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Original Research Article

ASSOCIATION OF METABOLIC SYNDROME WITH BENIGN ENDOMETRIAL PATHOLOGY IN WOMEN WITH ABNORMAL UTERINE BLEEDING – A STUDY AT A TERTIARY CARE TEACHING HOSPITAL

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ABSTRACT

Background: Benign endometrial pathology can cause significant gynecological morbidity which can affect the quality of life. Endometrial hyperplasia, endometrial polyp and disordered proliferative endometrium are the most common benign endometrial pathologies. Besides estrogen, metabolic disorders may also induce the occurrence and development of these proliferative lesions. **Aim:** This study was conducted with the aim to investigate metabolic syndrome and its components as risk factors for benign endometrial pathology. **Materials and Methods:** A case control study was conducted over a period of two years in the department of Obstetrics and Gynaecology, Mallareddy Medical College for Women, Hyderabad. Women presenting with abnormal uterine bleeding were included in the study and endometrial biopsy was done. Women with benign endometrial pathology constituted the case group and those with normal endometrial biopsy formed the control group. Waist circumference, blood pressure, fasting blood glucose and serum lipid profile were measured in both the groups and were compared using unpaired t test and chi-square tests. **Results:** A total of 97 and 211 women constituted the case and the control group respectively. These groups were again divided into two subgroups, premenopausal and postmenopausal groups, based on their menopausal status. Both the groups were comparable with respect to age and parity. Metabolic syndrome and some of its individual components like central obesity, high serum triglyceride level, low HDL cholesterol level and impaired blood glucose were found as risk factors for benign endometrial pathology whereas hypertension, high total cholesterol and high LDL cholesterol levels were not found to be associated with the occurrence of benign endometrial pathology. **Conclusion:** Continued efforts to make lifestyle interventions to control metabolic risk factors may reduce the prevalence of endometrial pathology and prevent the disease progression.

Keywords: Benign endometrial pathology, Endometrial hyperplasia, Endometrial polyp, Metabolic syndrome.

INTRODUCTION

Endometrium is the innermost layer of the uterus, formed by multilayered columnar epithelium which includes both gland cells and stromal cells. Benign endometrial pathology is one of the common diseases of the reproductive system which includes disordered proliferative endometrium, endometrial hyperplasia without atypia and endometrial polyps.

Endometrial hyperplasia is the thickening of the endometrium and is defined as irregular proliferation of the endometrial glands with an increase in the gland to stroma ratio.[1] The revised WHO classification for endometrial hyperplasia which is most widely used and is recommended by the Royal college of obstetricians and gynecologists/British society for gynecological endoscopy joint guideline

2016 separates endometrial hyperplasia into two groups based upon the presence of cytological atypia, hyperplasia without atypia and atypical hyperplasia.[2] Primary presenting symptom of endometrial hyperplasia is abnormal uterine bleeding (AUB), this includes heavy menstrual bleeding, intermenstrual bleeding, irregular bleeding and postmenopausal bleeding.[3] Fifteen percent of the women with postmenopausal bleeding and ten percent of the premenopausal women with AUB have endometrial hyperplasia.[4,5] Endometrial polyp is a localized overgrowth of the endometrium and its prevalence is 7.8 – 34.9%.[6] Polyps can remain silent or may present as intermenstrual bleeding or postmenopausal bleeding. Endometrial hyperplasia and polyps are the two benign structural endometrial pathologies recognized as causes of AUB according to the PALM-COEIN classification endorsed by the International Federation of Gynecology and Obstetrics working group on menstrual disorders (FIGO).[7] Metabolic syndrome is defined by National Cholesterol Education Program Adult Treatment Panel III (NCEP – ATP III) as clustering of at least three of the five following medical conditions, central obesity, high blood pressure, high fasting blood sugar, high serum triglyceride and low serum high density lipoprotein cholesterol.[8]

Endometrium exhibits various histological patterns depending upon the estrogen and progesterone hormone levels, any alteration in the normal balance of these hormones results in an altered histology. Overstimulation of the endometrium due to prolonged unopposed estrogen exposure causes proliferative endometrial disorders which includes a wide spectrum of lesions with disordered proliferative pattern at one end of the spectrum and carcinoma at the other end with intervening stages of hyperplasia. These traditional views do not explain why endometrial pathology still occurs in postmenopausal women with low estrogen level. Thus, other factors besides estrogen may also induce the occurrence and development of these proliferative lesions. Elevation of metabolites like blood sugar, insulin, insulin like growth factor and triglyceride may lead to abnormal endometrial proliferation.

Benign endometrial pathology causes significant gynecological morbidity due to problems associated with menstrual irregularities, abnormal uterine bleeding, anemia, undesirable side effects of prolonged hormonal therapy used in the treatment of these lesions and the risk of malignant transformation. Despite new emerging medical therapy, surgery is still preferred by many women with severe symptoms leading to surgical morbidity and irreversible infertility. It is one the most frequent causes of hospitalization and causes a major impact on a woman's physical, emotional and social quality of life. The incidence of endometrial hyperplasia is estimated to be at least three times higher than endometrial cancer and if left untreated, it can progress to carcinoma.[4,9] The risk of progression of non-atypical hyperplasia and atypical hyperplasia to endometrial carcinoma is < 5% and 28% respectively.[10] Endometrial polyps are associated with carcinogenesis and hyperplasia in 0.8 – 12.9% of patients, these also cause infertility.[11]

Epidemiological studies have shown that the risk of endometrial cancer in diabetic women was 2.4 times higher than that in the non diabetic women, 2.45 times higher in overweight women (BMI> 25 Kg/m) and 3.5 times higher in overweight women with hypertension.12 Increased risk of endometrial cancer in women with metabolic syndrome is reported in a meta-analysis of six studies.13A meta-analysis of 16 studies reported association of diabetes and endometrial carcinoma. A meta-analysis of 26 studies reported that with every 5 units increase in BMI, the risk of endometrial cancer in women increases by 50%.[14,15] There is less knowledge about these modifiable risk factors in relation to benign endometrial pathology.

This study aims to investigate metabolic syndrome and its components as risk factors for benign endometrial pathology.

MATERIALS AND METHODS

The study was conducted as a case control study over a period of two years from June 2021 to June 2023 in the department obstetrics and gynecology at Malla reddy medical college for women, a tertiary care teaching hospital in South India after obtaining approval from the institutional ethical committee. Written informed consent to participate in the research and to publish their data was taken from each participant.

Inclusion Criteria

- All the women aged above 35 years presenting with the complaints of abnormal uterine bleeding.

Exclusion Criteria

- Known cases of endometrial carcinoma.
- Current users of hormone therapy and oral contraceptives.
- Patients on long term tamoxifen therapy.
- Bleeding due to vaginal and cervical pathology.
- Women diagnosed with adnexal pathology like estrogen secreting tumors.
- Women diagnosed with fibroid uterus, adenomyosis, foreign body and endometrial tuberculosis.
- Women with bleeding diathesis.

The sampling frame was bounded by the above inclusion and exclusion criteria. This was a time-based study and all the patients falling in the sampling frame were included in the study. A detailed history regarding age, parity, socioeconomic status, duration and character of abnormal uterine bleeding, menopausal status, obstetric parameters, drug intake and medical co morbidities was taken. Physical examination including general examination, abdominal and bimanual examination was done.

Endometrial biopsy was done by endometrial aspiration curettage using Karman cannula (size 4, 5, 6) under paracervical block by 1% lignocaine and the specimen was placed in 10% formalin and sent for histopathological examination. The patients who were reported as inadequate tissue during histopathological workup were advised a repeat biopsy and those who were reported as having endometrial hyperplasia with atypia and endometrial carcinoma were excluded from the study as the study aims to investigate metabolic syndrome and its components as risk factors for benign endometrial pathology only. Patients were divided into two groups based on endometrial biopsy report. Patients with disordered proliferative endometrium, endometrial polyps and endometrial hyperplasia without atypia constituted the case group and those with proliferative, secretory and atrophic endometrium constituted the control group. The groups were further subdivided into premenopausal and postmenopausal women subgroups.

Height, weight, waist circumference and blood pressure were recorded in both the groups. Two measurements of height, weight, and waist circumference were taken using standardized methods for anthropometric measurements and the average was used as the final measurement. Waist circumference was measured at a point midway between lowest rib and iliac crest with the woman in standing position at the end of normal expiration using a retractable steel measuring tape and the measurement was taken to the nearest 0.1 cm. BMI was computed according to the Quetelet index and obesity was defined as BMI ≥ 30 Kg/m^2.

Blood pressure was recorded in sitting position on the right arm using a digital sphygmomanometer. The measurement was performed twice with an interval of five minutes and if there was a difference of ≥ 10 mm Hg between the two measurements either systolic or diastolic, then a third measurement was recorded after ten minutes resting period. The mean of two readings taken 5 minutes apart was recorded.

Blood was collected after a minimum of eight hours fasting from the antecubital vein following the standardized protocol. The blood sample for fasting blood sugar (FBS) measurement was collected in a vacutainer with sodium fluoride and potassium oxalate as an anticoagulant and glycolytic inhibitor. FBS was determined by Hexokinase method, serum total cholesterol by CHOD – PAP method, and serum HDL cholesterol and LDL cholesterol were determined by direct enzymatic method using Cobas Integra Geo Plus analysis. All the assays were carried out by the laboratory staff blinded with respect to the case - control status of the study participants.

Metabolic syndrome was diagnosed according to the criteria of NCEP – ATP III which defines metabolic syndrome as the presence of three or more of the following five risk factors, central obesity (waist circumference > 88 cm), high serum triglycerides ($\geq$ 150 mg/dl), low HDL cholesterol (< 50 mgs/dl), fasting blood glucose $\geq$ 110 mg/dl and increased blood pressure (systolic BP $\geq$ 130 mm Hg or diastolic BP $\geq$ 85 mm Hg).Serum triglyceride level of $\geq$ 160 mg/dl and total cholesterol level of $\geq$ 240 mg/dl were taken as high in accordance with the NCEP – ATP III criteria.

Values were expressed as numbers and percentages for categorical variables and analyzed statistically using chi square test. Mean ± standard deviation was calculated for continuous variables and analyzed statistically using unpaired t test. Odds ratios were calculated. Statistical analysis was done using Social Science and Graph Pad online software.

Research involving human participants

1. All the procedures performed on the patients were in accordance with the ethical standards of the institutional and national research committee and with the 1975 Helsinki declaration and its latest amendment in 2000 and other comparable ethical standards.

All the treatment and follow up protocols are according to the latest accepted RCOG and NICE guidelines.

RESULTS

A total of 352 women were enrolled in this study and endometrial biopsy was performed, of these 19 women were lost to follow and 34 women were reported as inadequate sample in endometrial biopsy report. Women who were reported as inadequate sample were advised a repeat endometrial biopsy, 27 of these women accepted a repeat biopsy and 7 patients denied. Hence the total number of women in whom endometrial biopsy report could be analyzed was 326 excluding 19 women who were lost to follow up and 7 women who rejected a repeat biopsy. Of the 326 women 89 (27.30%)were postmenopausal and 237 (72.69%) were premenopausal. 53 out of 89 postmenopausal women had a normal endometrial biopsy report and constituted the control group. 36 postmenopausal women had an abnormal biopsy report, of which 2 had atypical hyperplasia and 2 had endometrial carcinoma and were excluded from the study, thus the case group constituted 32 postmenopausal women. 158 out of 237 premenopausal women had a normal biopsy report and constituted the control group. 79 women in the premenopausal group had an abnormal biopsy report, of which 9 had atypical endometrial hyperplasia and 5 had endometrial carcinoma and were excluded, thus the case group was constituted by 65 subjects. Total number of subjects in the control group were 211(158+53) and the total number of subjects in the case group were 97 (32+65).

The demographic and metabolic parameters of the case and control group of the total study population are tabulated in Table 1. The difference between age and parity is statistically insignificant; hence both the groups are comparable. [Table 1]

The association between various metabolic risk factors and benign endometrial pathology in the total study population is shown in Table 2. [Table 2]

Table 3 shows comparison of the demographic and metabolic parameters of the case and the control group of premenopausal subjects. The difference between age and parity is statistically insignificant; hence both the groups are comparable. [Table 3]

Table 4 illustrates the association between various metabolic risk factors and benign endometrial pathology in premenopausal subjects. [Table 4]

Demographic and metabolic parameters of the case and the control group of postmenopausal subjects are tabulated in Table 5. [Table 5]

Table 6 shows the association between various metabolic risk factors and benign endometrial pathology in postmenopausal subjects. [Table 6]

Table 1: Comparison of baseline characteristics and metabolic parameters of the total study population

S.No.	Variable	Case Group[a] (N = 97)	Control Group[b] (N = 211)	P Value
1.	Age (years) (Mean ± SD)	46.26 ± 5.02	46.52 ± 6.13	0.70†
2.	Parity (Mean ± SD)	2.10 ± 0.95	2.20 ± 0.88	0.38†
3.	BMI (Kg/m^2) (Mean ± SD)	27.63 ± 4.40	26.10 ± 4.10	0.003*
4.	Waist Circumference (cm)			
	Mean ± SD	90.35±9.39	86.68±7.65	0.0003*
	> 88 cm (n) (%)	56 (57.73%)	81 (38.38%)	0.001*
5.	HDL Cholesterol (mg/dl)			
	Mean ± SD	42.73± 7.83	45.83±8.03	0.001*
	< 50 mg/dl (n) (%)	78 (80.41%)	133 (63.03%)	0.002*
6.	Triglyceride (mg/dl)			
	Mean ± SD	139.32 ± 38.16	125.61 ± 34.84	0.002*
	≥150 mg/dl (n) (%)	47 (48.45%)	63 (29.85%)	0.001*
7.	LDL Cholesterol (mg/dl)			
	Mean ± SD	110.92 ± 30.98	104.66 ± 28.75	0.08†
	≥ 160 mg/dl (n) (%)	11 (11.34%)	20 (9.47%)	0.61†
8.	Total Cholesterol (mg/dl)			
	Mean ± SD	163.88 ± 42.77	160.98 ± 38.14	0.55†
	≥ 240 mg/dl (n) (%)	10 (10.30%)	18 (8.53%)	0.61†
9.	Fasting Plasma Glucose (mg/dl)			
	Mean ± SD	97.99± 14.55	92.52± 12.90	0.001*
	≥110 mg/dl (n) (%)	27 (27.83%)	30 (14.21%)	0.004*
10.	Hypertension			
	≥130/85 mm Hg (n) (%)	33 (34.02%)	60 (28.43%)	0.32†
	Systolic BP mm Hg (Mean ± SD)	125.39± 13.71	122.34± 14.46	0.08†
	Diastolic BP mm Hg (Mean ± SD)	81.15± 9.80	78.83±9.56	0.05†
11.	Metabolic Syndrome (n) (%)	60 (61.85%)	88 (41.70%)	0.001*

[a] Case Group: Subjects with Benign Endometrial Pathology
[b] Control Group: Subjects with Normal Endometrium
*- Statistically significant P Value † - Statistically Insignificant P Value

Table 2: Odds ratio for Benign Endometrial Pathology according to metabolic risk factors in total study population

S. No.	Risk Factor	Case Group[a] N = 97	Control Group[b] N = 211	Odds Ratio (95% CI)	P Value
1.	Waist Circumference > 88cms				
	Yes	56 (57.73%)	81 (38.38 %)	2.19	0.001*
	No	41 (42.26%)	130 (61.61 %)	(1.34-3.57)	
2.	HDL Cholesterol < 50 mg/dl				
	Yes	78 (80.41%)	133 (63.03 %)	2.41	0.002*
	No	19 (19.58%)	78 (36.96 %)	(1.35-4.27)	
3.	Triglyceride ≥ 150 mg/dl				
	Yes	47 (48.45%)	63 (29.85 %)	2.21	0.001*
	No	50 (51.54%)	148 (70.14 %)	(1.34-3.62)	
4.	LDL Cholesterol ≥ 160 mg/dl				
	Yes	11 (11.34%)	20 (9.47 %)	1.22	0.613†
	No	86 (88.65%)	191 (90.52 %)	(0.56-2.66)	
5.	Total Cholesterol ≥ 240 mg/dl				
	Yes	10 (10.30%)	18 (8.53 %)	1.23	0.614†
	No	87 (89.69%)	193 (91.46 %)	(0.54-2.77)	
6.	Fasting Plasma Glucose ≥110 mg/dl				
	Yes	27 (27.83%)	30 (14.21 %)	2.33	0.004*
	No	70 (72.16%)	181 (85.78 %)	(1.29-4.19)	
7.	Hypertension				
	Yes	33 (34.02%)	60 (28.43 %)	1.30	0.32†
	No	64 (65.97%)	151 (71.56 %)	(0.77-2.17)	
8.	Metabolic Syndrome				
	Yes	60 (61.85%)	88 (41.70 %)	2.27	0.001*
	No	37 (38.14%)	123 (58.29 %)	(1.38-3.70)	

[a] Case Group: Subjects with Benign Endometrial Pathology
[b] Control Group: Subjects with Normal Endometrium
*- Statistically significant P Value † - Statistically Insignificant P Value

Table 3: Comparison of baseline characteristics and metabolic parameters of premenopausal subjects

S.No.	Variable	Case Group[a] (N = 65)	Control Group[b] (N = 158)	P Value
1.	Age (years) (Mean ± SD)	44.59 ± 4.30	43.49± 4.29	0.08†
2.	Parity (Mean ± SD)	2.06 ± 0.95	2.16 ± 0.87	0.43†
3.	BMI (Kg/m^2) (Mean ± SD)	27.66 ± 4.19	26.25 ± 4.20	0.02*
4.	Waist Circumference (cm)			
	Mean ± SD	89.25±9.01	86.20±7.76	0.01*
	> 88 cm (n) (%)	38 (58.46%)	64 (40.50%)	0.01*
5.	HDL Cholesterol (mg/dl)			
	Mean ± SD	42.52± 7.48	45.40±7.97	0.01*
	< 50 mg/dl (n) (%)	53 (81.53%)	103 (65.18%)	0.01*
6.	Triglyceride (mg/dl)			
	Mean ± SD	141.35 ± 38.38	128.98 ± 35.73	0.02*
	≥150 mg/dl (n) (%)	34 (52.30%)	54 (34.17%)	0.01*
7.	LDL Cholesterol (mg/dl)			
	Mean ± SD	110.31 ± 30.46	105.40 ± 28.43	0.25†
	≥ 160 mg/dl (n) (%)	7 (10.76%)	15 (9.49%)	0.70†
8.	Total Cholesterol (mg/dl)			
	Mean ± SD	165.38 ± 44.60	163.40 ± 39.02	0.74†
	≥ 240 mg/dl (n) (%)	7 (10.76%)	14 (8.86%)	0.76†
9.	Fasting Plasma Glucose (mg/dl)			
	Mean ± SD	96.42± 14.68	92.20± 12.53	0.03*
	≥110 mg/dl (n) (%)	17 (26.15%)	23 (14.55%)	0.04*
10.	Hypertension			
	≥130/85 mm Hg (n) (%)	21 (32.30%)	44 (27.84%)	0.50†
	Systolic BP mm Hg (Mean ± SD)	123.05± 13.44	120.78 ± 15.08	0.29†
	Diastolic BP mm Hg (Mean ± SD)	80.14± 9.54	78.42±9.66	0.22†
11.	Metabolic Syndrome (n) (%)	38 (58.46%)	64 (40.50%)	0.01*

[a] Case Group: Subjects with Benign Endometrial Pathology
[b] Control Group: Subjects with Normal Endometrium
*- Statistically significant P Value † - Statistically Insignificant P Value

Table 4: Odds ratio for Benign Endometrial Pathology according to metabolic risk factors in premenopausal subjects

S. No.	Risk Factor	Case Group[a](N = 65)	Control Group[b] (N = 158)	Odds Ratio (95% CI)	P Value
1.	Waist Circumference > 88cms				
	Yes	38 (58.46%)	64 (40.50%)	2.07	0.01*
	No	27 (41.53%)	94 (59.49%)	(1.14- 3.71)	
2.	HDL Cholesterol < 50 mg/dl				
	Yes	53 (81.53%)	103 (65.18%)	2.36	0.01*
	No	12 (18.46%)	55 (34.81%)	(1.16-4.78)	
3.	Triglyceride ≥ 150 mg/dl				
	Yes	34 (52.30%)	54 (34.17%)	2.11	0.01*
	No	31 (47.69%)	104 (65.82%)	(1.17-3.80)	
4.	LDL Cholesterol ≥ 160 mg/dl				
	Yes	7 (10.76%)	15 (9.49%)	1.15	0.77†
	No	58 (89.23%)	143 (90.50%)	(0.45-2.97)	
5.	Total Cholesterol ≥ 240 mg/dl				
	Yes	7 (10.76%)	14 (8.86%)	1.24	0.65†
	No	58 (89.23%)	144 (91.13%)	(0.48-3.23)	
6.	Fasting Plasma Glucose ≥110 mg/dl				
	Yes	17 (26.15%)	23 (14.55%)	2.08	0.04*
	No	48 (73.84%)	135 (85.44%)	(1.02-4.22)	
7.	Hypertension				
	Yes	21 (32.30%)	44 (27.84%)	1.24	0.50†
	No	44 (67.69%)	114 (72.15%)	(0.66-2.31)	
8.	Metabolic Syndrome				
	Yes	38 (58.46%)	64 (40.50%)	2.06	0.01*
	No	27 (41.53%)	94 (59.49%)	(1.15-3.72)	

[a] Case Group: Subjects with Benign Endometrial Pathology
[b] Control Group: Subjects with Normal Endometrium
*- Statistically significant P Value † - Statistically Insignificant P Value

Table 5: Comparison of baseline characteristics and metabolic parameters of postmenopausal subjects

S.No.	Variable	Case Group[a] (N = 32)	Control Group[b] (N = 53)	P Value
1.	Age (years) (Mean ± SD)	52.69 ± 4.63	51.25± 3.50	0.10†
2.	Parity (Mean ± SD)	2.19 ± 0.97	2.30 ± 0.91	0.58†
3.	BMI (Kg/m^2) (Mean ± SD)	25.65 ± 3.78	27.55 ± 4.88	0.04*
4.	Waist Circumference (cm)			
	Mean ± SD	92.59±9.91	87.81 ±7.30	0.01*
	> 88 cm (n) (%)	18 (56.25 %)	17 (32.07 %)	0.02*
5.	HDL Cholesterol (mg/dl)			
	Mean ± SD	43.16± 8.62	47.13±8.15	0.03*
	< 50 mg/dl (n) (%)	25 (78.12 %)	30 (56.60 %)	0.04*
6.	Triglyceride (mg/dl)			
	Mean ± SD	135.19 ± 37.98	115.55 ± 30.16	0.01*
	≥150 mg/dl (n) (%)	13 (40.62 %)	9 (16.98 %)	0.01*
7.	LDL Cholesterol (mg/dl)			
	Mean ± SD	112.19 ± 32.45	102.47 ± 29.83	0.16†
	≥ 160 mg/dl (n) (%)	4 (12.50 %)	5 (9.43 %)	0.65†
8.	Total Cholesterol (mg/dl)			
	Mean ± SD	160.84 ± 39.28	153.77 ± 34.74	0.38†
	≥ 240 mg/dl (n) (%)	3 (9.37 %)	4 (7.54 %)	0.76†
9.	Fasting Plasma Glucose (mg/dl)			
	Mean ± SD	101.19± 13.95	93.49± 14.03	0.01*
	≥110 mg/dl (n) (%)	10 (31.25 %)	7 (13.20 %)	0.04*
10.	Hypertension			
	≥130/85 mm Hg (n) (%)	12 (37.50 %)	16 (30.18 %)	0.49†
	Systolic BP mm Hg (Mean ± SD)	130.16± 13.19	126.98± 11.35	0.24†
	Diastolic BP mm Hg (Mean ± SD)	83.28 ±10.13	80.23±9.21	0.15†
11.	Metabolic Syndrome (n) (%)	22 (68.75%)	24 (45.28%)	0.03*

[a] Case Group: Subjects with Benign Endometrial Pathology
[b] Control Group: Subjects with Normal Endometrium
*- Statistically significant P Value † - Statistically Insignificant P Value

Table 6: Odds ratio for Benign Endometrial Pathology according to metabolic risk factors in postmenopausal subjects

S. No.	Risk Factor	Case Group[a](N = 32)	Control Group[b](N = 53)	Odds Ratio	P Value
1.	Waist Circumference > 88cms				
	Yes	18 (56.25 %)	17 (32.07 %)	2.72	0.02*
	No	14 (43.75 %)	36 (67.92 %)	(1.10-6.73)	
2.	HDL Cholesterol < 50 mg/dl				
	Yes	25 (78.12 %)	30 (56.60 %)	2.74	0.04*
	No	7 (21.87 %)	23 (43.39 %)	(1.00-7.43)	
3.	Triglyceride ≥ 150 mg/dl				
	Yes	13 (40.62 %)	9 (16.98 %)	3.35	0.01*
	No	19 (59.37 %)	44 (83.01 %)	(1.22-9.15)	
4.	LDL Cholesterol ≥ 160 mg/dl				
	Yes	4 (12.50 %)	5 (9.43 %)	1.37	0.65†
	No	28 (87.50 %)	48 (90.56 %)	(0.34-5.53)	
5.	Total Cholesterol ≥ 240 mg/dl				
	Yes	3 (9.37 %)	4 (7.54 %)	1.27	0.76†
	No	29 (90.62 %)	49 (92.45 %)	(0.26-6.06)	
6.	Fasting Plasma Glucose ≥110 mg/dl				
	Yes	10 (31.25 %)	7 (13.20 %)	2.99	0.04*
	No	22 (68.75 %)	46 (86.79 %)	(1.00-8.90)	
7.	Hypertension				
	Yes	12 (37.50 %)	16 (30.18 %)	1.39	0.48†
	No	20 (62.50 %)	37 (69.81 %)	(0.55-3.50)	
8.	Metabolic Syndrome				
	Yes	22 (68.75 %)	24 (45.28 %)	2.66	0.03*
	No	10 (31.25 %)	29 (54.71 %)	(1.06-6.69)	

[a] Case Group: Subjects with Benign Endometrial Pathology
[b] Control Group: Subjects with Normal Endometrium
*- Statistically significant P Value † - Statistically Insignificant P Value

DISCUSSION

The rising incidences of obesity, metabolic diseases and physical inactivity have been associated with an increase in the incidence of endometrial hyperplastic disorders and endometrial cancer worldwide. Endometrial cancer is the most common gynecological malignancy affecting women in the developed countries and the second most common

gynecological malignancy worldwide due to the high rate of cervical cancer in the developing world.[16] There are several lines of evidence that, diagnosis of endometrial hyperplasia may precede the development of endometrial cancer and that the two have common predisposing risk factors. Besides being a precursor for endometrial cancer, benign endometrial lesions cause AUB, anemia and side effects of prolonged hormonal therapy used in its treatment which significantly affects the quality of life of a woman. Endometrial polyps also affect her fertility.

Prevalence of endometrial pathology is increasing even in the postmenopausal women. The peak incidence of simple hyperplasia of 142 per 100 000 woman-years, and of complex hyperplasia of 213 per 100 000 woman-years, are seen in the early 50s; while that of atypical hyperplasia (56 per 100 000 woman-years) is in the early 60s.[9]

In this study we found that the prevalence of metabolic syndrome, central obesity, high fasting plasma glucose, high serum triglyceride level and low HDL cholesterol level was high in the case group with benign endometrial pathology when compared to the control group in both premenopausal and postmenopausal women and the difference was found to be statistically significant. Hypertension, high total cholesterol and high LDL cholesterol levels were not significantly related with the occurrence of benign endometrial pathology in this study.

In obese women, adipose derived aromatase converts circulating androstenedione into estrone and testosterone to estradiol, thereby increasing the serum estrogen level which causes endometrial hyperplasia.[17] As the estradiol level decreases after menopause, there is increase in the total body fat which mainly accumulates around the abdomen causing central obesity, this causes increased peripheral conversion of the androgens to estrone, leading to increase in total estrogen level and prolonged unopposed estrogen action on the endometrium. Endometrial pathology can occur in perimenopausal period due to anovulatory cycles. This can be further aggravated by obesity, as obesity also leads to chronic anovulation. In addition to the unopposed estrogen action due to anovulatory cycles causing endometrial hyperplasia in these women, the metabolic factors like increased insulin levels, increased blood glucose levels and inflammatory mediators can also cause increased proliferation of the endometrial cells leading to a synergistic effect.

Obesity also causes a state of chronic low-grade inflammation, leading to secretion of pro inflammatory factors by the adipocytes and enhancing the infiltration of macrophages and T lymphocytes. These factors further promote abnormal proliferation and transformation of normal cells.[18] Obesity and diabetes mellitus cause insulin resistance and hyperinsulinemia. Insulin which is an anabolic hormone, and insulin like growth factor 1 (IGF – 1) causes proliferation of the endometrium. Insulin resistance decreases the synthesis of sex hormone binding globulin (SHBG) and thus increases free estrogen level. High insulin and IGF1/2 level in diabetic patients accelerate the transformation of androstenedione to estrogen by aromatase. Systemic hyperglycemia even provides a favorable condition for energy metabolism of cancer cells.

In this study the mean value of BMI, prevalence of waist circumference of > 88 cm and the prevalence of metabolic syndrome was found to be significantly higher in case group with benign endometrial pathology than in the control group in both premenopausal and postmenopausal women. A study by Onalanet al has also shown obesity as a risk factor of benign endometrial pathology which is consistent with the present study.[19] A study by Alberti et al has shown that obesity is a key factor in the development of metabolic syndrome.[20] Obesity increases the risk of endometrial hyperplasia and cancer in young women < 25 years, most commonly in those with BMI > 30 kg/m2. The risk of relapse of benign endometrial pathology is also common and higher in obese women, 3 folds higher in women with a BMI > 30 kg/m2.[21] Low HDL cholesterol is associated with an increase in free estradiol but no effect on progesterone levels, thereby causing unopposed estrogen exposure. A large sample sized study showed positive correlation of high serum triglyceride, total cholesterol and LDL cholesterol level and negative correlation of low serum HDL cholesterol with endometrial cancer.[22] But this study did not find any positive correlation between high total cholesterol and LDL cholesterol level and the benign endometrial pathology. Cust et al reported that low HDL cholesterol and high triglyceride level was associated with increased risk of endometrial cancer while high total cholesterol and LDL cholesterol level were not.[23] Lindemann et al showed that high triglyceride level was associated with increase in the risk of endometrial cancer while high total cholesterol, high LDL cholesterol and low HDL cholesterol levels were not associated.[24] A causal association has been found between high fasting blood glucose level and benign endometrial pathology in both premenopausal and postmenopausal women in this study. Goldman et al found that high glucose level acts as an energy source for the proliferation of tumor cells and thus increases the risk of endometrial cancer.[25]

The limitation of this study was that hysteroscopic guided biopsy was not done and fasting plasma insulin level was not measured due to technical short comings.

Awareness regarding modifiable risk factors of endometrial pathology including obesity, dietary modifications, impaired glucose tolerance, diabetes, physical inactivity and dyslipidemia through health education programs will be beneficial.

CONCLUSION

Metabolic syndrome, obesity, dyslipidemia and raised blood glucose levels were found as risk factors for benign endometrial pathology. Besides being a precursor of endometrial cancer, benign endometrial pathologies are a common cause for abnormal uterine bleeding, anaemia and infertility, impairing a woman's physical, social and mental quality of life. Interventions to control the modifiable risk factors would reduce the burden of endometrial pathologies and its effects on the quality of life to a greater extent.

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