

## To study the Co-relation of Endometrial Thickness and Endometrial Biopsy in a group of peri and post menopausal women

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### ABSTRACT

**Aims:** To find out the Co-relation of endometrial thickness & endometrial biopsy in a group of peri and post menopausal women.

**Study design:** Comparative study

**Duration of study:** 8-11 months.

**Methods:** Endometrial thickness was measured in 50 women aged 39 to 65 years who later underwent endometrial biopsy. Women undergoing estrogen replacement were excluded from study. Diagnosis can be made by excluding intrauterine pathology like submucosal myomas using transvaginal sonogram. Women who reported 8 or more days of bleeding were included in the study. They were divided into two groups based on menstrual status i.e. peri and post menopausal status. A sonographic recommended pattern was encountered in the study.

**Results:** Endometrial biopsy showed that benign endometrial polyp, cystic glandular hyperplasia and adenomatous hyperplasia with atypia had average endometrial thickness of 17.25, 16.00 and 23.33 mm respectively. This sonographic pattern is more common in peri menopausal women. On the other hand mid to late secretory phase with endometrial thickness of 7.39mm were common in both pre and perimenopausal group. Endometrial biopsy in post menopausal women showed that this group of women was more susceptible to cystic glandular hyperplasia and moderate to well differentiate papillary carcinoma having an endometrial thickness of 16.0 and 18.60 mm respectively. On the other hand, both peri and post menopausal women are at high risk of developing endometrial adenocarcinoma (endometrial thickness, 29.33mm).

**Conclusion:** Women with perimenopausal status are at greater risk of developing endometrial cancer as compared to post menopausal women. In a postmenopausal woman if the endometrium measures > 4 mm in thickness a biopsy should be considered as the risk of cancer is 10.1%, whereas if the endometrium measures <or =4mm a biopsy is not needed as the risk of cancer is extremely low.

**Keywords:** Endometrial biopsy, endometrial thickness, peri and post menopausal women.

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### INTRODUCTION

Dysfunctional uterine bleeding (DUB) is a common debilitating problem amongst women in all age groups and accounts for 20% of gynecology office visits<sup>1</sup>. It is defined as abnormal, irregular bleeding in the absence of demonstrable pelvic disease, complications of pregnancy or systemic disease<sup>2,3</sup>. The exact mechanism is uncertain but is thought to be caused by dysfunction of hypothalamic-pituitary-ovarian axis i.e., from an imbalance in the hormonal-endometrial relationship, where persistent and unopposed stimulation of the endometrium by estrogen occurs. Disorders that cause sustained high estrogen levels are polycystic ovary syndrome, obesity, immaturity of the hypothalamic-pituitary-ovarian mechanism (in postpubertal teenagers), and anovulation (in women in their late 30s or early 40s)<sup>4</sup>.

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The most important risk factor in premenopausal women is irregular menstrual cycles, which is associated with a 14% risk of an abnormal endometrial biopsy, including benign and malignant lesions<sup>5</sup>. Peri and postmenopausal bleeding, with or without the use of hormone replacement therapy, is a common clinical problem. The exclusion of endometrial hyperplasia and carcinoma is the key issue in the evaluation of patients with abnormal uterine bleeding<sup>6</sup>. Women with PMB have around a 10% chance of having endometrial carcinoma and therefore PMB always needs further evaluation<sup>7</sup>.

In most cases of DUB, the endometrium shows no pathologic changes. However, in chronic unopposed estrogen stimulation (as from a hormone-producing ovarian tumor), the endometrium may show hyperplastic or malignant changes. DUB occurs in 20% of adolescents and in 40% of women older than age 40. It most commonly occurs within the 1st 2 years of menarche when >50% of cycles are

anovulatory. Older age at menarche results in longer duration of anovulation<sup>8</sup>.

Transvaginal ultrasound measurement of endometrial thickness has become a routine procedure and an initial investigation in patients with abnormal uterine bleeding. Its clinical importance and applications extend throughout the phases of the reproductive lives of women. Four distinct sonographic patterns were encountered. Pattern 1 consisted of echogenic endometrium with small cysts (endometrial polyp with cystic hyperplasia, atrophic endometrium). Pattern 2 was homogeneous echogenic endometrium (proliferative endometrium and adenomyomatous polyp. Pattern 3 was irregular, inhomogeneous endometrium (endometrial carcinoma, complex hyperplasia with atypia and atrophic endometrium). Pattern 4 was thin endometrium with fluid in the endometrial cavity (scant atrophic endometrium)<sup>9,10</sup>.

Women with an endometrial thickness of 4mm or less have an extremely low likelihood of endometrial cancer and thus do not need to undergo endometrial biopsy<sup>10</sup>. In premenopausal women, endometrial thickness is used to monitor infertility treatment, while in postmenopausal women with abnormal uterine bleeding it is useful as an initial investigation for endometrial hyperplasia or cancer. Studies involving endometrial cancer showed that endometrial volume estimation is more specific than endometrial thickness measurement for predicting endometrial cancer<sup>11</sup>. Moreover, endometrial thickness can vary with the menstrual cycle and with the use of hormone replacement therapy or selective estrogen receptor modulators<sup>12</sup>.

Endometrial biopsy is an important diagnostic tool in the evaluation of abnormal uterine bleeding. It is used to exclude the presence of pathologic conditions, such as endometrial cancer and its precursors, especially atypical endometrial hyperplasia<sup>13</sup>. Various combinations of hyperplastic, proliferative, secretory, and atrophic changes of endometrial glands, stroma, and blood vessels may result in confusing histologic patterns<sup>9</sup>.

## MATERIAL AND METHODS

Endometrial thickness was measured in 50 women ages 39 to 65 years who underwent transvaginal ultrasound screening. Women undergoing estrogen replacement were excluded from study. Endometrial thickness was measured by excluding intrauterine pathology like submucosal myomas using transvaginal sonogram (TVS). Women who reported 8 or more days of bleeding were included in the study. They were divided into two groups based on menstrual status i.e. peri and post menopausal

group. These women later underwent endometrial biopsy. Data was collected after obtaining fully informed, understood and voluntary consent of both patients and normal subjects.

The endometrial biopsy revealed different patterns in the study. These patterns were benign endometrial polyp, cystic glandular hyperplasia, Moderated to well differential papillary adenocarcinoma, Mid to late secretory phase, Early secretory phase, Secretory phase with pseudo decidual change, Atypical endometrial hyperplasia, Atrophic endometrium with pseudo decidual change, Chronic granulomatous endometritis, Proliferative phase, Cystic atrophy, Adenomatous hyperplasia with atypia and Endometrial adeno carcinoma.

**Statistical analysis:** Data was processed in SPSS (Statistical program for scientific studies) Software Computer Program. Variables were reported by using mean±S.D and presented as tabulated form.

## RESULTS

The relationship of endometrial thickness to endometrial biopsy in a group of peri (age range 40-53 years) and post menopausal women (age range 55-65 years) was tabulated. It was observed that in 8 cases (16%) of benign endometrial polyp the mean endometrial thickness was 17.25±4.80, range was 15-25. Mean age 48.0±6.30 and age range was 39-55 years. Cystic glandular hyperplasia was found in both groups (n=5, 10% cases). However the mean age was 55.20±9.44 with age range 40-62 year and mean endometrial thickness was 16.00±3.08 with a range of 12-20 mm. Moderated to well differential papillary adenocarcinoma (n=5, 10% cases). The mean age was 59.00±4.00 with age range 54-65 year and mean thickness was 18.60±9.86 with a range of 10-35mm. Mid to lateral secretory phase (n=8, 16% cases). The mean age was 45.44±6.17 with age range 35-52 year and mean thickness was 7.39±2.62 with a range of 03-11 mm.

Early secretory phase (n=2, 04% cases). The mean age was 43.00±2.83 with age range 41-45 year and mean thickness was 4.00±1.41 with a range of 03-05 mm. Secretory phase with pseudo decidual change (n=2, 04% cases). The mean age was 46.0±19.80 with age range 32-60 year and mean thickness was 10.50±0.71 with a range of 10-11mm. Atrophic endometrium with pseudo decedual change (n=2, 04% cases). The mean age was 62.5±3.54 with age range 55-60 year and mean thickness was 4.00±1.41 with a range of 3-5mm. Proliferative phase (n=07, 14% cases). The mean age was 40.0±7.70 with age range 25-47 year and mean thickness was 4.29±2.14 with a range of 2-8mm.

Cystic atrophy (n=05, 10% cases). The mean age was 64.75±10.66 with age range 50-75 year and mean thickness was 2.60±0.55 with a range of 2-3 mm. Adenomatous hyperplasia with atypia (n=03, 06% cases). The mean age was 53.33±5.71 with age range 50-60 year and mean thickness was

23.33±7.64 with a range of 15-30mm. Endometrial adeno ca (n=2, 04% cases). The mean age was 55.0±0.52 with age range 50-65 year and mean thickness was 29.33±0.5mm.

Table: Comparison of endometrial thickness and endometrial biopsy in a group of peri (age range 40-53 years) and post menopausal women (age range 55-65 years).

Endometrial biopsy	Age (years)	Endometrial thickness (mm)	%age of sonographic pattern
Benign endometrial polyp (8)	48.00±6.30 (1.70)	17.25±4.80(2.23)	16%
Cystic glandular hyperplasia(5)	55.20±9.44 (4.22)	16.00±3.08 (1.38)	10%
Moderated to well differential papillary adenocarcinoma (5)	59.00±4.00 (1.79)	18.60±9.86 (4.41)	10%
Mid to lateral secretary phase (9)	45.44±6.17 (2.06)	7.39±2.62 (0.87)	18%
Early secretary phase (2)	43.00±2.83 (2.00)	4.00±1.41 (1.00)	4%
Secretary phase with pseudo decidual change (2)	46.0±19.80 (14.0)	10.50±0.71 (0.50)	4%
Atropic endometrium with pseudo decidual change (2)	62.5±3.54 (2.50)	4.00±1.41 (1.00)	4%
Proliferative phase (7)	40.0±7.70 (2.91)	4.29±2.14 (0.81)	14%
Cystic atrophy (5)	64.75±10.66(5.33)	2.60±0.55 (0.24)	10%
Adenomatous hyperplasia with atypia (3)	53.33±5.71 (3.33)	23.33±7.64 (4.41)	6%
Endometrial adeno ca (2)	55.0±0.52	29.33±0.5	4%

## DISCUSSION

The majority of endometrial cancers are related to chronic unopposed endogenous or exogenous estrogen. Women at increased risk of endometrial cancer include those with a relatively longer period of exposure to estrogen, such as women with early menarche, late menopause, and nulliparous women. The pattern of abnormal bleeding is also important because women with irregular menstrual cycles are at higher risk of having endometrial cancer than women with regular cycles<sup>14</sup>.

Endometrial thickness of greater than 5 mm in postmenopausal women is associated with a variety of pathologic conditions. The endometrial biopsy in these cases may be helpful in differentiating benign cystic atrophy or cystic endometrial hyperplasia from malignant endometrial lesions<sup>15</sup>.

The endometrial biopsy was related to the sonographic pattern of endometrial thickness in a group of peri (age range 40-53 years) and post menopausal women (age range 55-65 years). It was observed that 16% cases of benign endometrial polyp were mostly observed in perimenopausal women with a mean endometrial thickness of 17.25±4.80. However a study identified 43.1% polyps in a group of postmenopausal women<sup>16</sup>. Another study found polyps in 37% patients (Hernandez 2009). Endometrial polyps were a frequent finding in tamoxifen-treated<sup>17</sup> postmenopausal women who had endometrial thickness > or =5mm. Endometrial

polyps are usually benign although some may be precancerous or cancerous<sup>18,6</sup>.

Cystic glandular hyperplasia was found in both groups (10%) with a mean age was 55.20 years and age range 40-62 year. Mean endometrial thickness was 16.00 with a range of 12-20 mm. A study reported that Cystic glandular hyperplasia (CGH) has been considered to be a precursor of endometrial carcinoma. Proliferative and mitotic activities of CGH were found to be similar to those of adenomatous hyperplasia, and the levels of these activities were between those of normal endometrium and atypical hyperplasia<sup>19</sup>. Another study reported that as a woman's age increases, her risk of cancer increases at each endometrial thickness measurement. For example, using the 11mm threshold, the risk of cancer associated with a thick endometrium increases from 4.1% at age 50 years to 9.3% at age 79 years<sup>8</sup>.

Moderated to well differential papillary adenocarcinoma was 10% and more common in post menopausal women. The mean age was 59.00±4.00 with age range 54-65 year and mean thickness was 18.60±9.86 with a range of 10-35mm. In postmenopausal women with abnormal bleeding, endometrial thickness of 4–5mm cut off value has a high negative predictive value in excluding endometrial hyperplasia or cancer<sup>21</sup> (Machado et al 2005). Another study reported that the risk of cancer for a postmenopausal woman with vaginal bleeding is

increased when the endometrial thickness measures  $> 5 \text{ mm}^8$  (Goldstein et al 2009).

Present study observed early secretory phase in 4%, mid to late secretory phase in 18% and secretory phase with pseudo decidual change in 2% perimenopausal women. Endometrial thickness was usually 7-10mm in mid to late and pseudo decidual secretory phase while in early secretory phase it was in normal limits. A study reported that perimenopausal women with abnormal bleeding are at increased risk of endometrial cancer secondary to their age and anovulatory cycles. The most suspicious patterns are persistently increased menstrual flow, decreased menstrual interval, and intermenstrual bleeding<sup>22</sup>.

Atropic endometrium with pseudo decidual change was observed in 2% post menopausal women with mean age was  $62.5 \pm 3.54$  and age range 55-60 year. Mean thickness was  $4.00 \pm 1.41$  with a range of 3-5 mm excluded the risk of endometrial cancer. A study found endometrial atrophy in 13% cases<sup>20</sup> (Hernandez 2009). A group of workers used cutoff level of 3 mm for exclusion of endometrial carcinoma in women with postmenopausal bleeding<sup>23</sup> (Timmermanns et al 2010). Another study reported that 4-5-mm threshold conventionally used to exclude endometrial malignancy in women with postmenopausal bleeding<sup>24</sup>.

Cystic atrophy with mean endometrial thickness 2.60mm and endometrial adeno carcinoma with endometrial thickness 29.33 mm was also found in 10% and 04% postmenopausal women respectively. However, a study observed that no specimens of post menopausal women were identified as adenocarcinoma<sup>16</sup>. It is reported that conditions associated with postmenopausal vaginal bleeding, such as endometrial atrophy, polyp, and hyperplasia, might be related to a decrease or increase in endometrial thickness. In some cases, the sonographic appearance of a thick endometrium may correspond not to a true thickening of the endometrial lining but rather to the unrecognized formation of endometrial polyps or accumulation of fluid within the endometrial cavity<sup>25</sup> (Sit et al ). However, a study found, endometrial atrophy in 13% and cystic hyperplasia in 8% post menopausal women<sup>17</sup>.

Proliferative phase (n=07, 14% cases) was mainly observed in both pre and peri menopausal women with mean age was  $40.0 \pm 7.70$  with age range 25-47 year and mean thickness was  $4.29 \pm 2.14$  with a range of 2-8 mm. In clinical studies, endometrial malignancy is uncommon in women with an endometrial thickness measurement  $< 5 \text{ mm}^26$ .

Adenomatous hyperplasia with atypia was observed only in 06% perimenopausal women. The mean age was  $53.33 \pm 5.71$  with age range 50-60 year

and mean endometrial thickness was  $23.33 \pm 7.64$  with a range of 15-30mm. According to a study adenomatous hyperplasia with atypia was ~16% without atypia progress to carcinoma, while ~47% with atypia progress to carcinoma<sup>27</sup>. Limitation of study: Number of cases are insufficient to reach a better conclusion

## CONCLUSION

Endometrial biopsy showed that benign endometrial polyp, cystic glandular hyperplasia, adenomatous hyperplasia with atypia is more common in peri menopausal women. On the other hand mid to lateral secretory phase are common in both pre and perimenopausal group. Study also showed that women with perimenopausal status are at greater risk of developing endometrial cancer as compare to post menopausal women. Sonographic pattern in post menopausal women showed that this group of women is more susceptible to cystic glandular hyperplasia, moderate to well differentiate papillary carcinoma. On the other hand, women with both peri and post menopausal status are at high risk of developing endometrial adenocarcinoma.

In a postmenopausal woman if the endometrium measures  $> 4 \text{ mm}$  a biopsy should be considered as the risk of cancer is 10.1%, whereas if the endometrium measures  $< \text{or} = 4 \text{ mm}$  a biopsy is not needed as the risk of cancer is extremely low.

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