

## Correlation of Clinical Characteristics with Histopathological Pattern of Endometrium in the Prediction of Endometrial Cancer in Postmenopausal Bleeding.

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### Abstract

**Background:** Postmenopausal bleeding is defined as uterine bleeding occurring after 12 months of amenorrhoea. The prevalence of spontaneous PMB was reported to be as high as 10% in the general population. 10% of all women with PMB are diagnosed to have endometrial cancer. Endometrial cancer is currently the most common malignancy of the female genital tract in Europe, USA, and Hong Kong. The aim in the evaluation of PMB is to exclude underlying malignancy. Endometrial cancer develops from precursor lesion, but the risk of progression varies from <1% for simple hyperplasia, 3% for complex hyperplasia to 29% for atypical hyperplasia. Thus, the clinical approach to postmenopausal bleeding requires prompt and efficient evaluation to exclude or diagnose carcinoma.

**Objectives:** To study the clinical characteristics and evaluate the histopathological findings of endometrium in postmenopausal women with postmenopausal bleeding. To associate the above features with endometrial cancer.

**Methodology:** This prospective observational study was conducted in SRI RAMACHANDRA MEDICAL COLLEGE AND RESEARCH INSTITUTE during the period between October 2014 and September 2016. 165 women with Post menopausal bleeding were enrolled in the study. All post menopausal women who presented with postmenopausal bleeding with Trans vaginal ultrasound showing double wall endometrial thickness of equal to and more than 4 mm.

**Results:** In our study out of the 165 women enrolled, 14 women were diagnosed with endometrial hyperplasia and 20 women were diagnosed with endometrial cancer.

**Conclusion:** Evaluation of women with postmenopausal bleeding helps in early diagnosis of endometrial cancer and its precursors.

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### I. Introduction

Postmenopausal bleeding is defined as uterine bleeding occurring after 12 months of amenorrhoea<sup>1-2</sup>. The prevalence of spontaneous PMB was reported to be as high as 10% in the general population<sup>3</sup>. Endometrial carcinoma is the leading cause and at least 10% of all women with PMB are diagnosed to have endometrial cancer. Endometrial cancer is currently the most common malignancy of the female genital tract in Europe, USA, and Hong Kong. Around 90% of women eventually diagnosed with endometrial cancer initially presented with postmenopausal bleeding<sup>3-7</sup>. The aim in the evaluation of PMB is to exclude underlying malignancy<sup>8-12</sup>. More than 90% of postmenopausal women diagnosed with endometrial cancer present with vaginal bleeding<sup>13</sup>. In most cases, the etiology of postmenopausal vaginal bleeding is due to benign conditions such as genital tract atrophy or endometrial polyps. There is substantial variability in the likelihood of endometrial carcinoma across postmenopausal women presenting with vaginal bleeding. The incidence of malignancy varies from 1% to 24% depending on the presence of risk factors for endometrial carcinoma and the population studied<sup>14-18</sup>. Thus, the clinical approach to postmenopausal bleeding requires prompt and efficient evaluation to exclude or diagnose carcinoma<sup>4</sup>. The aim of this study was to investigate whether the woman's age, body mass index, parity, age of menarche, age at menopause, duration of menopause, the number of episodes of bleeding, amount of postmenopausal bleeding and comorbidities may be used to predict the presence or absence of endometrial malignancy.

## II. Materials And Methods

**STUDY POPULATION:** This was a prospective observational study that allowed evaluation of clinical characteristics and histopathological pattern in patients with postmenopausal bleeding. 165 women with Post menopausal bleeding were enrolled in the study.

Study was conducted in SRI RAMACHANDRA MEDICAL COLLEGE AND RESEARCH INSTITUTE after ethical committee clearance during the period between October 2014 and September 2016.

### INCLUSION CRITERIA :

All post menopausal women who presented with postmenopausal bleeding with Trans vaginal ultrasound showing double wall endometrial thickness of equal to and more than 4 mm.

### EXCLUSION CRITERIA :

- Women who were subjected to invasive diagnostic interventions elsewhere.
- Women with bleeding disorders.
- Women diagnosed with carcinoma of cervix .

The Clinical characteristics of the patient were noted using a profoma:

- Age
- Body mass index
- Age at menarche
- Age at menopause
- Duration of menopause
- Number of bleeding episodes
- Duration of bleeding per episode
- Number of pads used per day
- Pad days
- History of medical disorders like diabetes mellitus / systemic hypertension/ thyroid disorder
- Past histories of any malignancies like a) breast, b) ovary, c) colon and others.
- Family history of any malignancies like a) breast, b) ovary, c) colon, d) endometrium and others.
- History of usage of any drugs like a ) anticoagulants, b) Tamoxifen and c) HRT
- Transvaginal ultrasound findings (endometrial thickness )

To quantify the amount of bleeding, Pad-day was calculated by multiplying the number of pads used per day by the number of days the patient has experienced bleeding.

Histopathological diagnosis of the endometrium was obtained from specimens obtained by endometrial biopsy or dilatation and curettage or operative hysteroscopy guided biopsy. The histopathology of the endometrium was considered gold standard.

The results were analyzed by suitable statistical methods.

## III. Results

165 women with postmenopausal bleeding were enrolled in to the study , clinical characteristics were taken into account and underwent transvaginal ultrasonography followed by endometrial biopsy . 131 women were diagnosed with benign histopathological findings , 14 women were diagnosed with endometrial hyperplasia and 20 diagnosed with endometrial cancer.

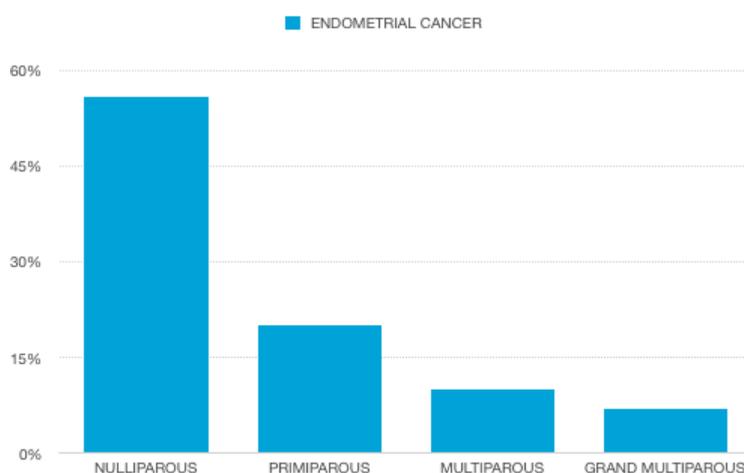
HISTOPATHOLOGICAL FINDINGS	NO OF PATIENTS N=165	PERCENTAGE
DISORDERED PROLIFERATIVE PATTERN	44	26.7
BENIGN ENDOMETRIAL POLYP	37	22.4
FRAGMENTED ENDOMETRIAL GLANDS	26	15.8
ATROPHIC ENDOMETRIUM	24	14.5
SIMPLE HYPERPLASIA WITHOUT ATYPIA	7	4.2
SIMPLE HYPERPLASIA WITH ATYPIA	2	1.2
COMPLEX HYPERPLASIA WITHOUT ATYPIA	0	0
COMPLEX HYPERPLASIA WITH ATYPIA	5	3
ENDOMETRIAL CARCINOMA	20	12.1

**3.1 AGE DISTRIBUTION WITH HISTOPATHOLOGICAL PATTERN :**

The age of women in this study ranged from 41 -72 years of age with maximum incidence of endometrial cancer seen in the 51-60 years of age group . There was no statistically significant association in the age of the patient and the presence of endometrial disease.

**3.2 BODY MASS INDEX DISTRIBUTION WITH HISTOPATHOLOGICAL PATTERN:**

Endometrial cancer was commonly seen in the obese group. There was no statistically significant association in the body mass index of the patient and the presence of endometrial disease.



**3.3 PARITY DISTRIBUTION WITH HISTOPATHOLOGICAL PATTERN :**

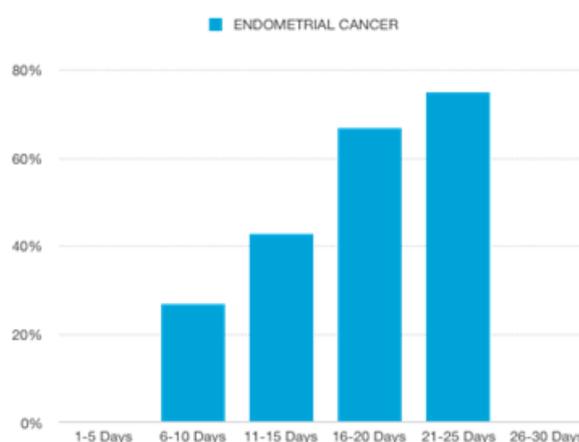
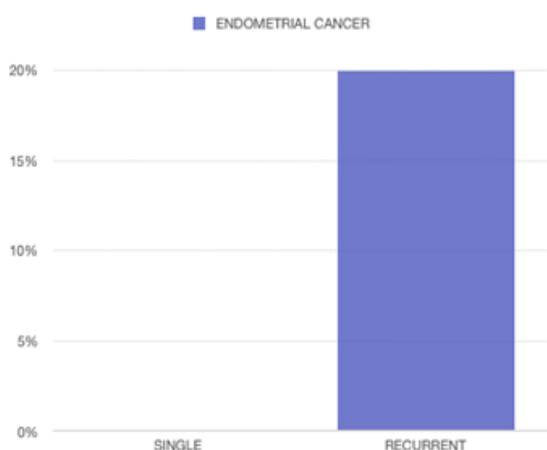
There was statistically significant association between parity and endometrial disease . Nulliparity is considered as an independent risk factor in the prediction of endometrial disease

**3.4 AGE AT MENARCHE , MENOPAUSE AND DUARTION OF MENOPAUSE WITH HISTOPATHOLOGICAL PATTERN:**

The age at menarche and menopause had no statistical significance with the presence of endometrial cancer .

**3.5 NUMBER OF BLEEDING EPISODES WITH HISTOPATHOLOGICAL PATTERN :**

Endometrial cancer was most commonly seen in women recurrent bleeding episodes . There was statistically significant association between the number of episodes.



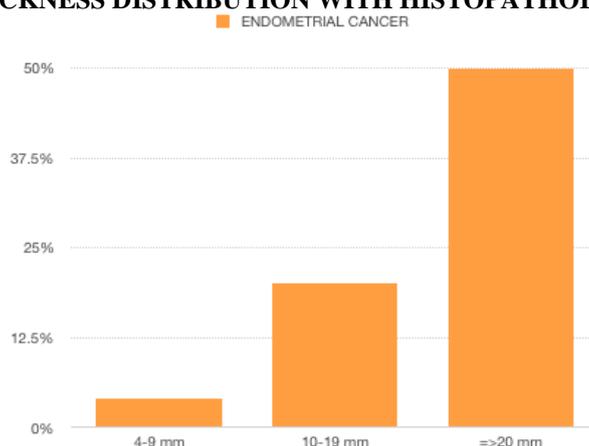
**3.6 PAD DAYS DISTRIBUTION WITH HISTOPATHOLOGICAL PATTERN**

Pad days was used to evaluate the amount of bleeding .

$$\text{PAD DAYS} = (\text{NUMBER OF PADS USED PER DAY}) \times (\text{NUMBER OF DAYS PATIENT HAD BLEEDING IN A SINGLE EPISODE})$$

There was statistically significant association between the amount of bleeding evaluated by pad days and the presence of endometrial disease.

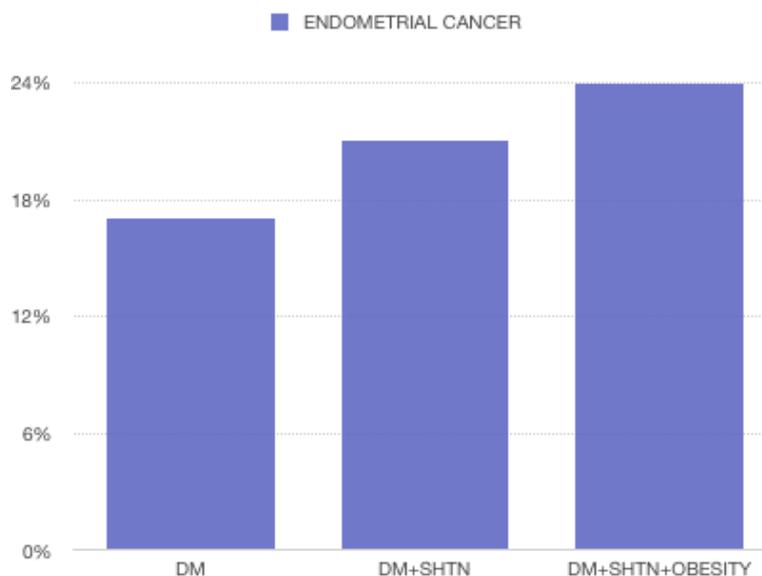
### 3.7 ENDOMETRIAL THICKNESS DISTRIBUTION WITH HISTOPATHOLOGICAL PATTERN :



There was a statistically significant association between the endometrial thickness and the presence of endometrial disease.

### 3.8 MEDICAL DISORDERS DISTRIBUTION WITH HISTOPATHOLOGICAL PATTERN :

There is a statistically significant association between patients with diabetes mellitus and endometrial disease. There is no statistically significant association between the presence of hypertension and endometrial disease.



There is a statistically significant association between the presence of diabetes, hypertension and obese group and endometrial disease when all the three variables were combined together.

## IV. Discussion

Postmenopausal bleeding is a frequent and alarming sign that may be associated with cervical or uterine pathology. It is often associated with either a benign or malignant endometrial pathology. Therefore prompt and efficient evaluation is required to differentiate between these two conditions and particularly to exclude cancer. In the modern era Transvaginal ultrasound is considered as the first line approach and has replaced dilatation and curettage as a first line investigation. Other invasive approaches which are used – Office endometrial aspiration, fractional curettage, hysteroscopy guided biopsy.

About 90% of women presenting with postmenopausal bleeding will finally be diagnosed with non malignant underlying condition. The probability of women having endometrial cancer may highly be influenced by their individual characteristics which includes the age at presentation, duration of menopause, Body Mass Index, amount of bleeding, duration of bleeding, medical disorders.

The inclusion of these individual case characteristics may allow for a more refined differentiation of patients, which could result in a more individualised and more accurate evaluation strategy. In this study we evaluated the correlation of known clinical risk factors, ultrasound findings with histopathological pattern in the prediction of endometrial cancer.

In our study 165 women with postmenopausal bleeding were evaluated . There clinical characteristics were noted using a pro forma and endometrial biopsy done.

In our study 131 (79.3% ) had benign histopathological findings , which included – atrophic endometrium, benign endometrial polyp, fragmented endometrial glands , disordered proliferation pattern endometrium. Premalignant conditions such as simple hyperplasia without atypia- 7 (4.2%) , hyperplasia with atypia seen in -7 (4.2 % ) . Malignancy – Endometrioid endometrial cancer , was diagnosed in 20 (12.1 %) patients .

#### **4.1 AGE AT PRESENTATION :**

In the study we observed that the maximum number of cases -was in the age group of 41-50 years. Minimum number of cases- 5.5%was seen at the age group greater than 60 years of age . In our study the age range was from 41-80 years , in studies done by *Wong SF et al* , *Sousa R et al* , *Bharani B et al* , *Sheikh M et al*<sup>19-21</sup> it was 38-94 , 43-82 , 52-65 , 42-84 respectively , which coincides with our study. Age is considered as an independent risk factor in studies done by *Opmeer et al*<sup>22</sup> , *Burbos et al*<sup>23</sup>.It was also observed that as the age of our subjects increases the incidence of postmenopausal bleeding decreased which coincides with the studies done by *Gredmark T et al* , *Yousaf S et al*<sup>33</sup>.

#### **4.2 PARITY :**

It was observed that endometrial cancer was most commonly seen in the nulliparity group (56%). In a study done by *Burbos et al*<sup>23</sup> , nulliparity as an isolated risk factor does not increase the risk of endometrial cancer . Whereas the study done by *Opmeer et al*<sup>22</sup> , nulliparity is considered as an combined risk factor, which coincides with our study .

#### **4.3 BODY MASS INDEX :**

In our study it was observed that 95% of the patients who were diagnosed with endometrial cancer , belonged to the obese group. In a study done by *Burbos et al*<sup>23</sup> and *Opmeer et al*<sup>22</sup> showed that obesity increased the risk of endometrial cancer by 40 % , which coincides with our study.

#### **4.4 AGE AT MENARCHE:**

In our study it was observed that the age at menarche was not an independent risk factor for the predictor of endometrial cancer in postmenopausal bleeding women . The mean age at menarche was found to be 12.63 yrs .

**4.5 AGE AT MENOPAUSE:** In our study the mean age at menopause was 46.3years and was not an independent risk factor for the prediction of endometrial cancer . In a study done by *Opmeer et al*<sup>22</sup> the mean age at menopause was found d to be 55yrs .

#### **4.6DURATION OF MENOPAUSE :**

In our study it was seen that endometrial cancer was seen in women who had attained menopause within 1-10 years of age with mean number of years as 7.5 years . It was not an independent risk factor for the prediction of endometrial cancer .In a study done by *Bruchim et al*<sup>24</sup> , the duration of menopause when combined with endometrial thickness has been diagnosed as a significant predictor for endometrial cancer.

#### **4.7 NUMBER OF EPISODES OF BLEEDING :**

In our study it was observed that women who presented with recurrent episodes of postmenopausal bleeding had 100% risk of having endometrial cancer.In studies done by *Burbos et al*<sup>23</sup> and *Keirse et al*<sup>25</sup> significant conclusions were obtained.

#### **4.8 MEDICAL COMORBIDS :**

Diabetes and hypertension are medical comorbidities which are frequently associated with endometrial cancer . In our study it was observed that , Diabetes mellitus is an independent risk factor in the prediction of endometrial cancer , supported by studies done by *Kalpan and Cole*<sup>26</sup> .

Where as systemic hypertension is not considered as an independent risk factor, which coincides with studies done by *Serdar sein et al*.

In our study it was observed that women who were obese , and who had history of diabetes mellitus and hypertension when combined where considered as significant risk factors .

#### **4.9 ENDOMETRIAL THICKNESS :**

In our study it was observed that patients with endometrial thickness of more than 10 mm – 25.8% , had increased incidence of endometrial malignancy and the percentage of endometrial cancer was 3.8% in the endometrial thickness range of 4-9 mm.

In a study done by *Burbos et al*<sup>23</sup>, it was observed that the endometrial thickness cut off of 5mm was very sensitive for predicting endometrial cancer .

In a study done by *Karlsson et al*<sup>27</sup>, the sensitivity and specificity of detecting abnormal endometrial histopathological patterns at endometrial thickness of greater than 4mm was 96% and 68 % respectively and accuracy was 78%.

#### **4.10 AMOUNT OF BLEEDING :**

When pad days was considered to quantify the amount of bleeding , cases diagnosed with endometrial cancer had significantly higher amount of bleeding and the risk was significantly higher if the patient experienced bleeding exceeding 5 pad days. In a study done by *Salman et al*<sup>28</sup> had similar findings .

#### **4.11 HISTOPATHOLOGICAL PATTERN OF ENDOMETRIUM:**

In our study it was observed that , disordered proliferative pattern of endometrium was the commonest histopathological pattern – 44 ( 26.7%) . Studies done by *Gredmark et al* , *Lee WH et al* , *Dangal G et al* and *Kaur M et al*<sup>29-31</sup> have observed atrophic endometrium has the most common histologic all diagnosis . *Philip H et al*<sup>32</sup> found atrophic endometrium (13.3 %) as the third most common cause after proliferative pattern endometrium, which is consistent with our present study .Endometrial hyperplasia is a condition of the endometrium which carries both clinical and pathological significance . It is one of the most important predisposing factor for endometrial carcinoma. The risk increases with atypical endometrial hyperplasia , which carries the risk of associated endometrial carcinoma more than endometrial hyperplasia without atypia. The percentage of risk explained earlier in detail.

In our study the percentage of patients presented with endometrial atypical hyperplasia was 4.2%.It was found to range from 1.8- 8% in others studies<sup>29,33</sup>. Endometrial carcinoma which is the most important and threatening cause of postmenopausal bleeding was found to be 12.1% in the present study. Other studies have found it to range from 6% to 12%<sup>29,33,34</sup> . Histologically all the cases were diagnosed to be Endometrioid endometrial cancer .

In conclusion, higher accuracy of diagnostic strategies with lower rates of unnecessary invasive sampling procedures may be achieved by the incorporation of patient and clinical history characteristics in the initial evaluation. The decision to proceed with either more invasive procedures or expectant management may be made more readily and confidently by this means even among women who requires sampling according to current guidelines. For a woman presenting with PMB, older age, recurrent bleeding history and higher amount of blood loss are strong predictors for endometrial cancer, and presence of these characteristics should immediately trigger invasive endometrial sampling. Using such risk models may also assist in appropriately allocating limited resources in developing countries.

### **V. Conclusion**

The study has proved the association of endometrial cancer with many of clinical characteristics, the amount and duration of bleeding and the endometrial thickness which are important in the diagnosis. From this study the risk factors with statistical significance were nulliparity, recurrent episodes of bleeding , amount of bleeding calculated using pad days , endometrial thickness of more than 10 mm, history of diabetes mellitus. Transvaginal sonography is safe, simple, non invasive and cost effective in the diagnosis of endometrial disease. Hence the combination of clinical characteristics , trans vaginal sonography and endometrial biopsy can be used in diagnosing endometrial cancer in post menopausal bleeding.

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