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Original Research Article

## Correlation of body mass index and abnormal uterine bleeding in premenopausal women

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### ABSTRACT

**Background:** As the rate of obesity is increasing in women in the recent years, the incidence of endometrial cancer increases as the body mass index (BMI) increases. Despite the clear evidence linking endometrial cancer and obesity, there is limited public awareness of this relationship. This study was undertaken to evaluate the association of BMI and endometrial pathology in premenopausal women with abnormal uterine bleeding (AUB).

**Methods:** An analytical case control study was conducted in 100 women between the age group of 40 to 55, with AUB in the Department of Obstetrics and Gynecology, ESIC-PGIMS Bangalore between January 2018 and June 2019. The menstrual patterns and endometrial pattern by histopathology were analysed in women with BMI of 18.5 to 24.99 and  $\geq 25$ .

**Results:** The mean age of women participated in the study group of between 40- 55 years was 44.83. The mean duration of symptoms was 10.18 months in the cases group and 8.52 months in the control group. The menstrual patterns were comparable and there was no significant difference in both the groups. The mean endometrial thickness, mean BMI, hyperplasia with or without atypia were all higher in the cases group. The frequency of occurrence of atypical endometrial hyperplasia was higher in women with increasing BMI.

**Conclusions:** We found increased BMI to be an important independent risk factor for the development of endometrial hyperplasia with atypia which is a precursor to endometrial carcinoma in premenopausal women with AUB.

**Keywords:** Abnormal uterine bleeding, Endometrial hyperplasia, Endometrial thickness, Body mass index

### INTRODUCTION

According to International Federation of Gynecology and Obstetrics (FIGO) abnormal uterine bleeding (AUB) is defined as bleeding from the uterine corpus that is abnormal in volume, regularity, frequency or duration and occurs in the absence of pregnancy. AUB is a common complaint encountered in Gynaecology outpatient department (OPD). It occurs in 9 to 14% of women from menarche to menopause affecting quality of life imposing financial burden.<sup>1</sup>

Recent global statistics showed that 35% of the adult population (age 20+) is overweight (body mass index  $\geq 25$  kg/m<sup>2</sup>) and 12% obese (body mass index  $\geq 30$  kg/m<sup>2</sup>). While the current prevalence of excess body mass index (BMI) is around 10% in many Asian and African countries.<sup>2</sup>

Over the past 2 decades there has been global recognition of increasing levels of obesity. At the same time, there is epidemiological evidence of increased incidence of endometrial cancer. Several systematic reviews have shown an association between obesity and endometrial cancer. However, given that the majority of endometrial

cancer occurs in postmenopausal women, it has not been widely recognized that obesity is a significant risk factor for endometrial hyperplasia and cancer in young, symptomatic, premenopausal women.<sup>3</sup>

Recent meta-analyses suggest that women who are overweight or obese have a 1.43 or 3.33 fold increase in risk for developing endometrial cancer, compared to women with normal weight.<sup>4</sup>

Developing a greater understanding of the leading risk factors for premenopausal women would lead to improved clinical pathways from primary to secondary care and improved targeting of invasive diagnostic testing. Deciding to biopsy primarily based on age, as currently recommended in national guidelines, potentially misses many cases or delays diagnosis. Body mass index should be the first stratification in the decision to perform endometrial biopsy and/or to refer secondary gynaecology services.

The current study was aimed to evaluate the association of body mass index and endometrial pathology in premenopausal women with AUB.

## METHODS

Our study was analytical, case control study conducted on 100 women after obtaining institutional ethical committee approval with AUB who attended the Department of Obstetrics and Gynaecology, ESIC-PGIMS Bengaluru between January 2018 and June 2019 (18 months), with the sample size of 100 cases. These women were subjected for height and weight measurement, calculation of BMI, and detailed history, examination, and baseline investigations including complete hemogram, LFT, renal function tests (RFT), coagulation profile and pelvic ultrasound followed by endometrial biopsy and the histopathological report was studied for the endometrial pattern. The diagnostic intervention was done with endometrial sampling by D and C or Pipelle for both groups.

BMI was calculated by:

$$\text{Quetelet index} = \frac{\text{weight in kgs}}{\text{height in meter square}}$$

### Sample size estimation

The sample size for the present case control study was calculated by considering the odds ratio for developing the endometrial cancer in overweight premenopausal women to the normal weight as 3.5 from the previously published literature. This gave disease exposure rate to be 70% in overweight and 40% in normal weight groups. The minimum sample size had been calculated to be 42 cases in each group with 30% as effect size at 5% level of significance which gives at least 80% power assuming two tailed hypotheses. Therefore, the minimum total sample

size of the study was set as 84 cases. But the study was conducted on 100 women. Following formula was used to calculate the sample size:

$$n = \frac{[Z_{\alpha/2} \sqrt{2 \times P(1-P)} + Z_{\beta} \sqrt{P_0(1-P_0)} + \sqrt{P_1(1-P_1)}]^2}{(P_0 - P_1)^2}$$

Where,  $Z_{\alpha/2}=1.96$ ,  $Z_{\beta}=0.84$ ,  $P_0=0.40$ ,  $P_1=0.70$  and

$$P = P_0 - P_1 \div 2$$

### Inclusion criteria

The inclusion criteria for the study was as follows: women who were willing to give written informed consent and all women attending Gynaecology OPD with complaint of AUB in the age group of 40 to 55 years with BMI of 18.5 to 24.99 and  $\geq 25$ .

### Exclusion criteria

The exclusion criteria for the study was as follows: existing cervical, uterine and ovarian cancer; pelvic inflammatory disease; premenopausal women with coagulation disorders; on-going pregnancy; and women with thyroid disorders, liver disorders, chronic kidney disease.

Results were analysed as continuous (age, duration of symptoms and endometrial thickness) and categorical (parity, menstrual pattern and ultrasound (USG) and histopathological analysis) variables using independent t test and chi square/Fischer exact test respectively. P value was considered significant if it is less than 0.05.

## RESULTS

The primary outcome of the study was the comparison of the menstrual pattern and the comparison of the histopathological report for the endometrial pattern of the women in both the groups. Mean age, duration of AUB, association of comorbidities were the secondary outcomes studied. Case- 50 women with BMI of  $\geq 25$ , control group- women with BMI of 18.5 to 24.99.

### Age group and parity

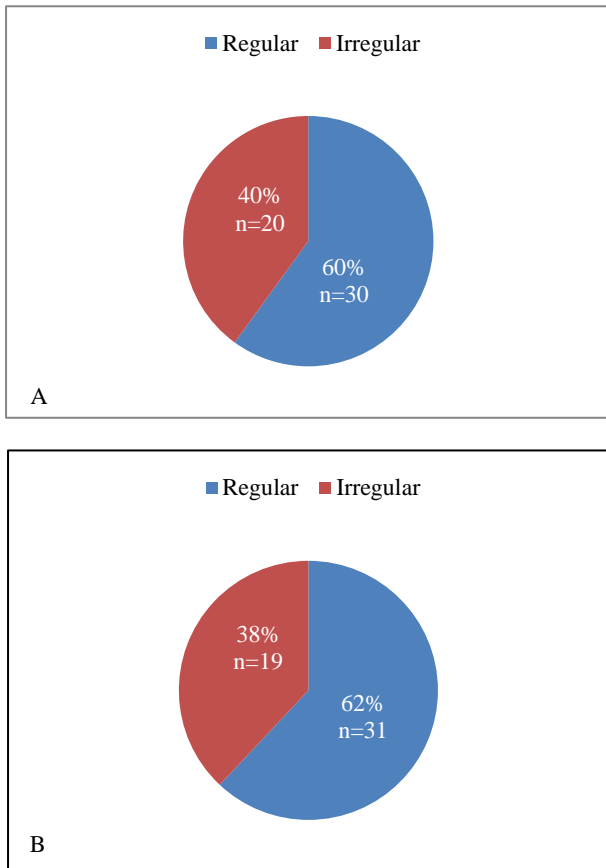
The mean age of women participated in the study group of between 40-55 years was 44.83 years while with the control group and cases group was 45.14 and 44.52 respectively. The p value was 0.3 which was not statistically significant, which rendered both the group comparable with respect to age. Maximum number of women were with parity 2, with 54% (27 women) and 48% (24 women) in control and cases group respectively. P value was 0.82. The second-high number of women fall under parity 3 with 14 women (28%) and 12 women (24%) in control and case group respectively.

**Duration of symptoms**

The duration of symptoms of AUB was compared in both the groups, with the mean duration in 100 women was 9.35 months. The mean duration of symptoms was 10.18 months in the cases group and 8.52 months in the control group, with the p value of 0.13

**Menstrual patterns**

The menstrual patterns were variedly studied in both the groups with respect to disturbance of frequency and regularity, disturbance of duration of flow, heaviness of flow. The menstrual patterns were comparable and there was no significant difference in both the groups. 61% of total women had regular menstrual bleeding and 39% had irregular menstrual bleeding. P value was statistically not significant which was 0.84.

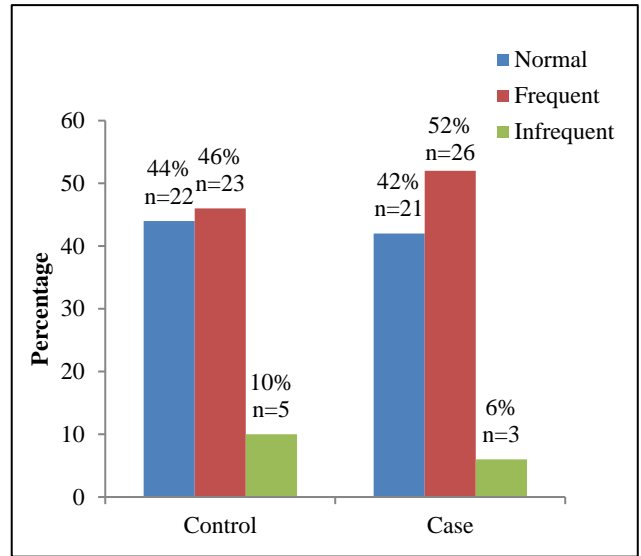


**Figure 1: Comparison of disturbance in regularity of menstrual bleeding among both the groups, (A) menstrual pattern control group, (B) menstrual pattern cases group.**

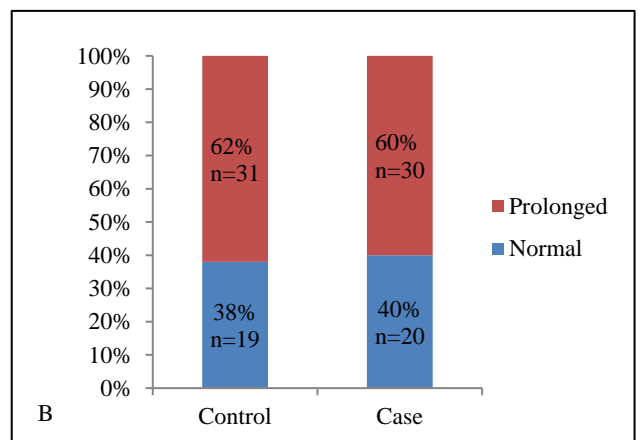
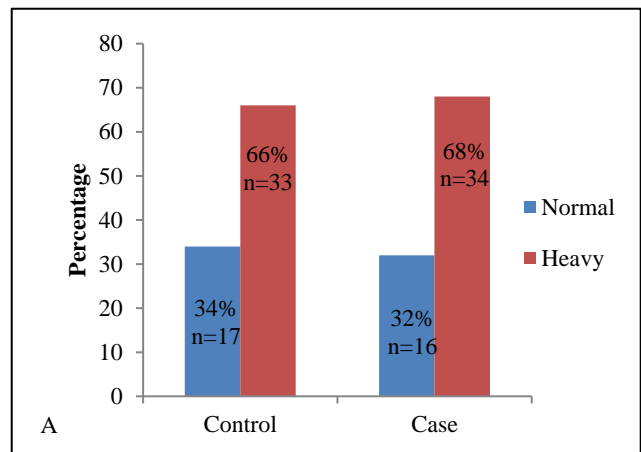
Among 100 women studied 43% had normal frequency of cycle, 49% had frequent menstrual cycle and 8% had infrequent cycles. 0.70 was the p value which was statistically not significant.

The amount of menstrual flow was comparable with both the case and control group as normal menstrual bleeding

and heavy menstrual bleeding. 33% of women had normal and 67% of women heavy menstrual bleeding. P value was 0.83 which was statistically not significant.



**Figure 2: Comparison of frequency of menstrual cycle (n=100).**

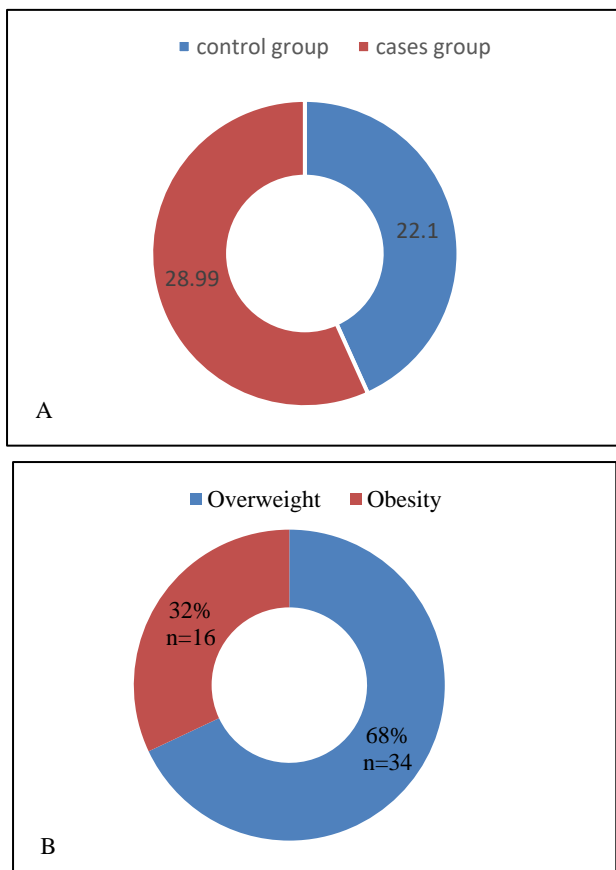


**Figure 3: (A) Comparison of menstrual flow among both the groups, (B) comparison of menstrual duration among both the groups (n=100).**

The duration of menstrual bleeding was compared in both the groups as normal menstrual bleeding and prolonged menstrual bleeding. Among 100 women in the study 39% had normal duration of flow and 61% had prolonged menstrual flow with the p value of 0.84 which was statistically not significant.

#### Comparison of body mass index

The mean BMI was compared in both the groups with the cases groups was 28.99 while the mean BMI in the control group was 22.1.



**Figure 4: (A) Comparison of mean body mass index, (B) distribution of overweight and obesity.**

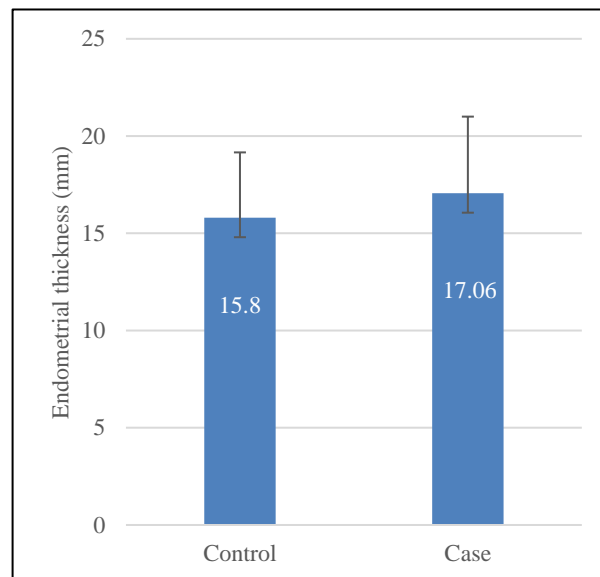
The total number of women with overweight (BMI of 25 to 29.99) was 34 (68%) and the total number of women with obesity (BMI of  $\geq 30$ ) was 16 (32%).

#### Ultrasonographic findings

All the women in the study group were subjected to ultrasound examination for uterine size, endometrial thickness and adnexa was looked for any pathology.

Among 100 women in both the groups, 68% (34) and 56% (28) of women had normal uterine size, rest 32% (16) and 44% (22) of women had bulky uterus in control group and cases group respectively.

With the comparison of endometrial thickness in both the groups the mean endometrial thickness was 16.43 mm. The minimal endometrial thickness studied was 8mm seen in the control group and the maximum was 26 mm seen in the cases group. The mean endometrial thickness in control group and cases group was 15.8 mm and 17.06 mm respectively. The p value was 0.09 which was statistically not significant.



**Figure 5: Comparison of endometrial thickness.**

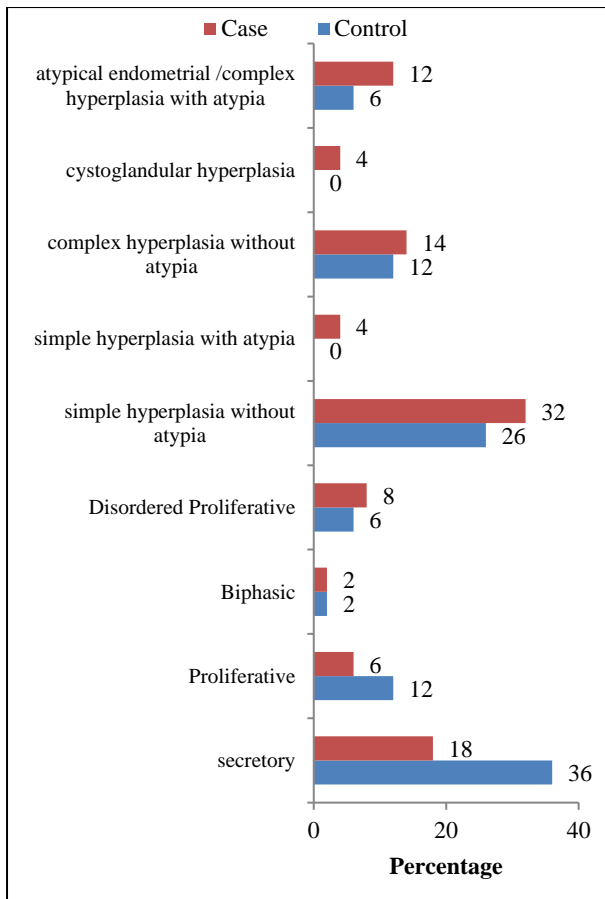
#### Comorbidities

With the comparison of comorbidities among both the groups, 60% (30 women) and 54% (27 women) of women had no comorbidities associated with AUB. Diabetes mellitus type 2 was seen in 20% (10 women) and 24% (12 women) in control and cases group respectively. The presence of anaemia was equal in both the groups of 12% (6 women). Hypertension was seen in 8% (4 women) in control group and 10% (5 women) in cases group. P value being 0.93 which was statistically not significant.

#### Histopathological correlation

Among the histopathological findings in both the groups, normal histopathological findings were more common in the control group with secretory phase endometrium in 36% (18 women) followed by proliferative endometrium of 12% (6 cases) and biphasic endometrium in 1 woman (2%). In the cases group the number of women with secretory and proliferative endometrium were 18% (9 cases) and 6% (3 cases) respectively, and biphasic endometrium was 2% (1 case).

Other patterns including disordered proliferative endometrium was seen in both control and cases group of 6% (3 women) and 8% (4 women) respectively.



**Figure 6: Comparison of histopathological findings (n=100).**

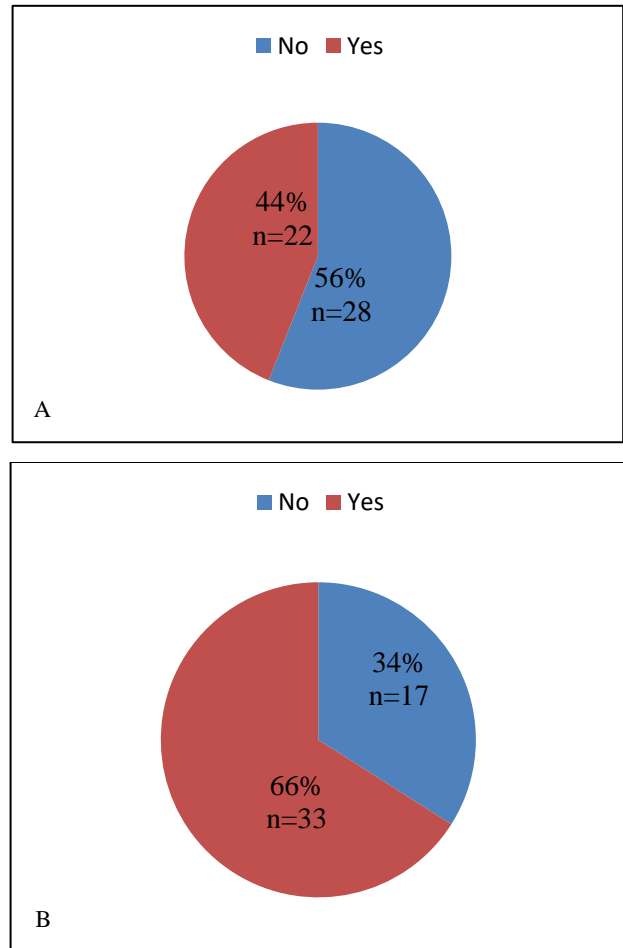
Among the endometrial patterns, the percentage of hyperplasia (all types) diagnosed by endometrial biopsy was high in both the groups. Of 100 women in the present study 55 women had endometrial hyperplasia and 46 women had other patterns with the p value of 0.07.

Simple hyperplasia without atypia was common with 26% and 32% respectively in control and cases group while simple hyperplasia with atypia was 4% in cases group and zero in control group.

Complex hyperplasia without atypia was seen in 12% (6 women) and 14% (7 cases) in AUB with control group and cases group respectively. Complex hyperplasia with atypia was 6% (3 women) and 12% (6 women) in control and cases respectively. Cysto-glandular hyperplasia was seen in 2 women (4%) in the cases group.

With the comparison of endometrial hyperplasia from the histopathology report of all 100 women, the percentage of women having hyperplasia with or without atypia was more in women with BMI of  $\geq 25$  (case group). 44% (22 women) and 66% (33 women) were diagnosed to have endometrial hyperplasia in both control and case group respectively. Though a greater number of hyperplasia was seen in the high BMI group, the p value of 0.07 was not statistically significant.

Out of 55 women with hyperplasia, 33 were in the cases group and 22 women in the control group. the mean endometrial thickness was 16.09 mm and 16.8 mm in the cases and control group respectively which was comparable, the mean BMI was 22.3 in the control group and 28.99 in the cases group respectively. P value of 0.5 which was statistically not significant.

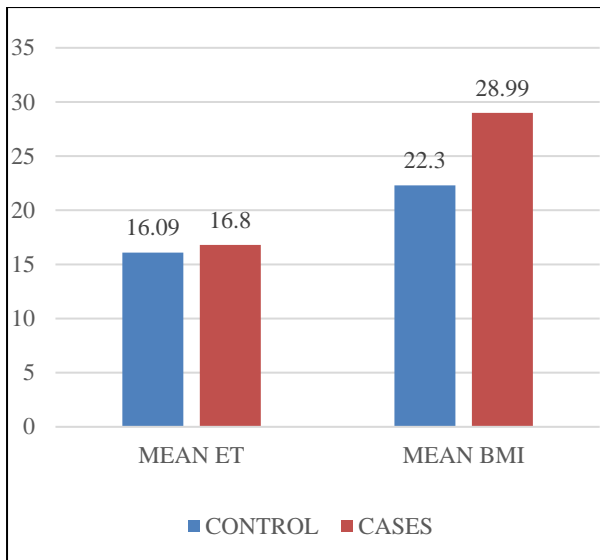


**Figure 7A: Comparison of endometrial hyperplasia among the study groups (A) endometrial hyperplasia in control group), (B) endometrial hyperplasia in cases.**

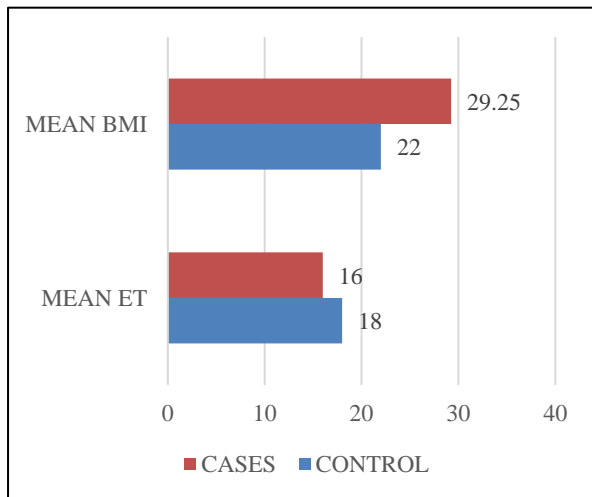
Among the 100 women in the present study group 11 women developed hyperplasia with atypia, 8 women from the cases group and 3 women from the control group. The mean endometrial thickness and the mean BMI were studied in these 11 women.

The mean BMI in both the groups was found to be 29.25 in the cases group and 22 in the control group, likewise the mean endometrial thickness was 16 mm and 18 mm in the cases and control group respectively. Among the 8 women in the cases group, 5 women were in the overweight category and 3 women in the obese category.





**Figure 8: Comparison of mean endometrial thickness and body mass index.**



**Figure 9: Comparison of mean endometrial thickness and mean body mass index among the study groups.**

## DISCUSSION

The primary outcome of the study was the comparison of the menstrual pattern and the comparison of the histopathological report of these women in both the groups. Mean age, duration of AUB, associated comorbidities were also studied.

The demographic characteristics of both the groups were found to be comparable, in terms of age with the mean age of women with the normal BMI and (control group) was 45.14 and in the cases group was 44.52 years. The mean duration of symptoms in control group was 8.52 months and in the cases group was 10.18 months.

In our study the most common endometrial pattern was secretory and proliferative endometrium which was 36%.

The endometrial biopsy compared by Wise et al<sup>3</sup> in 2016, the most common endometrial pattern seen in the biopsy was the normal endometrium like secretory and proliferative phase seen in 41.1% followed by disordered proliferative endometrium which was 20.5%. The incidence of endometrial cancer or hyperplasia with atypia was 4.9% in women with AUB with the BMI of more than 30 which was comparable with our study with the presence of endometrial hyperplasia with atypia seen in 8% of women with BMI of  $\geq 25$  and 3% in women with BMI  $< 25$ . In the present study obese women had more atypia along with hyperplasia in the endometrial patterns compared to the women with normal BMI.

The menstrual patterns were variedly studied in both the groups with respect to disturbance of frequency and regularity, disturbance of duration of flow, heaviness of flow.

The different menstrual irregularities did not significantly affect the outcome. Menstrual history had no effect on the endometrium according to Wise et al, 2016 which was comparable with our study, where the menstrual irregularities were similar in both the groups.<sup>3</sup>

Seif et al in 2015 reported that the prevalence of menstrual cycle irregularities was 8.4% in women who were 74% overweight, as compared to 2.6% in women who were  $< 20\%$  overweight.<sup>5</sup> A further study documented that being 15% overweight was associated with a significantly higher chance of having a menstrual cycle longer than 43 days.

In the present study 52% of women in the cases group had frequent cycles, 68% had heavy menstrual bleeding, 30% had prolonged menstrual bleeding and 38% had regular cycle length in comparison with the control group where 60% had regular cycles, 46% had frequent cycles, 66% had heavy menstrual bleeding and 31% had prolonged menstrual bleeding which was consistent with the previous studies.

In the study conducted by Wise et al, the mean duration of AUB in the control group was 3.4 years while the mean duration of AUB in the cases group was 3.8 years, which was comparable with the present study with the mean duration of AUB in the control group and the cases groups were 8.52 months and 10.18 months respectively.<sup>3</sup>

Comparison of endometrial thickness with respect to AUB was made by Wise et al, where the mean endometrial thickness in the control group and the cases group were 16.5 mm and 26 mm respectively which was comparable with the present study with the endometrial thickness of 15.8 mm and 17.06 mm in the control group and the cases group respectively.<sup>3</sup>

Nouri et al studied the pathological effects of obesity on triggering DUB, they suggested that thickened endometrium and uterine wall hyperplasia can predispose to AUB.<sup>6</sup>

In the present study the endometrial thickness in the cases group was 17.06 which was higher than control group (15.8) and the uterine size comparison was consistent with the study conducted by Nouri et al, where 44 % in the cases group and 32% in the control group had bulky uterus.<sup>6</sup>

In the cases group the mean BMI of women were studied for its correlation with AUB, according to Nouri et al, 2014 the mean BMI of women in the study group was 32.63 while the mean BMI according to Sharma et al, 2018 was 27.92 which was comparable with the present study where the BMI was 28.99 indicating the higher incidence of AUB in obese and overweight women.<sup>6,8</sup> According to Farquhar et al, 1999 they concluded that obesity and BMI were independent risk factors contributing to endometrial hyperplasia and endometrial cancer.<sup>7</sup>

**Table 1: comparison between overweight and obesity.**

Study conducted by	Overweight (25-29.99)	Obese (>30)
Sharma et al <sup>8</sup>	56.25%	25%
Present study	34 (68%)	16 (32%)

Sharma et al, in 2016, concluded that almost 81% of cases had abnormal BMI. More than half of cases in the study group (56.25%) were overweight and 8% that was one-fourth women were obese.<sup>8</sup>

Nouri et al concluded that two-third of studied women suffered from overweight status and other one third cases were obese.<sup>6</sup> In the present study (34 cases) 68% of women were overweight and 36% of women (18 cases) were obese according to World Health Organization (WHO) BMI classification which was consistent with the above two results.

Though the present study may be limited with smaller sample size, the relation of BMI with AUB and existence of longer duration of symptoms of AUB in overweight and obese women was well correlated.

The risk factors were comparable and the number of women having diabetes and hypertension were equal in both the groups. Wise et al, concluded that there was no association between diabetes and hypertension as a risk factor for the development of endometrial hyperplasia.<sup>3</sup>

Endometrial thickness of more than 12 mm was considered to be thickened endometrium in premenopausal women with AUB. In the present study the number of women with endometrial thickness of more than 12 mm were 92 out of 100 women which was comparable with the study conducted by Wise et al, 2016 where they concluded that women with endometrium thickness of 12 mm had significantly higher odds of having complex hyperplasia or cancer.<sup>3</sup>

In the present study, the mean endometrial thickness in women who developed endometrial hyperplasia with

atypia was 16 mm and 18 mm in cases and control group respectively which was found to highly associated with the development of endometrial hyperplasia as compared with the previous studies.

Likewise, the mean BMI between the women with hyperplasia with atypia was studied and was found to be 29.25 kg/m<sup>2</sup> in the cases group which was comparable with the study by Wise et al, 2016 where they had a significant association between high BMI and development of endometrial hyperplasia with atypia which was considered to be a precursor to endometrial carcinoma.<sup>3</sup> Obese women had significantly higher odds of having complex hyperplasia or cancer compared to women with normal BMI (adjusted OR, 4.00; 95% Confidence interval (CI), 1.36-11.74),

Renehan et al, 2008 in their study found that for every increase in BMI of 5 kg/m<sup>2</sup> which significantly increased a woman's risk of the development of endometrial cancer (relative risk (RR), 1.59; 95% CI, 1.50-1.68).<sup>9</sup> Therefore, we summarize that premenopausal women with a BMI of >25 kg/m<sup>2</sup> have an increased risk for developing higher grades of hyperplasia of the endometrium than compared to the premenopausal women with the same degree of endometrial thickness cut off of 12 mm.

#### **Limitations of the study**

Statistical significance could not be attained due to limited number of study group. Disease onset to endpoint cannot be commented as it is dependent on the onset of obesity and the menstrual abnormalities to presentation of symptoms. The cut off for different grades of BMI is narrow hence the outcome varies depending on the duration of exposure to different grades of BMI.

#### **CONCLUSION**

Obesity is considered to be an epidemic globally. In the present study we found that increased BMI to be an important independent risk factor for the development of endometrial hyperplasia with atypia which is a precursor to endometrial carcinoma in premenopausal women with AUB. Although age, duration of symptoms and duration of menopause were considered as an important parameter for the evaluation of the endometrium in premenopausal and post-menopausal women, this led to delay in the detection of endometrial carcinoma in these women. Therefore, body mass index should be set as the first criteria for premenopausal women to undergo evaluation of the endometrium for early detection and prevention of endometrial hyperplasia or carcinoma. The association of obesity with endometrial cancer, breast cancer and colonic cancer have been emphasised in the literature. Need for public awareness on the ill effects of cancer which can be prevented by maintaining a normal BMI need to be publicized.

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