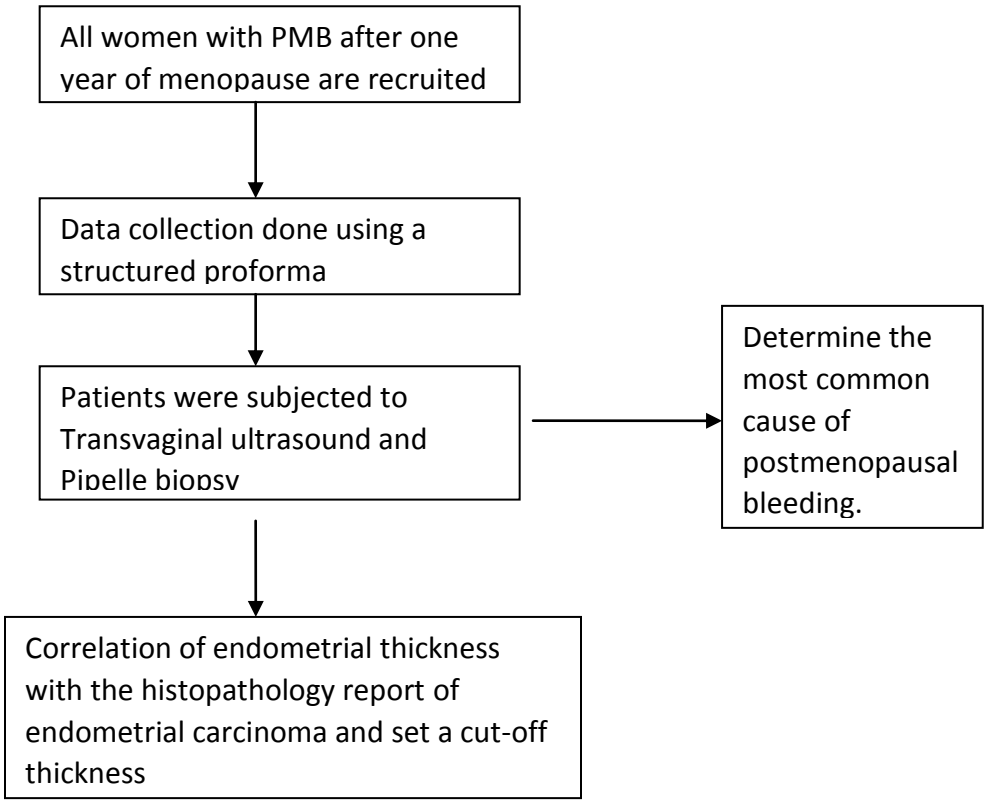
All women who have attained natural menopause after 45 years of age, presenting with postmenopausal bleeding after one year of menopause.

Exclusion criteria for the second aim of the study:

1. Women with other obvious causes of bleeding from cervix and vagina.
2. Women with known case of bleeding disorders
3. Premature menopausal women.
4. Postmenopausal women with postmenopausal bleeding who have been treated with hormones elsewhere.
5. Transvaginal ultrasound showing adnexal pathology.

The following flow diagram shows the methodology of the study

Flow diagram 1:



Setting:

The materials of the study were obtained from the patients who presented with postmenopausal bleeding to the Obstetrics and Gynaecologyoutpatient clinic. All postmenopausal women who presented with postmenopausal bleeding from February 2016 to July 2016 were recruited. Patient recruitment and data collection through a structured proforma was done by the principal investigator. Following data collection, a transvaginal ultrasound was done in the Out Patient department ultrasound room by a trained and experienced senior sonology technician and by

the principal investigator. After the ultrasound, endometrial sampling using pipelle was done by the principal investigator in minor operation theatre.

A woman who is recruited for the study was considered postmenopausal when one year has elapsed from the final menstrual period. No hormonal investigation like FSH was done to confirmher menopausal status. All these women except women who had a clinical diagnosis of carcinoma cervix underwent a transvaginal scan followed by endometrial sampling by Pipelle.

The endometrial samples were classified into following histopathological categories: 1.Endometrial carcinoma, 2.Endometrial hyperplasia, 3.Atrophic endometrium, 4. Proliferative endometrium, 5.Secretory endometrium, 6. Endometrial Polyps, 7. Shed endometrium with no hyperplasia./malignancy, 7.Sample inadequate for evaluation.

Statistical methods and sample size calculation:

Data were summarized using mean (S.D), and median (range) for continuous variables and by frequency (percentage) for categorical variables.

Prevalence of carcinoma was presented with 95% CI. (Exact method was used).

Independent‘t’ test was used to compare continuous variable among carcinoma and non- carcinoma group. Chi-square was used to test association between carcinoma and non-carcinoma and other categorical variables.

An ROC analysis was done to obtain the cut-off of endometrial thickness discriminating carcinoma and non-carcinoma. For the cut-off decided, the diagnostic accuracies with 95% CI were presented.

All analysis was done in STATA 13.1/I C.

Sample size calculation:

To detect a prevalence of 10% (1, 6, 7, 94), we collected a sample of 144 postmenopausal women, with 95% CI and 5% precision. The following formula was used.

$n = 4pq/d^2$

Where p denotes prevalence, taken as 10,

q is 100-p,

d is precision, which is taken as 5

Hence,
n = 4 x 10 x 90/25

Therefore the sample size is 144.

RESULTS

Results:

The baseline characteristics of our study population are as follows.

The baseline characteristics of our study population are tabulated below:

Table 1:

	No. of patients	Percentage (%)
Age of menarche		
Less than 11 years	4	2.78%
More than 11 years	144	97.22%
Age of menopause		
45-50 years	84	58.33%
50-55 years	59	40.97%
>55 years	1	0.69%
Parity		
Nulliparous	7	4.86%
Multiparous	137	95.14%
BMI		
<25 kg/m2	44	30.56%
25-30kg/m2	52	36.11%
30-35kg/m2	39	27.08%
35-40kg./m2	4	2.78%
>40kg/m2	5	3.47%
Diabetes	55	38.1%
Hypertension	62	43.06%

Age of presentation:

In our study, of the 144 women recruited with postmenopausal bleeding, 15.97% of them were between 45-50 years, 35.42% between 51-55 years, 21.53% between 56-60 years, and 27.08% beyond 60 years of age.

Table 2: Table showing the distribution of patients according to the age of presentation:

Age	No. of patients	Percentage
45-50 years	23	15.97%
51-55 years	51	35.42%
56-60 years	31	21.53%
>60 years	39	27.08%

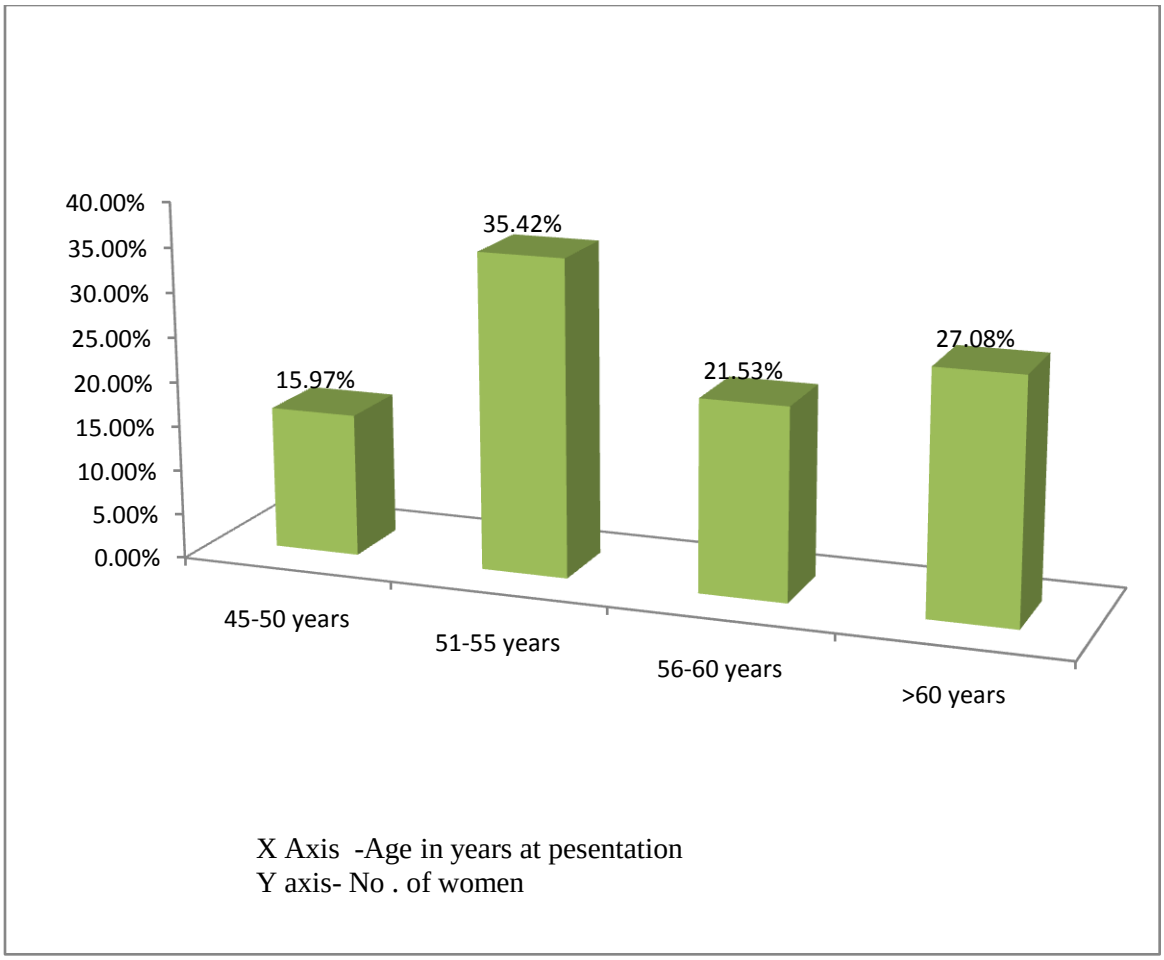


Figure 1: The bar diagram below depicts the study population according to their age groups.

It is evident from the above bar diagram, postmenopausal bleeding seems to occur most commonly within the next few years of menopause (i.e.) at 51-55 years constituting 35.4% and the next peak after 60 years of age at 27%.

Age of menarche:

97% of women had menarche beyond 11 years and only 2.7% had early menarche. The mean age of menarche was found to be 14 years.

Age of menopause:

58% of women in our study group had attained menopause between 45-50 years and 41% of them between 50-55 years and only one woman beyond 55 years. The mean age of menopause in our study group was found to be 48.7 years which is consistent with data from the Indian Menopause Society where the mean age of menopause for Indian women was noted to be 47.5 years (16).

Parity:

Multiparous women constituted 95% of our study population whereas 7 women (4.86%) were nulliparous. Among the women with endometrial hyperplasia and malignancy, 11.43% were nulliparous.

Table 3: Table showing the distribution of endometrial cancer/hyperplasia according to parity

Parity	Cancer	Others	p value
Nulliparous	4(11.43%)	3(2.78%)	0.039
Multiparous	31(88.57%)	105(97.22%)	

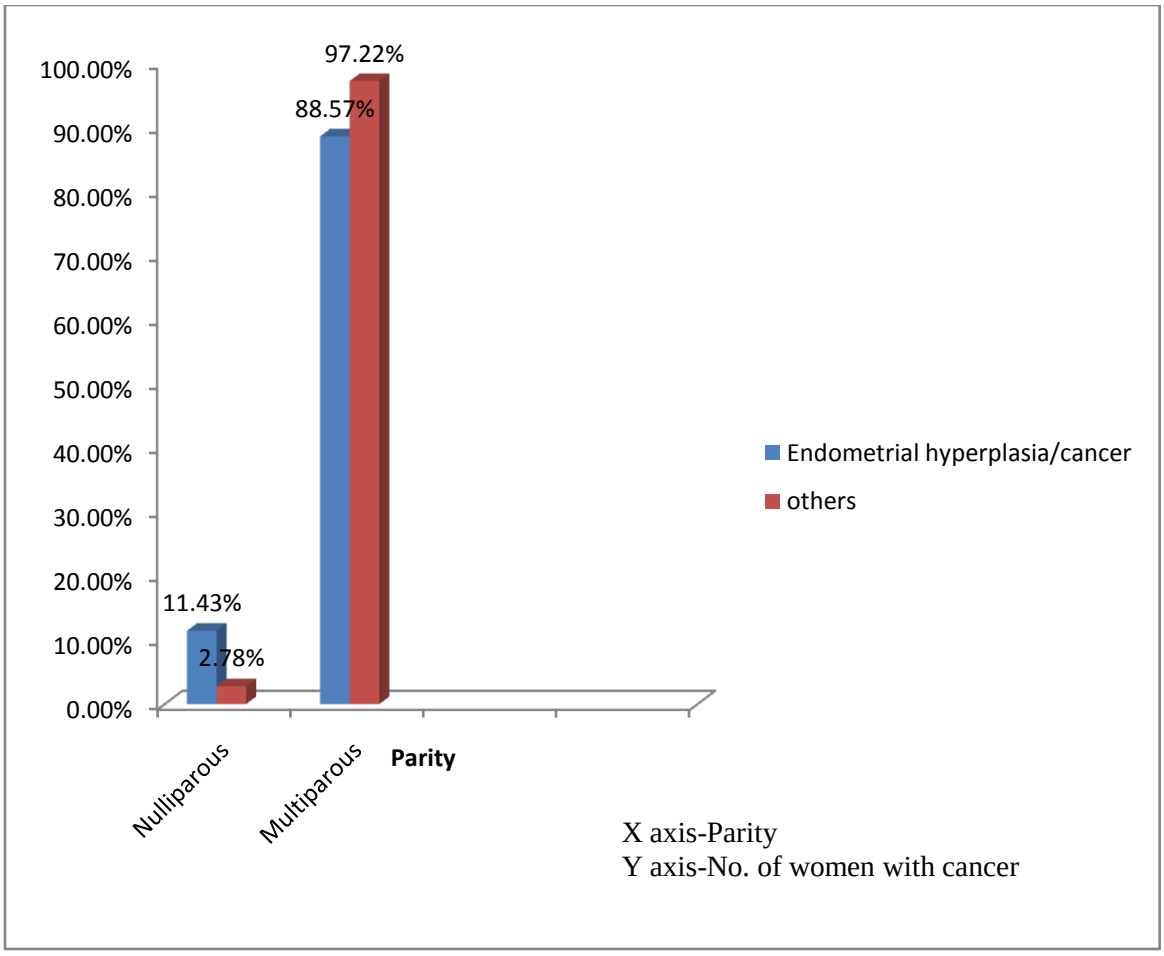


Figure 2: Bar diagram showing the prevalence of endometrial cancers/hyperplasia according to parity.

BMI:

On considering the BMI, about 36% of our women were overweight, 29.8% obese and 3.4% morbidlyobese. The mean BMI in our study population was 28.15 kg/m2.

Table 2 below shows the number of women with endometrial hyperplasia/cancer on the basis of their BMI:

Table 4:

BMI(Kg/m2)	Frequency	Percentage	p value
< 25	7	20%	0.0554
26-30	13	37.14%	
31-35	11	31.43%	
36-40	1	2.86%	
>40	3	8.57%	

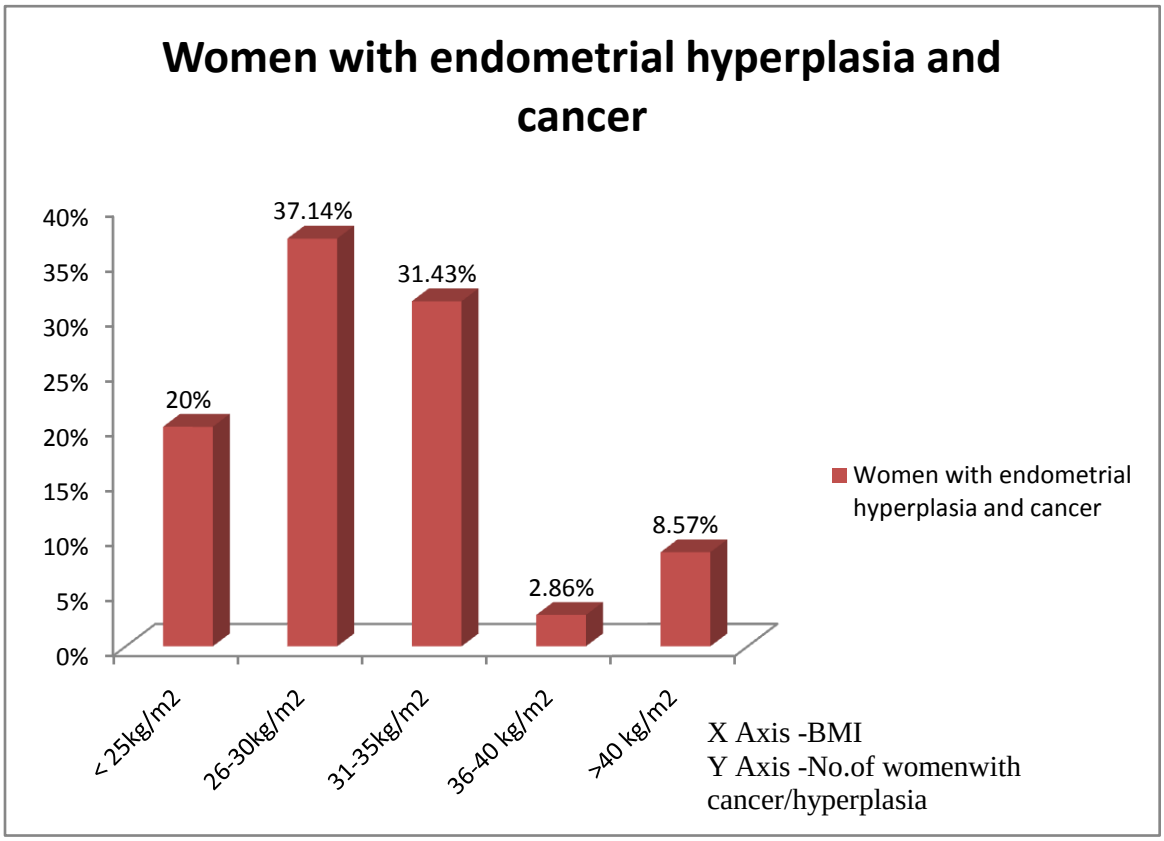


Figure 3: Picture showing the distribution of endometrial hyperplasia/cancer cases on the basis of BMI.

Diabetes and hypertension:

Medical comorbidities like diabetes and hypertension were found in 38% and 43% of our study women respectively.

The following table shows the number of diabetics and hypertensives with endometrial cancer/hyperplasia:

Table 5:

Comorbidities	Frequency	Percentage	p value
Diabetes	20	57.14%	0.006
Hypertension	21	60%	0.017

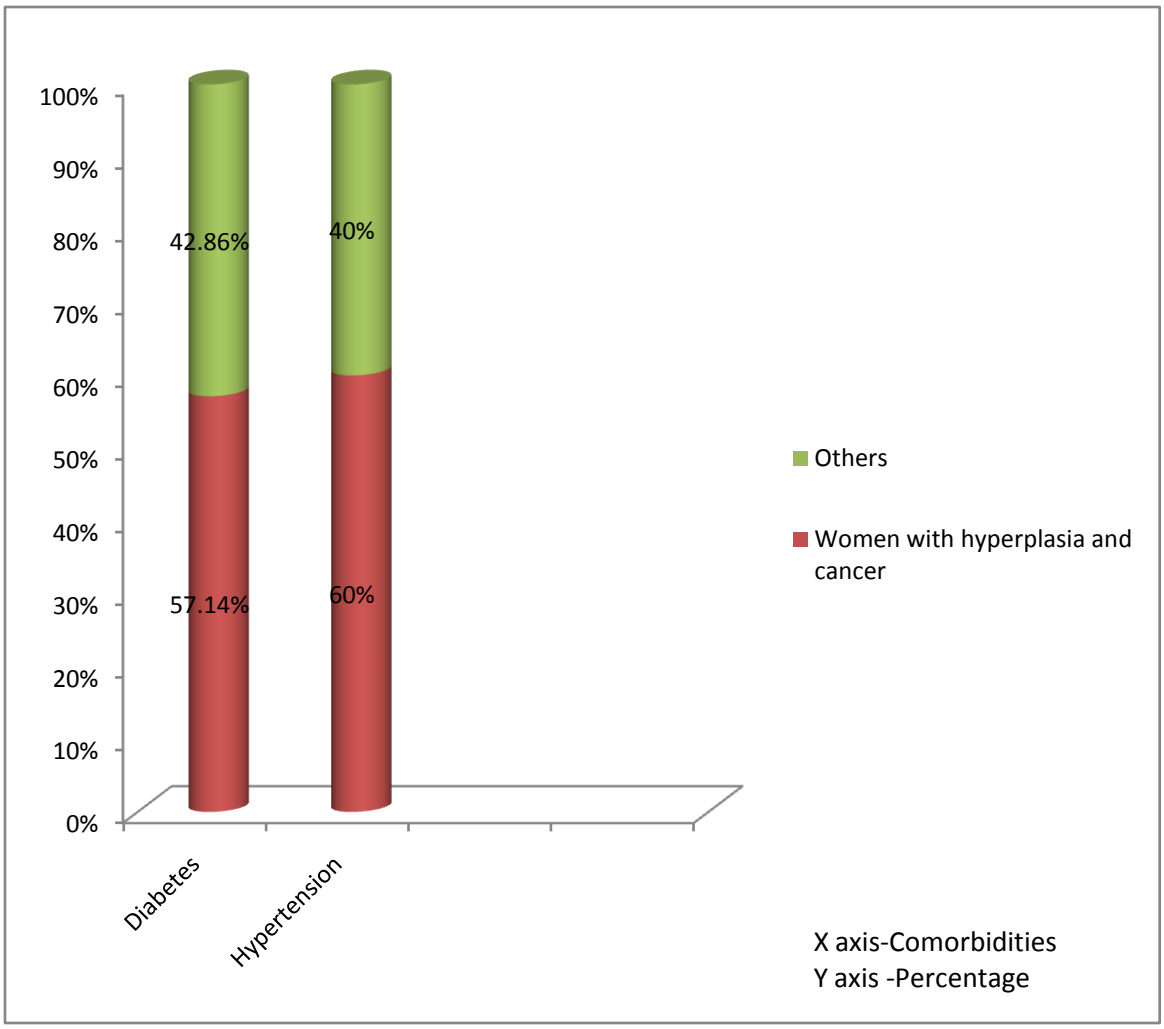


Figure 4: Figure showing the prevalence of endometrial cancer/hyperplasia among diabetics and hypertensives.

Age:

The mean and median age of women with postmenopausal bleeding was found to be 56.6 and 55 years respectively in our study population .The mean age noted in the

various studies ranged from 47.43 to 57.5 years (95). In the prospective study done by Thomas Gredmark et al the mean age quoted is 61.4 years (96).

In our study, it was found that, the age at which women presents with postmenopausal bleeding peaks at 51-55 years. Even though, there is a slight decrease in women presenting with postmenopausal bleeding after 56 years of age there is definitelyan increase in the incidence of malignancy in this group as compared to women in the early menopausal years.Studies done by Gredmark T et al, Bani et al and Youssef et al had a similar finding (8, 96, 97).Youssef et al, in his study showed that 25 patients (69%) who presented with postmenopausal bleeding were between 50-60 years where as only 5 patients (13%) were above 70 years and at the same time the incidence of malignancy was more after 60 years (97).

The frequency of postmenopausal bleeding decreased with increasing age but, the number of women with cancer (endometrium and cervix) increased proportionately. There were only 2 cases (5.71%) of endometrial malignancy in the age group of less than 50 years whereas there were 9 patients (25.71%) between 50-55 years and 12 patients (34.29%) between 55-60 years and another 12 patients (34.29%) beyond 60 years.

This was true with cervical cancer too. There was only one case (4.76%) of cancer cervix at age less than 50 years, whereas there were 6 patients (28.57%) between 50-55 years,5 patients (23.81%) between 55-60 years and 9 patients (42.86%) beyond 60 years.

On comparing endometrial malignancy and cervical malignancy, endometrial malignancy rates increased beyond 55 years of age and cervical malignancy peaked beyond 60 years.

The number of endometrial and cervical malignancies in each age group is summarized in table 6 and Figure 5:

Table 6:

Age	Endometrial cancer/ hyperplasia	Cervical cancer
<=50 years	2 (5.71%)	1(4.76%)
50-55 years	9 (25.71%)	6 (28.57%)
55-60 years	12(34.29%)	5 (23.81%)
>60 years	12 (34.29%)	9 (42.86%)

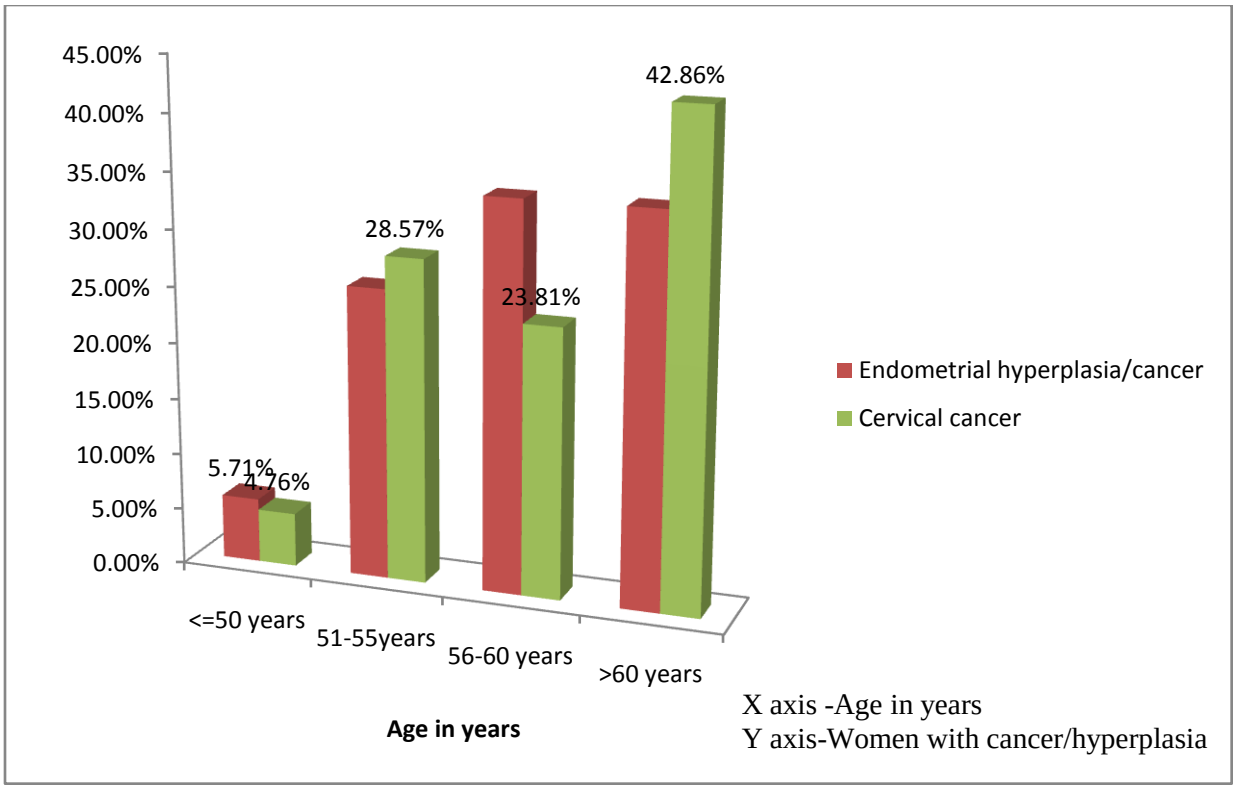


Figure 5:

It was also found in our study that, the mean age of developing premalignant and malignant diseases of the uterus i.e. endometrial hyperplasia and malignancy was found to be 58.8 years where as mean age for developing other benign conditions like atrophic endometrium, endometrial polyp etc. was found to be 55.71 years. Hence, it is evident in our study that, as age increases the chance of malignancy increases which is statistically significant with a p value of 0.0233. This is in consistent with the study done by Thomas Gredmark et al where he found the incidence of endometrial cancer was found in older women between 65-69 years (96, 98).

Other characteristics:

In our study, 86 women (59.7%) presented to the health care facility in the first episode of postmenopausal bleeding. The rest 40% of women had recurrent episodes of bleeding before they presented to the health care facility. The number of recurrent episodes ranged from 2 to 21 episodes. This is in consistent with the study done by Choo et al where 70% of women presented with the first episode of postmenopausal bleeding(98).The mean age at which our women in the study group experienced the first episode of postmenopausal bleeding is 55.85 years which is about 8-10 years post menopause. This is in consistent with the study done by Bani et al and Choo et al where the mean duration of menopause was 10 years (8, 98).

Table 7:

Episode of PMB	Frequency	Percentage
First	86	59.72%
Recurrent	58	40.28%

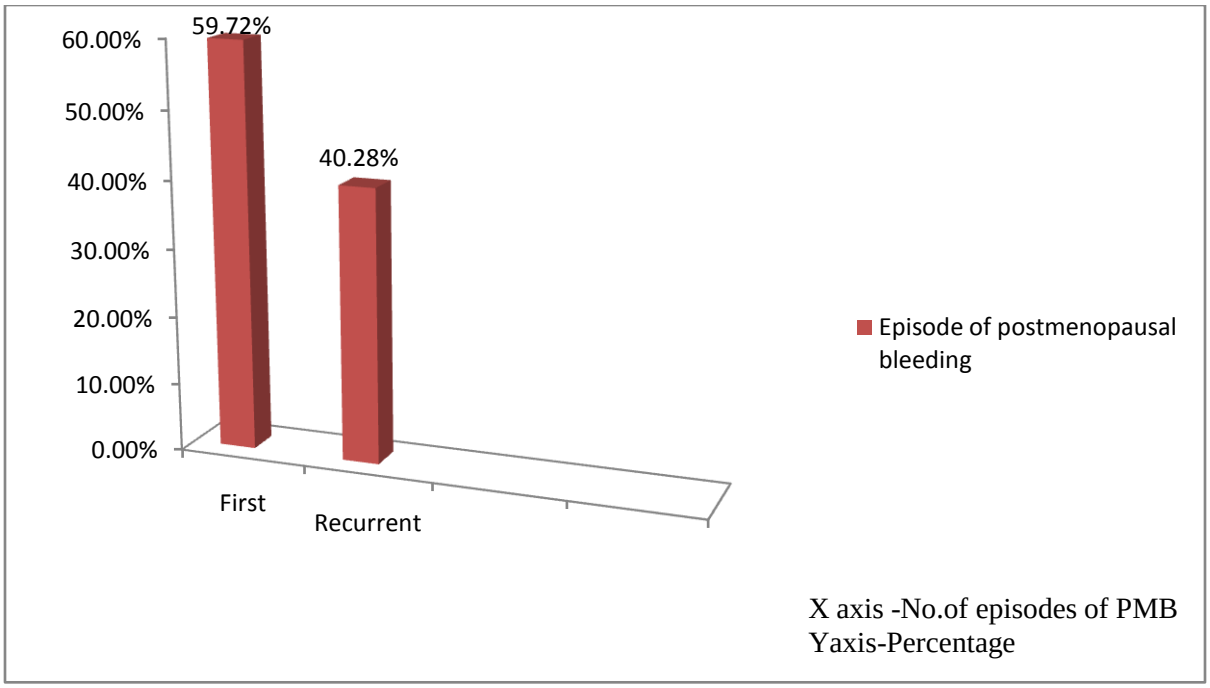


Figure 6: The above bar diagram shows the number of women with first and recurrent episodes of bleeding.

Amount of bleeding:

The bleeding was described as scanty bleeding in 46% of women, moderate bleeding in 35% of women and heavy bleeding in 18% of women. This is shown in the following table.

Table 8:

Type of bleeding	Frequency	Percentage
Scanty	67	46%
Moderate	51	35%
Heavy	26	18%

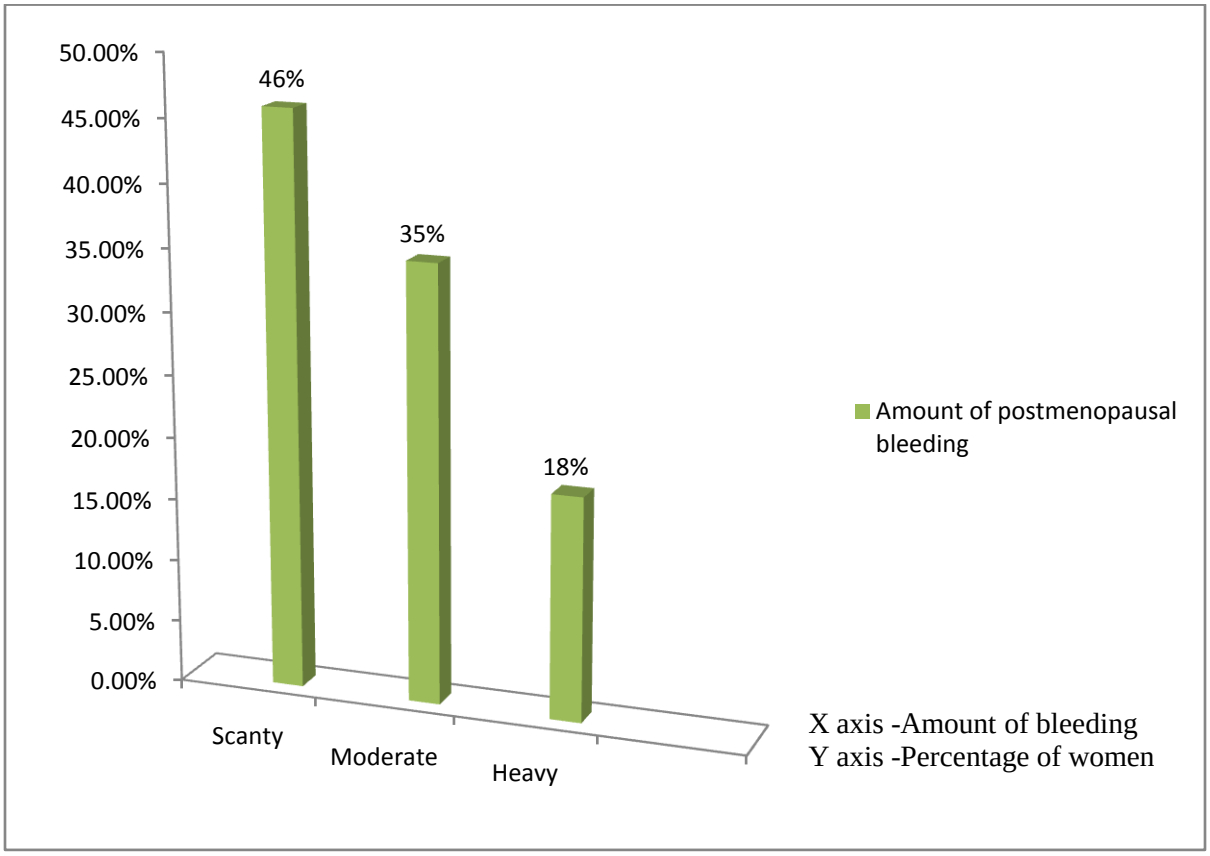


Figure 7: Bar diagram showing the distribution of study population based on amount of bleeding.

Menopausal hormone therapy:

No women in our study group had menopausal hormone therapy.

Drugs:

Of the 144 women, 8 women (5.55%) had exposure to drugs like anticoagulants, antiplatelet and Tamoxifen. Among the 8 women, 2 women had tamoxifen use, 4 ofthem had aspirin use and the rest two of them had anticoagulant use.

Aspirin:

Of the 4 women who were using aspirin, 2 had endometrial polyps, 1 patient had endometrial hyperplasia and the other had cancer cervix as their cause for postmenopausal bleeding.

Anticoagulants:

Of the 2 women who were using anticoagulants, one patient had cancer cervix and the other patient had endometrial hyperplasia.

It should be emphasized that, all the 6 women who were on aspirin and anticoagulants were older than 55 years, were obese and had the medical comorbidities, diabetes and hypertension. Hence all these confounding variables indirectly lead to the development of endometrial cancer/hyperplasia in them rather than anticoagulants/aspirin perse.

Tamoxifen:

Among the 2 women who were using Tamoxifen, one patient hadtamoxifen usage for 32 months and had endometrial polyp, whereas the other patient had tamoxifen usage for 48 months and had endometrial cancer.

The following table shows the cause of postmenopausal bleeding in the women who were on aspirin, anticoagulants and Tamoxifen:

Table 9:

Drugs	Endometrial cancer	Endometrial hyperplasia	Cancer cervix	Endometrial Polyp
Aspirin	-	1(25%)	1(25%)	2(50%)
Anticoagulants	-	1(50%)	1(50%)	-
Tamoxifen	1(50%)	-	-	1(50%)

The following figure depicts the causes of postmenopausal bleeding in women who were on drug intake:

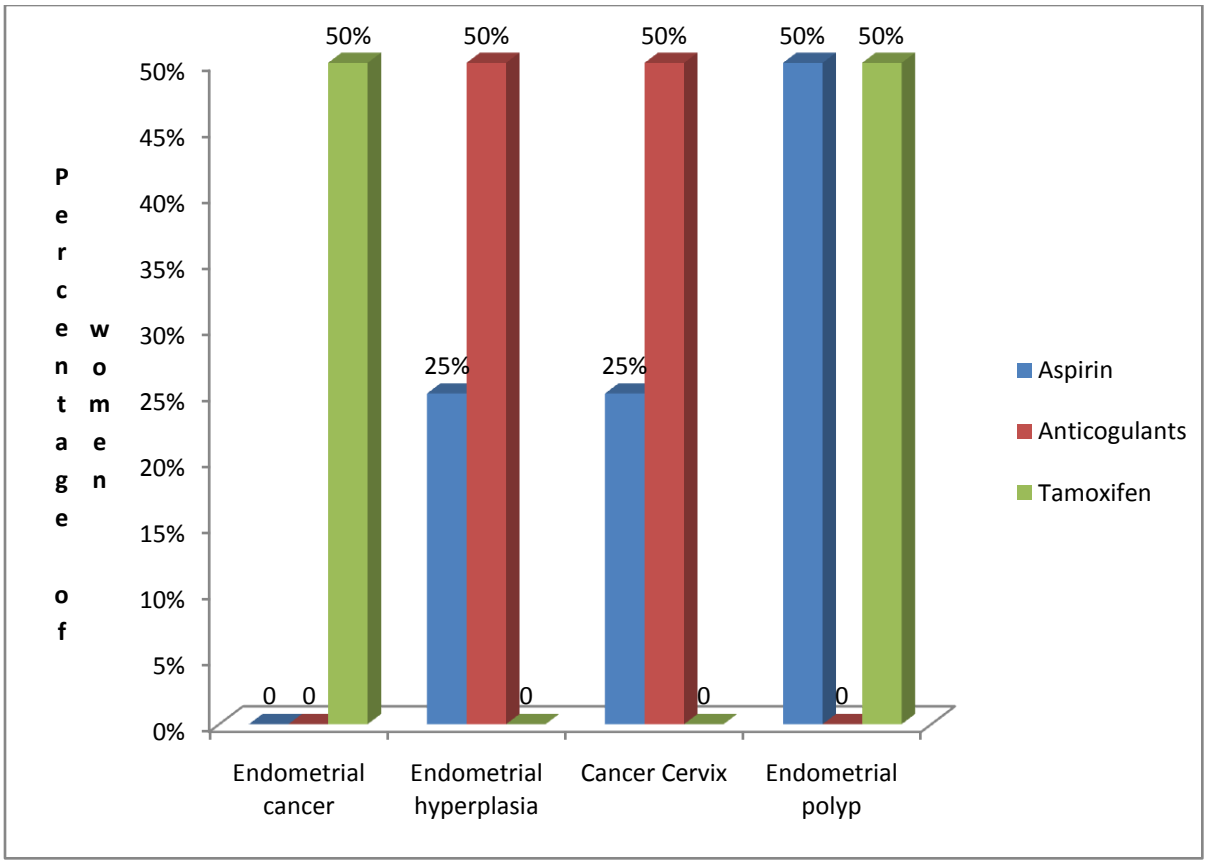


Figure 8: Bar diagram showing the endometrial pathologies in women with medications intake.

Family h/o malignancies:

Of the 144 women in our study population, 21 women (14.5%) had family h/o malignancies, like oral, upper GI, colonic, breast and uterine cancers. Of the 21 women, 12 women had malignancies, uterus -6 (28.5%), breast- 4 (19%) , colon-2 (9.5%) which are shown to have greater association with endometrial malignancy. 3 out of 12 (25%) of

those who have given h/o first degree relative having uterus, breast and colonic cancer had endometrial cancer.

Table 10 below shows the number of endometrial cancer in women with family h/o uterine, breast and colonic cancer.

Table 10:

Family h/o malignancy	Endometrial cancer	Others
Uterine cancer	1	5
Breast cancer	1	3
Colon cancer	1	1

Aetiology of postmenopausal bleeding:

The following table shows the aetiology of postmenopausal bleeding in our study population.

Table 11:

Histopathological report	No. of patients	Percentage (%)
Atrophic endometrium	28	19.44%
Endometrial polyp	24	16.66%
Endometrial malignancy	22	15.27%
Carcinoma Cervix	21	14.58%
Endometrial hyperplasia	14	9.72%
Ovarian cancers	6	4.16%
Secretory endometrium	4	2.77%
Proliferative endometrium	3	2.08%
Others	22	15.27%

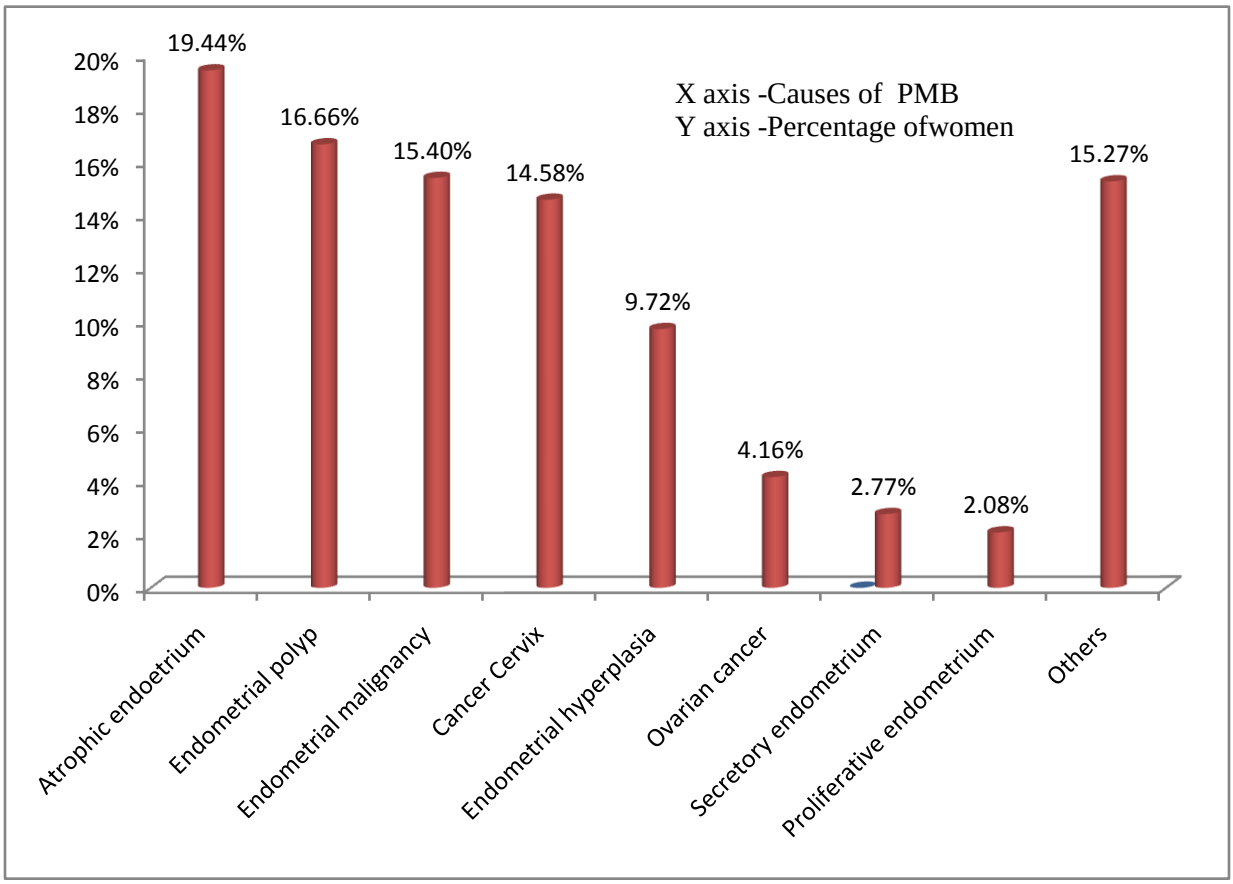


Figure 9: Bar diagram showing the aetiology of postmenopausal bleeding in our study population.

In our study, histopathological reports from the endometrial sampling by Pipelle were only included. Of the 144 samples, 123 patients had the endometrial sampling by Pipelle. Benign conditions including endometrial polyps, secretory endometrium, proliferative endometrium were found in 31 patients which accounted for 21.5%.

Premalignant conditions which included endometrial hyperplasia with/without atypia and Cervical intraepithelial neoplasia were seen in 14 patients (9.72%). Atrophic endometrium was evident in 28 patients (19.44%).

The malignancies diagnosed in our study were endometrial cancers, cervical cancers and ovarian malignancies. Among our study population, 22 women (15.27%) had endometrial malignancy, 20 (14.58%) had cancer Cervix and 6 patients (4.16%) had ovarian cancers.

Of the 144 women with postmenopausal bleeding, 22 women (15.27%) had no histopathological diagnosis for their bleeding and was reported as endometrium with no evidence of hyperplasia/malignancy.

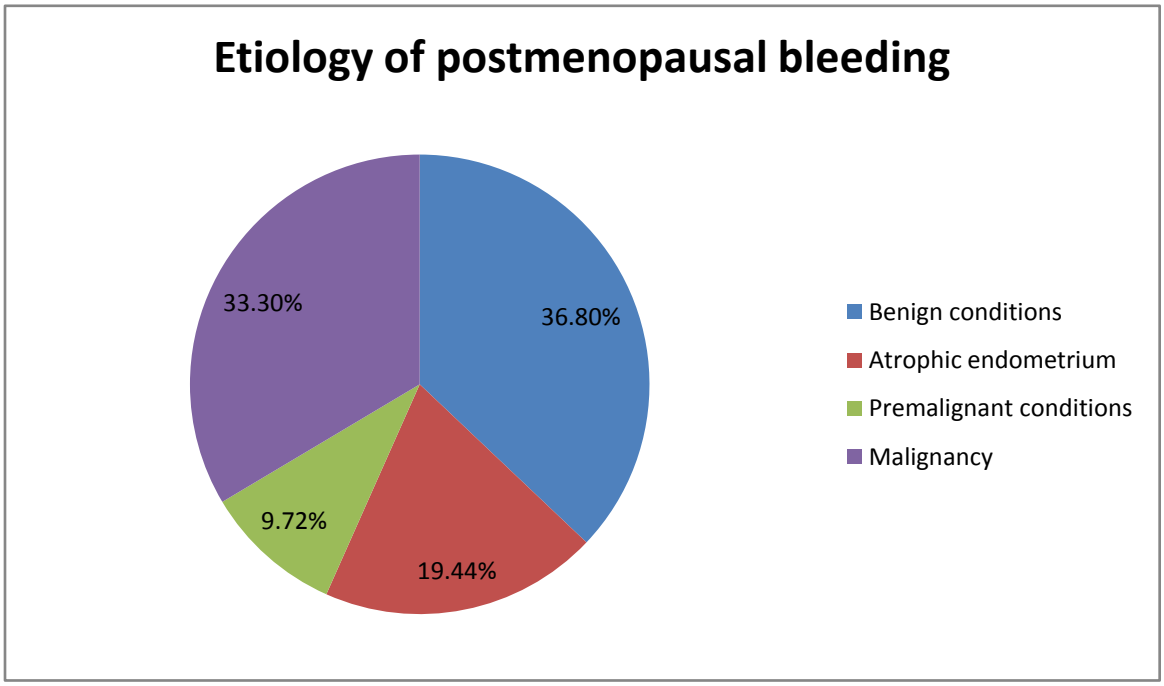


Figure 10: Pie chart showing the major attributable causes of postmenopausal bleeding.

Atrophic endometrium:

Of the 144 women with postmenopausal bleeding, 28 women (19.44%) had atrophic endometrium. Even though atrophic endometrium is found to top the list, it constituted only 19.44% which is in contrast to the other studies done by Choo et al, Praghathi et al, Goodmann et al where the incidence of atrophic endometrium was seen in 50%, 32%, 60-80% respectively(95,98,99). However, our results were consistent with the an Indian study done in a teaching hospital in Andhra Pradesh by Kavitha et al where atrophic endometrium was seen only in 16% of patients(5). In an Ethiopian study done by Wondwossen et al in 475 patients with postmenopausal bleeding, only 4.4% cases were reported as atrophic endometrium (100).

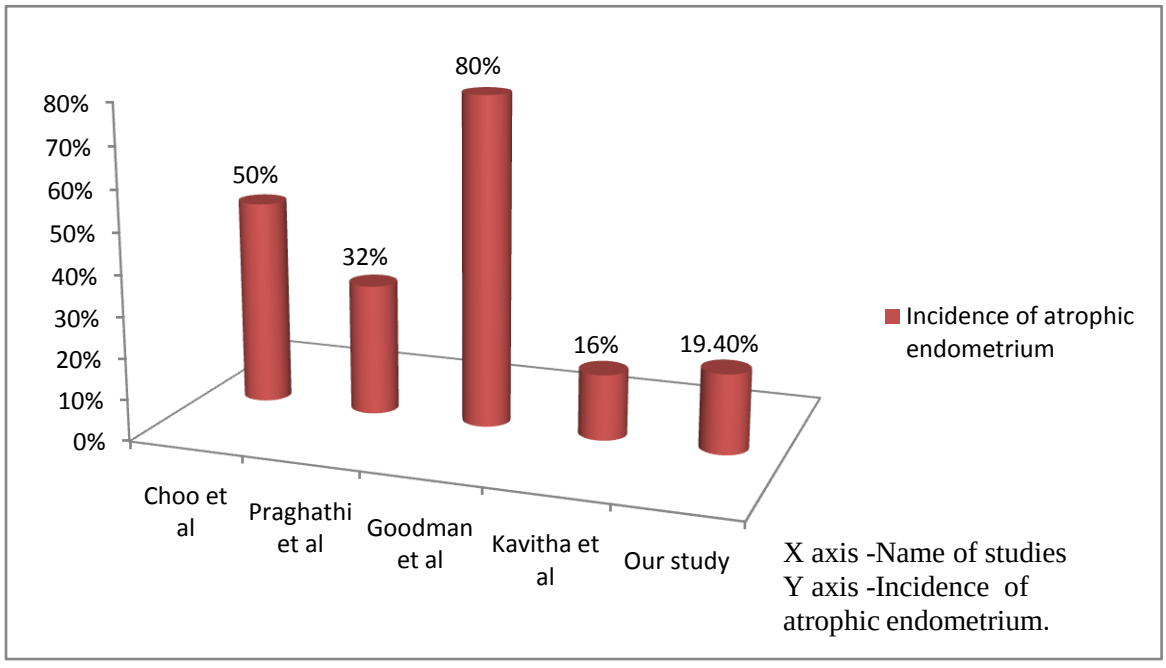


Figure 11: Bar diagram showing the incidence of atrophic endometrium in various studies.

Endometrial Polyps:

The second most common cause of postmenopausal bleeding in our study group is endometrial polyps, which accounted for 16%.This is in consistent with the retrospective study done by Pl So et al on 265 women with postmenopausal bleeding, where benign endometrial polyps were seen in 16% of patients (101). In studies done by Gredmark T et al, polyps accounted for 9%.(96) In the retrospective study by Kavitha et al and Praghathi et al the prevalence of endometrial polyps in their study population was very low which was only 3-4% (5,99).

Endometrial carcinoma:

Of the 144 women, endometrial cancer was found in 22 women, which accounted for 15.27% in the present study. The prevalence of endometrial cancer in our study population was 14.6% with 95% CI (9.3%-21.5%).From the literature review, it is evident that the prevalence of malignancies in patients with postmenopausal bleeding is lower in the developed country when compared to its prevalence in developing countries. The incidence of endometrial carcinoma varies between 3%-7% in the various studies published earlier in literature among Western women (6, 96, and 98). Few studies done in developing countries like Pakistan, India by Siyal et al and Kauser J et al found the incidence of endometrial cancer to be 16% which is consistent with our study (102,103). A study done by Alberico et al found a higher incidence of endometrial cancer of about 24%.(104).In an Indian study done by Nirupama et al, on 100 cases of postmenopausal

bleeding it was found that malignancies predominated the benign conditions and the endometrial cancer was seen in 12% of patients(94). However, few more Indian studies done by Pragathi et al and Kavitha et al reported a lower incidence of endometrial malignancy in their study population (5, 99).

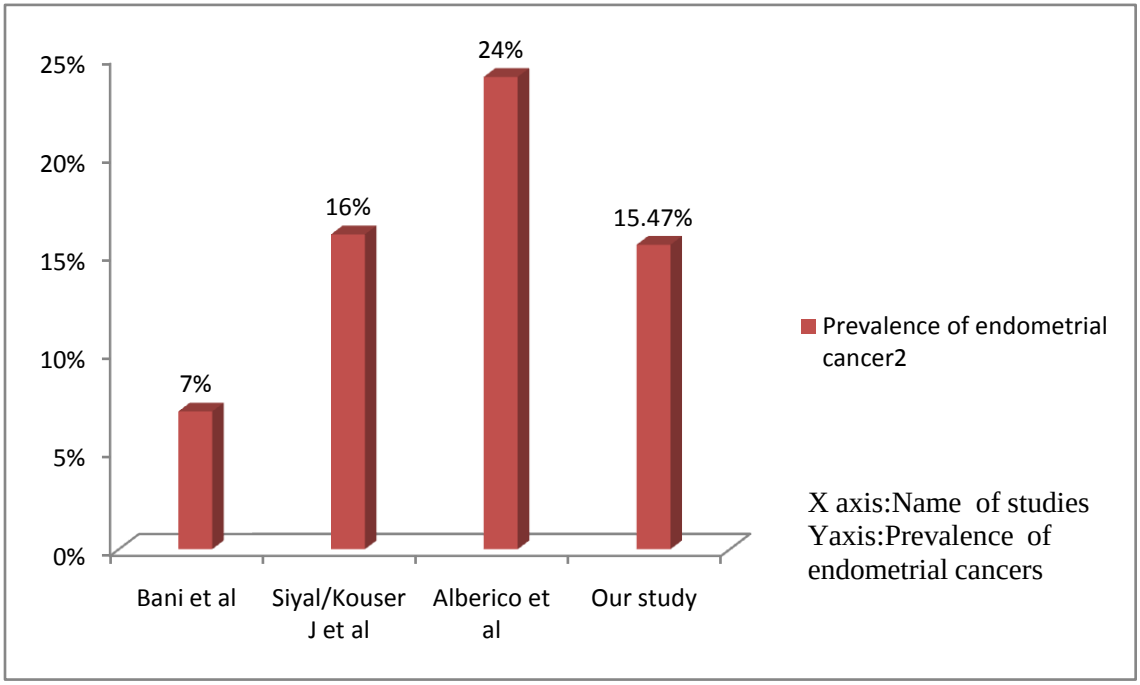


Figure 12: Figure showing the prevalence of endometrial cancer in various studies.

Endometrial hyperplasia:

Endometrial hyperplasia which is a premalignant condition was found in 9.7% of women in our studygroup.This is in consistent with the study done by Gredmark et al and kavitha et al where it was found in 10% of women with postmenopausal bleeding.(5,96). Another study done by Lidor et al in 226 women with postmenopausal bleeding also found a similar incidence of endometrial polyps. (6).

Cervical cancer:

Malignancy is the most important factor which should be ruled out in the evaluation of a woman with postmenopausal bleeding. In the various Indian studies done on the aetiology of postmenopausal bleeding, malignancy was noted as the most common cause .The reported prevalences were 40% by Nirupama et al, 63.6% by Pamela et al and 44% by Asif et al(94,105). In our study, it is found that the prevalence of malignancy in our study population was 34%, Of which cervical cancer was 14.5% and endometrial cancer was 15.27%.

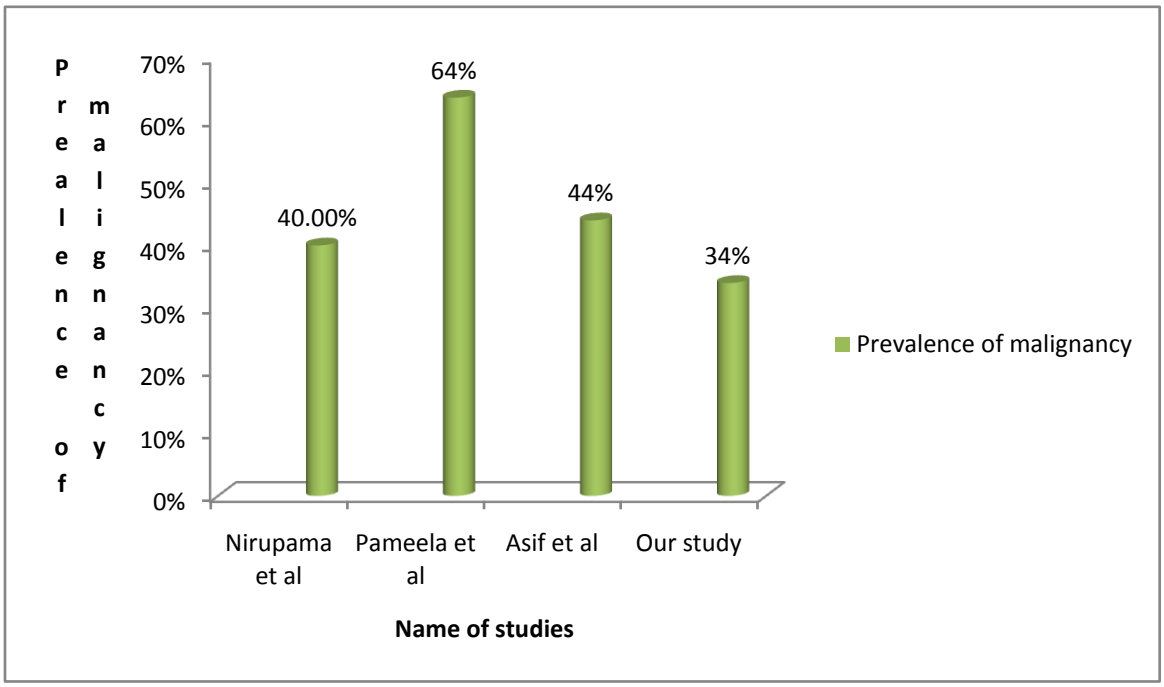


Figure 13: Bar diagram showing the prevalence of malignancies in women with postmenopausal bleeding

Of the 144 women with postmenopausal bleeding, cervical cancer was seen in 14.5% of women. Studies done in developed countries by Pl So et al found that cervical cancer was seen in only 0.8% of patients in their population (101).

Since cancer cervix is predominantly seen in developing countries, many Indian studies have looked on its prevalence among patients with postmenopausal bleeding. Indian studies done by Kavitha et al ,Pragathi et al found the prevalence of cancer cervix in their women with postmenopausal bleeding was found to be 6.6% and 6.4% respectively(5,99). The earlier studies done by Sengupta et al (1990), Naik et al (2004) has shown a higher prevalence of cervical cancer 32% and 39% respectively (106,107).

Another retrospective study done in Singapore by Lee et al, in 163 women with postmenopausal bleeding, the researchers found that out of the malignant causes of postmenopausal bleeding, Cervical cancer is the most common malignancy and it contributed to 12.9%.(9) .

A retrospective study done in Ethiopia byWondwosen et al in 475 women with postmenopausal bleeding showed that cervical cancer ranked as the first cause in their population which accounted for 52.6%(100).

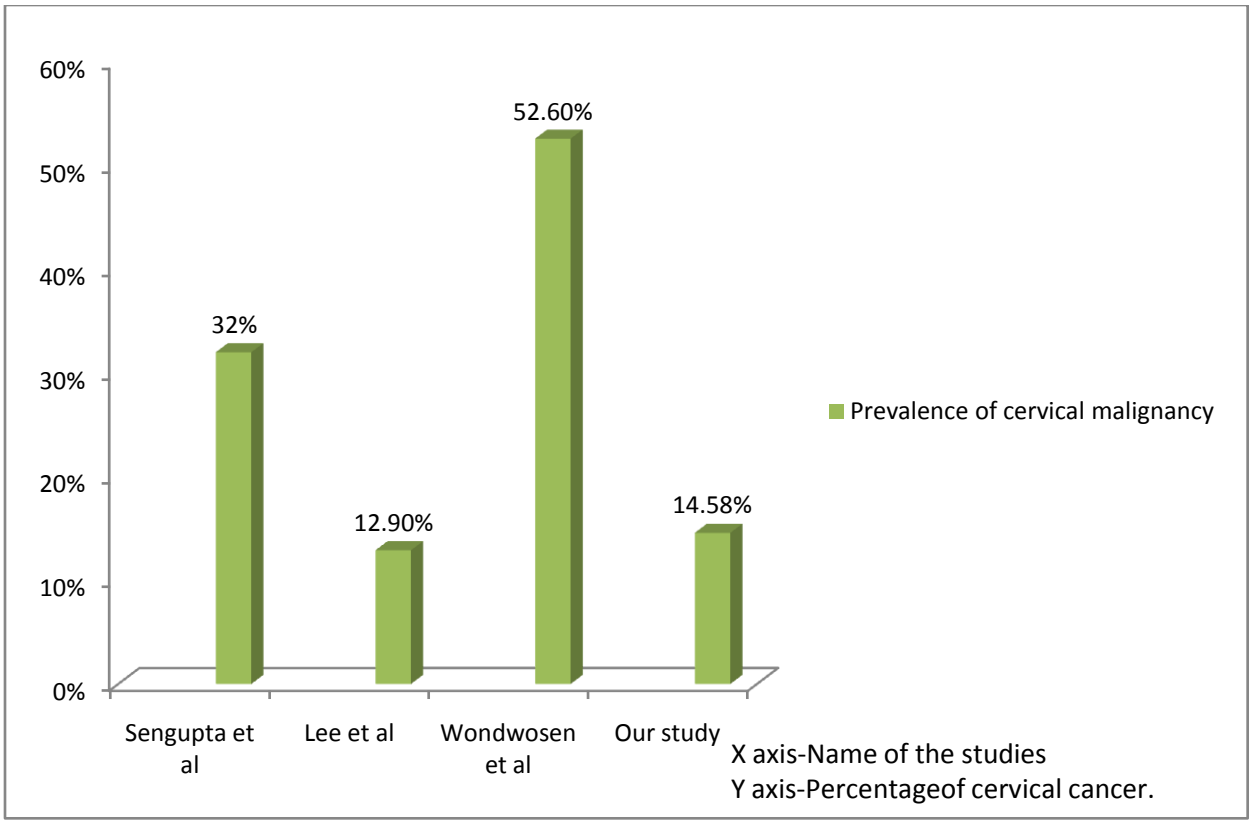


Figure 14: Figure showing the prevalence of cervical cancer in women with postmenopausal bleeding

The reason for the increased prevalence of malignancy in the developing countries are poor accessibility to the modern health care services, screening programmes and lack of education and awareness about the important aspects of health**. Moreover, it is difficult to estimate the prevalence of malignancy in postmenopausal women in developing countries because many women do not seek medical care for the symptom of postmenopausal bleeding (100).**

In the developed countries, the incidence of cancer cervix among postmenopausal women is very low due to the excellent screening services and infrastructure available in those

countries. In a Swedish study done by Gredmark T et al, of the 460 postmenopausal women with postmenopausal bleeding only 6 cases of cancer cervix was found (96).

Ovarian cancers:

Among the 144 patients with postmenopausal bleeding, 125 women had transvaginal ultrasound in their evaluation of postmenopausal bleeding. Of the 125 women 11 patients (8%) had adnexal mass. These 11 patients, similar to the rest of the study population underwent endometrial sampling by Pipelle and the histopathological findings were consistent with the proliferative, secretoryendometrium, endometrial hyperplasia. 2 samples were reported as estrogenic stimulation of the endometrium. All these 11 women underwent Staging laparotomy and the final histopathology of the surgical specimen showed ovarian malignancy in 6 patients (4%). Two patients had granulosa cell tumour, two serous cell carcinoma, one borderline serous ovarian cancer and another endometriod adenocarcinoma of the ovary.

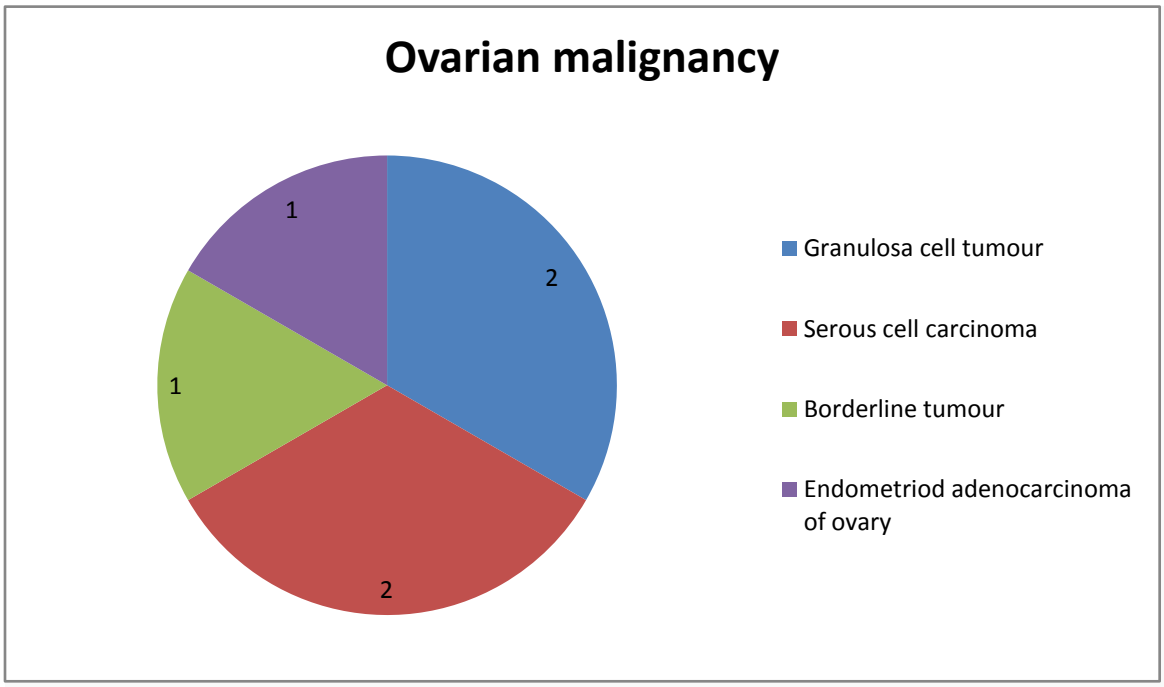


Figure 15: Pie chart showing the histopathology of ovarian cancer in women with postmenopausal bleeding.

Literature review shows ovarian malignancy to be one among the least causes for postmenopausal bleeding ranging from 1-3%. Gredmark et al, has reported 2% of postmenopausal bleeding to be associated with ovarian malignancy (96).

Others:

Secretory endometrium was found in 2.7% of patients in the present study, which is in parallel with the other studies by Gredmark T et al, Pragathi et al, Pl So et al where secretory endometrium was seen in 1%, 4%, 0.5% of patients respectively(96,99,101). It is being postulated that the reason behind the presence of secretory endometrium in

postmenopausal women is, as the ovarian function declines in menopause, the progesterone from the follicular remnants fluctuate leading to secretory endometrium (96).

Proliferative endometrium is seen in 2% of women in our study. This is in consistent with the retrospective studies done by Gredmak T et al, Praghathi et al, where they found it in 4% of patients (96, 99). Pl So et al in theirretrospective study on 265 patients with recurrent postmenopausal bleeding found that proliferative endometrium was the cause for the postmenopausal bleeding in 4% of cases (101).A analysis done by Kavitha et al on the aetiology of postmenopausal bleeding found proliferative endometrium was the most common cause of postmenopausal bleeding which accounted for 36% in their population (5).

Sample Inadequate for evaluation:

In our study, we found that out of 123 women who required endometrial sampling using Pipelle, 9 (i.e.) 7.3% of women had histopathology reported as sampling failure (or) tissue inadequate for evaluation. Among the nine women with sampling failure, 6 patients (4.8%) had endometrial thickness less than or equal to 5mm, whereas the remaining 3 patients (2.4%) had a thick endometrium. In a prospective cohort study done by Visser et al in 356 women with postmenopausal bleeding 29.8% of patients had tissue inadequate for evaluation. (108).

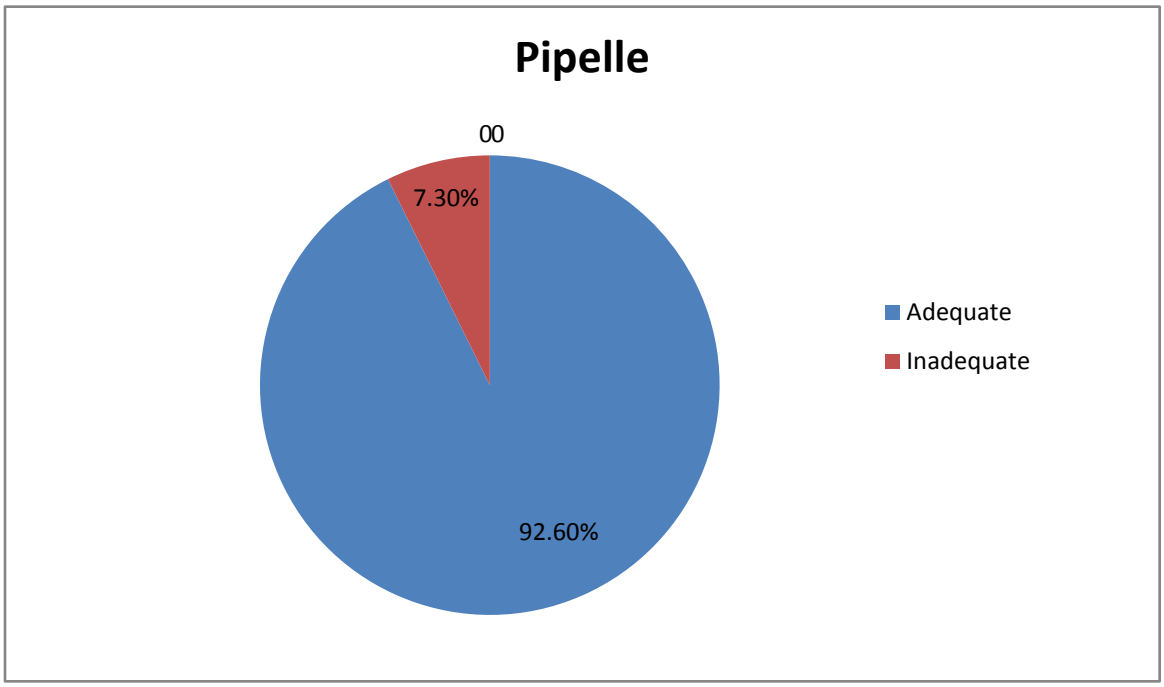


Figure 16: Pie chart showing distribution of pipelle samples in our study population

Diagnostic evaluation:

Evidence from the literature review suggests that the transvaginal ultrasound has excellent sensitivity, specificityand predictive value in the diagnostic evaluation of women with postmenopausal bleeding. Hence, it is noteworthy to start our initial evaluation of postmenopausal bleeding with transvaginal ultrasound.

In our study, all women with postmenopausalbleeding except women with clinical examination finding suggestive of cancer cervix underwent transvaginal ultrasound by an experienced sonology technician. Out of 144 women, 139 women underwent transvaginal ultrasound. During the transvaginalultrasound, endometrial thickness, growth/ polyp in

the endometrial cavity and adnexal mass if any are noted. After TVS, all these women underwent office endometrial sampling using Pipelle.

The mean endometrial with thickness in women endometrial cancer was found to be 13.81+/- 9.93mm. Of the 35 women who were diagnosed with endometrial cancer/hyperplasia, no women had cancer when the endometrial thickness was <=3mm.

The table below shows the no.of cases of endometrial cancer/hyperplasia diagnosed with each endometrial thickness

Table 12:

Endometrial Thickness	Frequency	Percentage
4mm	3	8.57%
5mm	2	5.71%
6-10mm	10	28.57%
11-15mm	10	28.57%
16-20mm	6	17.14%
>20mm	3	8.57%

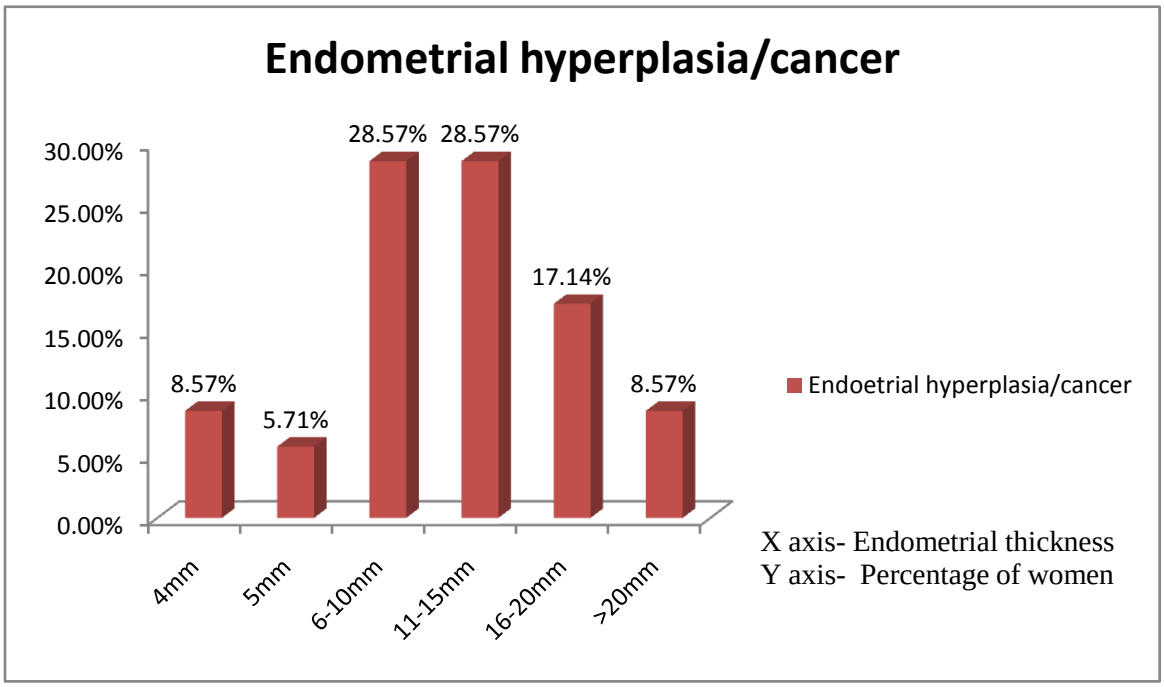


Figure 17: Bar diagram shows the distribution ofendometrial hyperplasia/cancer women corresponding to each endometrial thickness.

When a subgroup analysis was madebetween women with endometrial hyperplasia , endometrial cancer and atrophic endometrium it was evident that all women with hyperplasia with or without atypia had endometrial thickness between 6-15mm. The mean endometrial thickness in women with endometrial hyperplasia was found to be 11.7 +/-3.41mm.

Women with atrophic endometrium had endometrial thickness up to 10mm, and the mean endometrial thickness was found to be 5.07 +/- 2.23mm. Among the 28 women who had atrophic endometrium 10.7% had 2mm endometrial thickness , 14.2% women

had 3mm, 21.4% of them had 4 and 5mm and 32% of them had thickness between 6-10mm.

The following table and bar diagram summarizes the women with atrophic endometrium and their endometrial thicknesses:

Table 13:

Endometrial thickness	Frequency	Percentage
2mm	3	10.71%
3mm	4	14.29%
4mm	6	21.43%
5mm	6	21.43%
6-10mm	9	32.14%

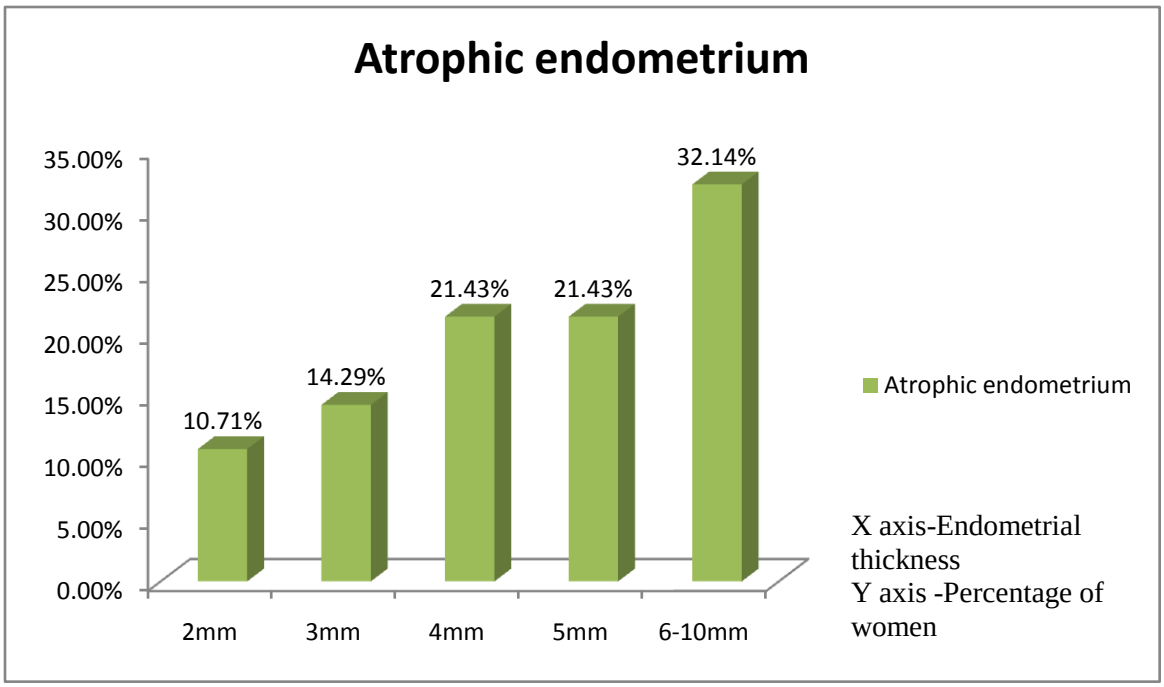

Atrophic endometrium
35.00%
30.00%
25.00%
20.00%
15.00%
10.00%
5.00%
0.00%
10.71%
14.29%
21.43%
21.43%
32.14%
2mm
3mm
4mm
5mm
6-10mm
Atrophic endometrium
X axis-Endometrial thickness
Y axis -Percentage of women

Figure 18:

Figure 19 below depicts the mean endometrial thickness in women with endometrial cancer, hyperplasia and atrophic endometrium:

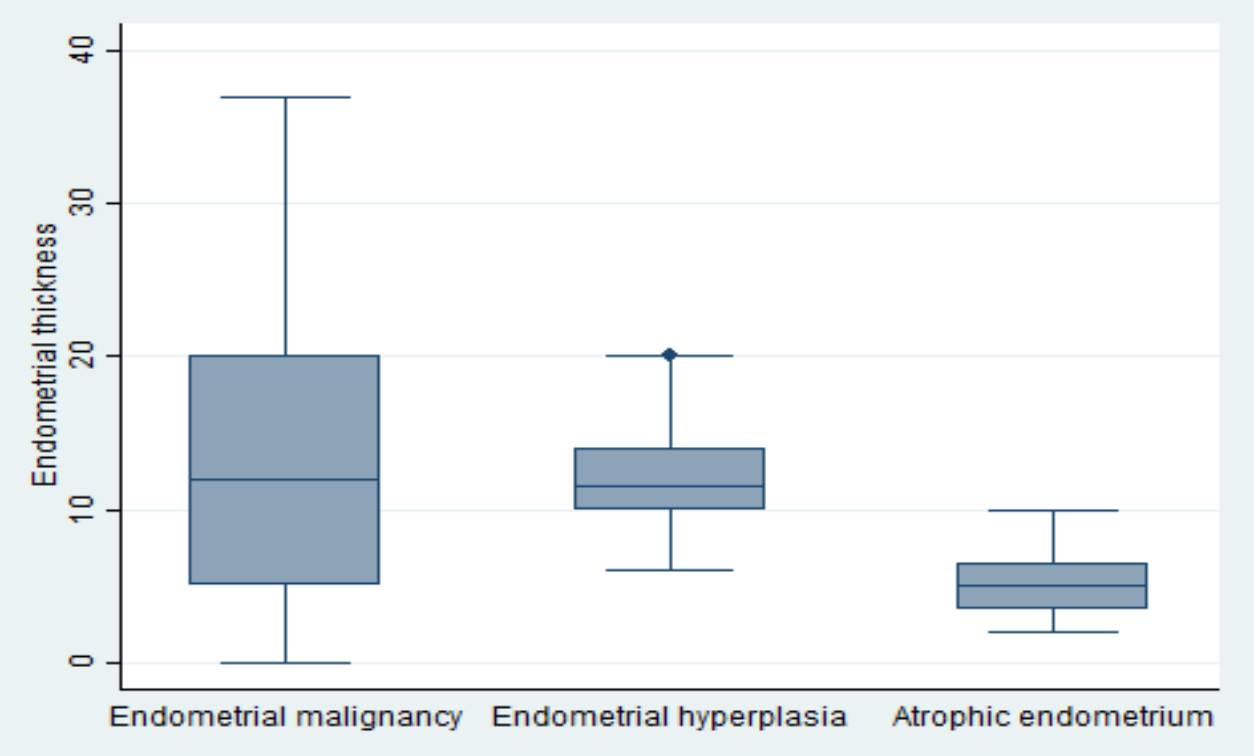


Figure 19:

To set a cut off endometrial thickness and to discriminate women who are at risk for endometrial cancer, we included the endometrial thickness of the 126 women after excluding women who had adnexal mass by USG and women with cancer cervix and constructed a 2*2 table that compared the endometrial thickness to the presence or absence of endometrial cancer and hyperplasia. Results were summarized in a Receiver Operator Characteristics Curve (ROC). In the ROC curve, it was found that the AUC was found to be 0.7621 with 95% CI (0.653-0.871)

The ROC curve is depicted below:

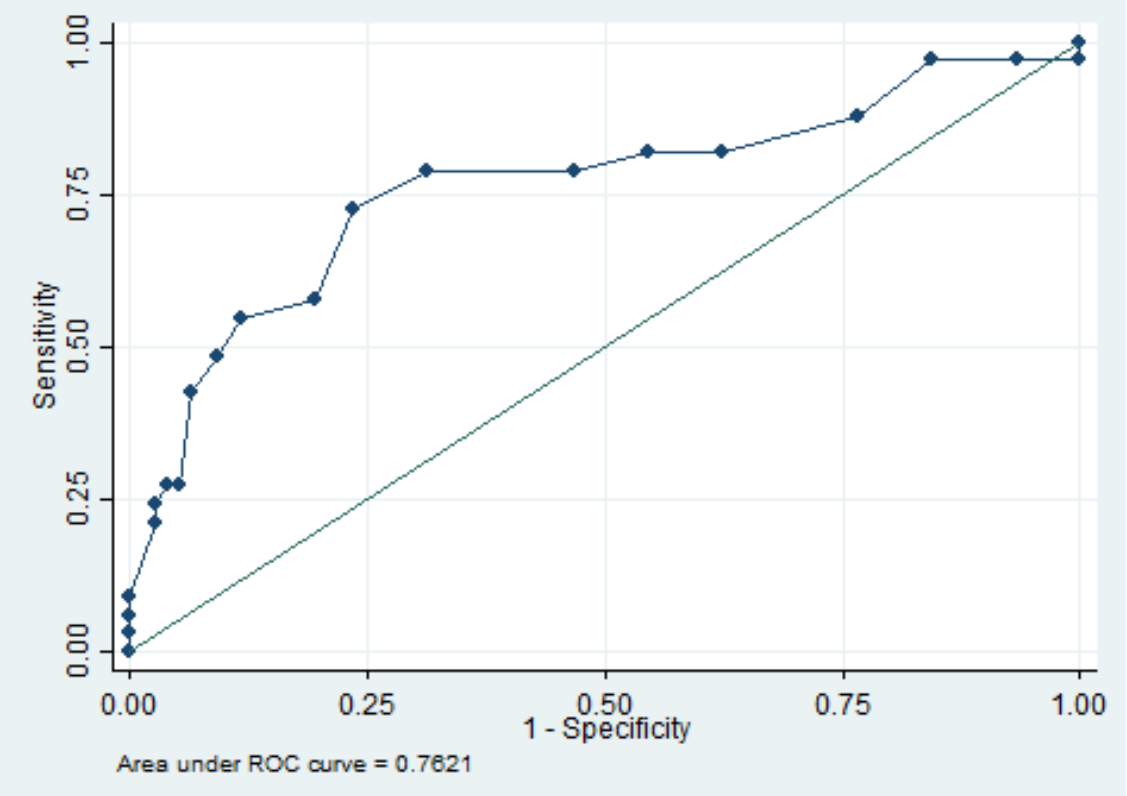


Figure 20: ROC curve comparing endometrial thickness Vs. endometrial cancers/hyperplasia

On comparison of the endometrial thickness 2mm, 3mm, 4mm all the three had good sensitivity of 96.97% whereas the specificity was very low in 2mm and 3mm (nil and 6% respectively). But, when 4mm is considered, the specificity increased to 15.58%. At endometrial thickness of 5mm, even though the specificity further increased to 23%, the sensitivity decreased to 87%.

Hence, in order to construct a particular cut off thickness, positive and negative predictive values were obtained for 3mm, 4mm and 5mm. At 3mm, 4mm, 5mm thickness

the positive predictive values were 30.8%, 33.4% and 33% respectively, whereas the negative predictive values were 83.3%, 92.3% and 81.8% respectively. Hence, based on this 4mm having the good negative predictive value is taken as a cut-off thickness in our study. When 4mm is taken as a cut off, it was found that the odds ratio was 5.91, whereas the odds ratio was only 2.22 and 2.21 when 3mm and 5mm were used.

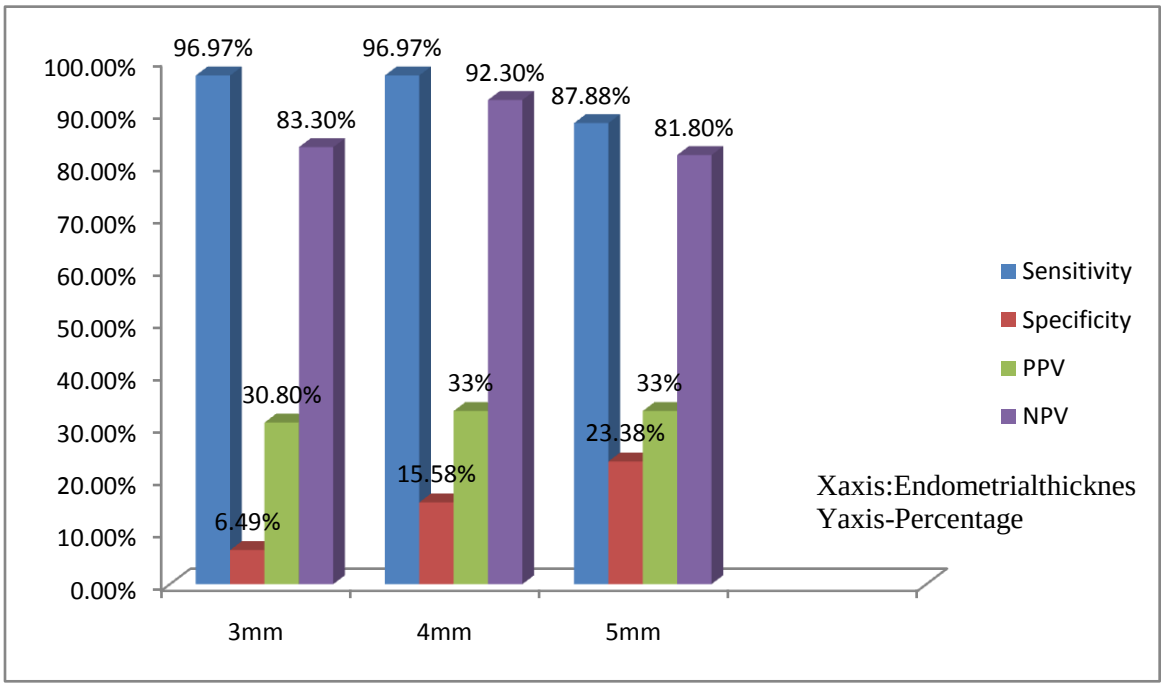


Figure 21: Above figure shows the sensitivity, specificity, PPV and NPV for the endometrial thickness 3mm, 4mm, and 5mm.

DISCUSSION

Discussion:

Postmenopausal bleeding (PMB) is one of the common symptom for which a menopausal women presents to the gynaecologists. PMB, being anominous symptom, needs proper evaluation in order to exclude malignancy. Evaluation begins from history, physical examination and diagnostic testing with ultrasound and endometrial sampling. It is being estimated that the risk of endometrial cancer increases with age which is 1% at the age of 50 years and 25% at 80 years. (96)

The incidence of malignancy in the postmenopausal period is very high. Hence it requires early diagnosis, strict follow up and prompt treatment. In our study, the reported prevalence of endometrial cancer was 14.6% with 95% CI (9.3%-21.5%). In this modern era of health services, the assessment and evaluation of PMB has moved from operation theatre procedures to outpatient non-invasive investigations. The primary diagnostic evaluation of all cases of PMB should start with transvaginal ultrasound (TVS), as measurement of endometrial thickness helps in delineating the presence of endometrial cancer/hyperplasia to a certain extent. In our study population, every womanhad transvaginal ultrasound irrespective of the amount or number of episodes of bleeding. TVS, due to its availability, easiness, less invasive nature is accepted by all patients.

Following TVS, pipelle endometrial sampling was performed. Of the pipelle sampling done in our study population, about 7% of the samples were inadequate for evaluation which is acceptable when compared with the studies done by Visser eta l,

Gordon et al where 28-30% of their samples were inadequate for evaluation (108-112). Based on the histopathological reports, the causes of postmenopausal bleeding in our study population were atrophic endometrium (19.4%), endometrial polyps((16.6%), endometrial malignancy(15.27%), cervical cancer (14.5%), endometrial hyperplasia (9.72%), ovarian cancers (4.16%) and other benign conditions like proliferative/secretory/unspecified diagnosis constituting another 20%. Among these causes, benign aetiologies constituted 56% and the malignancies 44%. Even though, atrophic endometrium tops the list, it is seen only in 19% of our women which is in contrast to the Western literature where the prevalence is 60-80 %(1, 6, 8, and 96). Malignant causes of postmenopausal bleeding are on a rising trend in developing countries compared to that in developed countries (9,94and100). In our study population also malignancies (cervical, endometrial, ovarian cancers) were seen in 44% of women, which is significantly a huge number. The reason for the increasing rates of malignancy in developing countries are poor accessibility to the modern health care services, screening programmes and lack of education and awareness about the important aspects of health.

Even though, cancer cervix is 2% less than cancer endometrium in our study, this may not be the true picture in developing countries as various Indian studies have quoted that, among the malignant causes of postmenopausal bleeding, cancer cervix ranks first followed by endometrial malignancy (9, 94, and 99,100).

Our second aim in the study was to get a cut off for endometrial thickness and so we focussed on the risk factors in developing endometrial cancer.

The frequency of postmenopausal bleeding decreased with age**,** and the number of women with cancer (both endometrium and cervix) increased proportionately. Older women had increased risk of endometrial malignancy with the mean age of 58.8 years , when compared to the benign conditions where the mean age was 55.71 years, which is statistically significant with a p value of 0.0233.The chance of developing malignancy is inversely proportional to the age. Cervical cancer had its peak age beyond 60 years in our study.

- Moreover, the mean age at which there was first episode of bleeding in women with endometrial hyperplasia/malignancy was 57.83+/-7.34, when compared to that of benign conditions was 55.04+/-6.96 years and it was statistically significant with a p value of 0.0298. About 60% of patients with cancer cervix patients and 55% with endometrial malignancy presented to us with the first episode of bleeding

- Nulliparous women had more risk for developing endometrial malignancy when compared to the multiparous women which is too statistically significant with a p value of 0.039.

- It is a well-known fact that, BMI is directly proportional to the endometrial malignancy risk. This is proved in our study too with statistical significance, p value of 0.0554.
- Medical co-morbidities like diabetes and hypertension had increased risk for developing endometrial malignancies with a significant p value of 0.006 and 0.017 respectively.
- Even though, early menarche and late menopause are risk factors for developing endometrial cancer we did not find any association in our study population, p values being 0.8865 and 0.0829 respectively.
- Other risk factors, like intake of drugs (tamoxifen, aspirin, anticoagulants), family h/o malignancies did not show any association in the endometrial cancer risk in our study.

The amount of bleeding whether it was scanty/moderate/heavy did not have any association with the development of either benign or malignant conditions in our study.

The other aim in the present study was to set a cut-off endometrial thickness in our women, so that women who are below that particular cut off thickness are considered to be at low risk for endometrial malignancy and hence invasive procedures like endometrial sampling/biopsy can be avoided in them. Meta-analysis done by Smith Bindman et al, Gupta et al have taken 5mm as the cut off endometrial thickness and they concluded that when the endometrial thickness is less than 5mm, further investigations are not required (113-115). Few authors have quoted 3mm too as the cut-off endometrial

thickness (73). In our study, we did not find any premalignant/ malignant conditions below endometrial thickness of 4mm. We found that the risk of developing endometrial cancer is increased 5 times when the endometrial thickness is>= 4mm

(Odds ratio 5.91) , with a sensitivity of 96.97% and a specificity of 15.5%. Moreover, with a cut off of 4mm, there is a good negative predictive value of 92.3%. Hence, we come forward with the evidence that any endometrial thickness below 4mm in women with postmenopausal bleeding need not be further investigated with other invasive tests. But, when awoman presentswith persistent bleeding, irrespective of the endometrial thickness she should be investigated because of the risk of developing type 2 endometrial cancers (64).

LIMITATIONS

Limitations:

1. In women with endometrial thickness less than 4mm, measurement of endometrial thickness followed by hysteroscopy and biopsy would have given a better light to the problem when compared to endometrial thickness measurement followed by blind endometrial sampling.
2. Due to the cost factor we did not include this aim in our study.
3. Follow-up of women with endometrial thickness <4mm, and in whom endometrial sampling was inadequate for histopathological diagnosis is also not done due to time and cost factors.

CONCLUSION

Conclusion:

1. The prevalence of endometrial cancer in women with postmenopausal bleeding in our population was 14.6%with 95% CI (9.3%-21.5%).
2. All women with postmenopausal bleeding should be evaluated even if it is the first episode.
3. Transvaginal ultrasound and Pipelle sampling still holds good for evaluation of women with postmenopausal bleeding.
4. The commonest aetiology of postmenopausal bleeding was found to be atrophic endometrium in our population, even though it contributes to only 19%. Totally, 43% were premalignant and malignant conditions and 56% being benign conditions.
5. Hence, it is very important not to miss these malignant cases when a woman presents with postmenopausal bleeding. More importantly, in developing countries like India, cervical cancer evaluation should also be a part in evaluating a woman with postmenopausal bleeding.
6. Like many other accepted studies, in our study we found that, endometrial thickness >=4mm correlates well with malignancy in our Indian woman too. Hence we suggest that, in a woman with postmenopausal bleeding irrespective of their risk factors if the endometrial thickness is <4mm, further invasive tests like endometrial sampling/biopsy is not required. Few exceptions to this are, if the postmenopausal bleeding is persistent even with endometrial thickness of <4mm

endometrial sampling is mandatory because of the risk of developing type 2 endometrial cancers. Also, in women with postmenopausal bleeding having abnormal ultrasound features like adnexal mass will also require further investigation irrespective of the endometrial thickness.

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Volume 188, Issue 2, Pages 401-408.

ANNEXURES

PATIENT INFORMATION SHEET

Title:Etiology of postmenopausal bleeding and correlation of endometrial thickness in endometrial carcinoma in our population.

Aims of the study:

1.To determine the most common cause of postmenopausal bleeding in our population.

2.To determine the correlation of endometrial thickness in uterine cancer and to set a cut-off thickness in our population.

Introduction:

This study is being conducted by the Department of Obstetrics and GynaecologyCMC,Vellore.

Menopause is permanent cessation of menstruation.The average age of menopause in Indian women is 47-50 years.By definition,Post menopausal bleeding is bleeding occuring one year after menopause.Postmenopausal bleeding accounts in 4-11% of menopausal women.It is one of the common presentation for which patients present to gynaecologists due to the suspicion of underlying uterine cancer. Patients with postmenopausal bleeding have 10-15% chance of having uterine cancer and therefore diagnostic workup is aimed at excluding malignancy.

Are you at increased risk of developing uterine cancer?

The risk factors for uterine cancer are:Nulliparity,earlymenarche,latemenopause,Polycystic Ovarian disease,obesity,diabetes, hypertension,and women on Hormone replacement therapy,Tamoxifen.

Postmenopausal bleeding is often caused by abnormalities of the endometrium whether benign or malignant. The malignant causes being uterine cancer, cervical cancer. Unlike other malignancies,uterine cancer presents at an early stage where there is definitive curative treatment available if detected in earlier stages.

Hence early intervention for postmenopausal bleeding is needed. So,when a patient comes with postmenopausal bleeding,she should be evaluated completely to exclude uterine cancer.The first investigation to be done is scan.By doing a scan,we get an idea about the uterine size,endometrial thickness, uterine cavity, any growth in the cavity etc. The transvaginal scan will be done by a senior sonologist.

Next step, the scan is followed by endometrial biopsy. The endometrial biopsy is done as an outpatient procedure in the minor theatre with a pipelle aspirator. The biopsy will be done by myself and in case of my absence, it will be done by a senior registrar or by M.S Registrar.

Complications of endometrial biopsy:

As such there are no severe complications following an endometrial biopsy. Patients may experience mild lower abdominal pain and mild spotting for 1 day.

Benefits of the study:

From literature,we find that few Western studies has come up with the cut-off endometrial thickness as 5mm/4mm,below which the risk of uterine cancer is low and these women will not require further investigation like endometrial biopsy.

But, no Indian studies has given any specific cut-off thickness for Indian women.Currently,in CMC we use the cut-off thickness in menopausal women as 4mm based on the Western studies.

So, at the end of this study we beleive that we will be able to set a cut-off thickness for our population so that patients in whom endometrial thickness is below the cut-off ,biopsies can be avoided because the risk of cancer in these women is low.

Informed Consent Form for Subjects

Informed Consent form to participate in a research study

Study Title:Etiology of postmenopausal bleeding and correlation of endometrial thickness in endometrial carcinoma in our population.

Study Number: _____

Subject's Initials: _____

Subject's Name: _____

Date of Birth / Age: _____

You are invited to participate in this study which is to find out the commenestetiology of postmenopausal bleeding and the correlation of endometrial thickness in endometrial carcinoma in our population.

Postmenopausal bleeding is indicative of underlying malignancy until proven otherwise.Unlike other malignancies, uterine cancer presents at an early stage when curative treatment is available.Hence when a postmenopausal women presents with bleeding per vaginum early diagnosis to exclude uterine cancer should be done.Diagnostic evaluation is done by doing a vaginal scan and a biopsy.

I understand that I will not receive any financial benefits or material incentive for participation in the study.

I understand that the study staff and institutional ethics Commitee members will not need my permission to look at my health records even if I withdraw from the trial.I agree to this access.

I understand that my identity will not be revealed in any information released to third parties.

The results of this study may be published in medical journal but you will not be identified by name in any publication/presentation of results.

Your participation in this study is entirely voluntary and you are also free to decide to withdraw permissin to participate in this study.If you do so,this will not affect your usual treatment in this hospital in any way.

Your participation is important and of immense value as the results of this study will be useful in improving the care in future.

Signature of the Investigator:

Signature of the participant:

Signature of the Witness:

Date:

(Subject)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). [ ]

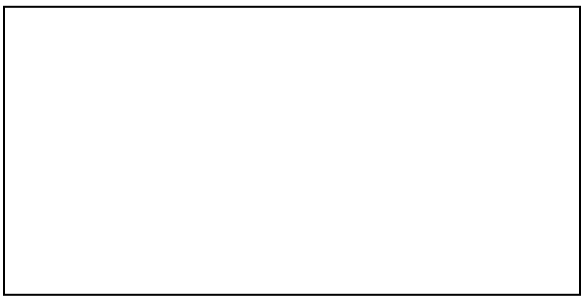
(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable

Date: _____/_____/_____

Signatory's Name: _____ Signature:

Or



Representative: _____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature or thumb impression of the Witness: _____

Date: _____/_____/_____

Name & Address of the Witness: _____

PROFORMA

Study Title:

ETIOLOGY OF POSTMENOPAUSAL BLEEDING AND CORRELATION OF ENDOMETRIAL THICKNESS IN WOMEN WITH ENDOMETRIAL CARCINOMA IN OUR POPULATION.

1.Study number :

2. Age :

3. Age of menarche : a)<11 years b)>11 years

4. Age of menopause : a)45-50 years b)50-55 years c)>55 years

5. Parity : a)Nulliparous b)Multiparous

6. Body Mass Index : a)less than 25 b)25-30 c)30-39 d)more than 40

7. Age of first episode of postmenopausal bleeding :

8. Is this the first episode of PMB a)Yes b)No

9. If no, how many episodes in the past ?

10. Amount of bleeding : a)Scanty(Brownish discharge/spotting) b)Moderate(soaking 1-2 diapers) c)Heavy(>3 diapers)

11. Associated comorbidities:

Diabetes a)Yes b)No.

Hypertension a)Yes b)No.

12. Any exposure to hormone replacement therapy:

a)Yes b)No

13. If Yes, When does bleeding occur with respect to estrogen and Progesterone phase : a)Estrogen phase, b)Progesterone phase

14. Any other drugs exposure like Tamoxifen or anticoagulants : a)Yes b)No

15. If yes, specify the drug exposed:

16. If on Tamoxifen, duration of exposure to Tamoxifen:

a)less than 5 years b)more than 5 years.

17. Any family history of malignancies:

a)Yes b)No

18. If yes, specify what malignancy:

19. Endometrial thickness : a)<=3mm, b)4mm, c)>=5mm

20. Endometrial biopsy done : a)Yes b)No.

21. Histopathological report:

a)Endometrial malignancy b)endometrial hyperplasia c)atrophic endometrium, d)others.

Data Sheet

slno	age	aomena	aomeno	parity	bmi	afepi	pmb	epi past	amt bleed	diabet	htn	hor mone	estro gen	oth drug	spec drug	tamo dur	malig nan	yes malig	endo met	endo biop	histo path	post diag
1	46	15	45	2	26.8	46	1		1	2	2	2		2			2		6	1	6	
2	58	15	48	2	32	57	2	1	1	1	1	2		2			2		7	1	6	
3	61	14	52	2	24.2	60	1		1	1	1	2		2			2		10	1	1	1
4	56	15	48	2	24	56	1		1	1	1	2		2			2		18	1	1	1
5	72	15	52	2	33.4	72	2	5	2	1	1	2		2			2		20	1	1	1
6	53	14	47	2	31.2	53	1		3	1	1	2		1	Aspirin		2		5	1	6	4
7	66	16	55	2	25	65	2	21	1	1	1	2		2	NIL	0	2		17	1	1	1
8	46	15	45	2	22	46	1		2	2	2	2		2	NIL	0	2	NIL	0	2	5	4
9	50	14	48	2	32	50	1		3	2	2	2		2	NIL		2	NIL	5	1	4	4
10	51	15	52	2	25.4	50	2	5	1	2	1	2		2	NIL	0	2	NIL	3	1	3	
11	47	15	45	2	26.2	46	1		3	1	1	2		2	NIL	0	2	NIL	8	1	3	
12	62	15	48	2	24	62	1		1	2	2	2		2		0	2		2	1	3	4
13	52	14	47	2	22	50	2	42	2	2	2	2		2		0	2		0	2	5	4
14	60	15	49	2	32.2	60	1		2	2	2	2		2		0	2	NIL	7	1	6	4
15	68	15	52	1	33.25	68	1		3	1	2	2		2			2		14	1	2	4
16	63	15	47	2	34.1	53	1		1	1	2	2		2			2		13	1	2	4
17	50	16	47	2	35	50	1		2	2	1	2		2			2		8	1	2	4
18	52	11	50	2	21.8	51	1		1	2	2	2		2			2		6	1	4	4
19	58	15	53	2	28.2	57	2	3	2	2	2	2		2			2		0	1	1	1
20	61	15	52	2	44.1	61	2	5	2	2	1	2		2			2		11	1	6	4
21	50	20	45	1	22.1	50	1		2	2	2	2		2			2		2	1	3	4
22	56	11	49	2	31	56	1		1	2	1	2		2			2		13	1	2	4
23	62	12	48	1	26	62	1		1	2	2	2		2			2			1	1	1
24	52	14	47	2	27	52	1		1	2	2	2		2			2		14	1	1	1
25	61	14	53	2	20.5	61	1		1	2	1	1		2			2		10	1	6	4
26	54	12	50	2	29	54	1		2	1	2	2		2			2		8	1	4	4
27	67	15	49	2	26.5	67	2	1	2	2	1	2		2			2		12	1	6	4
28	56	13	52	2	26	55	2	4	1	2	2	2		2			2		10	2	2	4
29	67	13	50	2	44	67	2	2	2	2	1	2		2			2		34	1	1	1
30	63	13	55	2	33.9	63	1		1	1	1	2		2			1	Uterine (	5	1	1	1
31	48	15	46	2	26	48	1		1	1	1	2		2			2		5	1	4	4
32	53	14	49	2	23.45	53	2	5	2	2	2	2		2			2			2	5	4
33	50	13	46	2	33.8	50	1		2	2	2	2		2			2		11	1	4	4
34	56	15	52	2	34.9	56	1		2	1	1	2		1	Aspirin		2		6	1	2	4
35	52	14	50	2	30.4	52	1		3	1	1	2		2			2		11	1	4	4
36	46	15	45	2	25.1	46	1		1	2	2	2		2			2		4	2	3	
37	55	15	52	2	25.7	55	1		2	2	2	2		2			1	Sister-Ut	5	1	4	4
38	47	14	47	2	24.2	47	1		2	2	2	2		2			2		5	1	3	
39	50	13	46	2	24.2	48	2	5	3	2	2	2		2			1		4	1	3	
40	56	14	52	2	41.4	55	2	4	2	1	2	2		2			2		10	1	2	4
41	55	13	50	2	26	54	2	3	3	1	2	2		2			1	Father-T	9	1	2	4
42	54	14	45	2	32	53	1		2	2	1	2		2			2		5	1	3	4
43	52	14	46	1	26.8	52	2	2	2	1	2	2		2			2		9	1	1	1
44	61	14	47	2	24.65	61	1		1	1	1	2		1	Clopidogrel		2			2	5	4
45	55	18	45	2	32	55	1		1	2	2	2		2			1	Sister ca	9	1	4	4

46	49	14	46	2	22.4	48	2	3	2	2	2	2		2			2		11	1	4	4
47	68	15	45	2	34.18	60	1		2	2	2	2		1	Aspirin		2		14	1	6	3
48	61	14	52	2	30.1	61	1		1	1	1	1	2	2			2		20	1	1	1
49	75	14	55	2	32.45	75	1		3	2	1	2		2			2		13	1	4	4
50	70	18	55	2	23	70	1		1	2	1	2		2			2		5	1	6	4
51	60	14	51	2	22.15	56	2	4	1	2	2	2		2			2		3	1	3	
52	55	12	52	1	34.8	53	2	2	2	1	1	2		2			1	Gall blad	4	1	1	1
53	57	13	46	2	31	56	1		1	2	2	2		2			2			2	5	4
54	68	13	48	2	26	68	2		2	2	2	2		2			2		4	1	4	4
55	60	15	49	2	20.7	58	2	5	1	2	2	2		2			2		2	1	3	2
56	55	14	45	2	30.1	53	1		2	2	2	2		2			2		9	1	3	1
57	68	13	48	2	26.9	68	1		2	2	2	2		2			2		10	1	6	4
58	60	12	46	2	26.38	60	1		1	2	2	2		2			1	Uterine cancer-S		2	5	4
59	54	17	46	2	23.45	54	2	2	2	1	2	2		2			2		7	2	5	4
60	55	14	45	2	29.8	54	2	5	1	2	2	2		2			2		2	1	4	4
61	51	15	49	2	35	50	2	2	2	2	2	2		2			2		3	1	4	4
62	52	15	51	2	27.98	52	1		1	2	2	2		2			2		8	1	3	
63	59	14	49	2	23.79	56	2	1	1	2	2	2		2			1	Mother (	20	1	4	
64	55	12	50	2	23.79	55	1		1	2	2	2		2			2		2	1	6	4
65	59	14	49	2	27	59	1		1	1	2	2		2			2		4	1	3	4
66	48	14	47	2	27.8	48	1		3	1	1	2		2			2		20	1	6	4
67	60	12	50	2	24.1	58	2		1	1	2	2		2			2			2	5	
68	66	13	45	2	27.4	66	1		1	2	1	2		2			2		9	1	6	2
69	61	15	51	2	22	61	1		1	1	1	2		2			2		6	1	6	
70	53	15	50	2	24.8	53	1		2	2	2	2		2			2			2	5	
71	60	15	54	2	34.9	60	1		3	1	2	2		2			2		6	2	5	
72	57	14	51	2	28	51	1		1	2	1	2		2			2		8	1	4	
73	49	18	46	2	26.8	49	1		3	2	1	2		2			1	Mother I	20	1	1	1
74	57	13	50	2	32.8	53	2	4	2	2	1	2		2			2		11	1	2	1
75	64	13	46	2	35.7	64	1		2	1	1	2		2			2		9	1	6	
76	48	10	46	2	34.4	47	2	4	1	2	1	2		2			2		10	1	6	
77	54	15	50	2	23.8	54	1		3	2	2	2		2			2		7	1	1	1
78	47	14	45	2	21	47	1		2	2	2	2		2			2		8	1	4	
79	46	13	45	2	32.1	46	1		1	1	1	2		2			2		10	1	3	2
80	59	12	51	2	33.9	59	1		2	2	1	2		2			2		20	1	2	4
81	70	13	50	2	23.56	70	2	5	2	1	1	2		2			1	Father c	37	1	1	1
82	51	18	49	2	32.9	51	1		2	2	2	2		2			2		7	1	4	
83	56	13	49	2	37.1	53	2	5	1	2	2	2		2			1	Nother-u	9	1	3	
84	50	14	45	2	29	50	1		3	1	1	2		2			2		5	1	3	
85	70	12	50	2	21	70	1		2	2	2	2		2			1	Husband -Throa		2	5	
86	50	12	48	2	25.18	50	1		1	2	2	2		2			1		5	1	3	
87	70	15	57	2	35	69	2	3	1	1	1	2		1	Aspirin		2			2	5	
88	50	10	45	2	27.99	49	2	2	1	1	1	2		2			2		12	1	1	1
89	48	13	46	2	31	48	1		1	1	1	2		2			1	Sister ca	6	1	1	1
90	54	15	52	2	31	52	1		3	2	2	2		2			2		6	1	6	4
91	47	14	45	2	21.1	47	1		3	2	2	2		2			2		7	1	6	2
92	50	15	48	2	20	50	2	1	1	2	2	2		2			1	Mother-	7	1	3	
93	58	12	48	2	23.9	58	1		3	2	2	2		2			2		7	1	5	4
94	61	14	51	2	33.5	61	1		1	1	1	2		2			2			1	4	
95	53	14	51	2	27.89	52	2	21	1	2	2	2		2			2		10	1	6	4

96	59	12	50	2	21.8	59	1		2	2	2	2		2			2		12	1	2	4
97	46	17	45	2	35.5	46	1		3	2	2	2		2			2		6	1	4	
98	48	11	45	2	21.7	46	2	3	1	2	2	2		2			2		3	1	3	
99	53	13	51	2	26	52	2	3	3	1	1	2		2			2		8	1	6	
100	56	14	52	2	29.8	54	2	4	3	2	2	2		2			2		5	1	3	
101	60	15	45	2	26.03	60	2	3	1	2	2	2		2		211	2		4	1	3	2
102	62	14	45	2	27	62	1		1	2	2	2		2			2		13	1	6	
103	55	11	51	2	29	55	1		2	2	2	2		2			1	Cancer e	3	1	6	
104	68	15	48	2	33.99	68	1		3	1	1	2		2			1	Neice-Ut	9	1	6	
105	47	14	45	2	30.7	49	2	2	1	2	1	2		2			2		11	1	4	
106	62	12	51	2	27.88	62	2	4	1	2	2	2		2			1	Breast cancer- a		2	5	4
107	58	14	45	2	27	58	1		1	1	2	2		2			2		14	1	2	4
108	50	14	46	2	32.88	50	1		2	2	2	2		2			2		8	1	4	
109	49	16	47	2	25.33	49	1		3	1	2	2		2			1	Father -T	8	1	4	
110	53	12	51	2	27.9	53	1		1	1	1	2		2			2		12	1	4	
111	53	16	52	2	27	53	1		2	2	2	2		2			2		8	2	4	
112	70	12	50	2	18.9	69	1		2	2	2	2		2			2			2	5	
113	49	13	45	1	32.9	49	2	2	2	2	2	2		2			2		4	1	4	
114	67	14	54	2	28.7	67	2	2	2	2	1	2		2			2		3	1	3	
115	47	14	46	2	26.6	47	1		1	2	2	2		2			2		4		3	2
116	47	13	45	2	28.9	47	1		1	2	2	2		2			2		4	1	1	1
117	50	14	48	2	30.8	50	2	2	3	2	2	2		2			2		7	1	3	
118	47	14	45	2	33	47	1		2	1	1	2		2			1	Father-c	13	1	4	
119	57	16	52	2	27.9	53	2	2	1	1	1	2		2			2		8	1	6	4
120	57	16	50	2	26	55	2	3	1	1	1	2		2			1		5	1	4	
121	52	16	48	2	22.1	52	1		2	2	2	2		2			2		17	1	4	
122	59	14	46	2	19.8	50	2	8	1	1	1	2		1	Acitrom		1		14	1	2	
123	54	14	52	2	27.7	54	1		3	2	2	2		2			1	Sisters-B	5	1	4	
124	52	14	49	2	23.4	51	2	2	1	2	2	2		1	Tamoxif	32	2		5	1	4	
125	65	10	45	2	23.2	65	1		1	1	2	2		2			2		2	1	4	
126	57	12	45	2	24.6	50	2	7	2	1	1	2		2			2		8	1	4	
127	59	12	49	2	53	58	2	5	2	1	1	2		2			2		11	1	4	
128	52	16	48	2	21	50	2	2	1	2	2	2		2			2		3	1	4	
129	48	13	46	2	32.9	48	1		3	1	1	2		2			2		6	1	4	
130	61	15	47	1	25.18	59	2	10	1	1	1	2		2			2		6	1	3	
131	52	14	50	2	33	51	2	3	1	2	2	2		2			2		16	1	6	
132	53	15	51	2	28.9	53	2	4	3	2	1	2		2			2		5	1	3	2
133	53	15	48	2	26	53	1		1	2	2	2		1	Tamoxif	48	1	Aunt-Bre	10	1	1	1
134	72	15	45	2	22.1	72	1		1	1	1	2		2			2		4	1	1	1
135	55	12	54	2	26.5	55	1		3	1	1	2		2			2		4	1	3	
136	52	15	50	2	27.1	52	1		2	1	1	2		2			2		8	1	4	
137	54	15	48	2	27	52	2	2	1	1	1	2		2			2		10	1	2	
138	56	16	48	2	39.06	56	2	8	1	2	1	2		2			2		5	1	1	1
139	55	16	53	2	21.3	53	1		3	1	2	2		2			1	Mother -Uterine		2	5	
140	65	12	50	2	27.8	65	2	3	2	2	1	2		2			2			2	5	
141	65	14	52	2	24.9	65	1		1	2	2	2		2			2			2	5	
142	55	15	50	2	24.8	54	2	3	2	2	2	2		2			2			2	5	
143	69	10	49	2	23	69	1		2	2	1	2		2			2		6	2	5	
144	77	16	52	2	40.9	76	2	2	1	1	1	2		2			2		26	1	1	2