



Hyperinsulinemia and Other Risk Factors in Endometrial Carcinoma

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Abstract

Thirty Patients of Histologically confirmed endometrial carcinoma admitted and treated over a period of three years in the department of obstetrics and Gynecology Govt Medical College Jammu, were studied to evaluate the risk factors in endometrial Carcinoma. The major risk factors in this study were hyperinsulinemia, hypertension, obesity and increasing age. Hyperinsulinemia has a potential role in growth and development of endometrial carcinoma, as insulin, in postmenopausal women with endometrial carcinoma, leads to increased stromal secretion of androstenedione which gets aromatized to form unbound oestradiol, having proliferative action on endometrium. The other risk factors noted in the study were early menarche, heavy menstrual flow, late menopause and diabetes. Since most of the risk factors are associated with hyperinsulinemia and insulin resistance, hyperinsulinemia can act as a good clinical marker in patients of endometrial carcinoma.

Key Words

Endometrial Carcinoma, Risk Factors, Hyperinsulinemia

Introduction

Carcinoma of endometrium is the fourth most common malignancy in women after breast, bowel and lung and accounts for 8% of all cancers in women. Familial and genetic predisposition is suggested by its association with other primary cancers out side the uterus(1). Certain risk factors are consistently associated with development of endometrial carcinoma which include increasing age, with 75% of the patients being postmenopausal, hypertension, obesity, early menarche, late menopause, menstrual disorders, gall bladder and liver disease, hypothyroidism and exogenous exposure to oestrogen (2). Women with android obesity as measured by waist-hip ratio have higher levels of non protein bound oestrogen and thus increased chances of endometrial carcinoma (3). Hyperinsulinemia has been noted as the most important risk factor associated with endometrial carcinoma (4). However, to best of our knowledge no similar study has been carried from Jammu. Hence the present study was designed with primary objective to study various risk factors for endometrial cancer in our population with emphasis on relationship between fasting insulin and fasting plasma glucose in these patients.

Materials and Methods

This study was conducted on a series of thirty patients with confirmed diagnosis of endometrial carcinoma. Detailed history regarding demographic factors, diet, menstruation, pregnancies, menopause, use of exogenous hormones, personal and family history of cancer, diabetes, hypertension and obesity was recorded. Patients were examined for hirsutism and acanthosis nigricans. Blood pressure was recorded and waist-hip ratio and body mass index were calculated. Manual examination of breast was done for malignancy. Transabdominal pelvic ultrasonography was also done in each patient to look for uterine size, endometrial thickness and any growth in the uterus or ovaries. The diagnosis of endometrial cancer was established by histopathology of the tissue taken by endometrial biopsy or from specimen after hysterectomy. Laboratory investigations included routine investigations and estimation of fasting plasma glucose by enzymatic method (glucose oxidase-peroxidase method). Serum insulin quantitative measurement was done by the radioimmunoassay using (RIA kit-BARC Mumbai). This method is based upon the competition of unlabelled insulin in the standard or samples and radioiodiated (I-125)

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insulin, for the limited binding sites on a specific antibody. At the end of incubation the antibody-bound and free insulin were separated by polyethylene glycol (PEG) aided separation method. Insulin concentration of samples was quantitated by measuring the radio activity associated with the bound fraction of sample and standard.

Results

The maximum number of patients (60%) with endometrial carcinoma were found in age group of 60-69 years. More than 60% of patients were multiparous. 63.3% of the patients belonged to social class I & II. 97% of the patients had menstrual irregularity with moderate to heavy flow. 50% had menopause after 50 years of age, only 16.7% of the patients were in premenopausal age group. More than 60% of the patients presented with pain lower abdomen and post menopausal bleeding. 16% of the patients were on exogenous hormone therapy (i.e oestrogen). Ratio of fasting glucose/ fasting insulin 4.5, an indicator of insulin resistance was present in 80% patients with endometrial carcinoma. Hypertension and diabetes was found in 46.7% and 16.7% patients respectively. All the patients with diabetes had co-existing hypertension. 10% of patients had associated cholelithiasis. Only 3.3% of patients had associated hypothyroidism

Discussion

The peak age of incidence for endometrial cancer in our study was 60-69 years. In postmenopausal women the incidence of hyperinsulinemia is high which has implications for the development of endometrial carcinoma (5). Women with gall bladder and chronic liver disease have higher risk of developing endometrial carcinoma because of impaired conjugation and inactivation of oestrogen with chronic exposure of endometrium to oestrogen (6). In this study 10% cases had gall bladder disease. The incidence of endometrial carcinoma is high in nulliparous females as suggested by previous studies (7), where as in the present series this incidence was only 3.3%, which is in contrast to risk factor, the reason being that the protective effect of pregnancy is for short term and tends to flatten off with advancing age (8). Some studies reported that parous women had only 30% lower risk of endometrial carcinoma. Obesity accelerates the peripheral conversions of androgen to oestrogen and unopposed oestrogen contributes to increased endometrial cancer risk (9). In our study 3.3% of the patients were obese but 56.7% of patients were overweight with a BMI ranging 25-30 kg/m². Women with upper body fat distribution as measured by waist-hip ratio appeared to

Table 1. Demographic Profile and Risk Factors of Endometrial Carcinoma (n=30)

S.No	Clinical Characteristics	No. of Patients	Percentage
1.	Age in Years (60-69 years)	14	46.7
2.	Parity >P4	18	60.0
3.	Socio Economic Class (Class II)	10	33.3
4.	Prolonged Menstrual Span (4-6 Days)	22	73.3
5.	Age at menopause (50-54 years)	13	43.3
6.	Clinical presentation		
	(a) Post menopausal bleeding	18	60.6
	(b) Pain lower abdomen	15	50.0
7.	Medical disorders		
	(a) Hypertension	14	46.7
	(b) Diabetes mellitus	5	16.7
	(c) Cholelithiasis	3	10.0
	(d) Thyroid disorders	1	3.3
	(e) History of other cancers	1	3.3
8.	Body Mass Index (BMI/ kg ²) 25.0-29.9)	17	56.7
9.	Waist-hip ratio (0.80-0.85)	22	73.5
10.	Fasting blood sugar (mg/100ml) 80-119	20	66.7
11.	Fasting insulin level (micro U/ml) >20	24	80.0



be at greater risk of endometrial carcinoma (10). In our study 16.7 % of patients had waist-hip ratio >0.85 , suggestive of android obesity. Higher prevalence of hypertension in patients with endometrial carcinoma could again be related to hyperinsulinemia and insulin resistance as established in other studies (11). Fasting hyperinsulinemia is considered a marker of insulin resistance and value of fasting glucose and serum insulin levels are often taken as clinical markers of magnitude of insulin resistance. Increased insulin resistance may result from a high calorie diet and inadequate exercise in genetically susceptible individuals. Specific changes in ovarian steroidogenesis may then lead to higher concentration of oestradiol and androstenedione which are responsible for increased risk of endometrial cancer (4). In our study 80% patients had elevated insulin level indicating hyperinsulinemia.

A Recent study from USA (12) showed that among 99 patients of endometrial carcinoma, diabetes was present in 30. Increased risk of IR was significantly associated with higher body mass index ($P < .001$), lower socioeconomic status ($P = .007$), and nulliparity ($P = .029$). Thereby, suggesting that IR is highly prevalent in endometrial cancer patients, including nonobese women.

In another study from Italy (13), the multivariate ORs of endometrial cancer were 2.18 for type 2 diabetes, 1.77 for hypertension, 1.20 for hyperlipidemia, between 1.62 and 2.23 for various definitions of central obesity, and 3.83 for women with a body mass index (BMI) >30 kg/m². The risk of endometrial cancer was significantly increased for subjects with MetS, the ORs ranging between 1.67 and 2.77 when waist circumference was included in MetS definition, and 8.40 when BMI was considered instead.

In an epidemiological study (14) Approximately 290,000 women from Austria, Norway, and Sweden were enrolled during 1974-2005, with measurements of height, weight, systolic and diastolic blood pressure, and circulating levels of glucose, total cholesterol, and triglycerides. A total of 917 endometrial carcinomas and 129 fatal cancers were identified. Increased risks of incident endometrial carcinoma and fatal uterine corpus cancer were seen for the metabolic syndrome factors combined, as well as for individual factors (except for cholesterol). The relative risk of endometrial carcinoma for the metabolic syndrome was 1.37 (95% confidence interval: 1.28, 1.46) per 1-unit increment of z score. The positive associations between metabolic syndrome factors (both individually and combined) and endometrial carcinoma were confined to the heaviest women. The association between the metabolic syndrome and

endometrial carcinoma risk seems to go beyond the risk conferred by obesity alone, particularly in women with a high body mass index. The current study though is of short duration and with less number of patient but provides for the first time a pivotal information regarding association of endometrial carcinoma and hyperinsulinemia from the region of J&K.

Conclusion

This study suggests that women with extremes of age, heavy menstrual flow, diabetes, obesity, hypertension and hyperinsulinemia are known risk factors for endometrial cancer. Hyperinsulinemia is the most important factor in growth and development of endometrial cancer. This stresses the need for detection and correction of insulin resistance in patients of endometrial carcinoma.

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